National Institute for Health and Care Excellence

Version 1.0 Pre-consultation

Oesophago-gastric cancer: assessment and management in adults

Appendix F

Clinical Guideline

Clinical evidence tables

12 May 2017

Draft for Consultation

Developed by the National Guideline Alliance, hosted by the Royal College of Obstetricians and Gynaecologists

Disclaimer
Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and/or their guardian or carer.

ISBN:

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Appendix F:Evidence tables

F.1 Radical treatment

What are the specific information and support needs before and after treatment for adults with oesophago-gastric cancer who are suitable for radical treatment and their carers?

Study details	Participants	Methods	Findings and Results	Comments
Full citation Andreassen, S., Randers, I., Naslund, E., Stockeld, D., Mattiasson, A., Family members' experiences, information needs and information seeking in relation to living with a patient with oesophageal cancer, European Journal of Cancer Care, 14, 426-434, 2005 **Ref Id** 476910 **Country/ies where the study was carried out** Sweden **Study type**	**Sample size** N=9 **Characteristics** The sample consisted of close family members: one brother, two husbands and six wives. Five family members had full-time or part-time employment and four family members were retired. **Inclusion criteria**	Sample selection Convenience sampling- family members of study participants Data Collection The first author conducted the interviews at a time and place chosen by the participants. That is, six interviews were carried out at the participant's home, two at the first researcher's office and one at a hospital. An interview guide was developed to identify the areas to be covered. However, all interviews started by an open-ended question: 'Will you tell us a little about your experiences	**Themes and Categories** **Results** **Category: Intrusions on Family** Theme: Children Family members in this study emphasized the importance of including the whole family in the care given, even the children, whatever their level of knowledge or ability to understand are, because the children were aware that a tremendous change had occurred in the family. (author's comment) *I don't think anyone has ever asked how old our children*	**Limitations** CASP Quality Assessment Tool Aims Was there a clear statement of the aims of the research? Yes Is a qualitative methodology appropriate? Yes Was the research design appropriate to address the aims of the research? Yes Sample selection

Study details	Participants	Methods	Findings and Results	Comments
Qualitative study- semi-structured interviews **Aim of the study** To describe family members' experiences, information needs and information seeking in relation to living with a patient suffering from oesophageal cancer. **Study dates** December 2003 and January 2004 **Source of funding** This work was supported by grants from Sophiahemmet University College, and The Sophiahemmet Foundation for Clinical Research, Stockholm, Sweden.	The selection criteria for the participants in this study were that they should be a close family member or significant other to the patient and interested in participating in the present study. So, from an ongoing study in which 13 patients are included, nine family members were identified. **Exclusion criteria** Not reported	of your family member's illness?' This question permitted the participants to talk freely about their experiences of information needs, and their information seeking. The interviews lasted about 1 hour (one of them about 20 min). All interviews were audiotaped with the participant's consent and transcribed verbatim. Data Analysis Content analysis was used in analysis of the data. When analysing the part of the interviews involving the illness experiences, an inductive approach (Berg 2004) was used, while a deductive approach (Berg 2004) was used when analysing the data covering the participants' information needs and information seeking. The inductive approach went as following; the interviews were read through to gain an overall picture. They were	*are, if they visit school or anything like that. They don't seem to care that there is a family around the patient and that we in fact have a sixteen-year-old son, who has grown up with this.* (family member comment) It was evident that the children became anxious and stressed which affected their school life. Moreover, they had to struggle much on their own. (author's comment) *Our son had his 18th birthday this year. Although he himself says that his mother's illness doesn't affect him at all, we have noted that his grades dropped disastrously during his first term.* (family member comment) The family members called attention to the importance of preparing the children for a changed family situation. Crucial for the family members was that their	Was the recruitment strategy appropriate to the aims of the research? Yes- purposive sampling of family member already participating in other study Has the relationship between researcher and participants been adequately considered? No Data collection Was the data collected in a way that addressed the research issue? Probably Yes; data saturation not discussed by author Have ethical issues been taken into consideration? Yes (private and confidentiality) Data Analysis

Study details	Participants	Methods	Findings and Results	Comments
		then reread several times with the aim of the study in mind. Text units, i.e. a word, a sentence or a whole paragraph, that answered the questions at issue were marked and condensed into a description of their manifest content. From these descriptions, different themes were formed and organized into categories. Representative quotations have been used to illustrate themes. The initial procedure used in the deductive analysis was the same as above, but text units were identified in relation to information needs and information seeking. In this study, three authors read the interviews and checked the categorization, and the agreement was considerably unambiguous.	children should participate in information giving. Participation could facilitate the children's preparedness. (author's comment) *I think it would be good to receive joint information, to involve the children, since the parent, who comes home is a little foreign. You can say: 'One parent left and another one came home who is also a patient at home.' (family member comment)* **Category: Uncertainty** Theme: Course and prognosis The family members experienced an everyday symptomatic uncertainty and looked for signs for deterioration. (author comment) *You know all the time that one day it will get worse. You may receive an answer*	Was the data analysis sufficiently rigorous? Details of content analysis provided as well as references for data analysis method, 3 different authors read interviews and checked categorization Findings/results Is there a clear statement of findings? Y Overall quality: MODERATE **Other information**

Study details	Participants	Methods	Findings and Results	Comments
			that it is a metastasis, exactly as we received now. I live constantly with this. (family member comment) A prognostic uncertainty is a medical reality in patients with oesophageal cancer, which even these family members had to live with: '*Since after five years one is considered be out of the danger zone, we can calculate that my husband will in some form be given a clean bill of health, but perhaps not quite be declared healthy*.' (family comment) Theme: Future The uncertainty of death and dying pervaded the family members' thoughts and plans for the future. They expressed: *Shall we sell the house or shall we not? Shall we renovate our house or shall we not. Shall I work full time or shall I not?' 'Will my husband die tomorrow, or what?*	

Study details	Participants	Methods	Findings and Results	Comments
			Heredity The family members expressed a genetic threat and concerns about the connection between genetics and cancer. They were also worried if the children would inherit the cancer. (author comment) *What worries me most is that the illness will affect the children. If they will get this . . . whether it is hereditary. (family member comment)* *Since my brother now has cancer of the oesophagus and all my other siblings and my mother and father also had cancer, I want to know if I am exposed to cancer and have it in my genes, so I can take some special tests. (family member comment)* **Category: Managing Uncertainty**	

Study details	Participants	Methods	Findings and Results	Comments
			Theme: seeking information from interpersonal sources Subtheme: experts In order to learn, receive understanding for the illness and handle the uncertainty, the family members entrusted themselves to the experts, i.e. the physicians, who were considered the major source of information. The family members accompanied the patient when consulting the physician and took an active part by listening and asking specific questions concerning oesophageal cancer. *The doctor is our lifeline. When you are so close to the experts as we are now, we ought to get the truth directly from the doctor if there is anything we wonder about. We have*	

Study details	Participants	Methods	Findings and Results	Comments
			entrusted ourselves to the experts. (family member comment) In this study the family members also felt connected to the nurses who could answer questions of importance, and give practical and emotional support. *It's easier to talk with a nurse when it concerns important questions. You may receive quite good and reassuring answers. / . . . / You get a feeling of trust when you talk with a nurse. (family member comment)* Moreover, the patients themselves were considered experts. *I haven't asked anything myself because I knew that*	

Study details	Participants	Methods	Findings and Results	Comments
			my husband would ask everything so minutely himself. I know he would look up everything himself. He has shared his knowledge with me and we have discussed it together. (family member comment) Despite knowing that the physicians are able to provide information about diagnosis, prognosis and treatment, the family members did not always turn to them with questions. They sometimes thought they could not formulate questions since they did not always know enough in order to ask. This lead to a feeling of being left out of certain knowledge that perhaps should be of value for understanding the situation. However, all of the family members did not want to discuss and ask specific questions with the physician when the patient listened. (author comment)	

Study details	Participants	Methods	Findings and Results	Comments
			I don't want to ask the doctor a question, which he has to respond to negatively when my husband is with me. Some of the family members reported that not asking questions was due to their lack of medical knowledge about oesophageal cancer. (author comment) *You are not enough medically knowledgeable. Therefore, you don't know what to ask.* Subtheme: social network and kinship The family members contacted persons in the family's circle who had specific knowledge of the illness and in whom they felt confidence.	

Study details	Participants	Methods	Findings and Results	Comments
			I trusted the judgements that doctors in our acquaintance circle gave, but not completely, since they are not in the field. They can't be well read in all areas. Theme: media sources Subtheme: daily newspaper and TV Through personal experiences and by following cancer reports in daily newspapers and on TV, the family members had general knowledge and understanding about different cancer diagnoses. Concerning oesophageal cancer, they were ignorant and had never heard of the disease. (author comment)	

Study details	Participants	Methods	Findings and Results	Comments
			I hadn't heard about that disease. I think you have heard about most of the variations, but not cancer of the oesophagus. (family member comment) However, the family members believed that the image of cancer given in Swedish mass media is that the survival rates are increasing. (author comment) *I receive most of the information through the mass media. In that way, I get my information and it is sort of positive, since more and more people pull through. (family member comment)* Subtheme: encyclopaedias and other written material	

Study details	Participants	Methods	Findings and Results	Comments
			The family members looked in encyclopaedias, medical books, material produced by the hospital, and brochures, to gain medical information about the illness and to get an overview of problems related to the illness. *We have received books on how you deal with the illness, quite thin pamphlets from the medical authorities both to us and to the children. (family member comment)* *I have an encyclopaedia at home, which certainly is a bit old. I also have a book for quick medical reference, where I can look up different things in order to be able to read briefly about them. (family member comment)* Family members did not only seek information in order to gain increased medical	

Study details	Participants	Methods	Findings and Results	Comments
			knowledge, but also because it gave them the feeling of doing something constructive. *Seeking information is much more than receiving knowledge, it also includes a feeling of doing something. (family member comment)* Subtheme: the internet Most of the family members had access to computers and necessary skills for seeking information. They used the Internet mainly to obtain an overview about the illness and illness-related problems as well as about the prognosis of oesophageal cancer. The information sites of most interest on the Net were medical sites from Sweden where they could read about research, and sites from the United Kingdom as their medical information about	

Study details	Participants	Methods	Findings and Results	Comments
			oesophageal cancer was extensive. *I think that the Internet was a great help, since it is difficult to telephone someone and pose relevant questions when I hardly know what I want to find out. Then it is possible that if you receive incorrect information, you can form an opinion later. (family member comment)* *The prognosis was so bad. It was so depressing and I started to believe that I would find my husband dead in bed. I got terrified and there was nothing positive at all in the information I read. (family member comment)*	

Study details	Participants	Methods	Findings and Results	Comments
			Subtheme: Face-to-face with the physician and the information found When the family members confronted the physicians with information about the prognosis of oesophageal cancer, they found that their reaction was positive. The physician discussed the findings with the family members. Moreover, the family members were told that the information they had found, especially about the prognosis, was not current and needed to be updated. (author comment) *I said to the doctor that I had been on the Net and read about a study where it said that there was a terribly poor prognosis. He said that the information was not really current and that the prognosis is better now. I*	

Study details	Participants	Methods	Findings and Results	Comments
			didn't go into greater detail. (family member comment) Theme: not seeking information Subtheme: balancing needs On the one hand, there was an oscillation between family members' desire for more information and the avoidance of new information. (author comment) *I want to know if the prognosis is terribly poor or if it is about one year. I want to know what will happen.. . . Actually, I really don't want to know. (family member comment)*	

Study details	Participants	Methods	Findings and Results	Comments
			On the other hand, knowledge about details relating to the illness could alleviate some of the scariness and unpleasantness. (author comment) *Perhaps it isn't so terrible. Everything you know something about loses its terribleness. (family member comment)* Subtheme: Time-consuming and frightening Seeking information was sometimes considered as an effort for the family members, which demanded a considerable amount of time, courage and energy. The family members were also afraid of what they might find. (author comment)	

Study details	Participants	Methods	Findings and Results	Comments
			Certainly I can search for information. That isn't the problem but the problem is that it takes time. I shall mobilise the courage, the power, the energy . . . call it whatever you want, to be able to sit down and go through things. I am not sure I am going to like the answers I get. Maybe it is better not to know so very much but to do like the ostrich, to bury your head in the sand and hope for the best and keep your fingers crossed. (family comment)	
Full citation Andreassen, S., Randers, I., Näslund, E., Stockeld, D., Mattiasson, A., Patients' experiences of living with oesophageal cancer, Journal	**Sample size** N=13 **Characteristics**	Setting Patients with oesophageal-cancer under care of hospital in Sweden. Sample Selection	**Themes and Categories** **Results**	**Limitations** CASP Quality Assessment Tool Aims

Study details	Participants	Methods	Findings and Results	Comments
of Clinical Nursing, 15, 685-695, 2006 **Ref Id** 476911 **Country/ies where the study was carried out** Sweden **Study type** Qualitative study, semi-structured interviews **Aim of the study** To describe patients' experiences of living with oesophageal cancer and how they seek information. **Study dates** December 2003 and March 2004	Their ages ranged from 44 to 77 years. **Inclusion criteria** The selection criteria for this study were as follows: women and men of different ages who had undergone different treatments for oesophageal cancer, i.e., a total thoracic oesophagectomy, oncological treatment with a curative intent and/or palliative treatment. Moreover, the participants should speak and understand Swedish, feel sufficiently well and be willing to take part in the present study. **Exclusion criteria** NR	Purposive sampling was used. The surgeon in charge of their care identified and constructed a list of 17 potential participants, based upon the earlier mentioned criteria, where after their names were given to the first author. All participants received a letter including information about the aim of the study, stating that participation was voluntary, the right to withdraw at any time and that data would be treated confidentially. After about one week, participation was confirmed through a telephone call by the first author and a time for the interview was agreed upon Data Collection: The first author carried out two pilot interviews at the participant's home which, according to their consent, were audio-taped. These	**Theme 1) Experiences of becoming a patient diagnosed with oesophageal cancer** Subtheme: Unprepared and without knowledge of oesophageal cancer Because of the silence of the illness, the participants had no premonitions of the seriousness of the outcome of the initial investigations. Nor did they know about this specific type of cancer: *I knew nothing about my condition before I got the diagnosis. I was completely dumbfounded. My wife said when the doctor discussed it, I looked like a little child. (patient comment)* *If the doctors had told me it was breast cancer, uterine cancer, gastric cancer or intestinal cancer, I would have understood. But I had*	Was there a clear statement of the aims of the research? yes Is a qualitative methodology appropriate? yes Was the research design appropriate to address the aims of the research? yes Sample selection Was the recruitment strategy appropriate to the aims of the research? yes-purposive sampling Has the relationship between researcher and participants been adequately considered? no Data collection Was the data collected in a way that addressed the research issue?

Study details	Participants	Methods	Findings and Results	Comments
Source of funding This work was supported by grants from the Sophiahemmet University College and the Sophiahemmet Foundation for Clinical Research, Stockholm, Sweden.		interviews were semi-structured. That is, the interviewer used an interview guide to cover specific themes, but had no specific order when and how to address them. However, each interview started with inviting the participants to describe their experiences freely of having been diagnosed with oesophageal cancer. The main 11 interviews, were carried out as follows: eight at the participant's home, one at a hospital, one at the first author's office and one in a separate place at a cafe´. They lasted about one hour and were audio-taped. Data Analysis: All interviews were transcribed verbatim. Data was analysed through content analysis. Qualitative content analysis with an inductive approach (Berg 2004) was used when analysing the data. The interviews were	*never expected this. (patient comment)* Subtheme: Existential concerns After receiving the diagnosis the participants became aware of the seriousness of the situation. Their existential concerns were shown in the following thoughts and reflection on life and death: '*What will happen?' 'Will I survive?' 'Will I die?' Will I only be lying in bed and die?'* Later, when the participants wondered why they had developed cancer, they tried to find out if there was anything in their lifestyle that had promoted tumour growth, for example, 'using snuff', 'drinking alcohol moderately', 'hot drinks and food', 'drinking coffee',	yes; author discusses how data has reached saturation Have ethical issues been taken into consideration? yes-privacy and confidentiality, ethics board approved Data Analysis Was the data analysis sufficiently rigorous? Yes-examples given of thematic analysis, data analysed by 3 authors Findings/results Is there a clear statement of findings? Yes Overall quality: HIGH **Other information**

Study details	Participants	Methods	Findings and Results	Comments
		read sentence by sentence to identify text units. These text units, i.e. words, sentences, or a whole paragraph, which answered the questions at issue, were marked and notes about the content were made in the margin. A code was generated for each text unit. Codes were compared with each other and those that appeared to belong together were grouped into preliminary themes. The first author conducted the processes of reading, rereading, coding and the preliminary thematization. The first author and two of the co-authors (IR, A-CM) thereafter discussed these preliminary themes, transformed them into themes and further analysed and transformed themes into sub themes. This organization was repeatedly discussed between these three authors until a consensus was reached. To be complete in data reporting and to illustrate the research findings quotations from all	'heartburn' and 'gastric ulcer'. This resulted in feelings of blame: *Haven't I taken care of myself well enough? (patient comment)* Also, they had questions regarding heredity. Not only did they wonder if they themselves had contracted the disease because of hereditary predisposition: 'My Dad and his brother died of cancer'; they also wondered if their children would inherit the disease. **Theme 2) Experiences of undergoing investigations and treatment**	Linked to 2005 family member study. Author a Registered Nurse. Unknown which patients are undergoing palliative or curative treatments.

Study details	Participants	Methods	Findings and Results	Comments
		participants will be represented.	Subtheme: Extreme tiredness Going through palliative therapy, oncological treatment, or a harrowing as well as an extensive operation caused the participants extreme tiredness. The unpredictability of changes in energy level caused frustration and distress: *The cancer itself hasn't given me any concerns, but it is the treatment that takes away my strength. When I finished the radiotherapy, I was so exhausted that I couldn't walk. The first week I rested at home. (patient comment)* *The doctor said that after the treatment I would be very, very tired. I thought that this*	

Study details	Participants	Methods	Findings and Results	Comments
			tumour was so small and that I could fix it in a month or two. But oh, how I deceived myself. I am terribly, terribly tired. This overwhelming tiredness remained for long time, which is confirmed in the following quotation: 'I really don't understand why I'm still so tired after 6 months…but I am'. **Theme 3) Experiences of intrusions in daily life** Subtheme: Daily-life activities affected The side effects of treatment, i.e. fatigue, made simple everyday activities	

Study details	Participants	Methods	Findings and Results	Comments
			such as going for a walk or catching the bus nearly impossible to accomplish. In addition, their hearing was affected, which made them feel like 'living in a vacuum': *I am terribly, terribly tired. Certainly, I am out walking every day, but not very long stretches. I must stop quite often to breathe and to rest a little while. (patient comment)* For some of the participants the percutaneous endoscopic gastrostomy (PEG), which was placed for ensuring an adequate nutritional intake, caused restrictions in travelling and swimming: *The PEG is an obstacle when I shower and when I travel. It has to be washed. I can't go to a public sauna*	

Study details	Participants	Methods	Findings and Results	Comments
			and places like that (patient comment) Subtheme: Dietary habits changed The participants' dietary habits altered in step with increased side effects of treatment, i.e. phlegm secretion, oral mycosis and fatigue and the progressive illness and dysphagia. This resulted in exhaustion and tiredness as well as loss of weight. Meals became time-consuming and eating mainly turned into a necessary source for nutrition intake and they lost the pleasure earlier associated with eating: *I can't eat the same food as I used to eat and I have no appetite right now. Cooking is no fun. Nothing tastes good anymore. I try to eat sour milk, but I keep vomiting. I have an*	

Study details	Participants	Methods	Findings and Results	Comments
			enormous amount of phlegm and it really bothers me. (patient comment) *I have no energy…and it is really hard for me to eat anything. Where I used to eat two potatoes, I can only eat one now and even that can be too much. Eating makes me so tired that I have to lie down, even though I haven't eaten a whole lot. (patient comment)* Subtheme: Roles and relationship between partners affected The relationship between the participants and their partners sometimes altered as fatigue fostered a dependence on the partner concerning care and different chores: *My husband does all the housework; he cooks, he irons, he does laundry, he*	

Study details	Participants	Methods	Findings and Results	Comments
			takes the dog for a walk five times a day and he helps our son iron his clothes. (patient comment) *I became somewhat dependent on my wife, who had to help me wash up around the gastrostomy. (patient comment)* Moreover, the participants experienced that their partners were more psychologically affected than they were themselves, clearly expressed in the following quotation: *'I feel that the cancer hasn't struck me too hard, but my wife has taken it much worse mentally'*. They therefore had a wish for homogeneous support groups for all family members. (author comment) Subtheme: Children's lives affected Being a parent with a life-threatening illness caused an imbalance in children's	

Study details	Participants	Methods	Findings and Results	Comments
			lives as they mostly were aware of the seriousness of the illness and therefore became worried and stressed. Their schoolwork was affected, which resulted in lower marks: *My 18-year-old son was feeling very badly when he got the information that his mother had cancer. From having excellent marks in all his subjects, he started to ignore school completely. He didn't discuss this with my husband or me. He didn't want to make me upset or his father unhappy. He was convinced that I would die. He gave up everything. (patient comment)* Information about the parent's illness ought to be adjusted to the children's age and intellectual capacity. This became apparent when one of the participants talked	

Study details	Participants	Methods	Findings and Results	Comments
			about her son, who was mentally retarded and his specific needs: *It's immensely important that he also has a chance to meet someone, who allows him to express himself in his own way. (patient comment)* Subtheme: Everyday uncertainty The ambiguity of the cancer's nature was profoundly stressful. There was an expressed everyday uncertainty about future, which caused feelings of 'being under sentence of death'. The participants did not know whether the treatment would be successful or if their cancer would be cured. Thus their sense of uncertainty made it difficult to make plans for the future:	

Study details	Participants	Methods	Findings and Results	Comments
			They tell me they don't know why I got it and they can't give me a prognosis. Of course, that's not what you want to hear from your doctor…but if you think about it, they really don't know either. Sometimes it feels so hopeless. (patient comment) For one of the participants this uncertainty was so emotionally devastating that she wished the physician to give her 'a last injection', although she intellectually understood that this kind of action was impossible. **Theme 4) Managing a life-threatening illness.** Subtheme: Viewing the future	

Study details	Participants	Methods	Findings and Results	Comments
			After having received the diagnosis of cancer, the participants tried to take control over their lives. Hence, they adapted their behaviours to a new life situation. Some participants reappraised time and priorities in life: *When I heard that I didn't have any metastases, I thought that perhaps this is only a respite and therefore I have been terribly active. I work frantically. I think that time is very valuable, something I never bothered about before. (patient comment)* Others set up a specific goal to strive for: 'We have a son who will graduate this summer. The whole time I've set up a goal to take part in his graduation day'. Others wanted to fight for being health: 'I think that as long	

Study details	Participants	Methods	Findings and Results	Comments
			as I want to live, I will fight to be healthy'. Subtheme: Subordinating themselves to medical experts The participants had faith in their physicians having the best knowledge concerning the complexity of the disease and the treatment procedures. They were the major resources for information about diagnosis, treatment, prognosis and side effects of medications: (author comment) *I thought 'I can't do anything now; I'll just hand myself over to the experts and let them do whatever they want with me'. I've handed my life over to the doctors. (patient comment)*	

Study details	Participants	Methods	Findings and Results	Comments
			The registered nurses had to answer many of the participants' questions about the disease and the treatment as they experienced that there were difficulties in continuity with the physicians and they were afraid of bothering them. Thus, the participants also felt connected to registered nurses, as they had necessary medical competence for answering questions and were able to give the participants necessary practical and emotional support: (author comment) *I've seen a lot less of the doctors in the hospital. I see mostly nurses there. And things are different there; you ask the nurses, rather than the doctors, a lot more often than you do outside the hospital. (patient comment)*	

Study details	Participants	Methods	Findings and Results	Comments
			Sometimes I have written down a lot of questions, but usually not more than half or in some cases a third part is answered…the doctors are so rushed and suddenly they are gone. (patient comment) The participants had a wish for information from health-care professionals not only about the disease, but also about being a patient with a life-threatening illness: *The health-care professionals perhaps could have had time to tell me more about how it really is to be a patient. Perhaps they could have devoted a few hours to talk about a number of things concerning this cancer…in another way. (patient comment)* Subtheme: Seeking knowledge from Family members and friends	

Study details	Participants	Methods	Findings and Results	Comments
			In the encounters with the physicians, family members were a significant source of information for the participants because the family members could ask questions from an outside perspective: *I have experienced it positive that my son has come with me to the doctor. It is good to have another pair of ears listening. He has asked questions from an outside perspective. (patient comment)* *It is my wife, who gathers the information that is needed. She is often with me when I visit the doctor. (patient comment)* The participants also sought further information among those friends and relatives who had medical knowledge and understood the participant's capacity to learn: 'I have a cousin who is a doctor and I also had my	

Study details	Participants	Methods	Findings and Results	Comments
			brother-in-law who was a doctor. I trust them a little more because they know what information I am capable of understanding'. Subtheme: Seeking knowledge from Fellow patients Exchanging experiences with fellow patients was found to be valuable to get a better understanding about the illness as their knowledge is based on personal experiences: *It is immensely important that a new patient can talk with a fellow patient. That information is much more valuable than the information the doctor gives. You can ask questions you wouldn't dare to pose otherwise. (patient comment)* Subtheme: Seeking knowledge from Media sources	

Study details	Participants	Methods	Findings and Results	Comments
			The participants attended lectures at the hospital to get an understanding of the illness and an overview of medical information about the illness and illness-related problems. In addition, they used encyclopaedias, medical books, material produced by the hospital and brochures. (author comment) Most of them had access to computers and necessary skills for seeking information on the Internet, but they used it to a limited extent. Information found on the Internet was not always experienced relevant or reliable and could consequently not be applied, which became apparent in the following quotation: 'It became apparent that I could just as well ignore the information since it dealt with men between 60- and 80 years old. You don't put up with this information when you are 44 years old. This	

Study details	Participants	Methods	Findings and Results	Comments
			information is completely irrelevant'. Later, while conferring with the physicians about facts found on the Internet, the participants were told that this information was not always current and should be more individualized. This clarification was found encouraging: (author comment) *I found a research report, brought it with me and discussed it with the doctor. He took it out of my hand and said, 'It doesn't apply to you'. I experienced it positively that he reacted so because it was a negative report. (patient comment)* There were participants who avoided further information due to their fear of unwanted knowledge. Moreover, weakness and fatigue caused by the extensive treatment and its side effects made them avoid additional information:	

Study details	Participants	Methods	Findings and Results	Comments
			I don't pose any questions because I think it is scary. I've left myself in the doctors' hands… they can help me. (patient comment) *There is a great deal I should have asked the doctor about, but I was so tired of everything that I got to the point that I didn't feel like doing it. I became worn out over everything and had enough. (patient comment)*	
Full citation Henselmans, I., Jacobs, M., van Berge Henegouwen, M. I., de Haes, H. C.,	**Sample size** N=20	Setting: - outpatient gastro-intestinal oncology centre of the	**Themes and Categories** **Results**	**Limitations** CASP Quality Assessment Tool

Study details	Participants	Methods	Findings and Results	Comments
Sprangers, M. A., Smets, E. M., Postoperative information needs and communication barriers of esophageal cancer patients, Patient Education & CounselingPatient Educ Couns, 88, 138-46, 2012 **Ref Id** 477763 **Country/ies where the study was carried out** The Netherlands **Study type** Qualitative study with semi-structured interviews. **Aim of the study** To examine the content and type of patients' information needs and patient perceived facilitators and barriers to patient participation. **Study dates**	**Characteristics** Patients' mean age was 62 years. Fourteen participants were male (70%); 10 had a low (50%), 4 had an intermediate (20%) and 6 had a high educational level (30%). Four patients were interviewed more than half a year after discharge (20%). Most patients either had an open transthoracic (n = 10; 50%) or a thoraco-laporoscopic (n = 8; 40%) esophageal resection; two patients had a transhiatal resection (10%). One patient (5%) had tumor in stage I, 25% in stage II, 50% in stage III and 20% in stage IV. Half of the patients had no complications, 30% had mild complications (grade I or II) and 20% had relatively severe complications (grades III and IV). One or more companions were present in 11 interviews (55%).	Academic Medical Center (AMC) in Amsterdam Sample selection: Sample size depended on data saturation, i.e., inclusion ended when the research team jointly decided that 3 consecutive interviews did not provide any new information. To ensure a diverse sample, patients were selected purposefully based on information in their medical files, i.e., time since discharge, age and sex. purposive Data Collection Consenting patients were contacted by telephone to plan an appointment for the interview. The usual companion of the patient was invited to attend the interview and patients were asked to think beforehand about their	**Category: Postoperative information needs** Theme: Nutrition Almost all patients had questions related to nutrition. In the top three were meal size, enteral nutrition (providing food through a stomach tube) and dysphagia. Theme: Other health-related quality of life concerns Other frequently mentioned information needs were related to the performance of specific activities (holiday, cycling, sports, work), cough and pain. One quarter of patients' information needs (26%) within the HRQL domain reflected a need for information about the likely course of symptoms or limitations. In addition, patients' information needs often reflected a need to understand the cause of symptoms and limitations	Aims 1. Was there a clear statement of the aims of the research? Y 2. Is a qualitative methodology appropriate? Y 3. Was the research design appropriate to address the aims of the research? Y Sample selection 4. Was the recruitment strategy appropriate to the aims of the research? Y; sample recruitment was based on data saturation 5. Has the relationship between researcher and participants been adequately considered? PY-

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NR **Source of funding** The first author is financially supported by a personal grant of the Dutch Cancer Society (UVA 2009-4439).	**Inclusion criteria** (1) underwent esophagectomy with curative intent for adeno- or squamous cell carcinoma of the esophagus or gastro-esophageal junction, (2) were discharged either recently (3 months) or more than half a year ago; (3) did not have a prior history of cancer; (4) were above 18; (5) understood and spoke Dutch; (6) did not have a mental disorder. **Exclusion criteria** No additional.	information needs at the first consultation after discharge. Semistructured interviews were conducted at patients' homes by two researchers with a background in psychology and trained in interviewing skills. Following open questions about patient's information needs, a list with topics categorized into physical, social, emotional well-being and prognosis was presented. Using the constant comparative method, newly mentionened topics or, if necessary, categories were added to the original 38-item list after a number of interviews, to be used in subsequent interviews. Next, the patient's perspective on communication barriers and facilitators was addressed. First, patients were prompted to elaborate on their (in)ability to communicate with their physician, using questions adopted from the Perceived Efficacy in Patient–Physician Interactions scale.	and whether or not a symptom was considered 'normal' (22%). Moreover, a number of information needs reflected requests for information about self-management (17%), i.e., how to deal with symptoms or limitations in daily life. Lastly, patients often reported a need to discuss a certain symptom with the physician, without indicating a specific reason or question (31%). Theme: medical care Many patients had questions about medication (the use of painkillers, antacid), the follow-up procedure and technical aspects of surgery. Patients' questions often reflected a need for explanation (54%), e.g., about how patients will be monitored and the necessity of tests (e.g., scans), about things that happened during hospital admission or about how surgery changed their body. Other questions within	interviewers were experts in interviewing without previous relationship with participants Data collection 6. Was the data collected in a way that addressed the research issue? Y 7. Have ethical issues been taken into consideration? Y Data Analysis 8. Was the data analysis sufficiently rigorous? Y- three researchers carried out the analysis Findings/results 9. Is there a clear statement of findings? Y Overall quality: HIGH

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		Data Analysis Content analysis was performed in parallel with data collection. Verbatim transcripts were read and analysed independently by 2–3 researchers, who wrote detailed memo's. Analysis was partly inductive (i.e., bottom up; based on open interpretation of patients' responses) and partly deductive (i.e., top-down; based on pre-formatted lists and theory. The exact content of patients' information needs was registered (e.g., when will the chest pain disappear?) and categorized into main domain (e.g., HRQL), sub-domain (e.g., pain) and type of information requested (e.g., inquiring about likely course). To enable overview and the selection of quotes, one researcher coded the transcripts digitally on the basis of the reached	this domain reflected a need for self-management information (33%), often related to medication (about prolongation or how to quit use), wound care and the availability of or referral to other care providers (physiotherapist, family support). Theme: prognosis Some patients emphasized that the outcome of surgery was most important in the first consultation after discharge and many reported a need to be informed about these results (70%). Fewer patients, but still 40%, reported a need to be informed about the likelihood of recurrence. **Category: Barries and facilitators** Theme: Values Some reported not wanting to be a bothersome patient and a few reported feeling	**Other information** Patient comments and quotes are either patient or companinon remarks.

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		consensus using MAXqda10 software. We use the following qualifiers to give an indication of patient numbers: a few (1–4), some (5–10) or many (>10)	embarrassed about certain subjects. 1. Not wanting to be a bothersome patient R2: (. . .) I think everybody has that in a certain way, you don't want to be too bothersome. You want to pose your question and you hope you will get an answer to that, but bothersome, no. No. You certainly don't want to be bothersome, no. (companion comment) I: And is it also because of that, that sometimes you don't ask something or keep your mouth shut? R: I think that in general, in that situation, most people are very modest, that is what I think. That is a human thing. You are visiting an expert who operated on you (patient comment) 2. Feeling embarrassed about a subject	

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			R: No. No, in the beginning, I did have certain limits, but I don't have them anymore. [laughter] I: Ok, they all disappeared. R2: That wasn't [the case in] this conversation, but in the very first conversation with xxx, you were wondering if your breath would smell after the surgery. You didn't dare to ask that then. R: We did ask that then, didn't we? R2: I asked that, yes. R: Well, I can't remember that I didn't dare to ask that. R2: Well, yes, you wanted to know that before, but you didn't ask it in the conversation. And then I asked it and then you downplayed it a little bit Theme: Beliefs	

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			The belief that a subject is not part of the physician's task, the belief that the physician cannot provide an answer or solution anyway, the perception that there is too little time, expecting a negative reaction from the physician, the belief that a subject is not important enough or that the physician will raise the subject if it is, expecting negative consequences of raising a subject (e.g., referral or further testing) and uncertainty about one's own understanding. 1. Belief that a subject is not part of the surgeon's task [R and R2 say they had a hard time in the post-operative period] I: Do you want to bring up these things the next time you see the surgeon?	

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			R: Yes, I am not sure if you should speak to the surgeon about that, I personally don't think so. You see, the surgeon conducts the surgery and the follow-up care after surgery and I think for everything else, there are other people for that, I believe. 2. Belief that the doctor cannot provide an answer or solution anyway I: So, you're saying, I'm also a little bit afraid, this issue with eating, that might also be because I don't dare to. Would you like to discuss that with the surgeon? R: No, he cannot provide an answer anyway. Probably, this surgeon will probably say, nonsense or it will improve naturally. 3. Perception there is too little time R: Well, I do sometimes have the feeling that	

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			everything has to take place within a certain time span, and that I find detrimental, that often you have to go over a number of things rather quickly. . . I think that is the disadvantage, that is hanging over it a little bit. Yes. Especially with the GP, then you have to leave within 10 minutes, back through the door. (. . .) R: I am not sure how much time with the surgeon . . . I: I think it is the same . . . 10, 15 minutes . . . R: So you know that, so you have to more or less. . . yes, give those answers fast and quickly, or pose those questions. 4. Expecting a negative response of the physician R2: Yes, that they should. . . that the surgeon should realize more that there are lay people in front of him who did not go to college and who are just lay people.	

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			And that for them, it is always very terrible, while for a surgeon it might be . . . like, well, is that all? But for the patient it is really terrible. Cause they know what they are talking about and for us it is something unfamiliar, that suddenly happens to you.(. . .) R2: Yes, so they should think more about the people, realize that for the patient it sometimes does . . . yes . . . Cause because of the response, you sometimes don't dare to [speak up] anymore. That's it. 5. Belief that a subject is not important I: And why didn't you receive an answer to that? R: I don't know what the reason is. I assume, that is what I assumed, that if that is not discussed by the other party, then the surgery was successful. That has been my opinion.	

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			(. . .) R: I assumed that, like I just said, no news is good news. I: Yes, but it is still something about which you say, I would have liked to know it. R: Yes. 6. Expecting consequences of bringing a subject up I: And would you like to talk about this kind of things in the hospital, I mean about anxiety or sadness? R: Not really, no. No, because it won't help me. (. . .) they might talk you into other things . . . while it is not really an issue for me [negative emotions]. I: No, cause what do you mean exactly, if you bring that up, then. . . R: Then they might refer you and then you end up with a shrink or something like that (. . .)	

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			7. Uncertainty about own understandinga,b I: Ok, any other things that makes it difficult to say or to ask what's on your mind? R2: That there are things of which we think like well, maybe it has something to do with it. Often you have, how should I say this . . . you see, that is what I mean . . . that's what stops you, because you can't say something completely clearly, you don't say it. Cause that's what it is like. That you think, like, I have the idea it might have something to do with it, but you don't want to raise it, because then you might stray off . . . Yes, I am not sure how to say this right. But that is also what stops you often [referring to husband]. Theme: skills A number of the reported barriers seemed to reflect a	

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			lack of skills or cognitive abilities, i.e., remembering questions onl afterwards, having no experience with this type of conversations not knowing how to interrupt during the physician's talk, no knowing what to ask and not being able to process the physicians information and ask subsequent questions. Lastly, a few patients mentioned that an unfriendly, ignoring or hasty attitude of the physician, as well as not knowing the consulting physician well hindered participation. 1.Remembering questions only afterwardsa,c (R2 says he would have liked to know about the possibility of recurrence) R2: Yes, the chance of. . . that is something I would like to know. Yes. That question I already wanted to pose, by the way, when we were there the last time, but then it did not happen.	

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			R: Yes, simply forgotten I think. . . R2: Yes, forgotten. 2. No experience with this type of conversations I: You say, because you have little experience with having such conversations, and you noticed that in. . .? R: Well yes, you are the subject of the conversation and everything is new and, yes, for some time that has. . . yes that has an impact, it's about you, and not about your work. 3. Not knowing how to interrupt during the doctor's talk I: Yes, so do you then succeed in getting attention for what you personally want to say? Did you succeed at that time? (. . .) R2: You are actually waiting for what she is going to say, cause otherwise you don't	

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			know any questions at all, while she is talking . . . then you think, that is what I am going to ask in a moment, but then she is actually already so far, before you get to ask that question. . . I:. . . then the moment is gone . . . R2: Then the moment is gone 4. Not knowing what to ask R: Maybe this kind of things, these questions here [referring to the preformatted lists used in the interview], and maybe even the largest part of the items where the question was, like, do you want to discuss that with the surgeon', this question could come from the surgeon, when you are visiting. I: Yes, that is a possibility, that he asks you, do you want to talk about that? R: Yes, cause you can't think of it yourself.	

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			5. Not being able to process information and ask subsequent questions R: What you could say related to that, is that, you know, because it is a whole new area and because it is about you personally, that the pace might be too high. That was not really a big issue in this conversation, I believe, but that could play a part. You always come home and then you think like, ah yes, maybe I should have enquired a bit further on that subject. Theme: Agenda barriers Some of the reported barriers seemed to prevent patients from putting subjects on the consultation agenda prior to the consultation, such as the belief that a subject is not part of the physician's task	

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			and the belief that the physician cannot provide an answer or solution anyway. Theme: communication barriers In contrast, other barriers seemed to prevent them from meeting their needs during the consultation (communication barriers), such as forgetting questions or not knowing how to interrupt. Theme: facilitators Patients mentioned several factors that facilitated participation, reflecting characteristics of the physician (i.e., communication style or personality), characteristics of the interaction (i.e., available time, duration of the relationship), personal characteristics (i.e., personality, experience with this type of conversations, belief in patients' right to have information), support of	

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			companions (i.e., preparing questions or prompting questions during the consultation) and pre-consultation preparation (i.e., making a note, searching the internet). Some were opposites of mentioned barriers (e.g., not knowing the consulting physician), while others were newly mentioned factors of influence (e.g., help of companions). 1. Attitude of the doctor R: It also depends a lot on the person, I believe. Yes, cause I know that with that other surgeon it was much more difficult. I: With doctor xxx. R: That is a totally different person. And maybe that is also a different type of conversation, that I don't know. But there it was more difficult, cause he was more in a hurry.	

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			2. Not knowing the consulting surgeon very well R: (. . .) I think is a pity . . . well yes, it is a holiday season, that you didn't see the surgeon that operated on you. Cause yes, that makes the conversation difficult. Although. . . well, yes, doctor xxx did . . . yes, we were out of there in no time. Well, I think we weren't in there for more than ten minutes, very short. Yes, I thought that was a pity. And for Wednesday, will I have more . . . yes, I expect that doctor xxx will be back . . . Theme: faciliating interventions Subtheme: Pre-visit preparatory interventions Many patients saw merit in the suggested types of pre-visit preparatory interventions, i.e., 13 endorsed a written question	

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			prompt sheet, 9 a preparatory website (including example questions) and 8 a preparatory conversation with a nurse prior to the consultation with the physician. Some patients would appreciate example questions (independent of the medium), because these show them the range and type of questions appropriate to ask a physician. A few patients compared example questions with the preformatted topic list used in the interview, to illustrate how this helped them think about their needs. A few patients warned that example questions might prevent patients from coming up with their own questions. Moreover, a few patients did not endorse internet-based preparation, as they did not have internet access, were not frequent users or disliked searching the internet for information. A few patientsmentioned additional	

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			benefits of preparing the consultation with a nurse, i.e., a nurse has more time to 'pull things out of you' and can already deal with some questions. Subtheme: skill building intervention Few patients endorsed the suggested skill-building interventions, i.e., 5 endorsed a brochure on how to talk to your doctor, while none endorsed video's modelling doctor-patient communication or a workshop in communication skills. A few patients mentioned that such interventions are 'too far fetched' and some considered every conversation to be unique, so 'examples won't help'. A few thought it might help other (older, less assertive) patients, but would not benefit them.	

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Full citation Malmstrom, M., Klefsgard, R., Johansson, J., Ivarsson, B., Patients' experiences of supportive care from a long-term perspective after oesophageal cancer surgery - a focus group study, European Journal of Oncology Nursing, 17, 856-62, 2013 **Ref Id** 478449 **Country/ies where the study was carried out** Sweden **Study type** Qualitative, focus group study **Aim of the study** To illuminate patients' experiences of supportive care from a long-term	**Sample size** N=17 (divided in 4 focus groups) **Characteristics** **Inclusion criteria** Patients that two to five years earlier had been through elective surgery for oesophageal (oesophagectomy) or cardia cancer (oesophagogastrectomy), had the ability to communicate in Swedish and place of residence in southern Sweden were included in the study. **Exclusion criteria** Patients that went through an acute surgery, had cognitive impairment or suffered relapse of the cancer disease were not asked to participate.	Setting: University hospital in southern sweden. Sample Selection: - purposively sampled from an oesophageal cancer database at a university hospital Data Collection Four focus group interviews with between three and five respondents in each group were conducted during data collection. The interviews focused on the patients' experiences during the whole recovery period and were conducted 2 e5 years after elective surgery. The interviews lasted between 110 and 135 min and were carried out in a separate room in the hospital library. When planning the interviews, variations in sex, age and type of surgery were taken into account but the patients	**Themes and Categories** **Results** **Theme: the need for guiding light in the new life situation** **Category: Hospital-based support** Subcategory: the importance of planning of the future Having a plan for the future was shown to be vital for the patients and the importance of following the plan after discharge was highlighted. Information regarding the care at the hospital was experienced satisfactory by most of the patients while the informationconcerning the plan for the future was experienced insufficient. Even though most patients stressed the importance of having a plan for the future some patients left all	**Limitations** CASP Quality Assessment Tool Aims 1. Was there a clear statement of the aims of the research? Y 2. Is a qualitative methodology appropriate? Y though focus groups allow for less depth of data for individual narratives than individual interviews. 3. Was the research design appropriate to address the aims of the research? Y Sample selection 4. Was the recruitment strategy

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perspective after oesophagectomy or oesophagogastrectomy for cancer. **Study dates** Patients were identified between January and April 2009. **Source of funding** This study was supported by grants from Skåne University Hospital, Södra sjukvårdsregionen [Southern Regional Health Care Committee] and Vårdakademin [Academy of Caring Science].		had the opportunity to wish which interview occasion they preferred to attend. Two authors conducted all the focus groups. One moderated the interviews with focus on helping the respondents to focus on the topic while another assisted by asking probing questions and keeping notes during the process. The interviews focused on two different areas; patients' experiences of quality of life, reported in a separate article and patients' experiences and need of supportive care which is addressed in this study. As support, an interview guide helping to focus on the different areas of supportive care was used. After the third interview the researchers experienced that no new information emerged. In order to confirm that no further information would appear a fourt interview was conducted and confirmed data saturation.	planning to the HCP and felt secure knowing that someone else had control of their follow-up. A meeting with the surgeon and a nurse at the hospital before discharge to be able to discuss plans for the future, what to expect with regard to recovery and where to turn to for help was suggested by several patients. These patients experienced that the lack of such a meeting resulted in insecurity about the future and a feeling of being out of control. The insecurity of not knowing if and when they should meet the surgeon or the clinical nurse specialist during the follow-up engendered a feeling of being alone without knowing if they were recovering as expected. After discharge the follow-up meetings were described as occasions on which the patients had the possibility of asking questions and conirming that they were recovering as expected. The	appropriate to the aims of the research? Y 5. Has the relationship between researcher and participants been adequately considered? N Data collection 6. Was the data collected in a way that addressed the research issue? Y; data saturation was reached and confirmed through a 4th interview 7. Have ethical issues been taken into consideration? Y Data Analysis 8. Was the data analysis sufficiently rigorous? Y- multiple carried out the data analysis,

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		Data Analysis conventional qualitative content analysis Conventional qualitative content analysis is used to interpret the content of the data through a systematic process and aims to describe the patients' experiences from different perspectives. The interviews were recorded as a data file and transcribed verbatim. All authors analysed the interviews individually and then came together to discuss the analysis. Each author had considerable experience in caring for patients with cancer and the chosen research method. The analysis started with reading the text repeatedly as a whole to get an overall understanding.	patients' expectations before the follow-up meetings differed. Some patients felt that they went to the meeting to confirm that they were on the right track regarding recovery while others were concerned about what the surgeon would say and always expected the worst. (author comment) *Up until then (discharge) we 'd received all the information we needed. But afterwards I thought of it today, when am I going to the doctor the next time? They told me it was the last time what did they mean by that? (patient comment)* Subcategory: the need of support in a complex healthcare system Most patients experienced that they had a hard time navigating through the big and complex healthcare system after discharge and the distinction between different sources of	data saturation was reached Findings/results 9. Is there a clear statement of findings? Y Overall quality: HIGH **Other information**

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		Thereafter, the text was read again, word for word, with a focus on identifying codes that captured key concepts and thoughts. As the analysis proceeded, labels for codes emerged that were reflective of more than one key word and together the code resulted in the initial coding scheme. In the next step the code were sorted into categories and sub-categories. During analysi similarities and differences in rating were discussed. In the fina step, a consensus was reached by all authors and resulted in on theme and two categories with sub-categories.	caregivers was experienced as impossible to understand. Lack of understanding of the system engendered a feeling of being alone and many patients described that they did not know what responsibility the different caregivers had and who they should contact if they needed help. (author comment) *There's no-one who gets in touch with me from healthcare now. And then, when I phone they say that: You can't be under our care any longer; you have to be well now. You'll have to phone another doctor. What do they mean, ".phone another doctor"? Who'm I supposed to phone? (patient comment)* The patients had a contact person at the open-care clinic (clinical nurse specialist) whom they could contact for help after discharge. This contactwas experienced as important for	

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			the patients and some of them stated that knowing who to turn to for help was enough to feel secure after discharge while other patients expressed that they would like to have a more active follow-up. Itwas proposed that one way of intensifying the contacts was by having regular telephone contacts with the clinical nurse specialist so that they could ask questions and detect possible deviations from normal recovery at an early stage, thus not leaving them with all the responsibility. *She's a clinical nurse specialist; she takes care of everyone. It was to her I phoned on the Friday. The doctor wasn't there, she said, but he would be coming on the Monday. "So I'll speak to him and then we'll get in touch with you." She phoned on Tuesday morning and said that I could come the next day. (patient comment)*	

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			Subcategory: information: a prerequisite for realistic expectations Expectations about recovery after surgery were generally based on the information that the patients received during their stay at the hospital. However, for most of the patients, the expectations that they had were not experienced as matching the reality after discharge. Knowing what to expect after discharge regardless of whether it was good or bad was expressed as being important and the lack of honest and clear information resulted in many patients misinterpreting signs that were connected with the disease. These misinterpretations resulted in situations in which normal postoperative symptoms were interpreted as signs of recurrence of the actual cancer disease rather than as normal postoperative symptoms. The importance	

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			of honest information about e.g. self care were, for most patients, fundamental but there were some patients that felt that the truth could be terrifying and therefore did not want all information. However, all patients expressed that they needed information about how to manage their health in terms of knowing what is normal and what is not normal and how to prevent and self-manage symptoms if they emerged. (author comment) Knowledge about how long time the recovery period was expected to take was important for the patients and most of them experienced that the information that they were given was too positive. The lack of accurate knowledge engendered a feeling of failure since several patients thought that they were not following the expected developments after surgery. The majority of the patients felt strongly about wanting to	

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			know more about the prognosis, side-effects and risks of getting a relapse of the cancer disease and only a few felt that they preferred not to know. (author comment) *One thing that I miss especially is this: What's the prognosis? Will I be around in five years' time, or three years or will I just kick the bucket? I'm not afraid of that//dying. It's just, I wonder about the future, I mean I've got kids and all. (patient comment)* Subcategory: Being transferred from specialist care to general care Apart from the medical follow-ups and the contacts with the clinical nurse specialist at the hospital, all nursing interventions were performed by the municipal nurse and nurse assistants after discharge. This change e from having a nurse who was specialized in their	

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			condition performing all the nursing interventions to having a person that had a limited knowledge about their condition was a big concern for the patients since most of them did not fully trust the knowledge of municipal nurses. Even though some patients experienced that they were given good and valuable support by the municipal nurses the majority experienced that their condition was so complex that it required specialist trained nurses to perform the care. A concern for most patients was that the organisation around the municipal nurseswas unclear and lacked continuity. This lack of transparency of the organisation resulted in that many patients felt insecure and some were even readmitted to the hospital in order to be able to get the help that they needed. For those patients that had had contact with the municipal	

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			nurses before the surgery the problem with the unclear organisation was not that troubling since they had a better understanding of the organisation based on earlier experiences. (author comment) *They [the municipal nurses] didn't really know what it was all about, many of them felt insecure. Maybe someone came who'd seen this sort of thing before and knew exactly what to do but then the next day someone else would come. I think they came about five times and it was a different person every time. So, I thought on the Sunday evening, no, now I 've had enough. They can't come anymore. (paitent comment)* Many patients experienced that the distinction between when to turn to which healthcare facility was unclear and when problems arose after discharge the patients did not know if they	

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			were supposed to contact the surgeon or the primary care physician. Most patients preferred to turn to the surgeons at the hospital for help since they are the experts in the area but there were some patients who decided to contact their primary care physician while they had a relation with that person since before the cancer diagnosis. The lack of knowledge about who to turn to resulted for some of the patients in delays because they did not want to disturb someone or risk contacting the wrong person. *General physicians in healthcare, they're supposed to know about everything, but they're not specialists. Maybe they can't intervene in cases like yours and mine. They listen and all and maybe give you certification of illness or something. But they can't help you in the way that specialists can. (patient comment)*	

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			Category: Support in daily life Subcategory: The importance of support from one's social network After surgery, support and understanding from one's social network, including relatives, friends and colleagues, was experienced as being important. After discharge, life was hampered by remaining symptoms and having to learn to live with the symptom was a challenge for the patients in which they needed support. Most patients stated that they wanted their relatives to be involved and informed about their condition since that resulted in a feeling of not being alone with the whole burden and enabled their relatives to support them in an appropriate way. However, there were also a	

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			few patients that did not want to involve their relatives because they were worried about how they would manage the information. Retrospectively, most patients wanted to involve their relatives in their care even more. However, the initiative to involve them was often made by the patients themselves without encouragement by the HCP. (author comment) *I had my wife with me from beginning to end. Every single visit to the doctor, everything. Very good I advise everyone to do the same because she gets to know exactly the same things as I do. I don't make anything look better than it is for her. I can't do anything. She's heard the same things as I have, and that feels good. (patient comment)* Energy and support was gathered from different sources and patients expressed that they received	

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			support when, for example, they attended social activities or religious gatherings. For many patients it was important that support was not only gained when talking about the disease itself or discussing disease-related issues. Being in a supportive environment where everyone knew about your condition without your having to talk about it was appreciated. Even though the support from the social network was important after surgery some patients experienced that the network of friends shrank successively, both due to their own lack of energy to maintain the contacts and to the fact that the social network began to evade contact because of the illness. For these patients the lack of support from their social network was experienced as a grief. There were also patients that experienced that the support from their social network was	

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			intensified after surgery and that people around them cared for them and their family even more. (author comment) *But there's one thing that I find enormously irritating and that is that previous friends//who I used to hang out with before the sickness. I haven't heard from them the last three years, that's irritating (patient comment)* Subcategory: the need of support for dealing with the demand's of society The value that the patients put into their work and the contacts with colleagues varied. Some patients experienced that going back to work was important both for the "normality" of it and for regaining the social contact they had missed. Other patients experienced work as a threat that demanded them to perform tasks that they were not sure that they would be able to	

Study details	Participants	Methods	Findings and Results	Comments
			handle. Regardless of however work was perceived as something positive or as a threat, thinking about work engendering ambiguous feelings. It was stated by several patients that they would have needed more information about their ability to go back to work after surgery so that they would know what was expected of them. The long-lasting negative effects that were the result of the disease and the surgery led to contacts with the social insurance of ice. Many patients experienced that they needed to convince them about their disease and their inability to work, and that they were not always believed. This lack of understanding engendered anxiety about the future for most patients and some of them were seriously concerned about how they would manage their economy if they would not receive financial support.	

Study details	Participants	Methods	Findings and Results	Comments
			The contacts with the social insurance office were experienced as being energyconsuming and most patients felt the need for support from the healthcare system when it came to these contacts. *It's a slap in the face for someone who's sick. It's not only that you're sick; the sicker you are the more rotten it is. So, it's not only the sickness that you need to have treated but you also have to be on the alert about what's going to happen. It means that a person who's sick hardly gets better psychologically of something like that, rather that they [the social insurance office] add to the psychological thing you're already carrying around when it comes to cancer, relapse and all that. (patient comment)* Subcategory: peer-support from other patients, two sides of the same coin	

Study details	Participants	Methods	Findings and Results	Comments
			Many patients experienced a lack of opportunities to meet patients who had been through similar surgery as themself which resulted in a feeling of being alone with the disease. When the patients attended the focus-group interview and met each other several of them felt the contact to be very beneficial. Theyexpressed that this meeting helped them to understand that many problems and symptoms were a part of the new life situation after surgery and that they needed to learn to live with these problems. Knowing that they were not alone and listening to how other patients managed their new life situation was reinforcing and gave them new strategies for handling their problems. Even if most patients experienced an unmet need of peer-support after surgery a few patients described how contact with other patients made them	

Study details	Participants	Methods	Findings and Results	Comments
			feel vulnerable. The knowledge about that people around them could get a recurrence of their cancer led to a greater awareness that they themselves were subject to the same risk. *I thought I was alone with this. When it's good to hear that there are others going through the same thing. I feel exactly the same way and then you know that you're not alone with the disease you've been through. (patient comment)*	
Full citation McCorry, N. K., Dempster, M., Clarke, C., Doyle, R., Adjusting to life after esophagectomy: the experience of survivors and carers, Qualitative Health Research, 19, 1485-94, 2009 **Ref Id**	**Sample size** N= 22 (12 patients, 10 carers) **Characteristics** In total, 12 survivors (9 men and 3 women) and 10 carers (8 women and 2 men) participated in the focus group discussions. The relationships between survivor and carer were: seven	Setting: Belfast, UK Sample selection: Recruited from members of the Oesophageal Patients' Association in Northern Ireland. Data Collection	**Themes and Categories** **Results** **Survivors** Theme: Coping with a death sentence. Without exception, participants described the immense shock of receiving	**Limitations** CASP Quality Assessment Tool Aims 1. Was there a clear statement of the aims of the research? Y

Study details	Participants	Methods	Findings and Results	Comments
478512 **Country/ies where the study was carried out** UK **Study type** Qualitative, focus group study. **Aim of the study** The current study explored the emotional and cognitive experiences of esophageal cancer survivors and those of their carers, using focus groups conducted with members of a patient support group **Study dates** NR **Source of funding** The authors received no financial support for the research and/or authorship of this article.	husband–wife dyads, two wife–husband dyads, and one mother–daughter dyad. Two male survivors were unaccompanied. Six survivors were aged 56 to 65 years, 3 were aged 66 to 75 years, 2 were aged 76 to 85 years, and 1 survivor was aged 46 to 55 years. All patients had undergone surgery as part of their treatment for esophageal cancer. At the time of participation, time since diagnosis (self-reported) ranged from 14 months to 17 years, and time since surgery ranged from 7 months to 17 years. **Inclusion criteria** **Exclusion criteria**	focus groups groups were separated for carers versus patients Data Analysis Recordings were subsequently transcribed and anonymized. Data were analyzed according to standard thematic analysis techniques (Denzin & Lincoln, 1998). Descriptive codes of analysis were attached to segments of text, and then reviewed to identify broad categories. All text belonging to the same category was compared. The researchers met to discuss, clarify, and refine the coding categories. The analysis process also involved a purposeful search for deviant cases and explanations. The categories were further refined through an inductive and iterative process of going back and forth between the text and our developing conceptual framework, culminating with	a diagnosis of esophageal cancer and its poor "reputation": "I thought when the diagnosis was made, it was a death sentence. It really shook me up and I thoughtsemiseriously about suicide." Transferring perceived responsibility to others (especially medical professionals) at this stage appeared to help patients cope with a situation in which they could exert little control. This type of denial appears to have helped protect patients' emotional well-being while they awaited surgery: (author comment) *When you are first diagnosed it hits you like a 10-ton hammer hitting you in the chest, but when you think about it, okay, you've got cancer, what can I do about it? Nothing. And that's what I said to my cancer specialist. "I don't have the problem, you have the problem, so I'm not going to worry about it. I'm giving it to*	2. Is a qualitative methodology appropriate? Y 3. Was the research design appropriate to address the aims of the research? Y Sample selection 4. Was the recruitment strategy appropriate to the aims of the research? PY-convenience sample of patients part of a patient association could have introduced bias 5. Has the relationship between researcher and participants been adequately considered? N Data collection 6.Was the data collected in a way

Study details	Participants	Methods	Findings and Results	Comments
		the emergence of three higher-order themes from the survivors' data, and three themes from the carers' data.	*you, you worry about it." And exactly the same thing with the surgeon. (patient comment)* Theme: Adjusting to and Accepting an Altered Self Subtheme: Adjusting to and accepting physical changes. Following surgery, the process of recovery was described as a mirror image of the deterioration observed prior to surgery, especially in relation to weight gain and eating ability: *Every day there was something else that you couldn't get down. Even different liquids. Suddenly I found even the tea couldn't go down. Then the coffee wouldn't go down and some solids as well . . . I would suddenly have to disappear because maybe a wee sandwich that I knew I could eat the previous day, I just couldn't get it down that day. You had to disappear to get*	that addressed the research issue? PY; data saturation not addressed 7. Have ethical issues been taken into consideration? Y Data Analysis 8. Was the data analysis sufficiently rigorous? Y Findings/results 9. Is there a clear statement of findings? Y Overall quality: MODERATE **Other information**

Study details	Participants	Methods	Findings and Results	Comments
			rid of it. It was awkward and I stopped eating in front of anybody, even my wife. . . . So before the surgery, every day there was something else you couldn't get down, and after the surgery, every day, there was something that you could get down. (patient comment) Sensory feedback from the body was altered following surgery, and patients described how they had to "learn" appropriate amounts to eat. They were unable to rely on feelings of satiety, often denying themselves food even if they were still feeling hungry: (author) *You can't really eat a lot, but I don't find something telling me that I'm full and if I enjoy something I would say, "Is there any more?" But after it is down, that extra [food] I feel as if I want to be sick then, but it's only after I've eaten it . . . I just find that you have to accept it, and this is how life is going to be*	

Study details	Participants	Methods	Findings and Results	Comments
			from now on. That's the way I look at it. (patient comment) *Well I've got to the stage now where I cut off [eating] at a certain level, because you can find yourself in the bathroom or you find it coming up again, so you try and measure your meal as you go and stop at the right time. It is hard to do. (patient comment)* Subtheme: Adjusting to social and emotional changes. The consequences of patients' altered eating behaviors were felt at an interpersonal and social level. Especially in the early period following surgery, when survivors described how they had less control over the body's reactions to eating (such as choking and vomiting), patients withdrew from the company of their family and friends. They were often embarrassed and nervous about eating in	

Study details	Participants	Methods	Findings and Results	Comments
			public places, and some described a perceived stigma associated with these altered eating behaviors (such as ordering small portion sizes and children's meals): "You feel so embarrassed and you are eating a wee corner of your meal, and the waiter says, 'Is there something wrong with that?'" Patients also described emotional struggles, and the "fear of the unknown": (author) *When you have the operation it changes your life. . . . It changes you mentally and I feel that eh . . . somewhere along the line I think a psychologist could talk to you and ease your worries, because we all know doubt. . . . You don't know when you'll be getting measured for the coffin. (patinet comment)* Although fear of recurrence appeared to be a significant some control over their situation, or maintaining	

Study details	Participants	Methods	Findings and Results	Comments
			a positive outlook about their health: *It's the fear of the unknown. If I get it again there's nowhere else to go, but . . . there's more chance of getting knocked down by a bus. . . . I had my surgery five and a half years ago and I keep very active, and eh, I think it's part of the cure.* Subtheme: Adjusting to role changes. Finding a new focus, and disciplining the self not to give in to negativity, was stressed by patients as an important goal of adjustment postsurgery, especially when faced with role and identity challenges, such as being unable to return to work, or altered familial roles. The following quote describes a patient's daily struggle after being "pensioned off": *You get up some mornings and you don't feel like doing anything. Those are the*	

Study details	Participants	Methods	Findings and Results	Comments
			mornings that you really say to yourself, "Right—start such and such, because if you get started you keep going." . . . Having something to do and something to think about is the best medicine of the whole lot. Theme: The unique benefits of peer support. Patients described the informational and practical support received from medical staff, and also highlighted the role of "being known" by their physician throughout their experience. They advocated the unique benefits for psychological well-being and hope provided by peer example and support, particularly the role of the support group. The following quote helps to demonstrate the processes of upward social comparison at work within the group: *I think that one of the things that helped me was*	

Study details	Participants	Methods	Findings and Results	Comments
			whenever I was in touch with Ben [member of support group] after the operation . . . and he wasn't there because he was on holiday in Australia, and I thought, "Oh, there is life after this." And that actually helped me a lot. Although most patients did not have contact with other survivors until they made contact with the support group (generally following their recovery from surgery), they still appreciated a role for peer example and support within the health care setting, both in preparation for and following surgery. A few patients had (informally) met other patients who had undergone surgery, and described the influence of this on their attitudes and behavior: (author) *The day I was actually diagnosed and they told me I needed to have an operation. And there was a lady in that day who had*	

Study details	Participants	Methods	Findings and Results	Comments
			come in to get a checkup and she had had the operation . . . six weeks ago. And me meeting that woman made my mind up for me—I'm going for the operation straight away. (patient comment) **Carers** Theme: The carer as buffer. Carers described their responsibility for protecting the patient and their family from distress, sometimes by choosing to withhold information from them, and needing to be strong for those around them. This however, appeared to contribute to the carer's feelings of isolation, at a time when they were clearly suffering from elevated levels of distress themselves, often resulting in altered sleeping and eating patterns and reduced self-care of their own health problems:	

Study details	Participants	Methods	Findings and Results	Comments
			He [the patient] wasn't aware of the severity of the operation. And also, he doesn't know himself that he hemorrhaged after the operation and that night they had to bring him back to stop the hemorrhage, they opened him, I think they said his lungs were full of blood. They also told me that if he hadn't had the operation, if they hadn't got him back to surgery that night it would have been too late. . . . He is not aware of that; as a matter of fact nobody else in the family is aware of that, because I think a secret's best kept if you really keep it to yourself. (carer comment) *I felt, em, I had to be strong for the whole family because I would be a strong person anyway, but they were all looking to me and I couldn't let the side down. And I had nobody to talk to. I was nursing my father with cancer, my sister had just died, I had cancer, John had*	

Study details	Participants	Methods	Findings and Results	Comments
			cancer. There was just nobody. I couldn't let myself down, my guard down, and I found the isolation terrible. (carer comment) Carers felt the burden of responsibility for the patient's recovery. One woman described herself as her husband's "whipping boy," as she relentlessly tried to encourage her husband to eat, and to take medication: (author comment) *You were trying to get him to eat, trying to get him to take his tablets and I was getting the brunt of everything. And that was the worst . . . and it was so hard you know, and I used to have to go out of the room because I started crying. (carer comment)* The carer was also a conduit who provided explanations to family and friends, and in social situations. The following quote is an account of a	

Study details	Participants	Methods	Findings and Results	Comments
			husband's private conversation with a waiter in a restaurant: (author comment) *I had to take the guy away to the side, and I says, "Look, would you mind coming back and removing the plate and not saying anything, because"—well, I told him the situation. (carer comment)* Theme: Representations of recovery and recurrence. Carers appeared to engage in an anxious process of tracking the patient's recovery and health in terms of their ability to eat, their meal sizes, and weight gain. Their discussion was permeated throughout with accounts of this. Although patients, on the one hand, recognized and accepted that smaller portion sizes were a more-or-less inevitable consequence of surgery, carers' representations of food and	

Study details	Participants	Methods	Findings and Results	Comments
			eating were heavily emotionally laden and the carers still perceived recovery in terms of the ability to eat larger quantities: “I can’t get Bernard out of the small meals. . . . I have to ring him every day from work to tell him to eat, but his eating has got a bit better and he’s put on a bit of weight.” (author comment) Carers were vigilant in their observation of patients’ “progress,” and often interpreted even slight weight loss, dumping, or feeling unwell as indicators of disease recurrence: “Every time that he would not feel well or would have the dumping syndrome, I keep wondering, is it back?” This was clearly a significant source of distress for the carers, permeating their daily thoughts, and was felt very keenly when attending for checkups: (author comment)	

Study details	Participants	Methods	Findings and Results	Comments
			I continually worry about him, he's never out of my mind. He's the first thing on my mind in the morning and the last thing at night—"Have you got pain? Where's the pain?" . . . I used to just look for a reaction from their faces, just to see is he doing a bit better, is he not? . . . If there's a slight smile it gave you hope. You know, I was very aware of people's reactions in the hospital around me. (carer comment) Theme: Normalizing experiences through peer support. Carers described varied experiences of support from health professionals, but recognized the value of peer support, especially for normalization of experiences (such as eating habits/ability), reducing feelings of isolation, and as a source of hope: (author comment)	

Study details	Participants	Methods	Findings and Results	Comments
			Carers are supposed to forage for information, you know: "Am I doing the right thing?" You know he's not eating right, I can't get him to eat and it was only when I came here that I started talking to people . . . the first lifeline we had was here [the support group] . . . it was just like a breath of fresh air . . . and things that Brian had, this dumping syndrome, he wasn't the only one. . . . My friends were good but I think they cared about us so much, they couldn't ask, they didn't want to, they just wanted life to go on. (carer comment)	
Full citation McNair, A. G. K., MacKichan, F., Donovan, J. L., Brookes, S. T., Avery, K. N. L., Griffin, S. M., Crosby, T., Blazeby, J. M., What	**Sample size** N= 31 (25 consultations, 27 interviews)	Setting: Three United Kingdom (UK) upper gastrointestinal (GI) cancer centres.	**Themes and Categories** **Results** **Theme: Emphasis on surgical techniques and in-hospital risks by surgeons**	**Limitations** CASP Quality Assessment Tool Aims

Study details	Participants	Methods	Findings and Results	Comments
surgeons tell patients and what patients want to know before major cancer surgery: a qualitative study, BMC Cancer, 16, 2016 **Ref Id** 478526 **Country/ies where the study was carried out** UK **Study type** Qualitative study (patient interviews and observation of patient-surgeon consultation) **Aim of the study** This study explored information provided by surgeons and patient preferences for information in consultations in which surgery for oesophageal cancer surgery was discussed.	Six consultations were not recorded because of equipment failure and four patients declined an interview. **Characteristics** mean age= 67 years (range 55-79) 24 male, 7 female 18 AC/ 13 SCC **Inclusion criteria** oesophageal adenocarcinoma or squamous cell cancer selected for surgery alone, or neoadjuvant treatment and surgery by an upper gastrointestinal cancer multi-disciplinary team. Patients were eligible only when aware of results of diagnostic and staging investigations. All surgeons in the participating centres were eligible.	Sample selection: Eligible participants were posted study information. Data Collection Consultations between consultant surgeons and patients before surgery were audio-recorded to study information exchange, and semi-structured interviews were undertaken with patients within two weeks to explore views on the information provided and their preferences for information. Interested participants were met by researchers prior to a routine appointment in which treatment, including surgery, would be discussed by a surgeon. Consultations took place in usual hospital facilities. Following the consultation, participants were invited to be interviewed at home, in the hospital or by telephone according to their choice. An interview topic	Subtheme: surgeons presented detailed technical information All consultations were dominated by information from surgeons about operative technique and in-hospital morbidity risks. The information flow was unidirectional, with surgeons disclosing information to patients frequently in a uniform way with limited patient involvement. Descriptions were often detailed, and large amounts of information were communicated in a single discourse. Information about operative technique followed a typical format involving an explanation of normal anatomy, identification of the tumour site defining the extent of the resection and the method of reconstruction. Surgeons did not enquire if patients wanted this level of detail. (author comment)	1. Was there a clear statement of the aims of the research? Y 2. Is a qualitative methodology appropriate? Y 3. Was the research design appropriate to address the aims of the research? Y Sample selection 4 Was the recruitment strategy appropriate to the aims of the research? Unclear-limited detail on recruitment strategy 5. Has the relationship between researcher and participants been adequately considered? N Data collection

Study details	Participants	Methods	Findings and Results	Comments
Study dates Interviews conducted 2010/2011. **Source of funding** This work represents independent research partially commissioned by the National Institute for Health Research (NIHR) under Research for Patient Benefit Program PB-PG-0807.	**Exclusion criteria** - Patients were excluded if a translator was required in the clinical consultation	guide was used to ensure that similar issues were covered in each interview, including expectations of the consultations, views on the information provided and information desired. This final topic included discussions about investigative tests, treatments, physical and psychological symptoms. Data Saturation Data collection and analyses occurred concurrently and iteratively and the sample size was guided by assessment of the saturation of insights drawn from the data. Saturation was defined as the point at which no new relevant themes/subthemes were emerging from the iterative process of analysis. Data Analysis Audio-recordings were anonymised and transcribed	Subtheme: the gravity of the surgery was emphasized The gravity of the surgery was emphasised, being described as 'major' or 'big' in 17 of the 25 consultations. *"Now, the operation is a very big operation. It's a very serious operation and there are risks involved, ok? It is one of the biggest operations a human being can actually undergo" (consultant)* Such descriptions allowed more detail about specific aspects of the procedure to be introduced, which reinforced the magnitude of the surgery may helped contextualise disclosure about in-hospital risks. (author comment) Subtheme: Short term risks were listed with little explanation Short-term risks were described in all consultations, and were	6. Was the data collected in a way that addressed the research issue? Y; data saturation was reached 7. Have ethical issues been taken into consideration? Y Data Analysis 8. Was the data analysis sufficiently rigorous? Y, multiple researchers carried out thematic analysis independent Findings/results 9. Is there a clear statement of findings? Y Overall quality: HIGH **Other information**

Study details	Participants	Methods	Findings and Results	Comments
		verbatim following standard notation guidelines. Qualitative analysis software was used to assist with data management. Analyses were undertaken by two researchers and followed principles of thematic analysis. Transcripts of consultations and interviews were read and re-read for data familiarisation, all transcripts of consultations and interviews were coded in an iterative process. Coding was partly theory driven, in that the focus of analysis was on information exchange and needs, but the researchers sought to ensure that themes emerged from the data. Researchers were aware literature describing cancer patients' information needs, but they did not apply a priori categorisation to these data. Coding was conducted independently by two researchers and a process of constant comparison used to compare transcripts.	listed in succession with little explanation. The exception was in-hospital mortality, which often included summary statistics. (author comment) *"The overall mortality rate with a major operation like this, in our hands, is less than two percent, so it 's a ninety-eight percent chance of getting through it " (consultant comment).* Subtheme: Patients generally accepted the necessity of technical information Information about surgical technique and morbidity were identified as desired information topics by only three patients. Most patients acknowledged that surgeons needed to give them the data, and was often described in the context of possible litigation. (author comment)	

Study details	Participants	Methods	Findings and Results	Comments
			“I think it’s, erm- ‘cause of litigation, isn’t it these days– they have to tell you everything” (patient comment) Subtheme: some patients did not want technical information There were seven patients that expressed a preference against being given technical information. This demonstrates a mismatch between surgeons’ and patients’ views. Explicitly not wanting to know about these things was potentially related to a sense of inevitability about the procedure and a desire to ‘get on with it’: that reflecting on their own vulnerability was unhelpful, and possibly contradicted a positive narrative that patients were trying to maintain. (author comment) *"I did have the fleeting thought going through my mind, ‘For goodness sake,*	

Study details	Participants	Methods	Findings and Results	Comments
			why are you telling me all this. I'm confident, you're confident. Let's get on with it" (patient) *"I don't think I was as interested in that sort of detail. I know that there are risks, I don't want to dwell on it. It's always near the front of your mind at this particular time- and you're trying to get away from that as much as possible" (patient)* *"I must confess it came as rather a blow and what I what I didn't like really were the statistics that he went into - I would have liked to have heard more about the sort of positive side of it" (patient)* or a general squeamishness: *"Surgeons see it every day. They're quite happy to talk about it. A lot of people seen somebody run over in the road and their insides hanging out, they'd be on the*	

Study details	Participants	Methods	Findings and Results	Comments
			side of the road throwing up. You know, and if they tell you they're gonna do something similar to you, you don't wanna know about it" (patient comment) *"obviously one needs a-some idea of the process but not necessary of- not necessarily every gory detail" (patient comment)* **Theme: Post-operative recovery, long-term quality of life and survival were key patient information needs** Subtheme: recovery, long-term quality of life information was desired by most, but not all, patients Information about post-operative recovery and QOL was identified as important to all but four patients. This was related to a wide range of topics including work, social activities and physical symptoms.	

Study details	Participants	Methods	Findings and Results	Comments
			"I was trying to gauge what the time would be before I could begin to embark upon relatively normal activities" (patient) *"Will I not be able to work any more?" (patient)* *"I wanted to know basically what you're like. Can you, erm, do the things that I now do? Bearing in mind I'm seventy-six years old and I can't run about like I used to …after six months, erm, how - what will it do? Can I- Will I be able to stretch? Will I be able to paint the ceiling- Will I be able to- to run about? What? I 'll be like- I'll be able to drive a car, I guess but- you know, so those are the things." (patient)* There were four patients who explicitly stated that they did not want information about QOL. Reasons for this included wanting the information later in their	

Study details	Participants	Methods	Findings and Results	Comments
			recovery or to maintain an idea of “hope”. (author) *“I don’t think that I would really want to know what would be the long-term problems if any. I want to stay on top– I want to keep on top of it… I don’t really want to think too far ahead, there is probably enough to think about, y’know, at the moment” (patient)* Subtheme: Long-term effects of surgery were minimised by surgeons Long-term QOL were discussed in fewer than half (10) of consultations, with notable variation in the level of detail. Descriptions of recovery varied, from surgeons portraying it as an ongoing process, to describing a clear trajectory. Topics covered largely concerned the control of symptoms, such as reflux. Explicit in descriptions was that patients would return to a normal, or near-normal,	

Study details	Participants	Methods	Findings and Results	Comments
			state of functioning. This had the effect of minimising the long-term impact of surgery. (author) *"it can take six months or so before you are back to where you were, maybe longer—six to nine months to how you're feeling now" (coonsultant).* *"He said, 'six months.' But that's to full fitness, you should be feeling a lot better a lot sooner" (patient)* Patients appeared satisfied with this information, though this may be based on the unrealistic belief that they would return to full health. Minimising the long-term impact of surgery may therefore suppress question-asking. There were no examples of surgeons eliciting patients' information needs regarding recovery. (author)	

Study details	Participants	Methods	Findings and Results	Comments
			Subtheme: survival infromation was desired by patients Survival information was often stressed as important by patients. *"I'd like to know is- is your thoughts on, erm- on whether you'd like to know the- the chances of a successful cure and these kinds of things. (patient)* It was provided in 17 consultations and quoted statistics were largely consistent between consultations and with published literature (50 % two year survival). Disclosure of survival information was often embedded within the technical description of the surgical procedure, and was brief. (author)	

Study details	Participants	Methods	Findings and Results	Comments
			Subtheme: surgeons presented the uncertainty around survival Although specific survival rates were conveyed in many consultations, surgeons made efforts to impress the uncertainty of the prognosis for the individual. *"But, you know, as- as I s- tell people, you know, if- say there was a percentage cure rate, you're not gonna be percentage cured, you're either gonna be cured or not- [Yeah. Mm.] cured and that's a problem – that's when we just don't know anything" (consultant)* These difficulties were manifested in consultations where survival statistics were often followed by caveats; "we don't have a crystal ball". This reflects tensions between providing population-based survival statistics and providing	

Study details	Participants	Methods	Findings and Results	Comments
			individualised information. Difficulties with personalising survival information were acknowledged and largely accepted by patients during interviews, with uncertainty viewed as an inherent aspect of the cancer trajectory. This was even the case when such information was potentially distressing. In one interview the patient and his wife describe feeling 'done down' when hearing of the survival statistics, although the patient reflected; (author comment) *"I thought, it's better that [surgeon] said that than, 'Oh look, we'll cure you'" (patient).* Subtheme: fear may inhibit patients' desire for survival information One patient initially described not wanting survival information but then clarified his opinion.	

Study details	Participants	Methods	Findings and Results	Comments
			"I've got to ask the question because clearly those are the answers you want to know, you know. Am I gonna die? Or, you know, how long am I likely to live? You know, these are sort of basic questions that you want answers to but you're scared that someone's gonna say well, actually not very long', you know (laughs) and you can't argue because they're the professional" (patient) Fear was an inhibitory factor in this example but this highlights an important distinction between patients wanting survival information in general and wanting to know how long they will live as an individual. (author comment)	
Full citation Mills, M. E., Sullivan, K., Patients with operable	**Sample size** N=7	Setting Sample Selection	**Themes and Categories** **Results**	**Limitations** CASP Quality Assessment Tool

Study details	Participants	Methods	Findings and Results	Comments
oesophageal cancer: their experience of information-giving in a regional thoracic unit, Journal of Clinical Nursing, 9, 236-46, 2000 **Ref Id** 478572 **Country/ies where the study was carried out** UK **Study type** Qualitative study of semi-structured interviews **Aim of the study** To gain an insight into the experiences of patients with operable cancer of the oesophagus and the information they received. **Study dates** NR	**Characteristics** 5 male, 2 female **Inclusion criteria** Having gained the permission of the thoracic surgeons, the researcher generated a list, from the thoracic database, of 42 patients who had undergone TTO in the 18-month period preceding the start date of the study. It was decided that those patients (n.11) who had been involved in a clinical trial of pre-operative chemotherapy would be excluded, as they would have received additional information and support. **Exclusion criteria** Those over the age of 70 were excluded (n.9), as, from experience, the researcher considered this age group to be less willing to critically evaluate care.	purposively sampled from list provided by surgeons Data Collection Seven questions were outlined on the interview guide. The first two questions were general in nature and were used to gain an insight into participants' demographic details, their social background and their path to diagnosis. The third question asked for details about the type information they received while in hospital. Following on from this, they were asked to describe who was involved in providing them with information and how the information was given to them, for example verbally or written. The sixth question was related to how they perceived the overall system of information-giving in the hospital and incorporated a description of the positive and negative aspects of	Category: SOURCES OF INFORMATION Theme: Information from Consultant surgeon Generally participants were very positive about the surgeons, commenting on how `attentive' or `helpful' they were or how they provided `a lot of information' and spoke to their families. Although no-one in the group criticized the surgeons, a few areas of discontent were implied. Firstly, at review appointments it was apparent that participants' fears or misconceptions were often not clarified. This may have been due to a lack of probing questions to determine how patients were really feeling. Second, two participants identi®ed that information was only provided if requested:	Aims Was there a clear statement of the aims of the research? Y Is a qualitative methodology appropriate? Y Was the research design appropriate to address the aims of the research? Y Sample selection Was the recruitment strategy appropriate to the aims of the research? N- those over 70 excluded, only 7 patients included Has the relationship between researcher and participants been adequately considered? N Data collection

Study details	Participants	Methods	Findings and Results	Comments
Source of funding NR		information giving. Finally, participants were asked to suggest any ways in which they considered information-giving within the hospital could be changed to help other patients. Interviews were conducted at a time and place chosen by the participant. Interviews lasted between 25 min and one hour and all were tape-recorded with the participants' consent. This ensured that no emphasis or details were lost. Each interview was then transcribed verbatim and data analysis began. Data Analysis Content analysis was carried out, whereby the transcripts were analysed for themes and each interview was segmented by these themes into categories. This involved	*If you ask you will be told, but if you don't know what to ask, then your questions will never be answered. (patient comment)* In general, the comments made indicated that participants appeared to feel overwhelming gratitude to their consultant surgeon. In their eyes this person had done something miraculous and saved their lives. One patient stated: *I was in awe of the doctor, these guys are God to me, they are life-savers. They are able to cut me in half and take bits out and throw them away. You are in awe! (patient comment)* This participant vocalized what others implied. It could be assumed that if an individual feels their life is indebted to someone, then they will have the utmost respect for them. Irrespective of the reason for	Was the data collected in a way that addressed the research issue? Y; data saturation reached Have ethical issues been taken into consideration? Y Data Analysis Was the data analysis sufficiently rigorous? Y coding by two independent coders Findings/results Is there a clear statement of findings? Y Overall quality: Moderate due to concerns over sample selection **Other information**

Study details	Participants	Methods	Findings and Results	Comments
		a series of steps. Initially, the whole script was read to get a sense of the entire material. On a second reading, key words or themes were highlighted. On the third reading, the highlighted areas were coded. The main subject areas relating to information that had been identified in the literature were used as coding categories. The coded themes were cut and pasted using a word processor into these categories. A high level of agreement was reached by the two coders but statistical analysis of intercoder reliability was not carried out.	this phenomenon, it was signi®cant in this study that the consultant thoracic surgeon received considerably less criticism than other groups. Even referring consultants were not held in the same high esteem. One participant remarked that he would not allow his referring consultant to carry out a repeat oesophagoscopy, `in case he undid the good work of the surgeon'. (author) Theme: Information from Nurses Six participants made positive comments about nurses' information-giving skills. These comments mostly related to the fact that nurses clari®ed what the doctor had discussed. In addition some participants made general statements, such as `the nurses were great' or `excellent'. However, they did not support these statements with any details of how they	

Study details	Participants	Methods	Findings and Results	Comments
			were `great' and indeed on some occasions made indirect criticisms at a later stage. One participant perceived that nursing staff lacked the necessary knowledge to provide patients with information. As a result of this, the participant felt devalued and had no confidence in nurses. (author comment) One participant also stated that on several occasions nurses told him `little white lies'. When probed further, this appeared to relate to occasions when nurses gave him vague or inaccurate information, perhaps in an attempt to reassure him. One example was at diagnosis, when the nurse tried to explain why he was waiting for some time to speak to the doctor: like why are they all away, they were after me.?? (author)	

Study details	Participants	Methods	Findings and Results	Comments
			And she said the doctor sees everybody before they go. She lied (patient comment) A comparable problem was that of conflicting advice among nursing staff. This was in relation to care of a central venous line and caused the patient undue anxiety. Another participant, although taking care to emphasize that he was not criticizing staff, highlighted two problems in one statement: (author) *But no-one (nursing staff) has time, it took me a while to find out what a TTO was about, actually what the letters stood for. Nobody sat down and actually explained that. (patient)* Primarily this identifies the problem of jargon and, in association with it, staff having insufficient time to provide explanations. (author)	

Study details	Participants	Methods	Findings and Results	Comments
			Theme: Information from Other medical staff In general participants gave few details about junior doctors. Even when probed, those interviewed often made bland statements, such as `oh, they were a great team' or `they were very nice.' As with nursing staff, junior doctors were criticized for using jargon and not having the necessary knowledge to provide information. However, on one occasion a participant related how a junior doctor admitted that he could not answer his question. His honesty was appreciated and made the person realize `these guys are only human'. This highlights the importance of being honest with patients. (author) A number of problem areas relating to other medical	

Study details	Participants	Methods	Findings and Results	Comments
			staff, namely those above the level of junior house officer, were highlighted by one participant in particular. This man felt that the doctors were not there to answer his questions when needed and that at the next ward round `yesterday's questions were no longer relevant!' (author) Another criticism related to doctors' lack of understanding of psychological needs: *Doctors have to realize that this is a very traumatic time for patients. (patient)* The participant talked at length about how frightening it is for patients to undergo such a major operation: *It doesn't matter how confident you are, and I am normally confident and used to standing up and speaking to people. Yet here I was, petrified. (patient)* Likewise another participant outlined how a doctor had	

Study details	Participants	Methods	Findings and Results	Comments
			treated him in general and not as an individual: *It was just some of the questions that she asked that made me feel that she is treating me in general. She doesn't specifically know about me. (patient)* Finally two participants discussed situations when they became upset because they overheard doctors discussing their care. One participant was about to have a central venous line inserted and heard it being described as `a very dangerous thing'. Another individual who had lost his voice postoperatively heard doctors saying that he might never regain his voice. This individual probably gave the best answer to this scenario himself: (author) *Doctors should be very careful what they say within the earshot of patients. Patients at this stage need*	

Study details	Participants	Methods	Findings and Results	Comments
			support and confidence that all will be well. (patient) Theme: Information from Professions allied to medicine Dieticians were mentioned by five participants, as they provided them with dietary information postoperatively. However, there were few details about the nature of this information. The other professionals who were positively portrayed by two participants were physiotherapists. They were described as one of the main sources of information and as having the time to sit down and talk. One woman stated: (author) *She (physiotherapist) was brilliant, she gave me more information than the doctors and nurses had. She was the only one that actually sat down. (patient)*	

Study details	Participants	Methods	Findings and Results	Comments
			This shows that all healthcare staff have an important role to play in relation to patient education and information-giving. Theme: Information from Other patients Those participants who spoke to other patients who had undergone the same operation were very positive about the experience. They used words such as `brilliant' and `terrific' to describe their encounters. One participant was particularly grateful: (author) *The main one there for me, that stands out in all of this, was talking to that woman [another patient]. That gave me the greatest hope. (patient)* In contrast, this participant also described how he was introduced to another patient. This meeting did not	

Study details	Participants	Methods	Findings and Results	Comments
			result in a positive outcome. On this occasion, the nurse mentioned that the other patient was an alcoholic. This blurred the participant's image of the patient and indeed he stated: `it didn't help me at all'. This illustrates that not all encounters with other patients are beneficial and that nurses should take care if initiating such an interaction. (author) Theme: need for nurse specialist Another significant finding relating to the sources of information was that six participants expressed the need for a nurse specialist in thoracic surgery. Four participants proposed that such a nurse would have been useful during the postoperative period, when they needed information and advice about matters such as returning to work. A nurse	

Study details	Participants	Methods	Findings and Results	Comments
			with counselling skills, who would have time to `sit down and talk' to the patient, was speci®cally identified by two participants. Another two participants suggested that such a nurse could have provided support and reassurance for families. (author)  In addition, a participant described at length how a nurse could establish a `back-up service' for patients by providing a telephone number with an answering machine that patients could contact day or night and leave a message. The nurse could then answer the query the following day. (author) Category: METHODS OF PROVIDING INFORMATION Theme: All participants stated that they received verbal information. Details about this verbal communication have already	

Study details	Participants	Methods	Findings and Results	Comments
			been discussed in relation to the sources that provided it. Theme: Written information All participants also received an information booklet produced by the Oesophageal Patients Association, and six participants spoke positively about this booklet. Some described it as `great' or `a tremendous help', while others just stated that it was useful. It was apparent from the data that participants used the booklet to refresh their memories and clarify any misconceptions. In addition, poor concentration postoperatively was experienced by three participants and this could also explain why they frequently relied on written material. (author) One participant was particularly keen on written data and stated that he `knew the booklet inside and out' and that he could easily	

Study details	Participants	Methods	Findings and Results	Comments
			refer to different sections when he needed to clarify anything. In contrast, two patients described their concentration as being so poor that they could not read the booklet. It was thus less useful to them. (author) Three participants also indicated that written information was useful to their families to help them understand what had occurred and what to expect. However, one family did seek additional written information from the charity Cancer BACUP which provides advice, support and literature for cancer patients and their families. This indicates that the current booklet did not satisfy all their information needs. (author) One participant was very critical of the information booklet. He described it as being `too optimistic' and of	

Study details	Participants	Methods	Findings and Results	Comments
			viewing the situation through `rose-coloured glasses'. This patient also contradicted some of the current literature regarding the usefulness of written information. He stated: *I have read the booklet and what I took out of it, and my wife has read it and what she has taken out of it, we never actually discussed. (patient)* As a result of this they had totally different impressions of what the postoperative recovery period would involve. (author) Theme: audio-visual information When asked about audio-visual methods of providing information, participants differed in their responses. Three participants, who highlighted some problems with written information, were in favour of audio-visual information, two were	

Study details	Participants	Methods	Findings and Results	Comments
			uncertain about the need for it and the remaining two, both from professional occupations, strongly opposed it, stating that training videos were generally of poor educational value and that videos were of little use for quick reference. Category: INFORMATION GIVEN TO PARTICIPANTS It became apparent during analysis that information given to participants could be categorized according to the list of information needs most frequently identified in the literature review, which were: details about treatment regimes, side-effects, extent of disease, likelihood of cure and prognosis and self-care or return to normality. Most participants (n.6) were given considerable details about the technical aspects of their operation both pre- and postoperatively. (author)	

Study details	Participants	Methods	Findings and Results	Comments
			Nevertheless, care has to be taken not to overwhelm patients with excessive technical data, while omitting information about less complex medical and nursing procedures. This was highlighted by one participant who stated: *Assumptions were made that people know what procedures are all about So a number of assumptions were made, are made, that people know about these things, and people don't. (patient comment)* Likewise, one woman stated that she had no idea what to expect about hospitalization in general as neither she nor any of her family had ever been in hospital. Staff should not assume that patients understand routine practices in hospital: for them and their families everything is novel and even simple procedures should be explained. (author comment)	

Study details	Participants	Methods	Findings and Results	Comments
			In relation to possible side-effects of the operation, participants appeared to be well informed, through both verbal and written means, about the possibility of having swallowing difficulties. Some other side-effects were also included in the information booklet, such as dietary problems, changes in gastric emptying and altered bowel habit. However, one participant felt that she did not receive satisfactory advice on discharge about postoperative complications and it was this woman's family that contacted the Cancer BACUP help-line to clarify some issues. Another stated `all the little set-backs made me feel that they were lying'. (author) Perhaps if this participant had been given more details about possible side-effects, he would not have seen them in such a negative light. These problems	

Study details	Participants	Methods	Findings and Results	Comments
			indicate a deficit in this area. (author) Five participants described how they were told about the extent of their disease, preoperatively: *He told me that it was localized, and all the good news, that it was in the lower third, which is highly survivable, or less fatal. He said `I don't know whether I can help you or not.' You can't get straighter than that, that was what I liked. I can't stand anybody beating around the bush. (author)*  Whether the information given was `good' or `bad', a number of participants appeared to appreciate being told the truth. (author comment) However, on a few occasions participants did mention that they would have preferred most positive information in the early postoperative period. This	

Study details	Participants	Methods	Findings and Results	Comments
			difference in opinion emphasizes that it is essential to assess each patient individually prior to providing information. Likewise, information given about cure and prognosis could be described as `hopeful' or `less hopeful'. (author) On the hopeful side: *We have your lab test back and you are completely clear. There is no cancer anywhere. He said it was a great success. (patient)* On the less hopeful side: *He told me, `You had four out of 14 nodes that were positive. The four nodes were small and that is good news. Anything that was left could take years to reoccur, if ever.' (patient)*  The `hopeful' quotes primarily aim to reduce patients' anxiety and generate feelings of safety and security. The `less	

Study details	Participants	Methods	Findings and Results	Comments
			hopeful' indicate that staff were providing participants with realistic expectations for the future. Six participants indicated that they were given some advice relating to their return to normality and self-care.`I just wanted to get back to my routine.' Four participants indicated that they required more information about convalescence. (author comment)	

<Insert search strategies here, broken down by database>

F.2 Palliative management

What are the specific information and support needs for adults with oesophago-gastric cancer who are suitable for palliative treatments and care only?

Study details	Participants	Methods	Findings and Results	Comments
Full citation Andreassen, S., Randers, I., Naslund, E., Stockeld, D., Mattiasson, A., Family members' experiences, information needs and information seeking in relation to living with a patient with oesophageal cancer, European Journal of Cancer Care, 14, 426-434, 2005 **Ref Id** 476910 **Country/ies where the study was carried out** Sweden **Study type** Qualitative study- semi-structured interviews **Aim of the study** To describe family members' experiences, information needs and	**Sample size** N=9 **Characteristics** The sample consisted of close family members: one brother, two husbands and six wives. Five family members had full-time or part-time employment and four family members were retired. **Inclusion criteria** The selection criteria for the participants in this study were that they should be a close family member or significant other to the patient and interested in participating in the present study. So, from an ongoing study in which 13 patients are included, nine family members were identified. **Exclusion criteria**	Sample selection Convenience sampling- family members of study participants Data Collection The first author conducted the interviews at a time and place chosen by the participants. That is, six interviews were carried out at the participant's home, two at the first researcher's office and one at a hospital. An interview guide was developed to identify the areas to be covered. However, all interviews started by an open-ended question: 'Will you tell us a little about your experiences of your family member's illness?' This question permitted the participants to talk freely about their experiences of information needs, and their information seeking. The interviews lasted about 1 hour (one of them about 20 min). All interviews were audiotaped with the participant's consent and transcribed verbatim.	**Themes and Categories** **Results** **Category: Intrusions on Family** Theme: Children Family members in this study emphasized the importance of including the whole family in the care given, even the children, whatever their level of knowledge or ability to understand are, because the children were aware that a tremendous change had occurred in the family. (authors comment) *I don't think anyone has ever asked how old our children are, if they visit school or anything like that. They don't seem to care that there is a family around the patient and that we in fact have a sixteen-year-old son, who has grown up with this.* (family member comment)	**Limitations** CASP Quality Assessment Tool Aims Was there a clear statement of the aims of the research? Yes Is a qualitative methodology appropriate? Yes Was the research design appropriate to address the aims of the research? Yes Sample selection Was the recruitment strategy appropriate to the aims of the research? Yes- purposive sampling of family member already participating in other study Has the relationship between researcher and participants been

Study details	Participants	Methods	Findings and Results	Comments
information seeking in relation to living with a patient suffering from oesophageal cancer. **Study dates** December 2003 and January 2004 **Source of funding** This work was supported by grants from Sophiahemmet University College, and The Sophiahemmet Foundation for Clinical Research, Stockholm, Sweden.	Not reported	Data Analysis Content analysis was used in analysis of the data. When analysing the part of the interviews involving the illness experiences, an inductive approach (Berg 2004) was used, while a deductive approach (Berg 2004) was used when analysing the data covering the participants' information needs and information seeking. The inductive approach went as following; the interviews were read through to gain an overall picture. They were then reread several times with the aim of the study in mind. Text units, i.e. a word, a sentence or a whole paragraph, that answered the questions at issue were marked and condensed into a description of their manifest content. From these descriptions, different themes were formed and organized into categories. Representative quotations have been used to illustrate themes. The initial	It was evident that the children became anxious and stressed which affected their school life. Moreover, they had to struggle much on their own. (author's comment) *Our son had his 18th birthday this year. Although he himself says that his mother's illness doesn't affect him at all, we have noted that his grades dropped disastrously during his first term.* (family member comment) The family members called attention to the importance of preparing the children for a changed family situation. Crucial for the family members was that their children should participate in information giving. Participation could facilitate the children's preparedness. (author's comment) *I think it would be good to receive joint information, to involve the children, since*	adequately considered? No Data collection Was the data collected in a way that addressed the research issue? Probably.Yes- data saturation not discussed by the author Have ethical issues been taken into consideration? Yes (privacy and confidentiality) Data Analysis Was the data analysis sufficiently rigorous? Details of content analysis provided as well as references for data analysis method, 3 different authors read interviews and checked categorization Findings/results

Study details	Participants	Methods	Findings and Results	Comments
		procedure used in the deductive analysis was the same as above, but text units were identified in relation to information needs and information seeking. In this study, three authors read the interviews and checked the categorization, and the agreement was considerably unambiguous.	*the parent, who comes home is a little foreign. You can say: 'One parent left and another one came home who is also a patient at home.' (family member comment)* **Category: Uncertainty** Theme: Course and prognosis The family members experienced an everyday symptomatic uncertainty and looked for signs for deterioration. (author comment) *You know all the time that one day it will get worse. You may receive an answer that it is a metastasis, exactly as we received now. I live constantly with this*. (family member comment) A prognostic uncertainty is a medical reality in patients with oesophageal cancer, which even these family members had to live with:	Is there a clear statement of findings? Yes Overall quality: Moderate **Other information**

Study details	Participants	Methods	Findings and Results	Comments
			'*Since after five years one is considered be out of the danger zone, we can calculate that my husband will in some form be given a clean bill of health, but perhaps not quite be declared healthy*.' (family comment) Theme: Future The uncertainty of death and dying pervaded the family members' thoughts and plans for the future. They expressed: *Shall we sell the house or shall we not? Shall we renovate our house or shall we not. Shall I work full time or shall I not?' 'Will my husband die tomorrow, or what?* Heredity The family members expressed a genetic threat and concerns about the connection between genetics and cancer. They were also worried if the children would	

Study details	Participants	Methods	Findings and Results	Comments
			inherit the cancer. (author comment) *What worries me most is that the illness will affect the children. If they will get this . . . whether it is hereditary. (family member comment)* *Since my brother now has cancer of the oesophagus and all my other siblings and my mother and father also had cancer, I want to know if I am exposed to cancer and have it in my genes, so I can take some special tests. (family member comment)* **Category: Managing Uncertainty** Theme: seeking information from interpersonal sources Subtheme: experts In order to learn, receive understanding for the illness and handle the uncertainty, the family members entrusted themselves to the	

Study details	Participants	Methods	Findings and Results	Comments
			experts, i.e. the physicians, who were considered the major source of information. The family members accompanied the patient when consulting the physician and took an active part by listening and asking specific questions concerning oesophageal cancer. *The doctor is our lifeline. When you are so close to the experts as we are now, we ought to get the truth directly from the doctor if there is anything we wonder about. We have entrusted ourselves to the experts. (family member comment)* In this study the family members also felt connected to the nurses who could answer questions of importance, and give practical and emotional support. *It's easier to talk with a nurse when it concerns important*	

Study details	Participants	Methods	Findings and Results	Comments
			questions. You may receive quite good and reassuring answers. / . . . / You get a feeling of trust when you talk with a nurse. (family member comment) Moreover, the patients themselves were considered experts. *I haven't asked anything myself because I knew that my husband would ask everything so minutely himself. I know he would look up everything himself. He has shared his knowledge with me and we have discussed it together. (family member comment)* Despite knowing that the physicians are able to provide information about diagnosis, prognosis and treatment, the family members did not always turn to them with questions. They sometimes thought they could not formulate questions since they did not always know enough in order	

Study details	Participants	Methods	Findings and Results	Comments
			to ask. This lead to a feeling of being left out of certain knowledge that perhaps should be of value for understanding the situation. However, all of the family members did not want to discuss and ask specific questions with the physician when the patient listened. (author comment) *I don't want to ask the doctor a question, which he has to respond to negatively when my husband is with me. (family member comment)* Some of the family members reported that not asking questions was due to their lack of medical knowledge about oesophageal cancer. (author comment) *You are not enough medically knowledgeable. Therefore, you don't know what to ask. (family member comment)* Subtheme: social network and kinship	

Study details	Participants	Methods	Findings and Results	Comments
			The family members contacted persons in the family's circle who had specific knowledge of the illness and in whom they felt confidence. *I trusted the judgements that doctors in our acquaintance circle gave, but not completely, since they are not in the field. They can't be well read in all areas. (family member comment)* Theme: media sources Subtheme: daily newspaper and TV Through personal experiences and by following cancer reports in daily newspapers and on TV, the family members had general knowledge and understanding about different cancer diagnoses. Concerning oesophageal cancer, they were ignorant and had never heard of the disease. (author comment)	

Study details	Participants	Methods	Findings and Results	Comments
			I hadn't heard about that disease. I think you have heard about most of the variations, but not cancer of the oesophagus. (family member comment) However, the family members believed that the image of cancer given in Swedish mass media is that the survival rates are increasing. (author comment) *I receive most of the information through the mass media. In that way, I get my information and it is sort of positive, since more and more people pull through. (family member comment)* Subtheme: encyclopaedias and other written material The family members looked in encyclopaedias, medical books, material produced by the hospital, and brochures, to gain medical information about the illness and to get an overview of problems related to the illness.	

Study details	Participants	Methods	Findings and Results	Comments
			We have received books on how you deal with the illness, quite thin pamphlets from the medical authorities both to us and to the children. (family member comment) *I have an encyclopaedia at home, which certainly is a bit old. I also have a book for quick medical reference, where I can look up different things in order to be able to read briefly about them. (family member comment)* Family members did not only seek information in order to gain increased medical knowledge, but also because it gave them the feeling of doing something constructive. *Seeking information is much more than receiving knowledge, it also includes a feeling of doing something. (family member comment)* Subtheme: the internet	

Study details	Participants	Methods	Findings and Results	Comments
			Most of the family members had access to computers and necessary skills for seeking information. They used the internet mainly to obtain an overview about the illness and illness-related problems as well as about the prognosis of oesophageal cancer. The information sites of most interest on the net were medical sites from Sweden where they could read about research, and sites from the United Kingdom as their medical information about oesophageal cancer was extensive. *I think that the internet was a great help, since it is difficult to telephone someone and pose relevant questions when I hardly know what I want to find out. Then it is possible that if you receive incorrect information, you can form an opinion later. (family member comment)*	

Study details	Participants	Methods	Findings and Results	Comments
			The prognosis was so bad. It was so depressing and I started to believe that I would find my husband dead in bed. I got terrified and there was nothing positive at all in the information I read. (family member comment) Subtheme: Face-to-face with the physician and the information found When the family members confronted the physicians with information about the prognosis of oesophageal cancer, they found that their reaction was positive. The physician discussed the findings with the family members. Moreover, the family members were told that the information they had found, especially about the prognosis, was not current and needed to be updated. (author comment) *I said to the doctor that I had been on the net and read about a study where it said*	

Study details	Participants	Methods	Findings and Results	Comments
			that there was a terribly poor prognosis. He said that the information was not really current and that the prognosis is better now. I didn't go into greater detail. (family member comment) Theme: not seeking information Subtheme: balancing needs On the one hand, there was an oscillation between family members' desire for more information and the avoidance of new information. (author comment) *I want to know if the prognosis is terribly poor or if it is about one year. I want to know what will happen.. . . Actually, I really don't want to know. (family member comment)* On the other hand, knowledge about details relating to the illness could	

Study details	Participants	Methods	Findings and Results	Comments
			alleviate some of the scariness and unpleasantness. (author comment) *Perhaps it isn't so terrible. Everything you know something about loses its terribleness. (family member comment)* Subtheme: Time-consuming and frightening Seeking information was sometimes considered as an effort for the family members, which demanded a considerable amount of time, courage and energy. The family members were also afraid of what they might find. (author comment) *Certainly I can search for information. That isn't the problem but the problem is that it takes time. I shall mobilise the courage, the power, the energy . . . call it whatever you want, to be able to sit down and go*	

Study details	Participants	Methods	Findings and Results	Comments
			through things. I am not sure I am going to like the answers I get. Maybe it is better not to know so very much but to do like the ostrich, to bury your head in the sand and hope for the best and keep your fingers crossed. (family comment)	
Full citation Andreassen, S., Randers, I., Näslund, E., Stockeld, D., Mattiasson, A., Patients' experiences of living with oesophageal cancer, Journal of Clinical Nursing, 15, 685-695, 2006 **Ref Id** 476911 **Country/ies where the study was carried out** Sweden **Study type**	**Sample size** N=13 **Characteristics** Their ages ranged from 44 to 77 years. **Inclusion criteria** The selection criteria for this study were as follows: women and men of different ages who had undergone different treatments for oesophageal cancer, i.e., a total thoracic oesophagectomy, oncological	Setting Patients with oesophageal-cancer under care of hospital in Sweden. Sample Selection Purposive sampling was used. The surgeon in charge of their care identified and constructed a list of 17 potential participants, based upon the earlier mentioned criteria, where after their names were given to the first author. All participants received a letter including information about the aim of the study, stating that participation was voluntary, the right to withdraw at any time and that	**Themes and Categories** **Results** **Theme 1) Experiences of becoming a patient diagnosed with oesophageal cancer** Subtheme: Unprepared and without knowledge of oesophageal cancer Because of the silence of the illness, the participants had no premonitions of the seriousness of the outcome of the initial investigations. Nor did they know about this specific type of cancer:	**Limitations** CASP Quality Assessment Tool Aims Was there a clear statement of the aims of the research? yes Is a qualitative methodology appropriate? Yes Was the research design appropriate to address the aims of the research? Yes Sample selection

Study details	Participants	Methods	Findings and Results	Comments
Qualitative study, semi-structured interviews **Aim of the study** To describe patients' experiences of living with oesophageal cancer and how they seek information. **Study dates** December 2003 and March 2004 **Source of funding** This work was supported by grants from the Sophiahemmet University College and the Sophiahemmet Foundation for Clinical Research, Stockholm, Sweden.	treatment with a curative intent and/or palliative treatment. Moreover, the participants should speak and understand Swedish, feel sufficiently well and be willing to take part in the present study. **Exclusion criteria** NR	data would be treated confidentially. After about one week, participation was confirmed through a telephone call by the first author and a time for the interview was agreed upon Data Collection: The first author carried out two pilot interviews at the participant's home which, according to their consent, were audio-taped. These interviews were semi-structured. That is, the interviewer used an interview guide to cover specific themes, but had no specific order when and how to address them. However, each interview started with inviting the participants to describe their experiences freely of having been diagnosed with oesophageal cancer. The main 11 interviews, were carried out as follows: eight at the participant's home, one at a hospital, one at the first author's office and one in a separate place at a cafe´. They lasted	*I knew nothing about my condition before I got the diagnosis. I was completely dumbfounded. My wife said when the doctor discussed it, I looked like a little child. (patient comment)* *If the doctors had told me it was breast cancer, uterine cancer, gastric cancer or intestinal cancer, I would have understood. But I had never expected this. (patient comment)* Subtheme: Existential concerns After receiving the diagnosis the participants became aware of the seriousness of the situation. Their existential concerns were shown in the following thoughts and reflection on life and death: '*What will happen?' 'Will I survive?' 'Will I die?' Will I only be lying in bed and die?'* Later, when the participants wondered why they had developed cancer, they tried	Was the recruitment strategy appropriate to the aims of the research? Yes- purposive sampling Has the relationship between researcher and participants been adequately considered? No Data collection Was the data collected in a way that addressed the research issue? Yes; author states data saturation was achieved in the interviews Have ethical issues been taken into consideration? Yes- privacy and confidentiality, ethics board approved Data Analysis

Study details	Participants	Methods	Findings and Results	Comments
		about one hour and were audio-taped. Data Analysis: All interviews were transcribed verbatim. Data was analysed through content analysis. Qualitative content analysis with an inductive approach (Berg 2004) was used when analysing the data. The interviews were read sentence by sentence to identify text units. These text units, i.e. words, sentences, or a whole paragraph, which answered the questions at issue, were marked and notes about the content were made in the margin. A code was generated for each text unit. Codes were compared with each other and those that appeared to belong together were grouped into preliminary themes. The first author conducted the processes of reading, rereading, coding and the preliminary thematization. The first author and two of the co-authors (IR, A-CM) thereafter discussed these	to find out if there was anything in their lifestyle that had promoted tumour growth, for example, 'using snuff', 'drinking alcohol moderately', 'hot drinks and food', 'drinking coffee', 'heartburn' and 'gastric ulcer'. This resulted in feelings of blame: *Haven't I taken care of myself well enough? (patient comment)* Also, they had questions regarding heredity. Not only did they wonder if they themselves had contracted the disease because of hereditary predisposition: 'My Dad and his brother died of cancer'; they also wondered if their children would inherit the disease. **Theme 2) Experiences of undergoing investigations and treatment** Subtheme: Extreme tiredness	Was the data analysis sufficiently rigorous? Yes- examples given of thematic analysis, data analysed by three authors Findings/results Is there a clear statement of findings? Yes Overall quality: HIGH **Other information** Linked to 2005 family member study. Author a Registered Nurse. Unknown which patients are undergoing palliative or curative treatments.

Study details	Participants	Methods	Findings and Results	Comments
		preliminary themes, transformed them into themes and further analysed and transformed themes into sub themes. This organization was repeatedly discussed between these three authors until a consensus was reached. To be complete in data reporting and to illustrate the research findings quotations from all participants will be represented.	Going through palliative therapy, oncological treatment, or a harrowing as well as an extensive operation caused the participants extreme tiredness. The unpredictability of changes in energy level caused frustration and distress. *The cancer itself hasn't given me any concerns, but it is the treatment that takes away my strength. When I finished the radiotherapy, I was so exhausted that I couldn't walk. The first week I rested at home. (patient comment)* *The doctor said that after the treatment I would be very, very tired. I thought that this tumour was so small and that I could fix it in a month or two. But oh, how I deceived myself. I am terribly, terribly tired. (patient comment)* This overwhelming tiredness remained for long time, which is confirmed in the	

Study details	Participants	Methods	Findings and Results	Comments
			following quotation: *'I really don't understand why I'm still so tired after 6 months…but I am'. patient comment)* **Theme 3) Experiences of intrusions in daily life** Subtheme: Daily-life activities affected The side effects of treatment, i.e. fatigue, made simple everyday activities such as going for a walk or catching the bus nearly impossible to accomplish. In addition, their hearing was affected, which made them feel like 'living in a vacuum': *I am terribly, terribly tired. Certainly, I am out walking every day, but not very long stretches. I must stop quite often to breathe and to rest a little while. (patient comment)* For some of the participants the percutaneous endoscopic gastrostomy (PEG), which was placed for ensuring an adequate nutritional intake, caused	

Study details	Participants	Methods	Findings and Results	Comments
			restrictions in travelling and swimming: *The PEG is an obstacle when I shower and when I travel. It has to be washed. I can't go to a public sauna and places like that. (patient comment)* Subtheme: Dietary habits changed The participants' dietary habits altered in step with increased side effects of treatment, i.e. phlegm secretion, oral mycosis and fatigue and the progressive illness and dysphagia. This resulted in exhaustion and tiredness as well as loss of weight. Meals became time-consuming and eating mainly turned into a necessary source for nutrition intake and they lost the pleasure earlier associated with eating: *I can't eat the same food as I used to eat and I have no*	

Study details	Participants	Methods	Findings and Results	Comments
			appetite right now. Cooking is no fun. Nothing tastes good anymore. I try to eat sour milk, but I keep vomiting. I have an enormous amount of phlegm and it really bothers me. (patient comment) *I have no energy…and it is really hard for me to eat anything. Where I used to eat two potatoes, I can only eat one now and even that can be too much. Eating makes me so tired that I have to lie down, even though I haven't eaten a whole lot. (patient comment)* Subtheme: Roles and relationship between partners affected The relationship between the participants and their partners sometimes altered as fatigue fostered a dependence on the partner concerning care and different chores:	

Study details	Participants	Methods	Findings and Results	Comments
			My husband does all the housework; he cooks, he irons, he does laundry, he takes the dog for a walk five times a day and he helps our son iron his clothes. (patient comment) *I became somewhat dependent on my wife, who had to help me wash up around the gastrostomy. (patient comment)* Moreover, the participants experienced that their partners were more psychologically affected than they were themselves, clearly expressed in the following quotation: *'I feel that the cancer hasn't struck me too hard, but my wife has taken it much worse mentally'*. They therefore had a wish for homogeneous support groups for all family members. (author comment) Subtheme: Children's lives affected	

Study details	Participants	Methods	Findings and Results	Comments
			Being a parent with a life-threatening illness caused an imbalance in children's lives as they mostly were aware of the seriousness of the illness and therefore became worried and stressed. Their schoolwork was affected, which resulted in lower marks: *My 18-year-old son was feeling very badly when he got the information that his mother had cancer. From having excellent marks in all his subjects, he started to ignore school completely. He didn't discuss this with my husband or me. He didn't want to make me upset or his father unhappy. He was convinced that I would die. He gave up everything. (patient comment)* Information about the parent's illness ought to be adjusted to the children's age and intellectual capacity.	

Study details	Participants	Methods	Findings and Results	Comments
			This became apparent when one of the participants talked about her son, who was mentally retarded and his specific needs: *It's immensely important that he also has a chance to meet someone, who allows him to express himself in his own way. (patient comment)* Subtheme: Everyday uncertainty The ambiguity of the cancer's nature was profoundly stressful. There was an expressed everyday uncertainty about future, which caused feelings of 'being under sentence of death'. The participants did not know whether the treatment would be successful or if their cancer would be cured. Thus their sense of uncertainty made it difficult to make plans for the future: *They tell me they don't know why I got it and they can't*	

Study details	Participants	Methods	Findings and Results	Comments
			give me a prognosis. Of course, that's not what you want to hear from your doctor…but if you think about it, they really don't know either. Sometimes it feels so hopeless. (patient comment) For one of the participants this uncertainty was so emotionally devastating that she wished the physician to give her 'a last injection', although she intellectually understood that this kind of action was impossible. **Theme 4) Managing a life-threatening illness.** Subtheme: Viewing the future After having received the diagnosis of cancer, the participants tried to take control over their lives. Hence, they adapted their behaviours to a new life situation. Some participants reappraised time and priorities in life:	

Study details	Participants	Methods	Findings and Results	Comments
			When I heard that I didn't have any metastases, I thought that perhaps this is only a respite and therefore I have been terribly active. I work frantically. I think that time is very valuable, something I never bothered about before. (patient comment) Others set up a specific goal to strive for: *We have a son who will graduate this summer. The whole time I've set up a goal to take part in his graduation day. (patient comment)* Others wanted to fight for being healthy: *I think that as long as I want to live, I will fight to be healthy. (patient comment)* Subtheme: Subordinating themselves to medical experts The participants had faith in their physicians having the	

Study details	Participants	Methods	Findings and Results	Comments
			best knowledge concerning the complexity of the disease and the treatment procedures. They were the major resources for information about diagnosis, treatment, prognosis and side effects of medications. (author comment) *I thought 'I can't do anything now; I'll just hand myself over to the experts and let them do whatever they want with me'. I've handed my life over to the doctors. (patient comment)* The registered nurses had to answer many of the participants' questions about the disease and the treatment as they experienced that there were difficulties in continuity with the physicians and they were afraid of bothering them. Thus, the participants also felt connected to registered nurses, as they had necessary medical competence for answering questions and were able to	

Study details	Participants	Methods	Findings and Results	Comments
			give the participants necessary practical and emotional support: (author comment) *I've seen a lot less of the doctors in the hospital. I see mostly nurses there. And things are different there; you ask the nurses, rather than the doctors, a lot more often than you do outside the hospital. (patient comment)* *Sometimes I have written down a lot of questions, but usually not more than half or in some cases a third part is answered…the doctors are so rushed and suddenly they are gone. (patient comment)* The participants had a wish for information from health-care professionals not only about the disease, but also about being a patient with a life-threatening illness: *The health-care professionals perhaps could have had time to tell me more about how it really is to*	

Study details	Participants	Methods	Findings and Results	Comments
			be a patient. Perhaps they could have devoted a few hours to talk about a number of things concerning this cancer…in another way. (patient comment) Subtheme: Seeking knowledge from Family members and friends In the encounters with the physicians, family members were a significant source of information for the participants because the family members could ask questions from an outside perspective: *I have experienced it positive that my son has come with me to the doctor. It is good to have another pair of ears listening. He has asked questions from an outside perspective. (patient comment)* *It is my wife, who gathers the information that is needed. She is often with me when I*	

Study details	Participants	Methods	Findings and Results	Comments
			visit the doctor. (patient comment) The participants also sought further information among those friends and relatives who had medical knowledge and understood the participant's capacity to learn: *I have a cousin who is a doctor and I also had my brother-in-law who was a doctor. I trust them a little more because they know what information I am capable of understanding. (patient comment)* Subtheme: Seeking knowledge from Fellow patients Exchanging experiences with fellow patients was found to be valuable to get a better understanding about the illness as their knowledge is based on personal experiences: *It is immensely important that a new patient can talk with a*	

Study details	Participants	Methods	Findings and Results	Comments
			fellow patient. That information is much more valuable than the information the doctor gives. You can ask questions you wouldn't dare to pose otherwise. (patient comment) Subtheme: Seeking knowledge from Media sources The participants attended lectures at the hospital to get an understanding of the illness and an overview of medical information about the illness and illness-related problems. In addition, they used encyclopaedias, medical books, material produced by the hospital and brochures. (author comment) Most of them had access to computers and necessary skills for seeking information on the Internet, but they used it to a limited extent. Information found on the Internet was not always experienced relevant or reliable and could	

Study details	Participants	Methods	Findings and Results	Comments
			consequently not be applied, which became apparent in the following quotation: *It became apparent that I could just as well ignore the information since it dealt with men between 60- and 80 years old. You don't put up with this information when you are 44 years old. This information is completely irrelevant. (patient comment)* Later, while conferring with the physicians about facts found on the Internet, the participants were told that this information was not always current and should be more individualized. This clarification was found encouraging. (author comment) *I found a research report, brought it with me and discussed it with the doctor. He took it out of my hand and said, 'It doesn't apply to you'. I experienced it positively that he reacted so*	

Study details	Participants	Methods	Findings and Results	Comments
			because it was a negative report. (patient comment) There were participants who avoided further information due to their fear of unwanted knowledge. Moreover, weakness and fatigue caused by the extensive treatment and its side effects made them avoid additional information: *I don't pose any questions because I think it is scary. I've left myself in the doctors' hands… they can help me. (patient comment)* *There is a great deal I should have asked the doctor about, but I was so tired of everything that I got to the point that I didn't feel like doing it. I became worn out over everything and had enough. (patient comment)*	

1

F.3 MDT

What is the most effective organisation of local and specialist MDT services for adults with oesophago-gastric cancer?

No evidence was available for this review.

F.4 Surgical services

What is the optimal provision and organisation of surgical services for people with oesophago-gastric cancer?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Dikken, J. L., Dassen, A. E., Lemmens, V. E. P., Putter, H., Krijnen, P., van der Geest, L., Bosscha, K., Verheij, M., van de Velde, C. J. H., Wouters, Mwjm, Effect of hospital volume on postoperative mortality and survival after oesophageal and gastric cancer surgery in the Netherlands between 1989 and 2009, European Journal of CancerEur J Cancer, 48, 1004-1013, 2012	**Sample size** n=24,246 non metastatic invasive carcinoma (oesophageal or gastric) **Characteristics** Resectable non-metastatic oesophageal cancer n=10,205 Resectable non-metastatic gastric cancer n=14,221 For very low volume, low volume, medium volume and high volume hospitals respectively: **Oesophageal cancer**	**Interventions** Type of surgery was not specified for every patient so oesophageal and gastric cancer differences were based on tumour location codes Definitions: Oesophagestomies: resections for cancers of the oesophagus (C15.0-15.9) and gastric cardia (C16.0)	**Details** Tumor staging: International Union Against Cancer (UICC) Tumour Node Metastases (TNM) classification in use in the year of diagnosis. Vital status: Municipal registries, from 1994 onwards from nationwide population registries network (cover all deceased Dutch residents) End of follow up: 31st December 2009	**Results** Volume-outcome relations for oesophagectomy and gastrectomy (1989-2009). Mortality and survival were calculated with multivariable Cox regression. Survival at 3 years was conditional on surviving the first 6 months. Very low (VL) (ref) : 1-5/year Low (L): 6-10/year Medium (M):11-20/year High (H):≥21/year <u>Survival at 6 months and 3 years by hospital volume</u>	**Limitations** Selection bias: low risk of bias Performance bias: Unclear risk. Unclear whether the comparisons groups received the same care, or if the participants were blinded to the volume status of the hospital. Attrition bias: low risk of bias. The registries are reported to have complete coverage of all deceased Dutch citizens. Some of the data was unknown e.g. tumour staging.

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>Ref Id

543467

Country/ies where the study was carried out

Netherlands

Study type

Retrospective cohort study

Aim of the study

To describe changes in annual hospital volumes, postoperative mortality, survival and lymph node yields for oesophagectomy and gastrectomy in the Netherlands between 1989 and 2009 and to explore whether there is any association between annual hospital volume for oesophagestomy and gastrectomy and postoperative</td>
<td>N values: 2914, 2695, 1494, 2922

sex (M %): 76%, 76%, 76%, 77%, p=0.73

Age: <60 years; 32%. 35%, 34%, 35%, 60-75 years; 56%, 54%, 54%, 56%, >75 years; 12%, 11%, 11%, 9%, p=0.002

Morphology: adenocarcinoma; 79%, 74%, 74%, 73%, SCC; 19%, 23%, 23%, 25%, other; 2%, 2%, 3%, 2%, p<0.001

TNM stage: I; 21%, 19%, 19%, 18%, II; 40%, 41%, 39%, 37%, III; 34%, 35%, 36%, 38%, IV (T4N1-3M0 and T1-4N3M0 gastric cancers were assigned stage IV in the 6th edition TNM classification); 1%, 1%, 2%, 1%, Unknown; 4%, 4%, 5%, 7%, p<0.001

Pre-operative therapy: Yes; 6%, 9%, 24%, 32%, p<0.001</td>
<td>Gastrectomies: resections for non cardia gastric cancer (C16.1-16.9)

(to ensure it didn't affect the results, analyses were repeated with cardia cancer coded as gastric cancer)

Yearly resection rates: number of resections relative to the number of cancers diagnosed in a year</td>
<td>Hospital volumes: number of oesophagectomies or gastrectomies per hospital per year

Very low: 1-5/ year

Low: 6-10/year

Medium: 11-20/year

High ≥21/year

Pre 2005: hospital where the surgery was done was only recorded in 53% cases and showed an 80% overlap with hospital of diagnosis. Those unknown the hospital of diagnosis was used to calculate the hospital volume.

Post 2005: Hospital performing the surgery was registered for all patients.</td>
<td>
<table>
<tr><th rowspan="2">Hospital volume</th><th colspan="2">Oesophagectomy HR (95%CI)</th><th colspan="2">Gastrectomy HR(95%CI)</th></tr>
<tr><th>6-mth</th><th>3-yr</th><th>6-mth</th><th>3-yr</th></tr>
<tr><td>VL</td><td>1.00</td><td>1.00</td><td>1.00</td><td>1.00</td></tr>
<tr><td>L</td><td>0.90 (0.78 - 1.03)</td><td>1.01 (0.94-1.10)</td><td>0.95 (0.84-1.07)</td><td>0.99 (0.91-1.07)</td></tr>
<tr><td>M</td><td>0.78 (0.62 - 0.97)</td><td>0.90 (0.81-0.99)</td><td>0.95 (0.83-1.08)</td><td>0.99 (0.90-1.08)</td></tr>
<tr><td>H</td><td>0.48 (0.38 - 0.61)</td><td>0.77 (0.70-0.85)</td><td>1.10 (0.82-1.49)</td><td>0.98 (0.86-1.12)</td></tr>
</table>
<u>Cox regression model of survival at 6 months and 3 years</u>

<table>
<tr><th></th><th>Oesophagectomy HR(95%CI)</th><th>Gastrectomy HR(95%CI)</th></tr>
</table>
</td>
<td>Detection bias:Unclear risk of bias. It is unclear if the investigators were blinded to the hospital volume status where the patients had their surgery and other important confounding factors.

Other limitations: pre 2005 place of diagnosis was used as the place of surgery (n=8). Survival is reported at 3 years rather than the protocol stated time points, so this will be classed as an indirect outcome. The protocol time points were read off the published survival curves, which will result in some inaccuracy.

Other information

Note: The study also reports lymph node harvest but this has not been extracted as not all of the protocol confounders were</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>mortality, survival and lymph node yield.

Study dates

January 1989 and December 2009

Source of funding

Funded by the Signalling Committee on Cancer of the Dutch Cancer Society (K W F Kankerbestrijding). The funding source had no role in study design, collection, analysis, analysis, interpretation, writing of the manuscript or in the decision to submit the manuscript for publication.</td>
<td>Post-operative therapy: Yes; 5%, 5%, 6%, 5%, p=0.43

Gastric cancer

N values: 3411, 6099, 4356, 355

sex (M %): 58%, 61%, 61%, 63%, p=0.045

Age: <60 years; 20%, 21%, 19%, 15%, 60-75 years; 47%, 48%, 48%, 46%, >75 years; 33%, 31%, 33%, 39%, p=0.016

Morphology: adenocarcinoma; 98%, 98%, 98%, 99%, other; 2%, 2%, 2%, 1%, p=0.11

TNM stage: I; 38%, 37%, 39%, 41%, II; 26%, 27%, 27%, 22%, III; 27%, 28%, 28%, 31%, IV (T4N1-3M0 and T1-4N3M0 gastric cancers were assigned stage IV in the 6th edition TNM classification); 5%,4%, 4%, 3%, Unknown; 3%, 3%, 3%,2%, p=0.014</td>
<td></td>
<td>Statistical analysis:

Type of surgery analysed separately

Changes in 6 month mortality and 3 year survival: stratified Cox regression, adjusted for sex, age, socioeconomic status, stage, morphology, preoperative therapy use and postoperative therapy use (only for 3 year survival).

Overall survival: day of diagnosis until death (because date of surgery was not available pre 2005)

Lymph node yield: adjusted for sex, age, stage and morphology. This has not been extracted as it does not adjust for neo-adjuvant therapy as per the protocol.</td>
<td>
<table>
<tr><th></th><th>6-mth</th><th>3-yr</th><th>6 mth</th><th>3-yr</th></tr>
<tr><td colspan="5">Year of diagnosis (Ref – 1989 to 1993)</td></tr>
<tr><td>1994-1997</td><td>0.91 (0.78-1.07)</td><td>0.92 (0.83-1.01)</td><td>0.96 (0.86-1.07)</td><td>0.98 (0.90-1.05)</td></tr>
<tr><td>1998-2001</td><td>0.82 (0.68-0.98)</td><td>0.88 (0.79-0.97)</td><td>0.89 (0.79-1.01)</td><td>0.94 (0.87-1.02)</td></tr>
<tr><td>2002-2005</td><td>0.69 (0.55-0.86)</td><td>0.69 (0.63-0.75)</td><td>0.74 (0.65-0.85)</td><td>0.88 (0.81-0.96)</td></tr>
<tr><td>2006-2009</td><td>0.67 (0.52-0.85)</td><td>0.75 (0.63-0.75)</td><td>0.70 (0.60-0.81)</td><td>0.78 (0.72-0.86)</td></tr>
<tr><td colspan="5">Sex(Ref-Male)</td></tr>
<tr><td>Female</td><td>0.75 (0.66-0.86</td><td>0.83 (0.78-0.89</td><td>0.79 (0.73-0.85</td><td>0.91 (0.85-0.97</td></tr>
<tr><td colspan="5">Age(Ref-<60 years)</td></tr>
<tr><td>60-75</td><td>1.83 (1.56-2.14</td><td>1.14 (1.07-1.21</td><td>2.03 (1.78-2.30</td><td>1.27 (1.18-1.37</td></tr>
<tr><td>>75</td><td>3.10 (2.54-3.79</td><td>1.41 (1.25-1.59</td><td>3.94 (3.47-4.49</td><td>1.57 (1.44-1.71</td></tr>
<tr><td colspan="5">SES(Ref-Low)</td></tr>
<tr><td>Medium</td><td>0.76 (0.64-0.9</td><td>1.05 (0.96-1.16</td><td>0.92 (0.81-1.04)</td><td>1.01 (0.92-1.12)</td></tr>
<tr><td>High</td><td>0.54 (0.38-0.78</td><td>1.00 (0.85-1.17</td><td>0.70 (0.55-0.91))</td><td>1.00 (0.84-1.20)</td></tr>
</table>
</td>
<td>adjusted for (neo-adjuvant treatment).</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td></td>
<td>Pre-operative therapy: Yes; 5%, 5%, 3%, 2%, p<0.001

Post-operative therapy: Yes; 4%, 4%, 3%, 3%, p=0.009

Annual no. of oesophagectomies doubled from 352 to 723, gastrectomies decreased from 1107 to 495 from 1989 to 2009.

% high volume hospital oesophagectomies increased from 7% to 64%, gastrectomies decreased from 8% to 5%.

In 2009: 44/92 hospitals in the Netherlands performed oesophagectomies, 91/92 performed gastrectomies.

Inclusion criteria

Patients who were registered on the Netherlands Cancer Registry (covers all hospitals in the country, 16.5 million inhabitants, data routinely</td>
<td></td>
<td>Volume outcome analyses: patient was the unit of analysis, volume the exposure factor

Differences in survival estimates, used Cox regression, stratified for hospital volume and adjusted (factors listed above) to analyse changes over time and clustering of deaths within hospitals

Hospital volume also analysed as a linear variable.</td>
<td>
<table>
<tr><td>Unknown</td><td>0.53 (0.38-0.74</td><td>1.04 (0.86-1.26</td><td>0.94 (0.73-1.21</td><td>1.03 (0.85-1.24)</td></tr>
<tr><td colspan="5">TNM stage (Ref – Stage I)</td></tr>
<tr><td>II</td><td>1.28 (1.08-1.52)</td><td>2.74 (2.46-3.04)</td><td>1.46 (1.31-1.63)</td><td>2.99 (2.78-3.22)</td></tr>
<tr><td>III</td><td>1.73 (1.41-2.13)</td><td>5.20 (4.46-6.05)</td><td>2.15 (1.93-2.38)</td><td>5.37 (5.01-5.75)</td></tr>
<tr><td>IV</td><td>3.85 (2.55-5.81)</td><td>9.76 (7.43-12.81)</td><td>3.50 (3.00-4.08)</td><td>8.45 (7.43-9.61)</td></tr>
<tr><td>Unkwn</td><td>1.92 (1.41-2.62)</td><td>2.37 (2.00-2.81)</td><td>1.91 (1.40-2.60)</td><td>2.36 (1.96-2.84)</td></tr>
<tr><td colspan="5">Morphology (Ref – Adenocarcinoma)</td></tr>
<tr><td>SCC</td><td>1.26 (1.11-1.43)</td><td>1.09 (0.98-1.21)</td><td>1.18 (0.86-1.64)</td><td>0.58 (0.44-0.78)</td></tr>
<tr><td>Other</td><td>1.28 (0.94-1.75)</td><td>1.05 (0.84-1.33)</td><td>1.18 (0.86-1.64)</td><td>0.58 (0.44-0.78)</td></tr>
<tr><td colspan="5">Preoperative therapy (Ref-No)</td></tr>
<tr><td>Yes</td><td>0.32 (0.23-0.43)</td><td>0.84 (0.76-0.93)</td><td>0.27 (0.17-0.43)</td><td>1.05 (0.84-1.31)</td></tr>
<tr><td colspan="5">Postoperative therapy (Ref – No)</td></tr>
<tr><td>Yes</td><td></td><td>1.07 (0.94-1.21)</td><td></td><td>1.01 (0.85-1.21)</td></tr>
</table>
</td>
<td></td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	collected by trained registrars from the hospital records 6-18 months after diagnosis. Quality and completeness of the data was stated to be high) with ICD-O codes for adenocarcinoma (8140-8145, 8190,8201-8211, 8243, 8255-8401, 8453-8520, 8572, 8573, 8576), squamous cell carcinoma (SCC) (8032, 8033, 8051-8074, 8076-8123) and other or unknown histology (8000-8022, 8041-8046, 8075, 8147, 8153, 8200, 8230-8242, 8244-8249, 8430, 8530, 8560, 8570, 8574, 8575). **Exclusion criteria** Those who did not undergo surgical treatment n=43,646 Patients without information on the hospital where the diagnosis was established, or where surgery was performed (n=8)			No data was shown but it was reported that there were no changes in the results when hospital volume was analysed as a linear covariate, and if surgery for cardia cancer was coded as gastrectomy. Survival curves were published and the % overall survival was estimated from the curves. **Oesophagectomy:** Overall survival at 30 days: 100% for all hospital volumes Overall survival at 90 days: 100% for all hospital volumes Overall survival at 1 year: high volume;90% , medium volume; 87%, low volume;85%, very low volume; 85% **Gastrectomy:** Overall survival at 30 days: 100% for all hospital volumes	

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr><td></td><td>Patients with insitu carcinoma (n=288) and with distant metastases (n=2902)</td><td></td><td></td><td>Overall survival at 90 days: 100% for all hospital volumes

Overall survival at 1 year: high volume;90% , medium volume; 88%, low volume;unclear ?88%, very low volume; unclear ?88%</td><td></td></tr>
<tr><td>Full citation

Anderson, O., Ni, Z., Moller, H., Coupland, V. H., Davies, E. A., Allum, W. H., Hanna, G. B., Hospital volume and survival in oesophagectomy and gastrectomy for cancer, European Journal of Cancer, 47, 2408-2414, 2011

Ref Id

476906

Country/ies where the study was carried out</td><td>Sample size

N=3870 patients resident in South East England (London, Kent, Surrey and Sussex Counties)

Characteristics

The following are for hospital volumes 1-10, 11-20, 21-30 and >30 respectively:

N values: 1790, 1211, 588, 277

Tumour topography: oesophageal; 23%, 32%, 32%, 43%, gastric; 77%, 68%, 68%, 57%,</td><td>Interventions

Hospital volume: calculated from each patient's record as the number of oesophagectomies and gastrectomies for cancer that were carried out in that patient's hospital in the same calendar year as their operation.

Split into the following volume groups: 1-10, 11-</td><td>Details

Thames Cancer Registry: ICD-10 codes and OPCS-4 coded operations (Office of Population, Censuses and Surveys (demographic info, SES, tumour stage, tumour topography and morphology and chemotherapy data). also receives death register data from the Office for National Statistics via the National Health Service Central Care Records Service.</td><td>Results

Results of the Cox proportional hazards regression analysis:

Hospital volume:

Very low(VL)=1-10 cases/yea(Ref)r
Low(L)=11-20cases/year
Medium(M)=21-30 cases/year
High(H)=>30 cases/year
<table><tr><td rowspan="3">Variable</td><td colspan="4">Survival stratification</td></tr><tr><td colspan="2">0-30 days</td><td colspan="2">31-365 days</td></tr><tr><td>Univariate</td><td>Multivariate</td><td>Univariate</td><td>Multivariate</td></tr></table></td><td>Limitations

Selection bias: Low risk of bias. Statistical methods adjusted for differences at baseline.

Performance bias: Unclear risk.

Unclear whether the comparisons groups received the same care, or if the participants were blinded to the volume status of the hospital.

Attrition bias: Unclear risk of bias

Unclear coverage of the Thames Cancer Registry.</td></tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>United Kingdom

Study type

Retrospective cohort study.

Aim of the study

To examine the relationship between hospital volume and survival from upper gastrointestinal cancer surgery using recent data from a population based cancer registration.

Study dates

1998-2008

Source of funding

No funding.</td>
<td>Median age: 69, 69, 68, 64 years

Sex (M:F): 7:3, 7:3, 7:3, 7:3

Stage: 1; 24%, 23%, 28%, 31%, 2; 7%, 9%, 7%, 5%, 3; 39%, 36%, 39%, 42%, 4; 13%, 14%, 11%, 8%, Unknown; 17%, 18%, 15%, 14%

Neo-adjuvant therapy: No; 88%, 83%, 79%, 54%, Yes; 12%, 17%, 21%, 46%

Tumour morphology: adenocarcinoma: 85%, 84%, 85%, 83%, squamous carcinoma; 6%, 9%, 8%, 9%, Other; 9%, 7%, 7%, 9%, unknown; 0% for all groups (n=2 in the 1-10 group)

Operation: oesophagectomy; 33%, 46%, 49%, 56%, gastrectomy; 67%, 54%, 51%, 44%

Median survival (days): 668, 703, 730, 1215</td>
<td>20, 21-30 and >30 per year.</td>
<td>Tumour staging: according to WHO

Neo adjuvant therapy: recorded dates of chemotherapy and surgery

Survival: calculated from the date of operation to the date of death from any cause. Censoring of follow up occurred on the 31st December 2008.

Blinding: data anonymised by the Thames Cancer Registry before being analysed, so the identity of the hospitals and the patients were blinded.

Statistical methods:

Cox proportional hazards regression analysis for uni and</td>
<td>
<table>
<tr><td>L</td><td>0.983</td><td>0.974</td><td>0.979</td><td>0.947</td></tr>
<tr><td>M</td><td>0.737</td><td>0.865</td><td>0.951</td><td>1.002</td></tr>
<tr><td>H</td><td>0.385 *</td><td>0.660</td><td>0.493 **</td><td>0.705</td></tr>
<tr><td>P trend</td><td>0.011</td><td>0.001</td><td><0.001</td><td>0.215</td></tr>
</table>
*≤0.01

**≤0.001

The paper does not report survival at 90 days, however this has been estimated from the Kaplan Meier survival curves:

Hospital volume:

1-10: 0.942

11-20: 0.959

21-30: Unable to determine

>30: 0.983

Paper also reports 5 year survival and has a Kaplan Meier curve showing up to 11 years survival.
</td>
<td>Unknown baseline data e.g. tumour stage and morphology

Detection bias: Low risk of bias

Long follow up (11 years). Survival defined. Investigators were blinded to hospital and patient identity.

Other limitations:

No confidence intervals for the hazard ratios were provided in the paper.

90 day survival has been estimated from the published Kaplan Meier Survival curve and will have high inaccuracy.

Other information</td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Inclusion criteria Patients diagnosed with oesophageal or gastric cancer and treated operatively over an 11 year period (1998-2008) **Exclusion criteria** None described.		multivariate analysis. Variables in the MVA were: hospital volume, year of diagnosis, tumour topography, age, sex, SES, Stage, neo-adjuvant chemotherapy, tumour morphology, and type of operation. Survival was stratified: 0-30 days, 31-365 days and >365 days. Only patients that survived a period were included in the analysis of the subsequent period.		
Full citation Viklund, P., Lindblad, M., Lu, M., Ye, W., Johansson, J., Lagergren, J., Risk factors for complications after esophageal cancer	**Sample size** N= 275 (147 oesophageal cancer, 128 cardia cancer) **Characteristics** Median age= 67	**Interventions** Surgical interventions We defined the surgical approaches as follows: 1) Esophageal	**Details** Methods The data were collected from the Swedish Esophageal and Cardia Cancer register (SECC register), an almost	**Results** At least 1 severe complication Surgeon volume: High(≥5/year) (n=74/176) (Ref) Low/L(<5/year) (n=49/99)	**Limitations** Selection bias: low risk of bias Performance bias: low risk of bias Attrition bias: low risk of bias. The registries are

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>resection: A prospective population-based study in Sweden, Annals of SurgeryAnn Surg, 243, 204-211, 2006

Ref Id

544276

Country/ies where the study was carried out

Sweden

Study type

Prospective cohort study.

Aim of the study

To identify risk factors for complications after resection for esophageal or cardia cancer.

Study dates

2001-2003</td>
<td>79% male

Histology: 77% adenocarcinoma/ 23% SCC

Tumour stage: 0-I 19%/ II 31%/ III 41%/ IV 10%

Inclusion criteria

All patients with a newly diagnosed adenocarcinoma or squamous cell carcinoma of the esophagus or gastric cardia who underwent tumor resection in Sweden during the period April 2, 2001 through December 31, 2003 were eligible for the study.

Exclusion criteria

None reported.</td>
<td>resection refers to removal of the main part of the esophagus with an anastomosis between an esophageal substitute (stomach, jejunum, or colon) and the proximal esophagus. 2) Cardia resection represents removal of the proximal part of the stomach and the distal part of the esophagus with an anastomosis between the remaining stomach and the remaining esophagus. 3) Extended total gastrectomy refers to removal of the entire stomach and the</td>
<td>complete nationwide register of esophageal and cardia cancer surgery in Sweden. The organization of this register is a continuation of a collaborative nationwide Swedish network of hospital departments and clinicians involved in the diagnosis or treatment of patients with cancer of the esophagus or gastric cardia.

The complications that were deemed to be severe were defined by a group of leading Swedish esophageal surgeons prior to the inclusion phase of the study. These complications included any of the following occurrences within 30 days after surgery: mortality (independently of the cause), anastomotic</td>
<td>
<table>
<tr><td></td><td colspan="2">OR (95%CI)</td></tr>
<tr><td></td><td>Basic model</td><td>Multivariate</td></tr>
<tr><td>L</td><td>1.33 (0.81-2.19)</td><td>1.32 (0.74-2.36)</td></tr>
</table>
At least 2 severe complications
Surgeon volume:

High(≥5/year) (n=31/176) (Ref)
Low/L(<5/year) (n=24/99)

<table>
<tr><td></td><td colspan="2">OR(95%CI)</td></tr>
<tr><td></td><td>Basic</td><td>Multivariate</td></tr>
<tr><td>L</td><td>1.49 (0.79-2.83)</td><td>1.36 (0.62-3.00)</td></tr>
</table>
Anastomotic Leakage
High(≥5/year) (n=5/176) (Ref)
Low/L(<5/year) (n=13/99)

<table>
<tr><td></td><td colspan="2">OR(95%CI)</td></tr>
<tr><td></td><td>Basic</td><td>Multivariate</td></tr>
</table>
</td>
<td>reported to have near complete data. 1 patient of 276 excluded because of incomplete data.

Detection bias: Unclear risk of bias. It is unclear if the investigators were blinded to the surgeon volume status where the patients had their surgery and other important confounding factors.

Reporting bias: low risk

Other limitations: Indirectness of population (cardia and oesophageal cancer)

Other information

Population indirectness- 54% oesophageal.</td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding Supported by the Swedish Cancer Society and the National Board of Health and Welfare in Sweden.		distal part of the esophagus with anastomosis between the jejunum and the esophagus. 4) Total gastrectomy and esophageal resection means that the entire stomach and the main part of the esophagus were removed with an anastomosis between an esophageal substitute (jejunum or colon) and the proximal esophagus. Patients with esophageal cancer were, with a few exceptions, operated with a transthoracic esophageal resection with a	leakage (causing clinical symptoms and verified by radiology or endoscopy), serious infections (intra-abdominal or intrathoracic abscess, sepsis with positive bacterial culture in the blood, or wound infection requiring intervention), respiratory insufficiency (need for reintubation, or severe pneumonia), cardiac failure (myocardial infarction, or arrhythmia with requiring for intervention), renal or liver failure (need for dialysis and jaundice, respectively), technical complications (postoperative bleeding 2000 mL or a need for reoperation, inadvertent damage to the recurrent laryngeal nerve or the thoracic duct), early	<table><tr><td>L</td><td>5.64 (1.89-16.81) (p<0.01)</td><td>7.86 (2.13-29.00) (p<0.01)</td></tr></table> Basic model adjusts for age, sex and tumour stage. Multivariate model adjusts for age, sex, tumour stage. histology, adjuvant treatment, type of surgery, surgical approach and substitute for oesophagus.	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
		gastric tube as esophageal substitute. The type of surgery among patients with cardia cancer varied between esophageal resection, cardia resection, extended total gastrectomy, or total gastrectomy and esophageal resection (see definitions above).	anastomotic stricture (with severe dysphagia and a need for endoscopic intervention), and others (embolus, deep venous thrombosis, rupture of the wound, intestinal obstruction, or stroke, all with a need for intervention). Statistics We used unconditional logistic regression model to estimate the relative risk of complications in the form of odds ratios (OR) with 95% confidence intervals (CI). In multivariable modeling, our basic model included adjustments for age (categorized into 3 groups: 60, 60–69, or 70 years), sex, and tumor stage (4 groups: 0–I, II, III, or IV). We also analyzed the variables in a more		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			extensive multivariable model in which we also adjusted for all other covariates under study, including histologic type of cancer (categorized into 2 groups: adenocarcinoma or squamous cell carcinoma), neoadjuvant treatment (2 groups: yes or no), preoperative bleeding volume (3 groups: 500, 500–1000, or 1000 mL), surgical approach (2 groups: transhiatal abdominal only or transthoracic), surgeon volume (3 groups: 5, 5–10, or 10 operations per year), type of hospital (2 groups: university or nonuniversity), and type of anastomosis (2 groups: stapled or hand-sewn).		

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr>
<td>Full citation

Derogar, M., Sadr-Azodi, O., Johar, A., Lagergren, P., Lagergren, J., Hospital and surgeon volume in relation to survival after esophageal cancer surgery in a population-based study, Journal of Clinical OncologyJ Clin Oncol, 31, 551-7, 2013

Ref Id

544475

Country/ies where the study was carried out

Sweden

Study type

Retrospective cohort

Aim of the study</td>
<td>Sample size

N=1,411 but it was only possible to retrieve the surgical charts of 1335 patients (94.6%).

Characteristics

<u>According to annual hospital volume</u>
<table>
<tr><td></td><td>Q1-2</td><td>Q3</td><td>Q4</td></tr>
<tr><td>n</td><td>726</td><td>310</td><td>299</td></tr>
<tr><td>Op</td><td>1-8</td><td>9-16</td><td>≥17</td></tr>
<tr><td>Male</td><td>72%</td><td>76%</td><td>74%</td></tr>
<tr><td colspan="4">Age, years</td></tr>
<tr><td><65
65-75
>75</td><td>46%
42%
12%</td><td>45%
42%
13%</td><td>39%
42%
19%</td></tr>
<tr><td colspan="4">Tumour stage</td></tr>
<tr><td>0-I
II
III
IV
Missing</td><td>18%
30%
24%
9%
19%</td><td>24%
34%
21%
10%
11%</td><td>12%
35%
30%
6%
17%</td></tr>
<tr><td colspan="4">Histology</td></tr>
<tr><td>Adenocarcinoma</td><td>38%</td><td>39%</td><td>29%</td></tr>
</table>
</td>
<td>Interventions

Hospital volume: annual number of esophagectomies performed for each hospital and year in 1987 to 2005

Hospitals divided into quartiles of annual hospital volume (two lowest quartiles collapsed because many hospitals only perform a few annually).

Surgeon volume: annual and cumulative. If >1 surgeon conducted the resection the surgery was assigned to the</td>
<td>Details

Swedish nationwide registers were used. Surgery and histopathological records from all Swedish hospitals conducting esophageal cancer surgery during the period.

Each patient has a personal identity number, unique to every resident in Sweden, which was used for individual register linkages and identification of hospital records.

Swedish Cancer Register: codes 150.0, 150.8, 150.9, ICD-7. Register has 98% nationwide completion rate for registration of oesphageal cancer.</td>
<td>Results

Primary outcome: mortality

Overall mortality: any death (all causes) occurring after the surgery

Short term mortality: any death within 3 months of surgery

Longer term mortality: any death occurring after 3 months from surgery

1,123 died, 177 of which was in the first 3 months post surgery. Causes of death documented as recurrence of oesophageal cancer was in 90% of the 1,125 that died.

Mortality:

Overall (O)
≤3 months(short-term/SM)
>3 months(long-term/LM)

Hospital volume:
Low (L): 1-8 surgeries</td>
<td>Limitations

Selection bias: Low risk of bias. Statistical methods adjusted for differences at baseline.

Performance bias: Unclear risk.

Unclear whether the comparisons groups received the same care, or if the participants were blinded to the volume status of the hospital.

Attrition bias: Low risk of bias

High registry coverage. 5.4% had unretrievable surgical case notes and were excluded. Unknown baseline data e.g. tumour stage and morphology

Detection bias: Low risk of bias</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>Aimed to clarify the independent association between hospital volume and surgeon volume in relation to survival after esophageal cancer surgery from both the short and long term perspective.

Study dates

1987-2005

Follow up until 2011

Median follow up 1.2 years (range 0-23 years), 4,251 person years at risk

Source of funding

Financial support: Two authors; Pernilla Lageren, Jesper Lagergren

Supported by The Swedish Research Council and the Swedish Cancer Society</td>
<td>
<table>
<tr><td>SCC
Missing</td><td>57%
5%</td><td>58%
3%</td><td>67%
4%</td></tr>
<tr><td colspan="4">Neoadjuvant therapy</td></tr>
<tr><td>Yes
Missing</td><td>24%
4%</td><td>30%
3%</td><td>32%
3%</td></tr>
</table>
<u>Acording to annual surgeon volume</u>
<table>
<tr><td></td><td>Q1-2</td><td>Q3</td><td>Q4</td></tr>
<tr><td>n</td><td>726</td><td>310</td><td>299</td></tr>
<tr><td>Op</td><td>1-8</td><td>9-16</td><td>≥17</td></tr>
<tr><td>Male</td><td>72%</td><td>76%</td><td>74%</td></tr>
<tr><td colspan="4">Age, years</td></tr>
<tr><td><65
65-75
>75</td><td>45%
42%
13%</td><td>43%
43%
14%</td><td>45%
41%
14%</td></tr>
<tr><td colspan="4">Tumour stage</td></tr>
<tr><td>0-I
II
III
IV
Missing</td><td>18%
31%
24%
9%
18%</td><td>19%
36%
21%
8%
16%</td><td>16%
32%
29%
8%
15%</td></tr>
<tr><td colspan="4">Histology</td></tr>
<tr><td>Adenocarcinoma
SCC
Missing</td><td>34%
61%
5%</td><td>37%
61%
2%</td><td>41%
55%
4%</td></tr>
</table>
</td>
<td>most experienced surgeon (algorithm to follow)

Annual surgeon volume: no. of times the surgeon had been responsible for a surgery during the index year

Cumulative surgeon volume: chronological no. of operations the surgeon had been responsible for at the time of the index surgery during the inclusion period, 1987-2005</td>
<td>Swedish Classification of Operations and Major Procedures: to include relevant operations

Swedish Patient Register. 100% coverage since 1987. Evaluated and found to have 95% accuracy, 98% completeness for surgical procedures, PPV of 99.6%.

Tumour classification: according to recommendations by the Union for International Cancer Control version6

Reviewer: blinded to the patients' survival time and name of the hospital

Surgical chart review: names of operating hospitals and surgeons</td>
<td>Medium (M): 9-16 surgeries
High(H): ≥17 surgeries

Annual surgeon volume

Low(L): 1-4 surgeries/year
Medium (M): 5-9 surgeries/year
High(H): ≥10surgeries/year

Cumulative surgeon volume
Low(L): 1-11 surgeries/year
Mediume(M): 12-32 surgeries/year
High(H): ≥33 surgeries/year
<table>
<tr><td colspan="4">Annual hospital volume</td></tr>
<tr><td></td><td>L</td><td>M</td><td>H</td></tr>
<tr><td>O</td><td>1.00</td><td>0.96 (0.82-1.11)</td><td>0.84 (0.72-0.98)*</td></tr>
<tr><td>SM</td><td>1.00</td><td>0.57 (0.38-0.85)**</td><td>0.47 (0.31-0.71)</td></tr>
<tr><td>LM</td><td>1.00</td><td>1.06 (0.90-1.25)</td><td>0.94 (0.80-1.10)</td></tr>
<tr><td colspan="4">Annual surgeon volume</td></tr>
</table>
</td>
<td>Median follow up 1.2 years (range 0-23 years) .
Reviewer: blinded to the patients' survival time and name of the hospital.

Other limitations:

Other information

Note: the majority of the patient data is pre 2002</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td></td>
<td>
<table>
<tr><td colspan="4">Neoadjuvant therapy</td></tr>
<tr><td>Yes
Missing</td><td>29%
4%</td><td>29%
3%</td><td>22%
3%</td></tr>
</table>
<u>According to cumulative surgeon volume</u>
<table>
<tr><td></td><td>Q1-2</td><td>Q3</td><td>Q4</td></tr>
<tr><td>n</td><td>686</td><td>319</td><td>330</td></tr>
<tr><td>Op</td><td>1-11</td><td>12-32</td><td>≥33</td></tr>
<tr><td>Male</td><td>74%</td><td>77%</td><td>70%</td></tr>
<tr><td colspan="4">Age, years</td></tr>
<tr><td><65
65-75
>75</td><td>44%
43%
13%</td><td>45%
39%
16%</td><td>44%
43%
13%</td></tr>
<tr><td colspan="4">Tumour stage</td></tr>
<tr><td>0-I
II
III
IV
Missing</td><td>18%
30%
24%
8%
20%</td><td>16%
39%
26%
8%
11%</td><td>22%
30%
24%
8
16%</td></tr>
<tr><td colspan="4">Histology</td></tr>
<tr><td>Adenocarcinoma
SCC
Missing</td><td>36%
60%
4%</td><td>38%
60%
2%</td><td>37%
59%
4%</td></tr>
<tr><td colspan="4">Neoadjuvant therapy</td></tr>
</table>
</td>
<td></td>
<td>The Causes of Death Register: 99.2% completeness for cause specific death

Statistical methods:

Person years from the date of surgery until the date of death or end of the study period (31 Jan 2011), whichever occurred first.

Multivariable parametric survival analysis used to calculate HR. Gompertz survival distribution resulted in the lowest Akaike information criteria score and was therefore used.

Clustering of patients and surgeons: shard frailty term with gamma distribution was added to the models.</td>
<td>
<table>
<tr><td></td><td>L</td><td>M (n=355)</td><td>H (n=300)</td></tr>
<tr><td>O</td><td>1.00</td><td>0.82 (0.70-0.96)*</td><td>0.82 (0.69-0.99)*</td></tr>
<tr><td>SM</td><td>1.00</td><td>0.91 (0.63-1.31)</td><td>0.48 (0.29-0.80)**</td></tr>
<tr><td>LM</td><td>1.00</td><td>0.79 (0.66-0.94)**</td><td>0.90 (0.74-1.09)</td></tr>
<tr><td colspan="4">Cumulative surgeon volume</td></tr>
<tr><td></td><td>L (n=686)</td><td>M (n=319)</td><td>H (n=330)</td></tr>
<tr><td>O</td><td>1.00</td><td>1.00 (0.85-1.17)</td><td>0.97 (0.80-1.17)</td></tr>
<tr><td>SM</td><td>1.00</td><td>0.93 (0.62-1.39)</td><td>1.12 (0.70-1.79)</td></tr>
<tr><td>LM</td><td>1.00</td><td>1.02 (0.86-1.21)</td><td>0.95 (0.77-1.16)</td></tr>
</table>
All of the results above are based on Model 1 which
</td>
<td></td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	<table><tr><td>Yes Missing</td><td>29% 5%</td><td>27% 1%</td><td>24% 2%</td></tr></table> n=number of patients op=number of operations **Inclusion criteria** All patients who underwent esophagectomy for esophageal cancer in Sweden from January 1, 1987 to December 31, 2005 with follow up for survival until February 2011. **Exclusion criteria**		MV models adjusted for: age (<65, 65-75, >75), sex, Charlson comorbidity index (0,1,≥2), tumour stage at the time of surgery (0-I, II, III, IV,missing), histology (adenocarcinoma, SCC, missing/undefined), neoadjuvant therapy (yes/no/missing), calendar period (1987-1990, 1991-1995, 1996-2000, 2001-2005) "After Cox regression analysis the results remained virtually unchanged (data not shown). However, some models adjusting for clustering could not be fitted with this analysis; this is why only the results of the parametric survival analyses are presented".	adjusted for age, sex, tumour stage, tumour histology, neo-adjuvant treatment, comorbidity according to Charlson comorbidity index, and calendar period. *p<0.05 **p<0.01 Note: other models were carried out adjusting for annual hospital volume, hospital clustering, and surgeon clustering which affected the statistical significance of the outcome making some outcomes no longer significant e.g ≤3 months mortality Q1-2 vs Q3 with the addition of hospital clustering to the model (this has not been extracted).	

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr>
<td>Full citation

Henneman, D., Dikken, J. L., Putter, H., Lemmens, V. E., Van der Geest, L. G., van Hillegersberg, R., Verheij, M., van de Velde, C. J., Wouters, M. W., Centralization of esophagectomy: how far should we go?, Annals of Surgical OncologyAnn Surg Oncol, 21, 4068-74, 2014

Ref Id

544606

Country/ies where the study was carried out

Netherlands

Study type

Retrospective cohort</td>
<td>Sample size

n=10,025 patients with esophageal or gastric cardia cancer who underwent surgery (non metastatic invasive carcinoma)

Characteristics

<u>Hospital volume category</u>

I=1-20 surgeries/year
II=21-40 sugeries/year
III=41-60 surgeries/year
IV=≥60 surgeries/year
<table><tr><td rowspan="2">Characteristic</td><td colspan="4">Hospital Volume category (%)</td></tr><tr><td>I</td><td>II</td><td>III</td><td>IV</td></tr><tr><td>Male</td><td>76</td><td>79</td><td>75</td><td>77</td></tr><tr><td>Age
<60 years
60-75
>75</td><td>
34
55
11</td><td>
34
56
10</td><td>
38
54
8</td><td>
35
57
8</td></tr><tr><td>Adenocarc</td><td>76
21</td><td>78
20</td><td>69
29</td><td>72
25</td></tr></table></td>
<td>Interventions

Annual hospital volumes: number of esophagectomies per hospital per year, was determined for each year of surgery and may have changed per/yr for individual hospitals.</td>
<td>Details

Netherlands Cancer Registry (NCR): routinely collects information on all newly diagnosed malignancies in all Dutch hospitals 6-18 months after diagnosis.

ICD-O coding: adenocarcinoma (8,140–8,145, 8,190, 8,201–8,211, 8,243, 8,255–8,401, 8,453–8,520, 8,572, 8,573, 8,576), squamous cell carcinoma (SCC) (8,032, 8,033, 8,051–8,074, 8,076–8,123), and other/unknown histology (8,000–8,022, 8,041–8,046, 8,075, 8,147, 8,153, 8,200, 8,230–8,242, 8,244–8,249, 8,430,</td>
<td>Results

<u>Mortality at 6 months and 2 years by annual hospital volume (n, surgeries per year)</u>

<table><tr><th></th><th colspan="2">HR (95%CI)</th></tr><tr><th>n</th><th>6mth</th><th>2-year</th></tr><tr><td>20</td><td>1.00</td><td>1.00</td></tr><tr><td>30</td><td>0.83 (0.76-0.91)</td><td>0.92 (0.89-0.96)</td></tr><tr><td>40</td><td>0.73 (0.65-0.83)</td><td>0.88 (0.83-0.93)</td></tr><tr><td>50</td><td>0.68 (0.6-0.78)</td><td>0.86 (0.79-0.93)</td></tr><tr><td>60</td><td>0.67 (0.58-0.77)</td><td>0.85 (0.75-0.97)</td></tr><tr><td>70</td><td>0.67 (0.54-0.83)</td><td>0.86 (0.71-1.05)</td></tr><tr><td>80</td><td>0.68 (0.49-0.94)</td><td>0.88 (0.66-1.16)</td></tr></table>
N values were not given for each hospital volume cut off. Sensitivity analyses using frailty models was stated to</td>
<td>Limitations

Selection bias: Low risk of bias. Statistical methods adjusted for differences at baseline.

Performance bias: Unclear risk.

Unclear whether the comparisons groups received the same care, or if the participants were blinded to the volume status of the hospital.

Attrition bias: Unclear risk of bias

Unknown registry coverage. Unknown baseline data e.g. tumour stage and morphology

Detection bias: Unclear risk of bias

Follow up unclear, ? only 2 years for the mortality</td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study Define a meaningful cutoff point for annual hospital volume for esophagectomy, using nonlinear statistical modelling techniques on a large dataset with a broad range in annual hospital volumes **Study dates** January 1989- 31 December 2009 **Source of funding** Funded by the Signalling Committee on Cancer of the Dutch Cancer Society (KWF Kankerbestrijding). The study sponsor had no role in the study design, in the collecdtion, analysis and interpretation of data, in writing the report or in the	inoma SCC Other: 2 / 1 / 2 / 2 I II: 20 / 17 / 15 / 20 III: 40 / 38 / 37 / 36 IV: 35 / 37 / 41 / 37 Unknown: 1 / 0 / 1 / 1 : 4 / 8 / 6 / 6 Preoperative surgery yes: 11 / 40 / 20 / 35 Postoperative surgery yes: 5 / 6 / 6 / 4 **Inclusion criteria** Patients who had under gone surgery for oesophageal or gastric cardia cancer (non metastatic invasive carcinoma) between January 1989- 31 December 2009. **Exclusion criteria** Those who did not undergo surgery (n=26,521)		8,530, 8,560, 8,570, 8,574, 8,575). Staging: International Union Against Cancer (UICC) Tumor Node Metastases (TNM) classification Vital status: municipal registries, 1994 onwards nationwide population registries network (complete coverage for deceased Dutch citizens). Statistical analysis: Main outcomes: 6 month and 2 year overall mortality. Calculated from the date of diagnosis until death (as date of surgery was not available pre 2005) Calculated using Cox regression adjusted for sex, age, SES, tumour stage, morphology, preoperative therapy use, postoperative	not qualitatively change the HRs or CIs (data was not shown).	outcome. Coverage for mortality was described as complete. Unclear blinding of investigators to patients details and hospital in which they had surgery. **Other information** Note: mortality calculated from date of diagnosis (date of surgery information was not available pre 2005) majority of the data is pre 2002. No n values were given with the hospital volume cut offs and their HRs.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
decision to submit the paper for publication.	In situ and M1 disease (N=1,014)		therapy use (only for 2 year mortality), and year of diagnosis. Adjust for clustering of patients in hospitals-robust SE using sandwich estimators. Frailty models with random hospital effects used in sensitivity analyses.		
Full citation Markar, S., Gronnier, C., Duhamel, A., Bigourdan, J. M., Badic, B., du Rieu, M. C., Lefevre, J. H., Turner, K., Luc, G., Mariette, C., Pattern of Postoperative Mortality After Esophageal Cancer Resection According to Center Volume: Results from a Large European Multicenter Study, Annals of Surgical	**Sample size** N=2944 **Characteristics** 82.4% male age >= 60: 51.6% tumour location: upper 13.7%; middle 33.3%; lower 53% TNM stage: I 24.7%; II 26.1%; III 47.9%; IV 1.3%	**Interventions** Approach to surgery varied between three techniques—Ivor–Lewis, three-stage, or transhiatal esophagectomy.	**Details** **Definition of centre volume:** Each center was classified by the number of patients undergoing esophagectomy during the 10-year study period. Centers were initially divided into quartiles based on contribution to the study cohort (\30, 31–80, 81–135, [135) and according to the	**Results** **30-day mortality** **Centre volume <= 80** 82/781 OR (95% CI)= 2.62 (1.77-3.87), p<0.001 (multivariate analysis) **Centre volume >80** 65/2163 OR= 1.00 (reference)	**Limitations** Selection bias: low risk of bias Performance bias: Unclear risk. Unclear whether the comparisons groups received the same care, or if the participants were blinded to the volume status of the hospital. Attrition bias: low risk of bias. Consecutive patients included.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
OncologyAnn Surg Oncol, 22, 2615-23, 2015 **Ref Id** 544924 **Country/ies where the study was carried out** Europe **Study type** Retrospective cohort study **Aim of the study** The aim of this study was to define the pattern of POM and major morbidity in relation to center procedural volume. **Study dates** 2000 to 2010 **Source of funding** None	Surgical technique: ivor-lewis 74.2%; three-stage 11.7%; transhiatal 14.1% Histology: SCC 46.3%; Adenocarcinoma 50.7%; other 3.0% **Inclusion criteria** Consecutive adult patients undergoing surgical resection for esophageal cancer (including Siewert type I and II junctional tumors) with curative intent in 30 French-speaking European centers between 2000 and 2010 were retrospectively collected. **Exclusion criteria** None reported		median (B80 defining LV centers, and [80 defining HV centers). **Definition of complications:** Pulmonary complications included bronchial congestion, disorders of ventilation, atelectasis, pneumonia, respiratory failure, and acute respiratory distress syndrome. Anastomotic leak was defined as any oesophagogastric anastomosis dehiscence that was clinically symptomatic (abscess, mediastinitis, digestive liquid externalizing drainage) or asymptomatic detected by contrast study. In case of doubt, the diagnosis was confirmed by gastroscopy without	**Anastomotic Leak** OR 0.54; 95 % CI 0.41–0.72; p<0.001 **Centre volume <= 80** 118/781 **Centre volume >80** 181/2163 p<0.001 OR= 1.00 (reference) **Surgical Site Infection** OR 0.63; 95 % CI 0.49–0.80; p<0.001 **Centre volume <= 80** 163/781	Detection bias: Unclear risk of bias. It is unclear if the investigators were blinded to the hospital volume status where the patients had their surgery and other important confounding factors. Other limitations: None Other information: Data was collected with an independent monitoring team auditing data capture to minimize missing data and to control concordance. Missing or inconsistent data were obtained from email exchanges or phone calls with the referral center. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			insufflation performed by an experienced physician. Surgical site infection was defined as superficial pus expressed from the abdominal, thoracic, or drains incision sites, requiring surgical debridement and antibiotic treatment. Postoperative haemorrhage was defined as blood loss requiring endoscopic or surgical intervention. **Statistical Analysis** Continuous variables were expressed as the mean ± standard deviation or the median (range), and categorical variables as a percentage. A Mann–Whitney test was used for	**Centre volume >80** 294/2163 p<0.001 **Pulmonary Complication** OR 0.47; 95 % CI 0.39–0.56; p<0.001 **Centre volume <= 80** 396/781 **Centre volume >80** 726/2163 p<0.001 **Reoperation** OR 0.54; 95 % CI 0.42–0.69; p<0.001 **Centre volume <= 80** 163/781 **Centre volume >80**	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			intergroup comparisons of continuous variables, whereas a Chi-square test or Fisher test was used to compare categorical data. A binary logistic regression was used to identify predictors of POM. In a second step, we conducted a propensity scorematching analysis to compensate for the differences in some baseline characteristics between the LV and HV groups.18 First, we compared all available patient and tumor variables using a Chi-square test, and a propensity score was then calculated using a logistic regression with the imbalanced variables. Finally, all analyses regarding POM and morbidity	266/2163 p<0.001	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			were adjusted based on the generated propensity score. Adjustment was also carried out for malnutrition as some missing variables did not allow us to integrate this into the propensity score. All tests were twosided and the threshold for statistical significance was set to p\0.05. Analyses were performed with SPSS version 19.0 software (IBM Corporation, Armonk, NY, USA).		
Full citation Rouvelas, I., Jia, C., Viklund, P., Lindblad, M., Lagergren, J.,	**Sample size** N=607 **Characteristics**	**Interventions** All patients treated with	**Details** **Definition of volume**	**Results** **30-day mortality: all patients** **Low-volume surgeon group**	**Limitations** Selection bias: low risk of bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Surgeon volume and postoperative mortality after oesophagectomy for cancer, European Journal of Surgical OncologyEur J Surg Oncol, 33, 162-8, 2007 **Ref Id** 545177 **Country/ies where the study was carried out** Sweden **Study type** Prospective cohort study **Aim of the study** Oesophagectomy remains the curative treatment of choice for patients with localised oesophageal or cardia cancer, but severe postoperative complications are	Mean age (SD)= 66.2 (10.1) 489 men/ 118 women Type of cancer: 328 oesophageal/279 gastric cardia Tumour stage: 25 Stage 0; 90 Stage I; 179 Stage II; 245 Stage III; 68 Stage IV Oesophageal tumour location: 17 upper; 90 middle; 231 lower Histology: 149 SCC; 171 adenocarcinoma of oesophagus; 278 adenocarcinoma of cardia; 9 dysphagia **Inclusion criteria** Eligible for inclusion were all Swedish residents diagnosed with oesophageal or cardia cancer who were treated with oesophagectomy during the period April 2, 2001 through December 31, 2005.	oesophagectomy.	Thus, the participating surgeons were divided into three categories on the basis of their average annual workload as recorded in the SECC register: Low-volume surgeons (LVS) performed <2 oesophagectomies, medium-volume surgeons (MVS) performed 2-6 oesophagectomies, and high-volume surgeons (HVS) performed >6 oesophagectomies annually. **Statistical Analysis** Unconditional logistic regression was used to examine associations between surgeon volume and 30- and 90-day mortality, expressed in odds ratios (OR) with	n=5 OR= 1.00 (ref) **Medium-volume surgeon group** n=4 Crude OR (95%CI)= 0.28 (0.07-1.07) Multivariate OR (95%CI)= 0.39 (0.09-1.70) **High-volume surgeon group** n=9 Crude OR (95%CI)= 0.34 (0.09-1.27) Multivariate OR (95%CI)= 0.42 (0.10 -1.80) **90-day mortality: all patients** **Low-volume surgeon group** n=8 OR= 1.00 (ref)	Performance bias: Unclear risk. Unclear whether the comparisons groups received the same care, or if the participants were blinded to the volume status of the surgeon. Attrition bias: low risk of bias. The registries are reported to have almost complete coverage of all oesophageal and cardiac cancer patients (97%). Detection bias: Unclear risk of bias. It is unclear if the investigators were blinded to the surgeon volume status where the patients had their surgery and other important confounding factors. Other limitations: none. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
common. Our aim was to assess the association between surgeon volume and postoperative mortality after oesophagectomy. **Study dates** April 2001 through December 2005 **Source of funding** Funding was provided by the Swedish Cancer Society and the Swedish Research Council.	**Exclusion criteria** None reported.		95% confidence intervals (CI). Three models were employed: a) a crude model without adjustments; b) a ‘‘basic’’ model with adjustment for age (categorised into four groups: <55, 55e65, 66e75, and >75 years), sex, and tumour stage (in five groups: 0, I, II, III, IV); and c) a full multivariable model including adjustments for all relevant covariates, i.e., patient (age, sex, and co-morbidity) and tumour characteristics (stage, location, and histology), preoperative oncological treatment (no or yes), and intention of the surgery (curative or palliative). yThe multivariable model included adjustments for age,	**Medium-volume surgeon group** n=9 Crude OR (95%CI)= 0.39 (0.14-1.08) Multivariate OR (95%CI)= 0.48 (0.16-1.38) **High-volume surgeon group** n=9 Crude OR (95%CI)= 0.75 (0.27-2.09) Multivariate OR (95%CI)= 0.86 (0.31 -2.38) To improve the statistical power, we also performed an analysis in which LVS were compared with the combined groups MVS and HVS. The adjusted ORs for 30- and 90-day mortality indicated a 59% and 28% lower risk, respectively, among the patients in the higher surgeon volume group, but the difference did not reach statistical significance	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			sex, co-morbidity, tumour stage, tumour location, tumour histology, preoperative oncological treatment, and curative intention.	(adjusted OR 0.41, 95% CI 0.11e1.54, and OR 0.72, 95% CI 0.28e1.87, respectively). **30-day mortality: oesophageal cancer only** **Low-volume surgeon group** n=1 OR= 1.00 (ref) **Medium-volume surgeon group** n=1 Crude OR (95%CI)= 0.14 (0.01-2.36) Multivariate OR (95%CI)= 0.12 (0.01-1.58) **High-volume surgeon group** n=4 Crude OR (95%CI)= 0.29 (0.03-2.74) Multivariate OR (95%CI)= 0.29 (0.02 -3.28)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				90-day mortality: oesophageal cancer only **Low-volume surgeon group** n=1 OR= 1.00 (ref) **Medium-volume surgeon group** n=2 Crude OR (95%CI)= 0.30 (0.02 - 3.53) Multivariate OR (95%CI)= 0.40 (0.05 - 3.38)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				High-volume surgeon group n=20 Crude OR (95%CI)= 1.58 (0.17 - 14.60) Multivariate OR (95%CI)= 2.16 (0.22-20.90)	
Full citation Rutegard, M., Lagergren, P., No influence of surgical volume on patients'	**Sample size** N=355 **Characteristics**	**Interventions** The following operative procedures were performed:	**Details** **Definition of surgical volumes**	**Results** **HRQL: EORTC QLQ-C30 questionnaire**	**Limitations** Selection bias: low risk of bias

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>health-related quality of life after esophageal cancer resection, Annals of Surgical OncologyAnn Surg Oncol, 15, 2380-7, 2008

Ref Id

505905

Country/ies where the study was carried out

Sweden

Study type

Prospective cohort study.

Aim of the study

This study was undertaken to examine the question whether hospital or surgeon volume influences HRQL as evaluated 6 months after such surgery.

Study dates</td>
<td>Age:

<60 26%; 60-70 36%; >70 39%

81% male/19% female

Tumour stage: 0-I 23%; II 34%; III 37%; IV 5%

Tumour location: upper or middle 15%; lower 415; cardia 44%

Histology: SCC 24%; adenocarcinoma 76%

Inclusion criteria

Patients newly diagnosed with esophageal or cardia cancer who underwent macroscopically and microscopically radical resection.

Exclusion criteria

Who died within 6 months after surgery or did not undergo a macroscopically and microscopically radical resection (R0) were not eligible for the current study.</td>
<td>Esophageal resection, referring to removal of the main part of the esophagus with an anastomosis between an esophageal substitute (stomach, jejunum, or colon) and the proximal esophagus; Cardia resection, representing removal of the proximal part of the stomach and the distal part of the esophagus with an anastomosis between the remaining stomach and the remaining esophagus; Extended total gastrectomy, referring to</td>
<td>Our cut-offs were predefined and based on previous research, using a similar number of patients in the comparison groups.1,3 This strategy meant that in the current study, LVHs conducted 0–9 operations annually and HVHs conducted more than 9 operations/year.

Surgeon volume was categorized in the same manner, producing two groups: low-volume surgeons (LVSs) with 0–6 operations/year, and highvolume surgeons (HVSs) with more than six procedures annually.

HRQL Score

The outcome was assessed through self-administered</td>
<td>Mean scores (all cancer types)

Low hospital volume (LH)= ≤9 surgeries/year, n=174
High hospital volume(HH)= >9 surgeries/year, n=181
Low surgeon volume(LS)= = ≤6 surgeries/year, n=148
High surgeon volume (HS)= >6 surgeries/year, n=207
<table>
<tr><th></th><th>LH</th><th>HH</th><th>LS</th><th>HS</th></tr>
<tr><td>Appetite loss</td><td>35 (30-41)</td><td>36 (30-41)</td><td>34 (28-39)</td><td>37 (32-42)</td></tr>
<tr><td>Dyspnoea</td><td>29 (25-34)</td><td>36 (31-41)</td><td>28 (23-33)</td><td>35 (31-40)</td></tr>
<tr><td>Fatigue</td><td>41 (37-44)</td><td>45 (41-49)</td><td>40 (36-44)</td><td>45 (41-49)</td></tr>
<tr><td>N & V</td><td>18 (15-21)</td><td>21 (17-25)</td><td>17 (14-20)</td><td>21 (18-25)</td></tr>
<tr><td>Pain</td><td>25 (20-29)</td><td>29 (25-33)</td><td>25 (20 - 29)</td><td>29 (25-33)</td></tr>
<tr><td>Physical function</td><td>79 (76-82)</td><td>76 (72-79)</td><td>80 (77-83)</td><td>75 (72-78)</td></tr>
<tr><td>Global QoL</td><td>60 (57-64)</td><td>60 (57-63)</td><td>62 (58-65)</td><td>59 (56-62)</td></tr>
</table>
</td>
<td>Performance bias: Unclear risk.

Unclear whether the comparisons groups received the same care, or if the participants were blinded to the volume status of the hospital.

Attrition bias: low risk of bias. The registries are reported to have almost complete coverage (97%) of all Swedish people with oesophageal or cardia cancer.

Detection bias: Unclear risk of bias. It is unclear if the investigators were blinded to the hospital volume status where the patients had their surgery and other important confounding factors.

Other limitations: none.

Other information

Among the 446 eligible patients, the registration in</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>2001-2005

Source of funding

Swedish Cancer Society</td>
<td></td>
<td>removal of the entire stomach and the distal part of the esophagus with an anastomosis between the jejunum and the esophagus; Total gastrectomy and esophageal resection, meaning that the entire stomach and the main part of the esophagus were removed with an anastomosis between an esophageal substitute (jejunum or colon) and the proximal esophagus. Minimally invasive esophagectomy was not performed during the study period.</td>
<td>questionnaires concerning HRQL, sent out to the patients 6 months after surgery. A cancer-specific core questionnaire, the QLQ-C30 (version 3.0)11 and an esophageal cancer-specific module QLQ-OES18,12 both developed and validated by the European Organization for Research and Treatment of Cancer (EORTC), were used.

Statistical Analysis

Mean scores with 95% confidence intervals (CIs) were calculated. Based on previous research, a mean score difference of 10 or more between comparison groups was considered of at least moderate clinical relevance.14,15</td>
<td>
<table>
<tr><td>Role function</td><td>67 (62-72)</td><td>61 (56-66)</td><td>69 (63-74)</td><td>60 (56-65)</td></tr>
</table>

Mean scores (oesophageal cancer only)

<table>
<tr><th></th><th>LH</th><th>HH</th><th>LS</th><th>HS</th></tr>
<tr><td>Appetite loss</td><td>35 (28-42)</td><td>35 (28–43)</td><td>33 (25–41)</td><td>37 (30–43)</td></tr>
<tr><td>Dyspnoea</td><td>32 (26-39)</td><td>37 (30–43)</td><td>30 (23–38)</td><td>37 (32–43)</td></tr>
<tr><td>Fatigue</td><td>42 (37-47)</td><td>44 (39–50)</td><td>41 (35–47)</td><td>44 (39–49)</td></tr>
<tr><td>N & V</td><td>18 (13-22)</td><td>20 (15–25)</td><td>18 (13–23)</td><td>20 (16–24)</td></tr>
<tr><td>Pain</td><td>24 (19-31)</td><td>26 (21–32)</td><td>25 (18–31)</td><td>26 (21–31)</td></tr>
<tr><td>Physical function</td><td>78 (74–83)</td><td>74 (70–78)</td><td>80 (75–85)</td><td>74 (70–78)</td></tr>
<tr><td>Global QoL</td><td>60 (56–65)</td><td>59 (55–64)</td><td>61 (56–66)</td><td>59 (55–63)</td></tr>
<tr><td>Role function</td><td>66 (59–73)</td><td>61 (54–68)</td><td>70 (62–77)</td><td>59 (53–65)</td></tr>
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</td>
<td>67 (15%) was delayed and 24 (5%) did not wish to participate or did not respond, thus leaving 355 patients (80% of those eligible) for final analyses.</td>
</tr>
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<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td>Whenever such a difference was found, a linear regression analysis was applied, including a crude analysis and two models adjusting for potential confounding factors. A basic model adjusted for age (\60, 60–70, or[70 years), gender, tumor stage (0–I, II, III, or IV), number of predefined co-morbidities (0, 1–2, or ‡3), and number of predefined complications occurring within 30 days of surgery (0, 1–2, or ‡3). In a second model, we further adjusted for histological type of tumor (squamous cell carcinoma or adenocarcinoma), tumor location (upper and middle esophagus, lower esophagus, or cardia), surgical approach</td><td>HRQL: EORTC QLQ-OES18 questionnaire

Mean scores (all cancer types)

A=Dry mouth
B=Choking with swallowing
C=Trouble with coughing
D=Dysphagia
E=Trouble when eating
F=Oesophageal pain
G=Reflux
H=Speech difficulties
I=Trouble with swallowing
<table><tr><th></th><th>LH</th><th>HH</th><th>LS</th><th>HS</th></tr><tr><td>A</td><td>23(18-28)</td><td>28 (24–33)</td><td>24 (19–29)</td><td>27 (23–31)</td></tr><tr><td>B</td><td>17 (13-20)</td><td>22 (18–26)</td><td>17 (13–22)</td><td>21 (17–24)</td></tr><tr><td>C</td><td>22 (18–27)</td><td>30 (25–35)</td><td>20 (15–24)</td><td>31 (26–35)</td></tr><tr><td>D</td><td>25 (21–30)</td><td>22 (18–25)</td><td>25 (20–29)</td><td>22 (19–26)</td></tr><tr><td>E</td><td>32 (29–36)</td><td>37 (33–41)</td><td>32 (28–36)</td><td>36 (33–40)</td></tr><tr><td>F</td><td>27 (23–30)</td><td>26 (23–30)</td><td>26 (23–30)</td><td>26 (23–30)</td></tr></table></td><td></td></tr>
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<td>(transthoracic or transhiatal), and neoadjuvant therapy (no or yes). Comorbidity was grouped into: (1) cardiopulmonary disorders, (2) diabetes, (3) hepatic or renal disease, (4) tobacco smoking, or (5) other malignancies or other significant disorders. Complications were grouped into: (1) technical surgical complications, (2) severe infections, and (3) severe respiratory complications. Comorbidities or complications occurring within the same group were counted only once. Foralldataanalysesthe statisticalsoftwareSTATA 9.2 for Windows was used.</td>
<td>
<table>
<tr><td>G</td><td>26 (21–30)</td><td>24 (20–28)</td><td>24 (20–29)</td><td>25 (21–29)</td></tr>
<tr><td>H</td><td>11 (8–15)</td><td>12 (8–16)</td><td>9 (5–13)</td><td>13 (10–17)</td></tr>
<tr><td>I</td><td>12 (8–16)</td><td>15 (11–19)</td><td>12 (8–16)</td><td>15 (11–18)</td></tr>
</table>
Mean scores (oesophageal cancer only)
<table>
<tr><th></th><th>LH</th><th>HH</th><th>LS</th><th>HS</th></tr>
<tr><td>A</td><td>22 (16–29)</td><td>27 (21–33)</td><td>24 (16–31)</td><td>25 (20–30)</td></tr>
<tr><td>B</td><td>21 (16–26)</td><td>23 (18–29)</td><td>22 (15–28)</td><td>23 (18–28)</td></tr>
<tr><td>C</td><td>28 (21–35)</td><td>36 (30–43)</td><td>24 (18–31)</td><td>38 (32–44)</td></tr>
<tr><td>D</td><td>23 (17–29)</td><td>21 (17–26)</td><td>26 (19–33)</td><td>20 (16–24)</td></tr>
<tr><td>E</td><td>33 (28–38)</td><td>36 (30–41)</td><td>31 (26–37)</td><td>36 (31–41)</td></tr>
<tr><td>F</td><td>27 (22–32)</td><td>23 (19–27)</td><td>28 (23–34)</td><td>22 (19–26)</td></tr>
<tr><td>G</td><td>29 (23–35)</td><td>26 (20–31)</td><td>28 (23–34)</td><td>27 (22–32)</td></tr>
<tr><td>H</td><td>13 (8–19)</td><td>14 (9–19)</td><td>10 (4–15)</td><td>16 (11–21)</td></tr>
</table>
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<td></td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				I 10 (5–15) 16 (10–21) 11 (5–18) 14 (9–19)	
Full citation Migliore, M., Choong, C. K., Lim, E., Goldsmith, K. A., Ritchie, A., Wells, F. C., A surgeon's case volume of oesophagectomy for cancer strongly influences the operative mortality rate, European Journal of Cardio-Thoracic SurgeryEur J Cardiothorac Surg, 32, 375-80, 2007 **Ref Id** 587964 **Country/ies where the study was carried out** United Kingdom **Study type** Prospective cohort	**Sample size** N=205 **Characteristics** mean age= 64 years (range 48-80) 140 men/ 55 women **Inclusion criteria** Patients who underwent oesophagectomy for malignant disease with palliative or curative intent. **Exclusion criteria** Patients treated by endoscopic techniques.	**Interventions** Surgeons: included if he had performed any operation as the primary surgeon during the study period. A consultant performed most of the operations. Few circumstances a senior trainee performed it under direct supervision of the consultant (operation was designated as having been done by the consultant). If two consultants (thoracic and general) operated	**Details** The following variables were evaluated to determine their influence on postoperative mortality: age, sex, presence of co-morbidities, neoadjuvant chemo radiotherapy, type of oesophagectomy, postoperative complications, pathology, pre and postoperative TNM stage, 30-day and in-hospital mortality, and the surgeon. Neoadjuvant chemotherapy was started in 2000.	**Results** **In-hospital mortality** High surgical volume 5/118 Low surgical volume 13/77 Crude OR= 4.59; 95% CI 1.57, 13.46, p=0.006 Adjusted OR for type of tumour= 2.26 (0.48, 10.52), p= 0.30 Adjusted OR for 10-year changes in age= 1.63 (0.93, 2.84) 0.087 **Overall Survival**	**Limitations** Selection bias: low risk of bias Performance bias: Unclear risk. Unclear whether the comparisons groups received the same care, or if the participants were blinded to the volume status of the hospital. Attrition bias: low risk of bias. The data is reported to be complete- all patients treated at one hospital. Detection bias: Unclear risk of bias. It is unclear if the investigators were blinded to the hospital volume status where the patients had their surgery and other important confounding factors.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study To determine the risks of in-hospital mortality and to define the relationship between surgeon volume and outcome. The secondary aim was to establish the numerical difference in case volume between high volume and low volume surgeons. **Study dates** January 1994 to December 2005 **Source of funding** Not reported		together, the operation was assigned to the surgeon who was first on the list. High volume surgeon: mean of >6 cases per year Operative mortality: in-hospital death	Preoperative staging: Upper GI series, endoscopy with biopsy and CT. Since 2002 PET and endosonography have also been used. Statistical analysis: Multiple logistic regression Between groups comparisons were performed using ttests for continuous variables and Fisher's exact test for categorical variables. Univariate logistic regression models were used to obtain unadjusted odds ratios (OR) (odds ratios from a model with a single variable) and these were used in addition to Wald test p-values of model parameters to assess significance of surgeon volume and	Median survival in months (95% CI) was 16.8 (13.8, 19.8) for the high-volume surgeons and 13.9 (11.0, 17.0) for the low-volume group. P log rank test= 0.476. HR calculated by NGA technical team (method described by Tierney 2007): HR (95% CI)= 0.89 (0.64-1.23) ln(HR)= -0.12, se(ln(HR))= 0.17	Other limitations: adjusted OR for in hospital mortality not clearly reported; multivariate analysis not conducted. **Other information** Some operations were done by trainees with consultant supervision. They were counted under that consultants name in terms of volume.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			other covariates of interest on in-hospital mortality. Survival curves were constructed using Kaplan—Meier methods. Survival in different groups was assessed using Wald test p-values for model parameters from Cox regression analysis. Multiple logistic regression was used to further assess the effect of surgeon volume on in-hospital mortality in the presence of covariates. In these models, the ORs reflect the relative increase (if greater than 1) or decrease (if less than 1) in the odds of in-hospital death for operations done by lowvolume surgeons while controlling for another variable.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			Due to a small number of patients, models with more than one covariate in addition to surgeon volume were not explored in this study.		

F.51 Staging investigations

What are the optimal staging investigations to determine suitability for curative treatment of oesophageal or gastro-oesophageal junctional cancer after diagnosis with endoscopy and whole-body CT scan?

What are the optimal staging investigations to determine suitability for curative treatment of gastric cancer after diagnosis with endoscopy and whole-body CT scan?

A joint table is provided for these two questions.

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>

Full citation

Chemaly, M., Scalone, I., Durivage, G., Napoleon, B., Pujol, B., Lefort, C., Hervieux, V., Scoazec, J. Y., Souquet, J. C., Ponchon, T., Miniprobe EUS in the pretherapeutic assessment of early esophageal neoplasia, EndoscopyEndoscopy, 40, 2-6, 2008

Ref Id

491282

Country/ies where the study was carried out

France

Study type

Retrospective cohort study

Aim of the study

To assess the use of a high-frequency endosonography miniprobe in the

</td>
<td>

Sample size

N = 91 participants

(assessed on a per lesion basis, with a total of 106 oesophageal lesions)

Characteristics

Characteristics	All cohort n = 91
Sex, M:F (%)	77:14 (84.6:15.4 %)
Mean age (range), years	67 (45-82)
Number of lesions, total	106
Mean size of lesion (range), cm	3.1 (1-15)
Location of lesions, n (%)	
Mid and proximal	70 (66%)
Distal	22 (20.8%)
Not recorded	13 (13.2%)

Inclusion Criteria

Assessed using endoscopic miniprobe

</td>
<td>

Tests

Miniprobe endoscopic ultrasound was conducted to assess the oesophageal lesions, by one of seven operators (all with at least 2 years experience).

</td>
<td>

Methods

Identification of mucosal invasion on endoscopic ultrasound was compared to histological examination of the specimen after resection.

</td>
<td>

Results

Differentiation of submucosal from mucosal invasion

2x2 table

	pSM	pM	Total
EUS (SM)	13	19	32
EUS (M)	8	62	70
	21	81	102

SM=submucosal
M=Mucosal
p=Pathological

Sensitivity: 61.9% (95% CI† 38.44 to 81.89)

Specificity: 76.5% (95% CI† 65.82 to 85.25)

Positive likelihood ratio‡: 2.64 (95% CI 1.57 to 4.43)

Negative likelihood ratio‡: 0.50 (95% CI 0.28 to 0.87)

Positive predictive value: 40.6% (95% CI† 28.98 to 53.43)

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<td>

Limitations

Other information

QUADAS 2 checklist

Patient selection

Risk of bias:

Was a consecutive or random sample of patients enrolled? Yes

Was a case-control design avoided? Yes

Did the study avoid inappropriate exclusions? Yes

Could the selection of participants have introduced bias? Low risk

Applicability:

Is there concern that the included participants do not

</td>
</tr>
</table>

assessment of early squamous cell carcinoma and superficial adenocarcinoma on Barrets oesophagus. **Study dates** January 1997 and April 2006. **Source of funding** Not reported.	Endoscopic or surgical resection following ultrasonographic assessment Diagnosis of superficial squamous cell carcinoma of the oesophagus, or adenocarcioma on Barrett's mucosa. **Exclusion Criteria** Locoregional invading tumour Stenosing tumour			Negative predictive value: 88.9% (95% CI† 81.60 to 93.13) † 95% confidence interval calculated by the NGA technical team from data reported i the article using https://www.medcalc.org/calc/diagnostic_test.php ‡ calculated by the NGA technical team from data reported i the article using https://www.medcalc.org/calc/diagnostic_test.php	match the review question? Low risk Index tests **Risk of bias:** Were the index tests interpreted without knowledge of the reference standard? Yes If a threshold was used, was it pre-specified? N/A Could the conduct or interpretation of the index test have introduced bias? Low risk **Applicability:** Is there concern that the index test, its conduct or interpretation differ from the review question? Low risk Reference standard **Risk of bias:**

					Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unclear Could the reference standard, its conduct or interpretation have introduced bias? Low risk **Applicability:** Is there concern that the target condition as defined by the reference standard does not match the review question? Low risk Flow and timing **Risk of bias:** Was there an appropriate interval

					between index tests and reference standard? Unclear Did all participants receive a reference standard? Yes Did participants receive the same reference standard? Yes Were all patients included in the analysis? No - one participant with T2 disease, and three lesions where invasion (mucosal or submucosal was unclear) were excluded. Could the participant flow have introduced bias? Unclear risk
Full citation Dhupar, R., Rice, R. D., Correa, A. M., Weston, B. R., Bhutani, M. S., Maru,	**Sample size** N = 181 **Characteristics**	**Tests** EUS procedures were performed by 4	**Methods** Pathological staging was based on	0	0

D. M., Betancourt, S. L., Rice, D. C., Swisher, S. G., Hofstetter, W. L., Endoscopic Ultrasound Estimates for Tumor Depth at the Gastroesophageal Junction Are Inaccurate: Implications for the Liberal Use of Endoscopic Resection, Annals of Thoracic SurgeryAnn Thorac Surg, 100, 1812-1816, 2015 **Ref Id** 491473 **Country/ies where the study was carried out** USA **Study type** Retrospective cohort study **Aim of the study** To assess the diagnostic accuracy for T staging of gastroesophageal junctional tumours. **Study dates**	<table><tr><td>Characteristics</td><td>All cohort n = 181</td></tr><tr><td>Sex, M:F</td><td>150:31 (83:17%)</td></tr><tr><td>Median age, years (range)</td><td>66 (40 to 86)</td></tr><tr><td>Adenocarcinoma</td><td>98%</td></tr><tr><td>Squamous cell carcinoma</td><td>2%</td></tr><tr><td>Well differentiated</td><td>5%</td></tr><tr><td>Moderately differentiated</td><td>54.7%</td></tr><tr><td>Poorly differentiated</td><td>36.5%</td></tr><tr><td>Undifferentiated</td><td>0.6%</td></tr><tr><td>Differentiation could not be assessed</td><td>3.3%</td></tr></table> **Inclusion Criteria**	gastroenterologists with advanced training. A radial echoendoscope was typically used (5 to 12 MHz). Miniprobes are used rarely.	the American Joint Committee on Cancer 7th edition, with invasion into duplicated muscularis mucosae considered as T1a.		

January 1995 and January 2014. **Source of funding** Not reported.	Patients undergoing oesophagectomy or endoscopic mucosal resection for primary adenocarcinoma or squamous cell carcinoma of the GE junction No preoperative chemo- or radiotherapy No previous esophagectomy Preoperative EUS tumor depth and pathologic tumor depth data available. **Exclusion Criteria** Not reported.				
Full citation Grotenhuis, B. A., Wijnhoven, B. P. L., Poley, J. W., Hermans, J. J., Biermann, K., Spaander, M. C. W., Bruno, M. J., Tilanus, H. W., van Lanschot, J. J. B., Preoperative Assessment of Tumor Location and Station-Specific Lymph Node Status in Patients with Adenocarcinoma of	Sample size n=50 Characteristics Out of 50 patients included, 26 patients underwent transthoracic oesophagectomy (TTE) with extended lymphadenectomy while the rest (n=24) had transhiatal oesophagectomy with locoregional lymphadenectomy	Tests All patients underwent upper GI endoscopy with endoscopic ultrasound, CT of the chest and abdomen and external ultrasound of the neck. The tests were performed by experienced	Methods The author did not report about 15 patients who underwent oesophagectomy but not included in analyses.	2	179

the Gastroesophageal Junction, World Journal of SurgeryWorld J Surg, 37, 147-155, 2013 Ref Id 491697 Country/ies where the study was carried out Netherlands Study type Prospective cohort study Aim of the study To evaluate the accuracy of preoperative endoscopic assessment and CT by comparing with histopathologic findings in the resection specimen Study dates April 2008 and December 2009 Source of funding Not reported	Age median (range) in years= 65 (48 -81) Male %: 78 Inclusion Criteria Patients having oesophagectomy for cancer of the oesophagus or gastroesophageal junction Exclusion Criteria Patients receiving neoadjuvant therapy Patients with irresectable tumour at surgery Patients with squamous cell carcinoma	gastroenterologist with a Q-endoscope and an electronic radial echoendoscope. The postoperative surgical resection of the tumour was analysed by a dedicated gastrointestinal pathologist. (gold standard)			

Full citation Lee, H. H., Lim, C. H., Park, J. M., Cho, Y. K., Song, K. Y., Jeon, H. M., Park, C. H., Low accuracy of endoscopic ultrasonography for detailed T staging in gastric cancer, World Journal of Surgical OncologyWorld J Surg Oncol, 10, 2012 Ref Id 492175 Country/ies where the study was carried out China Study type Retrospective cohort study Aim of the study To determine the accuracy of EUS for the staging of tumour depth and lymph node metastasis in gastric cancer.	Sample size N = 309 Characteristics M:F, n (%): 184:125 (59.5:40.5) Mean age, years (SD): 57.5 (12.2) T1 disease: n = 192 T2 disease: n = 70 T3 disease: n = 45 T4 disease: n = 2 N0 disease: n = 213 N1-3 disease: n = 96 M0 disease: n = 301 M1 disease: n = 8 Inclusion Criteria Surgery for gastric cancer performed. Pre-operative EUS performed. Exclusion Criteria Did not undergo resection	Tests EUS was performed with a radial transducer (12 to 20MHz) and in some cases a 20MHz miniprobe was also used.	Methods Pre-operative T and M staging was compared to the pathological stage.	2	179

<table>
<tr>
<td>Study dates

January to December 2009.

Source of funding

None reported.</td>
<td>Difficult pre-operative staging (including incomplete endoscopic dissection, neoadjuvant chemotherapy and remnant gastric cancer)

Pathological non-measureable lesions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full citation

Lee, S. J., Lee, W. W., Yoon, H. J., Lee, H. Y., Lee, K. H., Kim, Y. H., Park do, J., Kim, H. H., So, Y., Kim, S. E., Regional PET/CT after water gastric inflation for evaluating loco-regional disease of gastric cancer, European Journal of RadiologyEur J Radiol, 82, 935-42, 2013

Ref Id

492196

Country/ies where the study was carried out

Korea

Study type</td>
<td>Sample size

N = 44

Characteristics
<table><tr><td>Characteristics</td><td>n (%)</td></tr><tr><td>Age, years (SD)</td><td>62.1 (14.5)</td></tr><tr><td>Sex, M:F</td><td>30:14 (68.2:31.8)</td></tr><tr><td>Early gastric cancer</td><td>19 (43.2)</td></tr><tr><td>Advanced gastric cancer</td><td>25 (56.8)</td></tr><tr><td>Tumour location</td><td></td></tr><tr><td>Upper</td><td>10 (22.7)</td></tr></table></td>
<td>Tests

A PET-CT scanner integrated with a 64-slice multidetector row CT was used.</td>
<td>Methods

Patient information was partially known to the interpreters of the PET-CT scans - they were aware that patients had been diagnosed with gastric cancer and were undergoing pre-operative tests.</td>
<td>Results

Detection of lymph node metastasis

2x2 table
<table><tr><td></td><td>pN+</td><td>pN0</td><td>Total</td></tr><tr><td>PET-CT (N+)</td><td>12</td><td>0</td><td>12</td></tr><tr><td>PET-CT (N0)</td><td>12</td><td>20</td><td>12</td></tr><tr><td></td><td>24</td><td>20</td><td>44</td></tr></table>
(Per patient analysis)

Sensitivity† (95% CI): 50% (29-71)

Specificity† (95% CI): 100% (83-100)</td>
<td>Limitations

Other information

QUADAS 2 checklist

Patient selection

Risk of bias:

Was a consecutive or random sample of patients enrolled? No

Was a case-control design avoided? Yes

Did the study avoid inappropriate exclusions? Yes</td>
</tr>
</table>

Prospective cohort study Aim of the study To assess the diagnostic accuracy of PET-CT after water gastric inflation for locoregional staging of gastric cancer. Study dates February 2009 to December 2011. Source of funding Korea Healthcare Technology R&D Project, Ministry of Health and Welfare. National Research Foundation Ministry of Science and Technology Basic Science Research Program, Republic of Korea.	Middle 5 (11.4) Lower 29 (65.9) Inclusion Criteria Diagnosis of gastric cancer. Pathological confirmation of loco-regional lesions. Exclusion Criteria Received neoadjuvant or palliative systemic chemotherapy Due to undergo additional studies requiring nil by mouth immediately after PET-CT		Images were interpreted by two nuclear medicine physicians with at least 5 years experience. The presence of prominent FDG uptake in discrete lymph nodes was considered a positive finding for metastatic lymph nodes, regardless of the lymph node size.	Positive likelihood ratio† (95% CI): ∞ (not calculable) Negative likelihood ratio† (95% CI): 0.50 (0.34-0.75) Positive predictive value† (95% CI): 100% (not calculable) Negative predictive value† (95% CI): 63% (53-71) †calculated by the NGA technical team from data reported in the article using https://www.medcalc.org/calc/diagnostic_test.php	Could the selection of participants have introduced bias? Unclear Applicability: Is there concern that the included participants do not match the review question? No Index tests Risk of bias: Were the index tests interpreted without knowledge of the reference standard? Yes If a threshold was used, was it pre-specified? N/A Could the conduct or interpretation of the index test have introduced bias? Low risk Applicability:

					Is there concern that the index test, its conduct or interpretation differ from the review question? No Reference standard Risk of bias: Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unclear Could the reference standard, its conduct or interpretation have introduced bias? Low risk Applicability: Is there concern that the target condition as defined

					by the reference standard does not match the review question? No Flow and timing Risk of bias: Was there an appropriate interval between index tests and reference standard? Unclear Did all participants receive a reference standard? Yes Did participants receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the participant flow have introduced bias? Low risk
Full citation	Sample size	Tests	Methods	Results	Limitations

<table>
<tr>
<td>Liu, S., Zhu, H., Li, W., Zhang, B., Ma, L., Guo, Z., Huang, Y., Song, P., Yu, J., Guo, H., Potential impact of (18)FDG-PET/CT on surgical approach for operable squamous cell cancer of middle-to-lower esophagus, OncoTargets and therapyOnco Targets Ther, 9, 855-62, 2016

Ref Id

474790

Country/ies where the study was carried out

China

Study type

Randomised controlled study

Aim of the study

To assess whether PET-CT affects surgical approach in oesophageal cancer.

Study dates</td>
<td>N = 54

(additional participants in the trial did not undergo PET-CT).

Characteristics
<table>
<tr><th>Characteristics</th><th>PET-CT
n = 54</th></tr>
<tr><td>Sex (M:F), n</td><td>46:8</td></tr>
<tr><td>Tumour location</td><td></td></tr>
<tr><td>Lower</td><td>18</td></tr>
<tr><td>Middle</td><td>36</td></tr>
<tr><td>Tumour differentiation</td><td></td></tr>
<tr><td>Well</td><td>11</td></tr>
<tr><td>Moderate</td><td>28</td></tr>
<tr><td>Poor</td><td>15</td></tr>
<tr><td>Surgery</td><td></td></tr>
<tr><td>Curative surgery</td><td>51</td></tr>
</table>
</td>
<td>PET-CT

All participants fasted and rested for at least 6 hours prior to the scan.

Attenuation-corrected PET images, spiral CT images and fused PET-CT images were subsequently displayed as coronal, sagittal and transaxial slices. All studies were interpreted jointly and in consensus by 2 experience nuclear medicine physicians.

PET images were initially viewed to assess lesions indicative of malignancy. CT and fused PET-CT images were then reviewed together to amend the initial findings.</td>
<td>All participants underwent surgery, usually within 1 week of imaging. The choice of surgical approach was left to the surgeons discretion.

Resected lymph nodes were grouped according to their stations at pathology. The accuracy of detecting the involvement of nodal stations with PET-CT was determined</td>
<td>Detection of nodal metastasis by PET-CT

2x2 table*
<table>
<tr><th></th><th>p(+)ve</th><th>p(-)ve</th><th>Total</th></tr>
<tr><td>PET-CT (+)ve</td><td>77</td><td>17</td><td>94</td></tr>
<tr><td>PET-CT (-)ve</td><td>12</td><td>267</td><td>279</td></tr>
<tr><td></td><td>89</td><td>284</td><td>373</td></tr>
</table>
Sensitivity: 86.5% (95% CI† 77.63 to 92.83)

Specificity: 94.0% (95% CI† 90.59 to 96.47)

Positive likelihood ratio‡: 14.45 (95% CI 9.05 to 23.08)

Negative likelihood ratio‡: 0.14 (95% CI 0.08 to 0.24)

Positive predictive value‡: 81.91% (95% CI 73.93 to 87.85)

Negative predictive value‡: 95.70% (92.93 to 97.42)</td>
<td>Findings are reported on a per station basis, rather than a per patient basis. Therefore it is unclear how sensitivity and specificity for overall detection of nodal metastasis would compare (i.e. N stage for individual patients).

Other information

QUADAS 2 checklist

Patient selection

Risk of bias:

Was a consecutive or random sample of patients enrolled? Yes

Was a case-control design avoided? Yes

Did the study avoid inappropriate exclusions? Unclear - participants with</td>
</tr>
</table>

April 2009 to September 2012. Source of funding Grant from the Natural Science Foundation of Shandong Province.	Palliative surgery 3 Pathological stages IIa 11 IIb 4 III 36 IV 3 Inclusion Criteria Diagnosis of squamous cell cancer of the oesophagus, under consideration for surgery. Exclusion Criteria Upper oesophageal cancer Previous treatment Uncontrolled diabetes mellitus Inoperability due to medical reasons (e.g. severe pulmonary or cardiac disease)		and compared with the pathological results.	Station-based analysis used to determine diagnostic accuracy measures. *constructed by the NGA technical team from data reported in the article (sensitivity. specificity and prevalence) † 95% confidence interval calculated by the NGA technical team using https://www.medcalc.org/calc/diagnostic_test.php ‡ calculated by the NGA technical team using https://www.medcalc.org/calc/diagnostic_test.php	upper oesophageal cancer were excluded. Could the selection of participants have introduced bias? Low risk Applicability: Is there concern that the included participants do not match the review question? No Risk of bias Index tests Were the index tests interpreted without knowledge of the reference standard? Yes Is a threshold was used, was it pre-specified? Yes (SUV ≥2.5 considered abnormal) Could the conduct or interpretation of the index test have

					introduced bias? Low risk Applicability Is there concern that the index test, its conduct or interpretation differ from the review question? No Reference standard Risk of bias Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unclear Could the reference standard, its conduct or interpretation have introduced bias? Low risk Applicability

					Is there concern that the target condition as defined by the reference standard does not match the review question? No Flow and timing Risk of bias Was there an appropriate interval between index tests and reference standard? Yes Did all participants receive a reference standard? No - some participants did not undergo surgery due to scan findings, so were excluded from diagnostic accuracy analysis. Did participants receive the same reference standard? Yes

<table>
<tr><td></td><td></td><td></td><td></td><td></td><td>Were all patients included in the analysis? No, a further 27 participants were initially included, but did not undergo surgery due to the PET-CT findings.

Could the participant flow have introduced bias? Unclear risk.</td></tr>
<tr><td>Full citation

Lowe, V. J., Booya, F., Fletcher, J. G., Nathan, M., Jensen, E., Mullan, B., Rohren, E., Wiersema, M. J., Vazquez-Sequeiros, E., Murray, J. A., Allen, M. S., Levy, M. J., Clain, J. E., Comparison of positron emission tomography, computed tomography, and endoscopic ultrasound in the initial staging of patients with esophageal</td><td>Sample size

n=75

Characteristics

Inclusion Criteria

Newly diagnosed oesophageal cancer

Exclusion Criteria</td><td>Tests

All patients had PET and CT within one month prior to endoscopic ultrasound (EUS). EUS (a forward-viewing endoscope) and biopsy, as necessary was done by one expert for final diagnosis. All</td><td>Methods

Six patients were excluded from the study for diagnosis of other primaries.</td><td>Results

<table><tr><td>EUS</td><td>Sensitivity</td><td>Specificity</td></tr><tr><td>N+ve</td><td>0.86(38/44) [0.73, 0.95]</td><td>0.67(10/15) [0.38, 0.88]</td></tr><tr><td>M+ve</td><td>0.73 (19/26) [0.52, 0.88]</td><td>0.86 (19/22) [0.65, 0.97]</td></tr></table>
N=nodal spread
M=metastsis
<table><tr><td>EUS</td><td>Correct Dx</td><td>Under Dx</td><td>Over Dx</td></tr><tr><td>T</td><td>0.71(10/14) [0.42,0.92]</td><td>0.071(1/14) [0.002,0.33]</td><td>0.214(3/14) [0.05,0.51]</td></tr></table></td><td>Limitations

QUADAS 2 checklist

Patient selection

Risk of bias:

Was a consecutive or random sample of patients enrolled? Unclear

Was a case-control design avoided? Yes</td></tr>
</table>

cancer, Molecular Imaging and Biology, 7, 422-430, 2005 Ref Id 475992 Country/ies where the study was carried out USA Study type Prospective cohort study Aim of the study To assess the comparative accuracy of oesophageal cancer staging by CT, EUS and PET Study dates November 2000 to July 2002 Source of funding Mayo Foundation		patients received dilatation to pass the echoendoscope except for six patients and then radical EUS examination to assess perigastric and mediastinal lymph node for malignancy and for coeliac nodes and liver for metastases. Whenever a nonperitumoral lymph node or hepatic lesion is detected, linear EUS-guided needle aspiration is performed.		TNM | 0.75(43/57) [0.62,0.86] | 0.19(11/57) [0.10, 0.32] | 0.05(3/57) [0.01, 0.14]	Did the study avoid inappropriate exclusions? Yes Could the selection of participants have introduced bias? Unclear risk Applicability: Is there concern that the included participants do not match the review question? low risk Index tests Risk of bias: Were the index tests interpreted without knowledge of the reference standard? Unclear If a threshold was used, was it pre-specified? N/A Could the conduct or interpretation of the index test have introduced bias? Unclear risk

					Applicability: Is there concern that the index test, its conduct or interpretation differ from the review question? Low risk Reference standard Risk of bias: Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unclear Could the reference standard, its conduct or interpretation have introduced bias? Unclear risk Applicability:

					Is there concern that the target condition as defined by the reference standard does not match the review question? Low risk Flow and timing Risk of bias: Was there an appropriate interval between index tests and reference standard? Unclear Did all participants receive a reference standard? Yes Did participants receive the same reference standard? Yes Were all patients included in the analysis? No Could the participant flow have introduced bias? High risk

					Other information
Full citation Luo, L. N., He, L. J., Gao, X. Y., Huang, X. X., Shan, H. B., Luo, G. Y., Li, Y., Lin, S. Y., Wang, G. B., Zhang, R., Xu, G. L., Li, J. J., Endoscopic Ultrasound for Preoperative Esophageal Squamous Cell Carcinoma: a Meta-Analysis, PLoS ONE [Electronic Resource]PLoS ONE, 11, e0158373, 2016 Ref Id 490200 Country/ies where the study was carried out China Study type Systematic review Aim of the study	Sample size 44 included studies n = 2880 participants. Characteristics 43% of studies were prospective. Studies were conducted in 13 different countries. Inclusion Criteria EUS conducted pre-operatively Pathological confirmation of disease from surgery or endoscopic mucosal/submucosal resection Able to complete a 2x2 contingency table Exclusion Criteria Non-English publications Reviews, abstracts, editorials or letters and case reports.	Tests All used radial, linear or miniprobe EUS operating at 7.5, 12 or 20MHz	Methods Diagnostic accuracy measures were calculated as compared to the reference standard (histopathology).	Results Identification of T1 disease 24 studies Sensitivity (95% CI): 0.77 (0.73-0.80) Specificity (95% CI): 0.95 (0.94-0.96) Positive likelihood ratio (95% CI)†: 15.4 (not calculable) Negative likelihood ratio (95% CI)†: 0.24 (not calculable) Identification of T2 disease 32 studies Sensitivity (95% CI): 0.66 (0.61-0.70) Specificity (95% CI): 0.88 (0.86-0.89) Positive likelihood ratio (95% CI)†: 5.5 (not calculable)	Limitations Other information CASP systematic review checklist Clearly focused question. Appropriate papers included. All relevant papers apparently included. Sufficient quality assessment. Reasonable grounds for meta-analysis. Clear results. Appropriate precision. Results applicable to the population.

To systematically review the existing literature on the accuracy of endoscopic ultrasound for the staging of oesophageal squamous cell carcinoma. Study dates Articles published up to October 2015. Source of funding The Science and Technology Plan Projects of Guangdong Province Sun Yat-Sen University Cancer Center Clinical Research 308 Program and Plan Project of Guangdong Esophageal Cancer Research Institute.				Negative likelihood ratio (95% CI)†: 0.39 (not calculable) Identification of T3 disease 26 studies Sensitivity (95% CI): 0.87 (0.85-0.89) Specificity (95% CI): 0.87 (0.84-0.89) Positive likelihood ratio (95% CI)†: 6.69 (not calculable) Negative likelihood ratio (95% CI)†: 0.15 (not calculable) Identification of T4 disease 24 studies Sensitivity (95% CI): 0.84 (0.79-0.89) Specificity (95% CI): 0.96 (0.95-0.97) Positive likelihood ratio (95% CI)†: 21 (not calculable)	All important outcomes considered. Consideration given to benefits, harms and costs.

				Negative likelihood ratio (95% CI)†: 0.17 (not calculable) Identification of T1a disease 12 studies Sensitivity (95% CI): 0.84 (0.80-0.88) Specificity (95% CI): 0.91 (0.88-0.94) Positive likelihood ratio (95% CI)†: 9.33 (not calculable) Negative likelihood ratio (95% CI)†: 0.18 (not calculable) Identification of T1b disease 12 studies Sensitivity (95% CI): 0.83 (0.80-0.86) Specificity (95% CI): 0.89 (0.86-0.92) Positive likelihood ratio (95% CI)†: 7.55 (not calculable)	

				Negative likelihood ratio (95% CI)†: 0.19 (not calculable) Identification of N+ disease 34 studies Sensitivity (95% CI): 0.81 (0.79-0.82) Specificity (95% CI): 0.76 (0.73-0.78) Positive likelihood ratio (95% CI)†: 3.38 (not calculable) Negative likelihood ratio (95% CI)†: 0.25 (not calculable) † calculated by the NGA technical team from data reported in the article. Insufficient data are reported to allow determination of a confidence interval.	
Full citation	Sample size n=97	Tests	Methods	Results	Limitations

<table>
<tr>
<td>Mennigen, R., Tuebergen, D., Koehler, G., Sauerland, C., Senninger, N., Bruewer, M., Endoscopic ultrasound with conventional probe and miniprobe in preoperative staging of esophageal cancer, Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract, 12, 256-262, 2008

Ref Id

489222

Country/ies where the study was carried out

USA

Study type

Retrospective cohort study

Aim of the study

To evaluate the staging accuracy of conventional endoscopic ultrasound (EUS) miniprobe in</td>
<td>Characteristics

Mean±SD age: 64.7±10.7 years
Adenocarcinoma%: 71%
site of tumour: oesophagus (81%) and gastroesophageal junction (19%)

Inclusion Criteria

Histologically diagnosed oesophageal cancer or cancer of the gastrooesophageal junction

Preoperative EUS

Complete tumour resection with two-field lymphadenopathy

Exclusion Criteria

Patients without complete tumour resection

Patients receiving neoadjuvant therapy</td>
<td>All patients had a diagnostic endoscopy immediately prior to EUS.

EUS - Conventional probe was used if the probe can go through the lumen without any dilatation therapy. If the stenosis prohibited the passage of the probe, an EUS mini probe was used. Depth of tumour invasion into five layers indicated the T stage. Lymph nodes was considered positive if larger than 10mm or clearly delineated borders or hypo echoic or internal echo characteristics similar to the primary tumour or</td>
<td>The endoscopist was not blinded to other available clinical information (CT scan, endoscopy</td>
<td>Almost 60% of tumours were not traversable by the conventional EUS probe.

Overall staging results for T stage (n=97) EUS staging (uT) vs Pathohistological staging (pT)
<table>
<tr><td></td><td>pT0</td><td>pT1</td><td>pT2</td><td>pT3</td></tr>
<tr><td>uT1</td><td>2</td><td>13</td><td>1</td><td></td></tr>
<tr><td>uT2</td><td></td><td>6</td><td>16</td><td>12</td></tr>
<tr><td>uT3</td><td></td><td></td><td>5</td><td>42</td></tr>
</table>
Accuracy = 73.2%(63.2 to 81.7), overstating = 13.4%(7.3 to 21.8), understaging= 13.4%(7.3 to 21.8)

Overall staging results for N stage (n=97); EUS staging (uN) vs Pathohistological staging (pN)
<table>
<tr><td></td><td>pN -ve</td><td>pN +ve</td></tr>
<tr><td>uN -ve</td><td>23</td><td>10</td></tr>
<tr><td>uN +ve</td><td>15</td><td>49</td></tr>
</table></td>
<td>QUADAS 2 checklist

Patient selection

Risk of bias:

Was a consecutive or random sample of patients enrolled? Yes

Was a case-control design avoided? Yes

Did the study avoid inappropriate exclusions? Yes

Could the selection of participants have introduced bias? Low risk

Applicability:

Is there concern that the included participants do not match the review question? Low risk

Index tests

Risk of bias:</td>
</tr>
</table>

patients with oesophageal cancer Study dates January 2001 to July 2004 Source of funding Not reported		roundly shape. Postoperative pathohistological staging - N1 and N2 stage were combined as 'N positive' stage		Accuracy=74.2%(64.3 to 82.6), overstaging=15.5%(8.9 to 24.2%), understaging= 10.3%(5.1 to 18.1) Sensitivity= 83.1%(71 - 91.6), specificity = 60.5% (43.4 to 76), PPV=76.6%(64.3 - 86.2) NPV = 69.7%(51.3 to 84.4) If primary surgery was offered if T1-2 and N negative and neoadjuvant therapy if T3-4 and/or N positive in EUS finding, 84.5% of patients would have been assigned to the correct therapy. Of the patients, 8.2% would not have received neoadjuvant therapy despite indication whereas 7.2% would have been overtreated with neoadjvant therapy	Were the index tests interpreted without knowledge of the reference standard? No - presumably retrospective study and the examiner was not blinded to the available clinical information If a threshold was used, was it pre-specified? Unclear Could the conduct or interpretation of the index test have introduced bias? High risk Applicability: Is there concern that the index test, its conduct or interpretation differ from the review question? Low risk Reference standard Risk of bias:

					Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unclear Could the reference standard, its conduct or interpretation have introduced bias? Unclear risk Applicability: Is there concern that the target condition as defined by the reference standard does not match the review question? Low risk Flow and timing Risk of bias: Was there an appropriate interval

					between index tests and reference standard? Unclear Did all participants receive a reference standard? Yes Did participants receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the participant flow have introduced bias? Unclear risk Other information
Full citation Mitsunaga, A., Hamano, T., Teramoto, H., Tagata, T., Shirato, I., Shirato, M., Nishino, T., A new method of endoscopic ultrasonography for determining the depth of early gastric cancer,	Sample size n=92 (Of 97 consecutive eligible patients, five were excluded: four for the presence of cystic lesions and one for muscularis propria invasion.) Characteristics	Tests Mucosal and submucosal thickness measured by endoscopic ultrasound (EUS) was compared	Methods Submucosal thickness of 2.2 mm threshold was used to distinguish mucosal-submucosal	Results With the predermined cutoff in EUS, Sensitivity 93.2%, Specificity 94.7% accuracy 98.6%	Limitations QUADAS 2 checklist Patient selection Risk of bias: Was a consecutive or random sample

Gastrointestinal EndoscopyGastrointest Endosc, 73, AB168, 2011 Ref Id 489237 Country/ies where the study was carried out Japan Study type Prospective cohort study Aim of the study To establish a new diagnostic method for more accurate differential diagnosis by measurement of lesion depth using endoscopic ultrasonography as a preoperative diagnostic modality Study dates January 2007 to August 2010 Source of funding Not reported	Mean age: 68.8 years Male: 70/97 (72%) Inclusion Criteria Suspected early gastric cancer no indication of advanced cancer Exclusion Criteria	with pathological depth	(M-SM1) cancers from submucosal 2/3 (SM2/3) cancers.		of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes Could the selection of participants have introduced bias? Low risk Applicability: Is there concern that the included participants do not match the review question? Low risk Index tests Risk of bias: Were the index tests interpreted without knowledge of the reference standard? Yes If a threshold was used, was it pre-specified? Yes

					Could the conduct or interpretation of the index test have introduced bias? Low risk Applicability: Is there concern that the index test, its conduct or interpretation differ from the review question? Low risk Reference standard Risk of bias: Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unclear Could the reference standard, its conduct or interpretation have

					introduced bias? Low risk Applicability: Is there concern that the target condition as defined by the reference standard does not match the review question? Low risk Flow and timing Risk of bias: Was there an appropriate interval between index tests and reference standard? Unclear Did all participants receive a reference standard? Yes Did participants receive the same reference standard? Yes Were all patients included in the analysis? Yes

					Could the participant flow have introduced bias? Low risk Other information
Full citation Mocellin, S., Pasquali, S., Diagnostic accuracy of endoscopic ultrasonography (EUS) for the preoperative locoregional staging of primary gastric cancer, Cochrane Database of Systematic ReviewsCochrane Database Syst Rev, 2015 Ref Id 488126 Country/ies where the study was carried out Italy Study type Systematic review	Sample size 66 studies included in the review. Total number of participants: n = 7747 Characteristics Number of participants in each study, mean (range): 117 (14 to 930) Retrospective studies: 50/66 (76%) Gastric carcinoma: 60/66 (91%) Cancer arising in the cardia: 6/66 (9%) Radial array endoscopic ultrasound: 55/58 (95%) Inclusion Criteria	Tests Endoscopic ultrasound.	Methods The results of EUS were compared to pathological evaluation of tumour stage and nodal metastasis. To identify participants who would benefit most from pre-operative neoadjuvant chemo/radio therapy, EUS was assessed for its ability to distinguish	Results Ability to distinguish T1-2 from T3-4 tumours 50 studies included in meta-analysis. N = 4397 participants. Pooled sensitivity (95% CI): 0.86 (0.81 to 0.90) Pooled specificity (95% CI): 0.90 (0.87 to 0.93) Pooled positive likelihood ratio (95% CI): 8.9 (6.8 to 11.6) Pooled negative likelihood ratio (95% CI): 0.16 (0.12 to 0.22) Ability to distinguish T1 from T2 tumours	Limitations Other information The review addresses an appropriate and clearly focused question that is relevant to the review question: Yes The review collects the type of studies you consider relevant to the guidance review question: Yes The literature search is sufficiently rigorous to identify all the relevant studies: Yes

Aim of the study To systematically review the evidence on diagnostic accuracy of endoscopic ultrasound in the preoperative staging of gastric cancer. Study dates Publication between 1988 and January 2015. Source of funding None reported.	Minimum sample size of 10 participants with histologically proven primary carcinoma of the stomach. Evaluation of endoscopic ultrasonograpy (EUS) compared with histopathology of primary tumour (T stage) and regional lymph nodes (N stage). Sufficient data to construct a 2x2 contingency table such that cells could be labeled as true positive, false positive, true negative and false negative. Exclusion Criteria Studies with data overlapping with included studies (i.e. from the same study group, institution and period of inclusion) Studies reporting on the use of EUS before pre-operative chemotherapy and/or radiotherapy.		superficial (T1-2) from deep (T3-4) tumours. Participants with T1-2 tumours were designated positive, and those with T3-4 tumours were designated negative. To assess the ability to differentiate superficial tumours amenable to endoscopic resection (T1), the diagnostic accuracy of EUS in distinguishin g T1 from T2 tumours was assessed. Here,	46 studies included in meta-analysis. N = 2742 participants. Pooled sensitivity (95% CI): 0.85 (0.78 to 0.91) Pooled specificity (95% CI): 0.90 (0.85 to 0.93) Pooled positive likelihood ratio (95% CI): 8.5 (5.9 to 12.3) Pooled negative likelihood ratio (95% CI): 0.17 (0.12 to 0.24) Ability to distinguish T1a from T1b tumours 20 studies included in meta-analysis. N = 3321 participants. Pooled sensitivity (95% CI): 0.87 (0.81 to 0.92) Pooled specificity (95% CI): 0.75 (0.62 to 0.84) Pooled positive likelihood ratio (95% CI): 3.4 (2.3 to 5.0)	Study quality is assessed and reported: Yes An adequate description of the methodology used is included, and the methods used are appropriate to the question: Yes Are the results internally valid? Yes Are the results externally valid? Yes

			participants with T1 disease were deemed positive, and T2 deemed negative. Finally, within T1 tumours only, the ability to differentiate between T1a and T1b tumours was assessed, to identify those who benefit most from endoscopic resection (T1a). Here, T1a tumours were designated positive, and T1b designated negative.	Pooled negative likelihood ratio (95% CI): 0.17 (0.12 to 0.24) Ability to distinguish N+ from N- tumours 44 studies included in meta-analysis. N = 3573 participants. Pooled sensitivity (95% CI): 0.83 (0.79 to 0.87) Pooled specificity (95% CI): 0.67 (0.61 to 0.72) Pooled positive likelihood ratio (95% CI): 2.5 (2.1 to 2.9) Pooled negative likelihood ratio (95% CI): 0.25 (0.20 to 0.31)	

<table>
<tr>
<td>Full citation

Ramos, R. F., Scalon, F. M., Scalon, M. M., Dias, D. I., Staging laparoscopy in gastric cancer to detect peritoneal metastases: A systematic review and meta-analysis, European Journal of Surgical OncologyEur J Surg Oncol, 42, 1315-21, 2016

Ref Id

492728

Country/ies where the study was carried out

Brazil

Study type

Systematic review

Aim of the study

To evaluate the diagnostic accuracy of laparoscopy for staging of gastric cancer

Study dates</td>
<td>Sample size

5 studies included with a total of 240 patients (n=240)

Characteristics

Average resectability after laparoscopy = 68.75%

Inclusion Criteria

Studies of diagnostic test and accuracy in laparoscopic staging of gastric cancer confirmed by histopathologic examination for possible peritoneal metastases

Exclusion Criteria

studies with no standardised technique of staging laparoscopy, patients with early gastric cancer, complications (stenosis, bleeding) and patients with tumour in the gastrooesophageal junction

Studies without sufficient data to calculate the sensitivity and specificity</td>
<td>Tests

Laparoscopy was compared to histopathological examination as a standarised reference</td>
<td>Methods

Quality of the studies were assessed by QUADAS 2 by 2 independent reviewers. I2 of >50% was considered inconsistency.</td>
<td>Results
<table><tr><th>Study</th><th>TP</th><th>FP</th><th>FN</th><th>TN</th><th>R</th></tr><tr><td>Asencio 1997 (n=60)</td><td>16</td><td>0</td><td>2</td><td>42</td><td>58</td></tr><tr><td>Lavonius 2002 (n=47)</td><td>19</td><td>0</td><td>3</td><td>25</td><td>N/A</td></tr><tr><td>Munteanu 2009 (n=45)</td><td>14</td><td>0</td><td>2</td><td>29</td><td>62</td></tr><tr><td>Stell 1996 (n=65)</td><td>9</td><td>0</td><td>4</td><td>52</td><td>81</td></tr><tr><td>Tsuchida 2011 (n=23)</td><td>8</td><td>0</td><td>1</td><td>14</td><td>74</td></tr></table>
n=total number of patients: TP=True Positive; FP=False Positive; FN=False Negative; TN=True Negative; R=Resectability rate

Sensitivity: 84.6% (95%CI 0.747 to 0.918); p<0.64, I2=0 Specificity: 100% (95% CI 0.977 to 1.00; p=1.0, I2=0 Global accuracy (diagnostic odds ration): 291.31 with</td>
<td>Limitations

ROBIS tool for bias risk assessment in systematic reviews:

Study Eligibility Criteria

Did the review adhere to pre-defined objectives and eligibility criteria? Y

Were the eligibility criteria appropriate for the review question? Y

Were the eligibility criteria unambiguous? PN

Were all the restrictions on eligibility criteria based on study characteristics appropriate? Y

Were any restrictions in eligibility criteria</td>
</tr>
</table>

Not reported Source of funding None				PPV=0.197 and NPV=49.71 (AUC = 98%) No shoulder arm in ROC with Spearman correlation of 0.1	based on sources of information available? Y Concern regarding specification of study eligibility criteria: LOW Identification and Selection of Studies Did the search include an appropriate range of databases/electronic sources for published and unpublished reports? Y Were the methods additional to database searching used to identify relevant reports? Y Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible? PY

					Were restrictions based on date, publication format or language appropriate? PY Were efforts made to minimise error in selection of studies? Y Concern regarding methods used to identify or select studies: LOW Data Collection and Study Appraisal Were efforts made to minimise error in data collection? Y were sufficient study characteristics available? Y Were all relevant study results collected for use and synthesis? Y Was risk of bias formally assessed using appropriate criteria? PY

					Were efforts made to minimise error in risk of bias assessment? Y Concern: LOW Synthesis and Findings Did the synthesis include all studies it should? Y Were all pre-defined analyses reported and departures explained? Y Was the synthesis appropriate given the nature and similarity in the research questions? Y Was heterogeneity minimal or addressed? Y Were the findings robust as demonstrated though funnel plot or sensitivity analysis? Y

					Were biases in primary studies minimal or addressed in the synthesis? PY Concern= LOW Risk of bias in the review Did the interpretation of findings address all the concerns identifies in 1-4? Y Was the relevance of identified studies to the review's research question appropriately considered? Y Did the reviewers avoid emphasizing results on the basis of their statistical significance? PY Risk of bias= HIGH- quality assessment unclear with results not reported

<table>
<tr><td></td><td></td><td></td><td></td><td></td><td>Other information</td></tr>
<tr>
<td>Full citation

Roedl, J. B., Blake, M. A., Holalkere, N. S., Mueller, P. R., Colen, R. R., Harisinghani, M. G., Lymph node staging in esophageal adenocarcinoma with PET-CT based on a visual analysis and based on metabolic parameters, Abdominal ImagingAbdom Imaging, 34, 610-617, 2009

Ref Id

492756

Country/ies where the study was carried out

USA(ii)

Study type

Retrospective cohort study

Aim of the study</td>
<td>Sample size

N = 81

Characteristics
<table>
<tr><td>Characteristics</td><td>N0
n = 26</td><td>N1
n = 55</td></tr>
<tr><td>Age, years (SD)</td><td>68.4 (10.5)</td><td>66.3 (9.9)</td></tr>
<tr><td>Sex, M:F, n (%)</td><td>21:5 (81:19)</td><td>43:12 (67:33)</td></tr>
<tr><td>Grade of tumour, n (%)</td><td></td><td></td></tr>
<tr><td>Well differentiated</td><td>4 (15)</td><td>7 (13)</td></tr>
<tr><td>Moderately differentiated</td><td>19 (73)</td><td>39 (71)</td></tr>
<tr><td>Poorly differentiated</td><td>3 (12)</td><td>9 (16)</td></tr>
<tr><td>Location of tumour, n (%)</td><td></td><td></td></tr>
<tr><td>Proximal third</td><td>0</td><td>1 (2)</td></tr>
<tr><td>Middle third</td><td>7 (27)</td><td>13 (24)</td></tr>
<tr><td>Distal third</td><td>19 (73)</td><td>41 (74)</td></tr>
</table>
</td>
<td>Tests

Scans were obtained with a hybrid 3D PET-CT system.

2 radiologists (each with 4 years of experience in PET-CT interpretation) were blinded to the clinical data and performed visual interpretation independently.

FDG uptake in a presumed lymph node that was focally prominent compared with surrounding tissues was considered positive for malignancy.</td>
<td>Methods

Reference standard was pathology from resected surgical specimens for those participants who underwent primary surgery. Endoscopic ultrasound with fine needle aspiration was used as the reference standard for 42 patients who underwent neoadjuvant chemoradiot</td>
<td>Results

Detection of N1 (lymph node positive) disease versus N0

Visual interpretation only

2x2 table constructed from data reported in the article
<table>
<tr><td></td><td>pN1</td><td>pN0</td><td>Total</td></tr>
<tr><td>PET-CT N1</td><td>42</td><td>1</td><td>43</td></tr>
<tr><td>PET-CT N0</td><td>13</td><td>25</td><td>38</td></tr>
<tr><td></td><td>55</td><td>26</td><td>81</td></tr>
</table>
Sensitivity (95% CI)†: 0.76 (0.63-0.87)

Specificity (95% CI)†: 0.96 (0.80-1.0)

Positive likelihood ratio‡ (95% CI): 19.85 (2.89-136.45)

Negative likelihood ratio‡ (95% CI): 0.25 (0.15-0.40)</td>
<td>Limitations

Subset of participants found to have FDG avid tumours.

Other information

QUADAS 2 checklist

Patient selection

Risk of bias:

Was a consecutive or random sample of patients enrolled? No

Was a case-control design avoided? Yes

Did the study avoid inappropriate exclusions? Unclear - only those with FDG avid tumours were included due</td>
</tr>
</table>

<table>
<tr>
<td>To investigate the use of PET-CT in the assessment of lymph node status for participants with oesophageal cancer.

Study dates

Not reported.

Source of funding

Not reported.</td>
<td>Inclusion Criteria

Oesophageal lesions with increased FDG uptake in pre-treatment PET-CT images.

Exclusion Criteria

Diabetes mellitus.

Previous treatment (chemotherapy/ radiotherapy/ endoscopic laser therapy) before PET-CT

Previous primary or secondary malignancy.</td>
<td>In addition, tumour length parameters were assessed for thsi ability to diagnose lymph node metastasis.</td>
<td>herapy before surgery.</td>
<td>Positive predictive value‡ (95% CI): 98% (86-100)

Negative predictive value‡ (95% CI): 66% (54-76)

Quantitative analysis with tumour diameter, threshold >25.5mm

2x2 table constructed from data reported in the article
<table>
<tr><td></td><td>pN1</td><td>pN0</td><td>Total</td></tr>
<tr><td>PET-CT N1</td><td>48</td><td>4</td><td>52</td></tr>
<tr><td>PET-CT N0</td><td>7</td><td>22</td><td>29</td></tr>
<tr><td></td><td>55</td><td>26</td><td>81</td></tr>
</table>
Sensitivity (95% CI)†: 0.87 (0.75-0.95)

Specificity (95% CI)†: 0.85 (0.65-0.96)

Positive likelihood ratio‡ (95% CI): 5.67 (2.29-14.05)

Negative likelihood ratio‡ (95% CI): 0.15 (0.07-0.31)</td>
<td>to the nature of the study.

Could the selection of participants have introduced bias? Unclear

Applicability:

Is there concern that the included participants do not match the review question? Some concern - participants are likely to represent only a subset of "typical" oesophageal cancer patients therefore sensitivity/specificity may be different in the full population.

Index tests

Risk of bias:

Were the index tests interpreted without knowledge of the reference standard? Yes</td>
</tr>
</table>

Positive predictive value‡ (95% CI): 92% (83-97)

Negative predictive value‡ (95% CI): 76% (61-86)

Combined visual interpretation and quantitative analysis with tumour diameter, threshold >37.8mm

2x2 table constructed from data reported in the article

	pN1	pN0	Total
PET-CT N1	52	1	53
PET-CT N0	3	25	28
	55	26	81

Positive nodal metastasis identified as FDG avid nodes on visual inspection and/or a tumour diameter of ≥37.8mm

Sensitivity (95% CI)†: 0.95 (0.85-0.99)

Specificity (95% CI)†: 0.96 (0.80-1.0)

If a threshold was used, was it pre-specified? No

Could the conduct or interpretation of the index test have introduced bias? Unclear

Applicability:

Is there concern that the index test, its conduct or interpretation differ from the review question? Quantitative and qualitative interpretation of PET-CT was used.

Reference standard

Risk of bias:

Is the reference standard likely to correctly classify the target condition? Yes

Were the reference standard results interpreted without

				Positive likelihood ratio‡ (95% CI): 24.58 (3.59-168.17) Negative likelihood ratio‡ (95% CI): 0.06 (0.02-0.17) Positive predictive value‡ (95% CI): 98% (88-100) Negative predictive value‡ (95% CI): 89% (73-96) † 95% confidence interval calculated by the NGA technical team from data reported, using https://www.medcalc.org/calc/diagnostic_test.php ‡ calculated by the NGA technical team from data reported in the article, using https://www.medcalc.org/calc/diagnostic_test.php	knowledge of the results of the index test? Unclear Could the reference standard, its conduct or interpretation have introduced bias? Low risk Applicability: Is there concern that the target condition as defined by the reference standard does not match the review question? Low risk Flow and timing Risk of bias: Was there an appropriate interval between index tests and reference standard? Unclear Did all participants receive a reference standard? Yes Did participants receive the same

<table>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>reference standard? No - FNA was used for those undergoing neoadjuvant treatment.

Were all patients included in the analysis? Yes

Could the participant flow have introduced bias? Low risk</td>
</tr>
<tr>
<td>Full citation

Roedl, J. B., Prabhakar, H. B., Mueller, P. R., Colen, R. R., Blake, M. A., Prediction of Metastatic Disease and Survival in Patients with Gastric and Gastroesophageal Junction Tumors. The Incremental Value of PET-CT over PET and the Clinical Role of Primary Tumor Volume Measurements, Academic Radiology, 16, 218-226, 2009</td>
<td>Sample size

N = 59

Characteristics
<table>
<tr><th>Characteristics</th><th>M0 disease

n = 34</th><th>M1 disease

n = 25</th></tr>
<tr><td>Sex, M:F</td><td>26:8</td><td>16:9</td></tr>
<tr><td>Age, years (SD)</td><td>65.1 (12.6)</td><td>66.1 (8.6)</td></tr>
</table>
Inclusion Criteria</td>
<td>Tests

PET-CT images were acquired with a coupled PET-CT device.

Distant metastasis was first evaluated by visual inspection of the images by two experienced nuclear medicine physicians, who performed the analysis independently.</td>
<td>Methods

All suspected sites of metastasis were verified by MRI, biopsy or post surgical pathology within 3 weeks of the PET-CT scan, to provide the</td>
<td>Results

Identification of M1 disease

Visual interpretation only

2x2 table constructed by the NGA technical from data reported.
<table>
<tr><th></th><th>M1</th><th>M0</th><th></th></tr>
<tr><td>PET-CT M1</td><td>20</td><td>1</td><td>21</td></tr>
<tr><td>PET-CT M0</td><td>5</td><td>33</td><td>38</td></tr>
</table>
</td>
<td>Limitations

Other information

QUADAS 2 checklist

Patient selection

Risk of bias:

Was a consecutive or random sample of patients enrolled? Unclear

Was a case-control design avoided? Yes</td>
</tr>
</table>

<table>
<tr>
<td>Ref Id

492757

Country/ies where the study was carried out

USA(i)

Study type

Retrospective cohort study

Aim of the study

To assess whether tumour volume is associated with tumour stage, and can help to predict metastatic disease with PET-CT.

Study dates

Not reported.

Source of funding

Not reported.</td>
<td>Histopathologically proven adenocarcioma of the gastroesophageal junction

Pre-treatment PET-CT

Exclusion Criteria

Not reported.</td>
<td>Images were then interpreted by a combined team of nuclear medicine physicians and radiologists.

Primary tumour volume was then measured by two of the report authors, and the mean values were used for analysis.</td>
<td>reference standard.

Accuracy of visual interpretation alone was assessed, as was quantitative assessment of tumour volume as a predictive factor for identifying metastasis.</td>
<td>
<table>
<tr><td></td><td>25</td><td>34</td><td>59</td></tr>
</table>
Sensitivity (95% CI)†: 0.80 (0.59-0.93)

Specificity (95% CI)†: 0.97 (0.85-1.00)

Positive likelihood ratio‡ (95% CI): 27.20 (3.91-189.45)

Negative likelihood ratio‡ (95% CI): 0.21 (0.09-0.45)

Positive predictive value‡ (95% CI): 95% (74-99)

Negative predictive value‡ (95% CI): 87% (75-93)

Quantitative analysis of tumour volume (threshold >39ml)

2x2 table constructed by the NGA technical from data reported.
<table>
<tr><td></td><td>M1</td><td>M0</td><td></td></tr>
<tr><td>PET-CT M1</td><td>24</td><td>5</td><td>29</td></tr>
</table>
</td>
<td>Did the study avoid inappropriate exclusions? Yes

Could the selection of participants have introduced bias? Low risk

Applicability:

Is there concern that the included participants do not match the review question? Low risk

Index tests

Risk of bias:

Were the index tests interpreted without knowledge of the reference standard? Yes

If a threshold was used, was it pre-specified? No

Could the conduct or interpretation of the index test have introduced bias? Low risk</td>
</tr>
</table>

				<table><tr><td>PET-CT M0</td><td>1</td><td>29</td><td>30</td></tr><tr><td></td><td>25</td><td>34</td><td>59</td></tr></table> Sensitivity (95% CI)†: 0.96 (0.80-1.00) Specificity (95% CI)†: 0.85 (0.69-0.95) Positive likelihood ratio‡ (95% CI): 6.53 (2.89-14.73) Negative likelihood ratio‡ (95% CI): 0.05 (0.01-0.32) Positive predictive value‡ (95% CI): 83% (68-92) Negative predictive value‡ (95% CI): 97% (81-100) Combination of visual interpretation and quantitative analysis of tumour volume (visual identification of metastasis and/or tumour volume >59ml) 2x2 table constructed by the NGA technical from data reported. <table><tr><td></td><td>M1</td><td>M0</td><td></td></tr></table>	Applicability: Is there concern that the index test, its conduct or interpretation differ from the review question? Low risk Reference standard Risk of bias: Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unclear Could the reference standard, its conduct or interpretation have introduced bias? Low risk Applicability:

				<table><tr><td>PET-CT M1</td><td>24</td><td>2</td><td>26</td></tr><tr><td>PET-CT M0</td><td>1</td><td>32</td><td>33</td></tr><tr><td></td><td>25</td><td>34</td><td>59</td></tr></table> Sensitivity (95% CI)†: 0.96 (0.80-1.00) Specificity (95% CI)†: 0.94 (0.80-0.99) Positive likelihood ratio‡ (95% CI): 16.32 (4.24-62.76) Negative likelihood ratio‡ (95% CI): 0.04 (0.01-0.29) Positive predictive value‡ (95% CI): 92% (76-98) Negative predictive value‡ (95% CI): 97% (82-100) † 95% confidence interval calculated by the NGA technical team from data reported in the article ‡ calculated by the NGA technical team from data reported in the article, using https://www.medcalc.org/calc/diagnostic_test.php	Is there concern that the target condition as defined by the reference standard does not match the review question? No Flow and timing Risk of bias: Was there an appropriate interval between index tests and reference standard? Yes Did all participants receive a reference standard? Yes Did participants receive the same reference standard? No - the reference depended on the site of metastasis. Were all patients included in the analysis? Yes Could the participant flow

<table>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>have introduced bias? Low risk</td>
</tr>
<tr>
<td>Full citation

Roedl, J. B., Sahani, D. V., Colen, R. R., Fischman, A. J., Mueller, P. R., Blake, M. A., Tumour length measured on PET-CT predicts the most appropriate stage-dependent therapeutic approach in oesophageal cancer, European RadiologyEur Radiol, 18, 2833-40, 2008

Ref Id

492758

Country/ies where the study was carried out

USA

Study type

Retrospective cohort study

Aim of the study</td>
<td>Sample size

N = 82

(n = 29 additional participants with benign pathology)

Characteristics
<table>
<tr><th>Characteristics</th><th>Curable disease

n = 52</th><th>Palliative disease

n = 30</th></tr>
<tr><td>Sex, F:M</td><td>13:39 (25%: 75%)</td><td>8:22 (27%: 73%)</td></tr>
<tr><td>Age, years, mean (SD)</td><td>68.2 (19.5)</td><td>66.1 (9.2)</td></tr>
<tr><td>Tumour type</td><td></td><td></td></tr>
<tr><td>Dysplasia</td><td>7 (13%)</td><td>0</td></tr>
<tr><td>Squamous</td><td>25 (48%)</td><td>19 (63%)</td></tr>
</table></td>
<td>Tests

PET-CT

All participants were asked to fast for 6 hours prior to imaging. Imaging started 60 minutes after IV injection of 555MBq of 18F-FDG and was performed using an integrated PET-CT system.

Attenuation corrected PET data were iteratively reconstructed and co-registered with the CT data.</td>
<td>Methods

Tumour staging and assignment to a treatment group (surgery with curative intent or palliation) were performed based on a visual analysis of PET images with a side-by side review of the CT. This analysis was done by a team of experience nuclear medicine physicians. Fused PET-</td>
<td>Results

Differentiation of palliative versus curable stages of oesophageal carcinoma (T1-T3NxM0, versus T4NxM0 or TxNxM1)

Standardised uptake value, threshold 7.4

2x2 table*
<table>
<tr><th></th><th>Disease positive

(palliative stage)</th><th>Disease negativ

(curabl stage)</th></tr>
<tr><td>Test positive</td><td>25</td><td>13</td></tr>
<tr><td>Test negative</td><td>5</td><td>39</td></tr>
<tr><td></td><td>30</td><td>52</td></tr>
</table>
Sensitivity: 83% (95% CI† 65.28 to 94.36)</td>
<td>Limitations

Participants deemed to have inoperable disease included PET-CT findings as part of the reference standard.

Other information

QUADAS 2 checklist

Patient selection

Risk of bias:

Was a consecutive or random sample of patients enrolled? Unclear

Was a case-control design avoided? Yes

Did the study avoid inappropriate exclusions? Yes</td>
</tr>
</table>

<table>
<tr>
<td>To assess the accuracy of PET-CT (and CT) in determining the appropriate management in oesophageal cancer (curative resection versus palliation).

Study dates

Not reported/

Source of funding

Not reported.</td>
<td>
<table>
<tr><td>Adenocarcinoma</td><td>20 (39%)</td><td>11 (37%)</td></tr>
<tr><td>Location</td><td></td><td></td></tr>
<tr><td>Proximal</td><td>11 (21%)</td><td>6 (20%)</td></tr>
<tr><td>Middle</td><td>21 (40%)</td><td>12 (40%)</td></tr>
<tr><td>Distal</td><td>20 (39%)</td><td>12 (40%)</td></tr>
<tr><td>GE junction</td><td>0</td><td>0</td></tr>
</table>
Inclusion Criteria

Patients with oesophageal lesions who had undergone pre-operative PET-CT imaging.

Exclusion Criteria

Diabetes melllitus

Secondary or previous malignant disease

Previous anticancer therapy, including surgery, chemo- or radiotherapy.
</td>
<td></td>
<td>CT images were then interpreted by a combined team of nuclear medicine physicians and radiologists.

In addition, quantitative tumour length parameters were measured by two readers independently. Tumour length and standardised uptake value (SUV) were assessed on PET-CT. A length-SUV index was then calculated by</td>
<td>Specificity: 75% (95% CI† 61.05 to 85.97)

Positive likelihood ratio‡: 3.33 (95% CI 2.03 to 5.48)

Negative likelihood ratio‡: 0.22 (95% CI 0.10 to 0.50)

Positive predictive value‡: 65.79% (95% CI 53.91 to 75.97)

Negative predictive value‡: 88.64% (95% CI 77.53 to 94.63)

Tumour length, threshold 69.0mm

2x2 table*
<table>
<tr><td></td><td>Disease positive (palliative stage)</td><td>Disease negativ (curabl stage)</td></tr>
<tr><td>Test positive</td><td>27</td><td>9</td></tr>
<tr><td>Test negative</td><td>3</td><td>43</td></tr>
</table>
</td>
<td>Could the selection of participants have introduced bias? Low risk

Applicability:

Is there concern that the included participants do not match the review question? No

Index tests

Risk of bias:

Were the index tests interpreted without knowledge of the reference standard? Yes

If a threshold was used, was it pre-specified? No

Could the conduct or interpretation of the index test have introduced bias? High risk - threshold for SUV and tumour length was identified during the study.</td>
</tr>
</table>

			multiplying the SUV by the tumour length. The diagnostic accuracy of visual analysis alone (interpretation by radiologists and nuclear medicine physicians), quantitative assessment with the tumour-SUV index, and the combination of these two measures were calculated. Reference standard All participants	<table><tr><td></td><td>30</td><td>52</td><td>82</td></tr></table> Sensitivity: 90% (95% CI† 73.47 to 97.89) Specificity: 83% (95% CI† 69.67 to 91.77) Positive likelihood ratio‡: 5.20 (95% CI 2.84 to 9.53) Negative likelihood ratio‡: 0.12 (95% CI 0.04 to 0.36) Positive predictive value‡: 75.00% (95% CI 62.07 to 84.61) Negative predictive value‡: 93.48% (95% CI 82.95 to 97.69) SUV Index (Standardised uptake value x length, threshold 505) 2x2 table* <table><tr><td></td><td>Disease positive (palliative stage)</td><td>Disease negativ (curabl stage)</td></tr></table>	Applicability: Is there concern that the index test, its conduct or interpretation differ from the review question? No Reference standard Risk of bias Is the reference standard likely to correctly classify the target condition? Unclear. Patients not suitable for surgery only underwent pre-operative staging. Were the reference standard results interpreted without knowledge of the results of the index test? Unclear Could the reference standard, its conduct or interpretation have

			underwent endoscopic ultrasound, PET-CT and contrast enhanced CT for pre-therapy staging. The reference standard for assessment of tumour wall invasion (T stage) and nodal disease (N stage) was EUS with fine needle aspiration and/or histology after surgery. Patients with suspected pulmonary, hepatic or adrenal metastases underwent	<table><tr><td>Test positive</td><td>28</td><td>5</td><td>33</td></tr><tr><td>Test negative</td><td>2</td><td>47</td><td>49</td></tr><tr><td></td><td>30</td><td>52</td><td>82</td></tr></table> Sensitivity: 93% (95% CI† 77.93 to 99.18) Specificity: 90% (95% CI† 78.97 to 96.80) Positive likelihood ratio‡: 9.71 (95% CI 4.20 to 22.46) Negative likelihood ratio‡: 0.07 (95% CI 0.02 to 0.28) Positive predictive value‡: 84.85% (95% CI 70.76 to 92.83) Negative predictive value‡: 95.92% (95% CI 86.00 to 98.90) Visual analysis 2x2 table*	introduced bias? Low risk Applicability: Is there concern that the target condition as defined by the reference standard does not match the review question? No Flow and timing Risk of bias: Was there an appropriate interval between index tests and reference standard? Yes Did all participants receive a reference standard? Yes Did participants receive the same reference standard? No Were all patients included in the analysis? Yes

			definitive biopsy to prove or disprove distant metastatic stage. If bone or brain metastases were suspected, MRI was considered the standard reference. Participants who were T1N0M0 after pre-therapy staging underwent surgery, and histopathological results were used as the reference standard for staging. For those participants	<table><tr><td></td><td>Disease positive (palliative stage)</td><td>Disease negative (curable stage)</td><td></td><td></td></tr><tr><td>Test positive</td><td>23</td><td>2</td><td></td><td>25</td></tr><tr><td>Test negative</td><td>7</td><td>50</td><td></td><td>57</td></tr><tr><td></td><td>30</td><td>52</td><td></td><td>82</td></tr></table> Sensitivity: 77% (95% CI† 57.72 to 90.07) Specificity: 96% (95% CI† 86.79 to 99.53) Positive likelihood ratio‡: 19.93 (95% CI 5.05 to 78.70) Negative likelihood ratio‡: 0.24 (95% CI 0.13 to 0.47) Positive predictive value‡: 92.00% (95% CI 74.44 to 97.85) Negative predictive value‡: 87.72% (95% CI 78.84 to 93.21)	Could the participant flow have introduced bias? Low risk.

<table>
<tr>
<td></td>
<td></td>
<td></td>
<td>who did not undergo surgery (T4 and/or M1 disease) or who underwent neoadjuvant chemoradiotherapy followed by surgery (N1 or >T1), pre-therapy staging was considered the reference standard.</td>
<td>Visual analysis plus SUV index, threshold 505

2x2 table*
<table>
<tr><td></td><td>Disease positive

(palliative stage)</td><td>Disease negativ

(curabl stage)</td></tr>
<tr><td>Test positive</td><td>28</td><td>2</td></tr>
<tr><td>Test negative</td><td>2</td><td>50</td></tr>
<tr><td></td><td>30</td><td>52</td></tr>
</table>
Sensitivity: 93% (95% CI† 77.93 to 99.18)

Specificity: 96% (95% CI† 86.79 to 99.53)

Positive likelihood ratio‡: 24.27 (95% CI 6.21 to 94.77)

Negative likelihood ratio‡: 0.07 (95% CI 0.02 to 0.26)

Positive predictive value‡: 93.33% (95% CI 78.19 to 98.20)</td>
<td></td>
</tr>
</table>

Negative predictive value‡: 96.15% (95% CI 86.75 to 98.96)

Differentiation of T4 versus lower T stages

Standardised uptake value, threshold 7.7

2x2 table*

	Disease positive (T4)	Disease negative (Dysplas or T1-3)
Test positive	19	13
Test negative	3	47
	22	60

Sensitivity: 86% (95% CI† 65.09 to 97.09)

Specificity: 78% (95% CI† 65.80 to 87.93)

Positive likelihood ratio‡: 3.99 (95% CI 2.40 to 6.63)

Negative likelihood ratio‡: 0.17 (95% CI 0.06 to 0.50)

Positive predictive value‡: 59.38% (95% CI 46.77 to 70.86)

Negative predictive value‡: 94.00% (95% CI 84.44 to 97.84)

Tumour length, threshold 75.0mm

2x2 table*

	Disease positive (T4)	Disease negative (Dysplas or T1-3)
Test positive	19	7
Test negative	3	53
	22	60

Sensitivity: 86% (95% CI† 65.09 to 97.09)

Specificity: 88% (95% CI† 77.43 to 95.18)

Positive likelihood ratio‡: 7.40 (95% CI 3.62 to 15.14)

Negative likelihood ratio‡: 0.15 (95% CI 0.05 to 0.44)

Positive predictive value‡: 73.08% (95% CI 57.02 to 84.74)

Negative predictive value‡: 94.64% (95% CI 86.01 to 98.07)

SUV index (standardised uptake value x tumour length, threshold 600)

2x2 table*

	Disease positive (T4)	Disease negative (Dysplas or T1-3)
Test positive	22	8

Test negative	0	52		52			
	22	60		82			

Sensitivity: 100% (95% CI† 84.56 to 100.00)

Specificity: 87% (95% CI† 75.41 to 94.06)

Positive likelihood ratio‡: 7.50 (95% CI 3.93 to 14.30)

Negative likelihood ratio‡: 0.00 (95% CI not calculable)

Positive predictive value‡: 73.33% (95% CI 59.06 to 83.98)

Negative predictive value‡: 100% (95% CI not calculable)

Visual analysis

2x2 table*

	Disease positive (T4)	Disease negative (Dysplas or T1-3)

				<table><tr><td>Test positive</td><td>17</td><td>5</td><td></td><td>22</td></tr><tr><td>Test negative</td><td>5</td><td>55</td><td></td><td>60</td></tr><tr><td></td><td>22</td><td>60</td><td></td><td>82</td></tr></table> Sensitivity: 77% (95% CI† 54.63 to 92.18) Specificity: 92% (95% CI† 81.61 to 97.24) Positive likelihood ratio‡: 9.27 (95% CI 3.89 to 22.12) Negative likelihood ratio‡: 0.25 (95% CI 0.11 to 0.54) Positive predictive value‡: 77.27% (95% CI 58.77 to 89.02) Negative predictive value‡: 91.67% (95% 83.53 to 95.98) Visual analysis plus SUV index, threshold 600 2x2 table*	

	Disease positive (T4)	Disease negative (Dysplasia or T1-3)		
Test positive	22	5		27
Test negative	0	55		55
	22	60		82

Sensitivity: 100% (95% CI† 84.56 to 100.00)

Specificity: 92% (95% CI† 81.61 to 97.24)

Positive likelihood ratio‡: 12.00 (95% CI 5.18 to 27.77)

Negative likelihood ratio‡: 0 (95% CI not calculable)

Positive predictive value‡: 81.48% (95% CI 65.53 to 91.06)

Negative predictive value‡: 100.00% (95% not calculable)

<table>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>* 2x2 table reconstructed by the NGA technical team from data reported in the article

† 95% confidence interval calculated by the NGA technical team using https://www.medcalc.org/calc/diagnostic_test.php

‡ calculated by the NGA technical team using https://www.medcalc.org/calc/diagnostic_test.php</td>
<td></td>
</tr>
<tr>
<td>Full citation

Shen, H., Li, X., Meng, L., Ni, Y., Wang, G., Dong, W., Du, J., Confirmation of histology of PET positive lymph nodes recovered by hand-video-assisted thoracoscopy surgery, GeneGene, 509, 173-7, 2012

Ref Id

492857

Country/ies where the study was carried out</td>
<td>Sample size

N = 80

Characteristics

n = 52 males

n = 28 females

Age range 43-85 years, mean 61.5 years (SD 9.47).

Inclusion Criteria

Karnofsky performance score ≥70</td>
<td>Tests

The GE Discovery LS4PET/CT was used. All participants fasted for a minimum of 6 hours before the scan. 5.55 MBq/kg 18F-FDG was administered IV. 40 minutes later an emission full body scan was performed from thigh to head. CT images were collected</td>
<td>Methods

Three doctors familiar with nuclear medicine and CT diagnosis used the visual and semi-quantitative method to analyse the PET-CT images. SUV of >2.5</td>
<td>Results

Detection of malignant lymph nodes with PET-CT

2x2 table*
<table>
<tr><td></td><td>Disease positive</td><td>Disease negative</td></tr>
<tr><td>Test positive</td><td>123</td><td>8</td></tr>
<tr><td>Test negative</td><td>19</td><td>177</td></tr>
<tr><td></td><td>142</td><td>185</td></tr>
</table>
</td>
<td>Limitations

Diagnostic accuracy measures are calculated based on individual malignant nodes, rather than per patient basis (i.e. they do not show whether participants were correcntly identified as N0, N1 etc.).

Other information

QUADAS 2 checklist</td>
</tr>
</table>

China Study type Prospective cohort study Aim of the study To explore the diagnostic accuracy of PET-CT in the diagnosis of lymph node metastasis in oesophageal cancer. Study dates January 2004 to December 2007. Source of funding The National Natural Science Foundation of China, the Provincial Natural Science Foundation of Shandong and the Provincial Science and Technology Development Planning of Shandong.	Weight loss≤ 5% in the prior 3 months T≤3N≤1M0 on PET-CT Exclusion Criteria Other chronic disease, such as hypertension or diabetes mellitus. Previous treatment	immediately prior to the PET images.	was considered to be malignant. Results of pathology were cosidered to be gold standard for the comparison of diagnostic imaging. The diagnostic accuracy of PET-CT for lymph node metastasis was calculated.	Sensitivity: 86.62% (95% CI† 79.90 to 91.75) Specificity: 95.85% (95% CI† 91.66 to 98.11) Positive likelihood ratio‡: 20.03 (95% CI 10.14 to 39.57) Negative likelihood ratio‡: 0.14 (95% CI 0.09 to 0.21) Positive predictive value: 93.89% (95% CI† 88.61 to 96.81) Negative predictive value: 90.31% (95% CI† 85.96 to 93.41) Data shown are for identification of individual metastatic nodes, rather than per patient basis. *constructed by the NGA from data reported in the article † 95% confidence interval calculated by the NGA technical team	Patient selection Risk of bias: Was a consecutive or random sample of patients enrolled? Unclear Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes Could the selection of participants have introduced bias? Low risk Applicability: Is there concern that the included participants do not match the review question? Low risk Index tests Risk of bias: Were the index tests interpreted without knowledge

				using https://www.medcalc.org/calc/diagnostic_test.php ‡ calculated by the NGA technical team using https://www.medcalc.org/calc/diagnostic_test.php	of the reference standard? Yes Is a threshold was used, was it pre-specified? Yes Could the conduct or interpretation of the index test have introduced bias? Low risk Applicability: Is there concern that the index test, its conduct or interpretation differ from the review question? No Reference standard Risk of bias: Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the

					results of the index test? Unclear Could the reference standard, its conduct or interpretation have introduced bias? Low risk Applicability: Is there concern that the target condition as defined by the reference standard does not match the review question? No Flow and timing Risk of bias: Was there an appropriate interval between index tests and reference standard? Yes Did all participants receive a reference standard? Yes Did participants receive the same

					reference standard? Yes Were all patients included in the analysis? Yes Could the participant flow have introduced bias? Low risk
Full citation Shi, W., Wang, W., Wang, J., Cheng, H., Huo, X., Meta-analysis of 18FDG PET-CT for nodal staging in patients with esophageal cancer, Surgical OncologySurg Oncol, 22, 112-6, 2013 Ref Id 492868 Country/ies where the study was carried out China Study type Systematic review	Sample size 6 studies included that assessed metastasis on a per-patient basis. N = 245 participants in total. Characteristics All retrospective studies. Inclusion Criteria 18FDG PET-CT was used to detect regional nodal metastasis without any neoadjuvant treatment before surgery. Reference standard was pathological staging of resected nodes after surgery.	Tests PET-CT was used to identify nodal metastases.	Methods Diagnostic accuracy measures were calculated, based on pathology as the reference standard.	Results Detection of lymph node metastasis 6 studies included n = 245 patients Pooled sensitivity (95% CI): 0.55 (0.34-0.74) Pooled specificity (95% CI): 0.76 (0.66-0.83) Pooled positive likelihood ratio (95% CI): 2.2 (1.2-4.2) Pooled negative likelihood ratio (95% CI): 0.59 (0.35-1.0)	Limitations Other information Checklist for systematic reviews, from the NICE manual 2014 The review addresses an appropriate and clearly focused question that is relevant to the review question. Yes The review collects the type of studies you consider relevant to the

Aim of the study To systematically review the diagnostic accuracy of PET-CT for nodal staging in oesophageal cancer. Study dates Articles published until 31 Dec 2012 were included. Source of funding None reported.	Able to construct a 2x2 table for true/false positives and negatives. If data or subsets of data were reported in more than one article, the article with the most comprehensive details, or the most recent data was used. At least 10 patients were included The studies were based on per-patient analysis Exclusion Criteria Studies based on a per-lymph node analysis were excluded by the authors. For the purposes of this report, studies based on a per-station analysis were also excluded.				guidance review question. Yes The literature search is sufficiently rigorous to identify all the relevant studies. Yes Study quality is assessed and reported. Yes An adequate description of the methodology used is included, and the methods used are appropriate to the question. Yes Overall assessment of internal validity. Are the results internally valid? Yes Overall assessment of external validity. Are the results externally valid? Yes
Full citation	Sample size	Tests	Methods	Results	Limitations

<table>
<tr>
<td>Smyth, E., Schoder, H., Strong, V. E., Capanu, M., Kelsen, D. P., Coit, D. G., Shah, M. A., A prospective evaluation of the utility of 2-deoxy-2-[18F] fluoro-D-glucose positron emission tomography and computed tomography in staging locally advanced gastric cancer (Provisional abstract), CancerCancer, 118, 5481-5488, 2012

Ref Id

492903

Country/ies where the study was carried out

USA

Study type

Prospective cohort study

Aim of the study

To assess the benefit of adding PET-CT to the routine pre-operative staging of patients with gastric cancer.</td>
<td>N = 113

Characteristics
<table><tr><th>Characteristics</th><th>Number (%)</th></tr><tr><td>Male</td><td>68 (60)</td></tr><tr><td>Female</td><td>45 (40)</td></tr><tr><td>Median age, y</td><td>61 (range 25-83)</td></tr><tr><td>Site</td><td></td></tr><tr><td>Gastric</td><td>71 (63)</td></tr><tr><td>Proximal/GE junction</td><td>42 (37)</td></tr><tr><td>Lauren's classification</td><td></td></tr><tr><td>Intestinal</td><td>38 (34)</td></tr><tr><td>Diffuse</td><td>52 (46)</td></tr><tr><td>Mixed</td><td>12 (11)</td></tr><tr><td>Not reported</td><td>11 (9)</td></tr></table></td>
<td>PET-CT was performed on Biograph (Siemens Healthcare) of Discovery LS (GE Medical Systems) machines.

Participants fasted for at least 6 hours prior to the procedure. Imaging started 60 minutes after IV FDG administration.

Low dose CT and PET images were obtained from the skull base to the upper thigh. PET, CT and PET-CT fusion images were displayed on a workstation and prospectively reviewed by the responsible study nuclear medicine physician.</td>
<td>Individual lesions were graded according to the following scale: 0 = normal, 1 = probably benign, 2 = equivocal, 3 = probably malignant, 4 = definitely malignant. Lesions with a certainty of 3 or 4 were considered FDG avid.

All sites of M1 disease were confirmed, either pathologically by fine needle aspirate or core biopsy, or radiographically with</td>
<td>Detection of metastatic disease

2x2 table
<table><tr><th></th><th>Metastasis confirmed</th><th>Metastasis not confirme</th></tr><tr><td>Test positive</td><td>11</td><td>1</td></tr><tr><td>Test negative</td><td>20</td><td>81</td></tr><tr><td></td><td>31</td><td>82</td></tr></table>Sensitivity: 35% (95% CI 19-55)

Specificity: 99% (95% CI 93-100)

Positive likelihood ratio†: 29.10 (95% CI 3.92 to 216.08)

Negative likelihood ratio†: 0.65 (95% CI 0.50 to 0.85)</td>
<td>Other information

QUADAS 2 checklist

Patient selection

Risk of bias:

Was a consecutive or random sample of patients enrolled? Unclear

Was a case-control design avoided? Yes

Did the study avoid inappropriate exclusions? Yes

Could the selection of participants have introduced bias? Low risk

Applicability:

Is there concern that the included participants do not match the review question? Unclear - only locally advanced cancers</td>
</tr>
</table>

Study dates June 2003 to August 2010. Source of funding None reported.	<table><tr><td>Differentiation</td><td></td></tr><tr><td>Moderate</td><td>25 (22)</td></tr><tr><td>Moderate-poor</td><td>11 (10)</td></tr><tr><td>Poor</td><td>77 (68)</td></tr><tr><td>Stage</td><td></td></tr><tr><td>≥T3</td><td>112 (99)</td></tr><tr><td>≥N1</td><td>70 (62)</td></tr></table> Inclusion Criteria Locally advanced gastric cancer Suitable for surgical resection Karnofsky performance score ≥60% Exclusion Criteria None reported.		additional imaging (MRI or radionucleotide bone scan).	Positive predictive value†: 91.67% (95% CI 59.70 to 98.79) Negative predictive value†: 80.20% (95% CI 75.70 to 84.04) † calculated by the NGA technical team from data reported in the article using https://www.medcalc.org/calc/diagnostic_test.php	included (almost all were T3 or greater). Index tests Risk of bias: Were the index tests interpreted without knowledge of the reference standard? Yes Is a threshold was used, was it pre-specified? N/A Could the conduct or interpretation of the index test have introduced bias? Low risk Applicability: Is there concern that the index test, its conduct or interpretation differ from the review question? Low risk Reference standard Risk of bias:

					Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unclear Could the reference standard, its conduct or interpretation have introduced bias? Low risk Applicability: Is there concern that the target condition as defined by the reference standard does not match the review question? Low risk Flow and timing Risk of bias: Was there an appropriate interval

<table>
<tr><td></td><td></td><td></td><td></td><td></td><td>between index tests and reference standard? Unclear

Did all participants receive a reference standard? Yes

Did participants receive the same reference standard? Yes

Were all patients included in the analysis? Yes

Could the participant flow have introduced bias? Low risk</td></tr>
<tr><td>Full citation

Williams, R. N., Ubhi, S. S., Sutton, C. D., Thomas, A. L., Entwisle, J. J., Bowrey, D. J., The early use of PET-CT alters the management of patients with esophageal cancer, Journal of Gastrointestinal SurgeryJ Gastrointest Surg, 13, 868-73, 2009</td><td>Sample size

N = 38

Characteristics
<table><tr><td>Characteristics</td><td>n (%)</td></tr><tr><td>Median age (range)</td><td>65 (43-85)</td></tr></table></td><td>Tests

Co-registered PET-CT was performed with a GE Discovery ST PET-CT scanner. Acquisition was performed from eyes to knees.</td><td>Methods

Proformas detailing patient demographics, tumour type, site and stage were constructed for each</td><td>Results

Change in definitive staging by PET-CT

10/38 patients: 26% (95% CI† 13-44)

Change in management plan with PET-CT (assuming</td><td>Limitations

Other information

High risk of bias: MDT participants were asked to review the findings on their own to make the treatment plans, which is in contrast to the</td></tr>
</table>

Ref Id 487848 Country/ies where the study was carried out UK Study type Non-comparative study Aim of the study To determine how often PET-CT influenced the management plan for patients with oesophageal carcinoma. Study dates November 2006 - December 2007 Source of funding Not reported.	<table><tr><td>Histological subtype</td><td></td></tr><tr><td>Adenocarcinoma</td><td>28</td></tr><tr><td>Squamous cell carcinoma</td><td>10</td></tr></table> Inclusion Criteria Patients with carcinoma of the oesophagus or gastroesophageal junction. Staged as T1-3 N0-1 on initial CT scan Pre-operative staging with both CT and PET-CT Exclusion Criteria Not reported.	The threshold for the diagnosis of metastatic disease on PET-CT was a standardised uptake value in excess of 2.5/	patient. Duplicate profromas were created - one with and one without the PET-CT findings. Each proforma was independently reviewed in a random, blinded fashion by five consultant members of the multidisciplinary team. Their treatment strategy (palliative or curative) was recorded, along with their specific	majority decision, with 60% concordance) 7/38 patients: 18% (95% CI† 7-4) - 3 patients would have been changed from palliative approach to curative approach, 4 from curative to palliative, with the addition of PET-CT findings. † calculated by the NGA technical team from data reported in the article using http://statpages.info/confint.html	typical clinical situation. Small number of patients involved, therefore it would be easy to remember individual cases from the proformas.

<table>
<tr><td></td><td></td><td></td><td>managemen t plan.</td><td></td><td></td></tr>
<tr>
<td>Full citation

Yang, Q. M., Kawamura, T., Itoh, H., Bando, E., Nemoto, M., Akamoto, S., Furukawa, H., Yonemura, Y., Is PET-CT suitable for predicting lymph node status for gastric cancer?, Hepato-GastroenterologyHepatogastroenterology, 55, 782-785, 2008

Ref Id

493332

Country/ies where the study was carried out

Japan

Study type

Retrospective cohort study

Aim of the study

To determine the value of PET-CT for identifying</td>
<td>Sample size

N = 78

Characteristics

n = 57 male (73%)

n = 21 female (27%)

Mean age 65.6 years, range 38-84

No further information provided.

Inclusion Criteria

Pre-operative PET-CT performed

Radical gastrectomy procedure.

Pre-operative histological confirmation of gastric cancer.

Exclusion Criteria

Not reported.</td>
<td>Tests

The Discover-ST (GE) PET-CT scanner was used. Participants fasted for 4 hours pre-imaging, and were given 200MBq 18F-FDG 60 minutes before image acquisition.</td>
<td>Methods

Not reported. Visual interpretatio n of PET-CT is assumed.</td>
<td>Results

Detection of lymph node metastasis

2x2 table
<table>
<tr><td></td><td>Metastasis on pathology</td><td>No metasta on patholo</td></tr>
<tr><td>Test positive</td><td>13</td><td>1</td></tr>
<tr><td>Test negative</td><td>29</td><td>35</td></tr>
<tr><td></td><td>42</td><td>36</td></tr>
</table>
Sensitivity: 31.0% (95% CI† 17.62 to 47.09)

Specificity: 97.2% (95% CI† 85.47 to 99.93)

Positive likelihood ratio‡: 11.14 (95% CI 1.53 to 81.08)</td>
<td>Limitations

Other information

QUADAS 2 checklist

Patient selection

Risk of bias:

Was a consecutive or random sample of patients enrolled? Unclear

Was a case-control design avoided? Yes

Did the study avoid inappropriate exclusions? Yes

Could the selection of participants have introduced bias? Low risk

Applicability:</td>
</tr>
</table>

lymph node metastasis in gastric cancer. Study dates November 2002 to January 2006. Source of funding Not reported.				Negative likelihood ratio‡: 0.71 (95% CI 0.58 to 0.88) Positive predictive value: 92.9% (95% CI† 64.11 to 98.95) Negative predictive value: 54.7% (95% CI† 49.45 to 59.82) † 95% confidence interval calculated by the NGA technical team from data reported in the article using https://www.medcalc.org/calc/diagnostic_test.php ‡ calculated by the NGA technical team from data reported in the article using https://www.medcalc.org/calc/diagnostic_test.php	Is there concern that the included participants do not match the review question? Low risk Index tests Risk of bias: Were the index tests interpreted without knowledge of the reference standard? Yes Is a threshold was used, was it pre-specified? N/A Could the conduct or interpretation of the index test have introduced bias? Low risk Applicability: Is there concern that the index test, its conduct or interpretation differ from the review question? No Reference standard

					Risk of bias: Is the reference standard likely to correctly classify the target condition?Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unclear Could the reference standard, its conduct or interpretation have introduced bias? Low risk Applicability: Is there concern that the target condition as defined by the reference standard does not match the review question? Low risk Flow and timing Risk of bias:

<table>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Was there an appropriate interval between index tests and reference standard? Unclear

Did all participants receive a reference standard? Yes

Did participants receive the same reference standard? Yes

Were all patients included in the analysis? Yes

Could the participant flow have introduced bias? Low risk</td>
</tr>
<tr>
<td>Full citation

Burke, E. C., Karpeh, M. S., Conlon, K. C., Brennan, M. F., Laparoscopy in the management of gastric adenocarcinoma, Annals</td>
<td>Sample size

111

Characteristics

Not reported

Inclusion Criteria</td>
<td>Tests

Laparoscopy was performed with the patient under general anesthesia. Insufflation was performed after</td>
<td>Methods

Laparoscopic staging (M0 versus M1) - criteria not reported.</td>
<td>Results

Staging M0 vs M1 (intra-abdominal metastasis)

2x2 table
<table><tr><td></td><td>Histopathology M1</td><td>Histopathology M</td></tr></table></td>
<td>Limitations

QUADAS 2 checklist

Patient selection

Risk of bias:</td>
</tr>
</table>

<table>
<tr>
<td>of SurgeryAnn Surg, 225, 262-7, 1997

Ref Id

608061

Country/ies where the study was carried out

USA

Study type

Retrospective cohort study

Aim of the study

To determine the accuracy of laparoscopy in detecting metastatic disease in patients with gastric adenocarcinoma.

Study dates

December 1991 to December 1995

Source of funding

A grant from the Lillian S. Wells Foundation.</td>
<td>Patients with gastric adenocarcinoma deemed candidates for possible curative resection before surgery on the basis of physical examination, laboratory values, and modem generation computed tomographic imaging of the abdomen and pelvis.

Exclusion Criteria

Not reported</td>
<td>placing a Hasson trocar under direct vision in the patient. A 30-degree telescope was used for exploration.

The liver, diaphragm, serosal surfaces, peritoneum, omentum, bowel, mesentery, and pelvic organs were inspected

A second port was placed in the right upper quadrant for palpation, exploration, and biopsy of suspicious lesions.</td>
<td>Reference standard was pathological confirmation of findings at laparoscopy or laparotomy.</td>
<td>
<table>
<tr><td>Laparoscopy M1</td><td>32</td><td>0</td></tr>
<tr><td>Laparoscopy M0</td><td>6</td><td>65</td></tr>
<tr><td></td><td>38</td><td>65</td></tr>
</table>
32
71
10
3
</td>
<td>Was a consecutive or random sample of patients enrolled? Unclear

Was a case-control design avoided? Yes

Did the study avoid inappropriate exclusions? Yes

Could the selection of participants have introduced bias? Low risk

Applicability:

Is there concern that the included participants do not match the review question? Low risk

Index tests

Risk of bias:

Were the index tests interpreted without knowledge of the reference standard? Yes</td>
</tr>
</table>

					Is a threshold was used, was it pre-specified? N/A Could the conduct or interpretation of the index test have introduced bias? Low risk Applicability: Is there concern that the index test, its conduct or interpretation differ from the review question? unclear Reference standard Risk of bias: Is the reference standard likely to correctly classify the target condition?Yes Were the reference standard results interpreted without knowledge of the results of the index test? No

					Could the reference standard, its conduct or interpretation have introduced bias? Unclear risk Applicability: Is there concern that the target condition as defined by the reference standard does not match the review question? Unclear risk Flow and timing Risk of bias: Was there an appropriate interval between index tests and reference standard? Unclear Did all participants receive a reference standard? Yes Did participants receive the same reference standard? No

<table>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Were all patients included in the analysis? No

Could the participant flow have introduced bias? Unclear risk

Other information</td>
</tr>
<tr>
<td>Full citation

Fujimura, T., Kinami, S., Ninomiya, I., Kitagawa, H., Fushida, S., Nishimura, G., Kayahara, M., Shimizu, K., Ohta, T., Miwa, K., Diagnostic laparoscopy, serum CA125, and peritoneal metastasis in gastric cancer, EndoscopyEndoscopy, 34, 569-74, 2002

Ref Id

608096

Country/ies where the study was carried out

Japan</td>
<td>Sample size

31

Characteristics

22 women, 17 men; age range 26 – 80.

The macroscopic appearance of the primary gastric cancer indicated that one patient had type 1 tumour, four had type 2, 14 had type 3, and 20 type 4 tumours. Differentiated and undifferentiated carcinomas were diagnosed pathologically in 16 and 23 patients, respectively.

Inclusion Criteria</td>
<td>Tests

Laparoscopy with biopsy was done in an operating room with the patient under general anesthesia. A 10-mm or 2-mm laparoscope was inserted into the peritoneal cavity through an incision just caudal to the umbilicus. The parietal peritoneum and the surface of the stomach, liver and omentum were</td>
<td>Methods

Laparoscopic diagnosis for peritoneal metastasis was determined through macroscopic, pathological and cytological diagnoses.

Reference standard was pathological confirmation</td>
<td>Results

Peritoneal metastases

2x2 table
<table><tr><td></td><td>Final diagnosis - peritoneal metastases</td><td>Final diagnc - no peritor metast es</td></tr><tr><td>Laparoscopy - peritoneal metastases</td><td>9</td><td>0</td></tr><tr><td>Laparoscopy - no peritoneal</td><td>4</td><td>18</td></tr></table></td>
<td>Limitations

QUADAS 2 checklist

Patient selection

Risk of bias:

Was a consecutive or random sample of patients enrolled? Unclear

Was a case-control design avoided? Yes

Did the study avoid inappropriate exclusions? Yes</td>
</tr>
</table>

Study type Nested case-control study Aim of the study To investigate the utility of laparoscopy in the detection of peritoneal metastasis in gastric cancer Study dates 1992-2000 Source of funding	Tumor larger than 8 cm in diameter, tumor occupying two or more sections of stomach, or type 4 gastric cancer. Ultrasound and CT negative for peritoneal metastasis. Exclusion Criteria Distant metastases.	inspected. Another 5-mm port was then created, to insert a forceps for manipulating organs in order to disclose small metastases of the mesentery and the pouch of Douglas, and ascites.	of findings at laparoscopy or laparotomy.	metastases 13 18 31	Could the selection of participants have introduced bias? Low risk Applicability: Is there concern that the included participants do not match the review question? Low risk Index tests Risk of bias: Were the index tests interpreted without knowledge of the reference standard? Yes Is a threshold was used, was it pre-specified? N/A Could the conduct or interpretation of the index test have introduced bias? Low risk Applicability:

					Is there concern that the index test, its conduct or interpretation differ from the review question? Low risk Reference standard Risk of bias: Is the reference standard likely to correctly classify the target condition?Yes Were the reference standard results interpreted without knowledge of the results of the index test? No Could the reference standard, its conduct or interpretation have introduced bias? Unclear risk Applicability: Is there concern that the target condition as defined

					by the reference standard does not match the review question? Unclear risk Flow and timing Risk of bias: Was there an appropriate interval between index tests and reference standard? Unclear Did all participants receive a reference standard? Yes Did participants receive the same reference standard? No Were all patients included in the analysis? No Could the participant flow have introduced bias? Unclear risk Other information

<table>
<tr>
<td>Full citation

Lowy, A. M., Mansfield, P. F., Leach, S. D., Ajani, J., Laparoscopic staging for gastric cancer, SurgerySurgery, 119, 611-4, 1996

Ref Id

608162

Country/ies where the study was carried out

USA

Study type

Retrospective cohort study

Aim of the study

To determine the usefulness of laparoscopy for staging gastric adenocarcinoma in the era of CT scanning.

Study dates

1991 to 1995

Source of funding</td>
<td>Sample size

71

Characteristics

Not reported

Inclusion Criteria

All patients were believed to have resectable disease (T1 to T4, N0 to N2, M0) on the basis of the results of abdominal CT and physical examination.

Exclusion Criteria

Patients with obvious evidence of hepatic metastases or ascites were excluded from the study.</td>
<td>Tests

Staging laparoscopy with an open cannula technique.. At laparoscopy all peritoneal surfaces, the liver, and the omentum were inspected. Evaluation of the lesser sac was not routinely performed routinely until 1993.</td>
<td>Methods

Reference standard was pathological confirmation of findings at laparoscopy or laparotomy.</td>
<td>Results

Laparoscopy was attempted in 71 patients and successfully completed in 69 (97%), O f the 69 patients who
had a complete laparoscopic exploration, 41 underwent laparotomy with curative intent, and 38 (93%) of these underwent resection of all gross disease.

No reference standard for 12/53 with no peritoneal metastases on laparoscopy due to rapid disease progression (N=9) or loss to follow-up (N=3).

41/53 had laparotomy.

Peritoneal metastases

2x2 table
<table>
<tr><td></td><td>Final diagnosis - peritoneal metastases</td><td>Final diagnc - no peritor metast es</td></tr>
</table></td>
<td>Limitations

QUADAS 2 checklist

Patient selection

Risk of bias:

Was a consecutive or random sample of patients enrolled? Unclear

Was a case-control design avoided? Yes

Did the study avoid inappropriate exclusions? Yes

Could the selection of participants have introduced bias? Low risk

Applicability:

Is there concern that the included participants do not match the review question? Low risk

Index tests</td>
</tr>
</table>

Not reported				Laparoscopy - peritoneal metastases: 16 / 0 Laparoscopy - no peritoneal metastases: 3 / 38 : 19 / 38	Risk of bias: Were the index tests interpreted without knowledge of the reference standard? Yes Is a threshold was used, was it pre-specified? N/A Could the conduct or interpretation of the index test have introduced bias? Low risk Applicability: Is there concern that the index test, its conduct or interpretation differ from the review question? Low risk Reference standard Risk of bias: Is the reference standard likely to correctly classify the target condition?Yes

					Were the reference standard results interpreted without knowledge of the results of the index test? No Could the reference standard, its conduct or interpretation have introduced bias? Unclear risk Applicability: Is there concern that the target condition as defined by the reference standard does not match the review question? Unclear risk Flow and timing Risk of bias: Was there an appropriate interval between index tests and reference standard? Unclear

<table>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Did all participants receive a reference standard? No

Did participants receive the same reference standard? No

Were all patients included in the analysis? No

Could the participant flow have introduced bias? High risk

Other information</td>
</tr>
<tr>
<td>Full citation

Meister, T., Domagk, D., Heinzow, H. S., Osterkamp, R., Wehrmann, T., Kucharzik, T., Domschke, W., Seifert, H., Miniprobe endoscopic ultrasound accurately stages esophageal cancer and guides therapeutic decisions in the era of neoadjuvant therapy:</td>
<td>Sample size

N=143

Characteristics
<table><tr><td>Characteristics</td><td>Variable</td></tr><tr><td>Total N</td><td>143</td></tr><tr><td>Mean age (SEM)</td><td>63.8 (10.7)</td></tr></table></td>
<td>Tests

EUS with high frequency catheter probes. EUS miniprobes in a water filled lumen were used.

Reference: histopathology</td>
<td>Methods

EUS classification and histological diagnoses of all patients with esophageal cancer seen at hospital of Munster</td>
<td>Results

Sensitivity specificity and accuracy rates of miniprobe EUS for T stage diagnostics:<table><tr><td>T stage</td><td>Sensitivity (95%CI)</td><td>Specificity (95%CI)</td><td>Ac (95</td></tr><tr><td>T1</td><td>0.68(0.58-0.79)</td><td>0.97(0.96-1)</td><td>0.87-0</td></tr></table></td>
<td>Limitations

QUADAS 2 checklist

Patient selection

Risk of bias: Was a consecutive or random sample of patients enrolled? Unclear</td>
</tr>
</table>

results of a multicenter cohort analysis, Surgical Endoscopy and Other Interventional Techniques, 27, 2813-2819, 2013

Ref Id

488119

Country/ies where the study was carried out

Germany

Study type

Retrospective cohort study

Aim of the study

to study role of miniprobe EUS in tumour staging of esophageal malignancies and to guide the appropriate clinical decision making process

Study dates

Patients seen from December 2002 and July 2009

Source of funding

Not reported

Age range	34-85
Sex (male/female)	114/29
Esophageal tumour distribution	
proximal third	3(2)
mid third	7(5)
distal third/GE junction	133/38 (93)
Histology	
squamous cell carcinoma	31(22)
Adenocarcinoma	112 (78)
Therapy	
endoscopic mucosal resection	50(35)
surgical esophageal resection	93(65)

Inclusion Criteria

university, Oldenburg, Luneburg and Wiesbaden December 2002-July 2009 were retrospectiv ely analysed.

Histopatholo gy was available after surgical or endoscopic mucosal resection.

T2	0.39(0.23-0.56)	0.84(0.75-0.89)	0.75(0.65-0.79)
T3	0.72(0.56-0.89)	0.81(0.7-0.86)	0.79(0.7-0.84)
T4	0.13(0-0.35)	0.97(0.95-1)	0.93(0.89-0.97)
T1-2	0.73(0.64-0.81)	0.81(0.68-0.94)	0.75(0.68-0.82)
T3-4	0.78(0.65-0.92)	0.82(0.72-0.89)	0.81(0.73-0.86)
T1-4			0.6(0.52-0.68)

Sensitivity specificity and accuracy rates considering only tumours of the GE junction (n=38)

T1	0.7(0.42-0.98)	0.1(0-1)	0.9(-1)
T2	0.27(0.04-0.49)	0.82(0.67-0.98)	0.6(-0.7
T3	0.83(0.62-1)	0.58(0.39-0.77)	0.6(-0.8

Was a case-control design avoided? Yes

Did the study avoid inappropriate exclusions? Yes

Could the selection of participants have introduced bias? Low risk

Applicability: Is there concern that the included participants do not match the review question? No

Index tests Risk of bias: Were the index tests interpreted without knowledge of the reference standard? No

If a threshold was used, was it pre-specified? No

Could the conduct or interpretation of the index test have

	patients with esophageal cancer seen at the hospitals of Munster University, Oldenburg, Luneburg and Wiesbaden from December 2002 until July 2009 Exclusion Criteria prior neoadjuvant radio- or chemotherapy or esophageal surgery			<table><tr><td>T4</td><td>nc</td><td>0.97(0.92-1)</td><td>0.94(0.88-1)</td></tr><tr><td>T1-2</td><td>0.56(0.37-0.75)</td><td>0.92(0.78-1)</td><td>0.68(0.54-0.83)</td></tr><tr><td>T3-4</td><td>0.84(0.65-1)</td><td>0.56(0.3-0.82)</td><td>0.66(0.51-0.81)</td></tr><tr><td>T1-4</td><td></td><td></td><td>0.55(0.39-0.71)</td></tr><tr><td></td><td></td><td></td><td></td></tr></table> Sensitivity specificity and accuracy rates of miniprobe EUS for N stage diagnostics <table><tr><td>N stage</td><td>Sensitivity (95%CI)</td><td>Specificity (95%CI)</td><td>Ac (95</td></tr><tr><td>N0</td><td>0.71(0.56-0.84)</td><td>0.76(0.65-0.89)</td><td>0.7 5-0</td></tr><tr><td>N1</td><td>0.76(0.65-0.89)</td><td>0.71(0.56-0.84)</td><td>0.7 5-0</td></tr></table>	introduced bias? Low risk Applicability: Is there concern that the index test, its conduct or interpretation differ from the review question? No Reference standard Risk of bias Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? No Could the reference standard, its conduct or interpretation have introduced bias? Low risk Applicability: Is there concern that the target condition as defined by the reference standard

					does not match the review question? No Flow and timing Risk of bias: Was there an appropriate interval between index tests and reference standard? Yes Did all participants receive a reference standard? Yes Did participants receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the participant flow have introduced bias? Low risk Other information
Study details	Participants	Tests	Methods	Outcomes and results	Comments
Full citation	Sample size n=50	Tests	Methods	Results	Limitations

<table>
<tr>
<td>Berrisford, R. G., Wong, W. L., Day, D., Toy, E., Napier, M., Mitchell, K., Wajed, S., The decision to operate: role of integrated computed tomography positron emission tomography in staging oesophageal and oesophagogastric junction cancer by the multidisciplinary team, European Journal of Cardio-Thoracic SurgeryEur J Cardiothorac Surg, 33, 1112-6, 2008

Ref Id

558731

Country/ies where the study was carried out

UK

Study type

Nested case-control study

Aim of the study

To assess the additional role of fusion PET-CT in staging patients for</td>
<td>Characteristics

Mean age (range) years: 66.4 years (44 -81)
Male %: 44/50 (88%)
OGJ: 28/50; Lower 1/3: 16/50 and middle 1/3: 6/50
Adenocarcinoma/SCC/small cell: 45/4/1

Inclusion Criteria

patients with potentially operable, biopsy-proven carcinoma of the oesophagus or gastrooesophageal junction

Exclusion Criteria</td>
<td>All patients underwent pretreatment CT scan and were categorised into group A (N0M0 on CT) and group B (N1 and/or borderline M1 on CT). Thirty-two patients underwent endoluminal ultrasound. Patients who completed resection were analysed for pathological overall nodal status, pathological regional nodal status and outcome

PET-CT:

if positive regional lymph nodes confined to left gastric artery group, they underwent</td>
<td></td>
<td>Diagnostic accuracy for N staging of PET-CT
<table>
<tr><td>test</td><td>True</td><td>False</td></tr>
<tr><td>PET +ve</td><td>12</td><td>18</td></tr>
<tr><td>PET -ve</td><td>4</td><td>3</td></tr>
</table>
Sensitivity 75%; Specificity 14%:

PPV 40% and NPV 43%</td>
<td>QUADAS 2 checklist

Patient selection

Risk of bias:

Was a consecutive or random sample of patients enrolled? Yes

Was a case-control design avoided? Yes

Did the study avoid inappropriate exclusions? Yes

Could the selection of participants have introduced bias? Low risk

Applicability:

Is there concern that the included participants do not match the review question? Low risk

Index tests

Risk of bias:</td>
</tr>
</table>

minimally invasive oesophagectomy (MIO) with potentially resectable disease Study dates Not reported Source of funding Not reported		neoadjuvant chemotherapy followed by MIO if patents with bulky (>2 cm) but localised left gastric artery disease went on to staging laparoscopy prior to neoadjuvant chemotherapy if T3 and/or N1 stage, they underwent neoadjuvant chemotherapy with 1-3 cycles of platinum based chemotherapy followed by repeat CT scan to look for disease progression			Were the index tests interpreted without knowledge of the reference standard? Unclear If a threshold was used, was it pre-specified? N/A Could the conduct or interpretation of the index test have introduced bias? Unclear risk Applicability: Is there concern that the index test, its conduct or interpretation differ from the review question? Low risk Reference standard Risk of bias: Is the reference standard likely to correctly classify the target condition? Yes

					Were the reference standard results interpreted without knowledge of the results of the index test? Unclear Could the reference standard, its conduct or interpretation have introduced bias? Unclear risk Applicability: Is there concern that the target condition as defined by the reference standard does not match the review question? Low risk Flow and timing Risk of bias: Was there an appropriate interval between index tests and reference standard? Yes

					Did all participants receive a reference standard? Yes Did participants receive the same reference standard? Yes Were all patients included in the analysis? No - six excluded for unexpectedly inoperable, one unfit for surgery; two progressed to chemotherapy; one for primary pancreative ampullary tumour; one had fixed nodal disease at laparoscopy; two had unexpected metastases in pleura and lung Could the participant flow have introduced bias? Unclear risk Other information

<table>
<tr>
<td>Full citation

Bonavina, L., Incarbone, R., Lattuada, E., Segalin, A., Cesana, B., Peracchia, A., Preoperative laparoscopy in management of patients with carcinoma of the esophagus and of the esophagogastric junction, Journal of Surgical OncologyJ Surg Oncol, 65, 171-4, 1997

Ref Id

558752

Country/ies where the study was carried out

Italy

Study type

Prospective cohort study

Aim of the study

To assess the diagnostic value of laparoscopy in the preoperative staging of patients with cancer of</td>
<td>Sample size

N = 50

Characteristics

n = 39 male

n = 11 female

Mean age 58 years (range 31-81)

n = 14 squamous cell carcinoma

n = 36 adenocarcinoma

Inclusion Criteria

Known oesophageal carcinoma (distal oesophagus or gastric cardia).

Exclusion Criteria

Not reported.</td>
<td>Tests

Laparoscopy was performed under general anaesthetic at the same time as the planned surgical resection. Exploration of the abdominal cavity included the peritoneal surface, lesser omentum and liver. Diagnostic peritoneal lavage with 200ml saline solution was also performed.</td>
<td>Methods

All participants initially underwent preoperative staging with transabdominal ultrasonography and CT of the chest and abdomen.

Diagnostic laparoscopy was then conducted immediately prior to planned surgical resection.

Diagnostic accuracy measures were calculated.</td>
<td>Results

Procedure related morbidity

1/50 (2%, 95% CI 0 to 11)[1]

(n = 1 participant suffered moderate bleeding due to manipulation of a liver haemangioma)

Change in treatment plan

5/50 (10%, 95% CI 3 to 22)[1]

Identification of liver metastasis
<table>
<tr><td></td><td>Liver metastasis confirmed by histology</td><td>No liver metastas on histolo</td></tr>
<tr><td>Liver metastasis</td><td>6</td><td>0</td></tr>
</table></td>
<td>Limitations

QUADAS 2 checklist

Patient selection

Risk of bias:

Was a consecutive or random sample of patients enrolled? Yes

Was a case-control design avoided? Yes

Did the study avoid inappropriate exclusions? Yes

Could the selection of participants have introduced bias? Low risk

Applicability:

Is there concern that the included participants do not match the review question? Low risk</td>
</tr>
</table>

the oesophagus and the oesophageal junction. Study dates November 1995 to December 1996. Source of funding Not reported.				identified during laparoscopy			Index tests Risk of bias: Were the index tests interpreted without knowledge of the reference standard? Yes If a threshold was used, was it pre-specified? N/A Could the conduct or interpretation of the index test have introduced bias? Low risk Applicability: Is there concern that the index test, its conduct or interpretation differ from the review question? Low risk Reference standard Risk of bias: Is the reference standard likely to correctly classify the
				No liver metastasis identified during laparoscopy	1	43	
					7	43	
				Sensitivity (95% CI)[2]: 85.7% (42.1 to 99.6) Specificity (95% CI)[2]: 100% (91.8 to 100) Positive likelihood ratio[3] (95% CI): ∞ (not calculable) Negative likelihood ratio[3] (95% CI): 0.14 (0.02 to 0.88) Positive predictive value (95% CI)[2]: 100% (not calculable)			

				Negative predictive value (95% CI)[2]: 97.7% (87.5 to 99.6) Identification of macroscopic nodal metastasis Nodal metastasis confirmed by histology: Nodal metastasis identified during laparoscopy: 7; No nodal metastasis identified during laparoscopy: 2 No nodal metastasis confirmed on histology: Nodal metastasis identified during laparoscopy: 0; No nodal metastasis identified during laparoscopy: 41	target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? No Could the reference standard, its conduct or interpretation have introduced bias? Low risk Applicability: Is there concern that the target condition as defined by the reference standard does not match the review question? Low risk Flow and timing Risk of bias: Was there an appropriate interval between index tests and reference standard? Yes

				<table><tr><td></td><td>9</td><td>41</td><td>9 0</td></tr></table> Sensitivity (95% CI)²: 77.8% (40 to 97.2) Specificity (95% CI)²: 100% (91.4 to 100) Positive likelihood ratio³ (95% CI): ∞ (not calculable) Negative likelihood ratio³ (95% CI): 0.22 (0.07 to 0.75) Positive predictive value (95% CI)²: 100% (not calculable) Negative predictive value (95% CI)²: 95.4% (85.8 to 98.6) Identification of peritoneal metastasis <table><tr><td></td><td>Peritoneal carcinosis confirmed by</td><td>No peritoneal carcinosis on histology</td></tr></table>	Did all participants receive a reference standard? Yes Did participants receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the participant flow have introduced bias? Low risk

					histology			
				Peritoneal carcinosis identified during laparoscopy	5	0		5
				Peritoneal carcinosis identified during laparoscopy	2	43		45
					7	43		50
				Sensitivity (95% CI)[2]: 71.4% (29.0 to 96.3) Specificity (95% CI)[2]: 100% (91.8 to 100) Positive likelihood ratio[3] (95% CI): ∞ (not calculable) Negative likelihood ratio[3] (95% CI): 0.29 (0.09 to 0.92)				

				Positive predictive value (95% CI)[2]: 100% (not calculable) Negative predictive value (95% CI)[2]: 95.56 (87.0 to 98.6) [1] calculated by the NGA technical team using http://statpages.info/confint.html [2] 95% confidence interval calculated by the NGA technical team using https://www.medcalc.org/calc/diagnostic_test.php [3] point estimate and 95% confidence interval calculated by the NGA technical team using https://www.medcalc.org/calc/diagnostic_test.php	
Full citation Clements, D. M., Bowrey, D. J., Havard, T. J., The role of staging investigations for oesophago-gastric	Sample size n = 90 participants who underwent staging with laparoscopy	Tests Laparoscopy was performed using a 10mm port at the umbilicus and either one or two	Methods All study participants were initially staged by CT scan. If	Results Change of management plan following laparoscopy 16/90 (18%, 95% CI 11 to 27)†	Limitations QUADAS 2 checklist Patient selection

carcinoma, European Journal of Surgical OncologyEur J Surg Oncol, 30, 309-12, 2004 Ref Id 558847 Country/ies where the study was carried out UK Study type Retrospective cohort study Aim of the study To assess the frequency with which unresectable disease was identified on various pre-operative staging investigations for patients with oesophago-gastric cancer. Study dates 2000 to 2002. Source of funding Not reported.	(n = 255 total participants in the study, but many underwent CT and/or endoscopic ultrasound only) Characteristics Total study population: n = 169 male n = 86 female Median age 70 years (range 31-98) n = 98 oesophageal carcinoma (n = 56 squamous cell) n = 89 gastrooesophageal junction adenocarcinoma n = 68 gastric carcinoma Inclusion Criteria Gastroesophageal carcinoma Exclusion Criteria Metastatic disease identified on CT scan.	additional 5mm ports. The lesser sac was not opened for inspection.	metastatic disease was identified, no further staging investigations were undertaken. Participants with adenocarcinoma of the lower oesophageal third (and negative endoscopic ultrasound) underwent endoscopic ultrasound, as did participants with gastroesophageal carcinoma.	(All 16 had surgical resection precluded following laparoscopy for the following reasons: n = 11 peritoneal disease, n = 2 hepatic metastases, n = 2 poorly tolerated pneumoperitoneum, n = 1 atrial fibrillation developed during laparoscopy) † calculated by the NGA technical team from data reported in the article using http://statpages.info/confint.html	Risk of bias: Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes Could the selection of participants have introduced bias? Low risk Applicability: Is there concern that the included participants do not match the review question? Low risk Index tests Risk of bias: Were the index tests interpreted without knowledge

	Study assesses the staging accuracy of different procedures (CT and endoscopic ultrasound as well as laparoscopy). Not all participants underwent laparoscopy. Laparoscopy was not performed in the following cases: mid/upper oesophageal carcinoma (staged with EUS and CT only) gastric carcinoma with symptoms of outlet obstruction gastric carcinoma not visible on CT (assumed to be early disease, at low risk of metastases)				of the reference standard? Yes If a threshold was used, was it pre-specified? N/A Could the conduct or interpretation of the index test have introduced bias? Low risk Applicability: Is there concern that the index test, its conduct or interpretation differ from the review question? Low risk Reference standard Risk of bias: Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the

					results of the index test? No Could the reference standard, its conduct or interpretation have introduced bias? Low risk Applicability: Is there concern that the target condition as defined by the reference standard does not match the review question? Low risk Flow and timing Risk of bias: Was there an appropriate interval between index tests and reference standard? Yes Did all participants receive a reference standard? Yes Did participants receive the same

					reference standard? Yes Were all patients included in the analysis? Yes Could the participant flow have introduced bias? Low risk
Full citation Convie, L., Thompson, R. J., Kennedy, R., Clements, W. D., Carey, P. D., Kennedy, J. A., The current role of staging laparoscopy in oesophagogastric cancer, Annals of the Royal College of Surgeons of EnglandAnn R Coll Surg Engl, 97, 146-50, 2015 Ref Id 558856 Country/ies where the study was carried out UK	Sample size n = 295 Characteristics n = 225 male n = 70 female Type of tumour: n = 159 gastric adenocarcinoma n = 136 oesophageal (including junctional) adenocarcinoma Mean age 68 years Inclusion Criteria	Tests Laparoscopy was conducted with a three-port technique, with the abdominal viscera being inspected in a systematic fashion. Between 150ml and 500ml warm saline solution was instilled into the peritoneal cavity before being aspirated for cytological evaluation.	Methods Pre-operative staging for participants included CT and PET-CT.The results of these investigations had indicated disease resectability. The additional benefit of laparoscopy (in	Results Change of management plan following laparoscopy 63/295 (21%, 95% CI 17 to 26)† (n = 52 macroscopic metastasis, n = 11 positive cytology) Procedure related morbidity 1/295 (0.3%, 95% CI 0 to 2)† (n = 1 bowel injury requireing conversion to laparotomy in a patient with adhesions due to previous surgery)	Limitations QUADAS 2 checklist Patient selection Risk of bias: Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes

Study type Retrospective cohort study Aim of the study To determine the value of staging laparoscopy and peritoneal cytology for oesophagogastric cancer. Study dates March 2007 to August 2013. Source of funding Not reported.	Oesophageal adenocarcinoma or gastric cancer Exclusion Criteria Squamous cell oesophageal carcinoma involving the distal oesophagus. Evidence of metastatic disease on CT or PET-CT		identifying unresectable disease) was assessed.	†calculated by the NGA technical team from data reported in the article using http://statpages.info/confint.html	Could the selection of participants have introduced bias? Low risk Applicability: Is there concern that the included participants do not match the review question? Low risk Index tests Risk of bias: Were the index tests interpreted without knowledge of the reference standard? Yes If a threshold was used, was it pre-specified? N/A Could the conduct or interpretation of the index test have introduced bias? Low risk Applicability:

					Is there concern that the index test, its conduct or interpretation differ from the review question? Low risk Reference standard Risk of bias: Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? No Could the reference standard, its conduct or interpretation have introduced bias? Low risk Applicability: Is there concern that the target condition as defined

					by the reference standard does not match the review question? Low risk Flow and timing Risk of bias: Was there an appropriate interval between index tests and reference standard? Yes Did all participants receive a reference standard? Yes Did participants receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the participant flow have introduced bias? Low risk
Full citation	Sample size	Tests	Methods	Results	Limitations

<table>
<tr>
<td>de Graaf, G. W., Ayantunde, A. A., Parsons, S. L., Duffy, J. P., Welch, N. T., The role of staging laparoscopy in oesophagogastric cancers, Ejso, 33, 988-992, 2007

Ref Id

487990

Country/ies where the study was carried out

UK

Study type

Retrospective cohort study

Aim of the study

To assess whether staging laparoscopy significantly change the treatment decision for patients with oesophagogastric cancer.

Study dates

January 1997 to December 2003.</td>
<td>N = 416

Characteristics

n = 308 male

n = 108 female

Median age 68 years (range 30 to 87)

Tumour site:

n =307 oesophagus and cardia

n = 109 gastric

Inclusion Criteria

Known oesophagogastric cancer.

Considered fit for surgery with potentially resectable disease.

Exclusion Criteria

Unfit for surgery.

Known metastatic or locally advanced disease on CT and/or abdominal ultrasonography.

Declined surgery.</td>
<td>Staging laparoscopy was performed under general anaesthesia, usually as a day case one week before intended definitive surgery. In some cases, laparoscopy was immediately followed by definitive curative resection.

Careful and thorough inspection of the primary tumour and adjacent structures was conducted, including lymphovascular network, diaphragm, liver, peritonem, greater omentum, pelvis and sometimes the lesser sac. Biopsies were taken of suspicious lesions</td>
<td>Preoperative imaging: 385 participants underwent a CT scan of the chest and abdomen , while the remaining 31 participants had abdominal ultrasound only. 48 of the participants had endoscopic ultrasonography in addition to CT.

The additional benefit of laparoscopy at identifying patients with unresectable disease</td>
<td>Change in management plan following laparoscopy

84/416 (20%, 95% CI 16 to 24)†

(n = 63 peritoneal and/or liver metastases, n = 17 locally advanced disease, n = 4 extensive lymph node involvement).

Procedure related morbidity

0/416 (0%, 95% CI 0 to 1)†

Detection of unresectable disease
<table>
<tr><th></th><th>Disease unresectable</th><th>Disease resectable</th></tr>
<tr><td>Disease unresectable at laparoscopy</td><td>84</td><td>0</td></tr>
</table></td>
<td>N.B. authors report sensitivity of 88% and specificity of 100% for detection of resectable disease. However, these figures do not match the raw data reported in the article.

Other information

QUADAS 2 checklist

Patient selection

Risk of bias:

Was a consecutive or random sample of patients enrolled? Yes

Was a case-control design avoided? Yes

Did the study avoid inappropriate exclusions? Yes

Could the selection of participants have</td>
</tr>
</table>

Source of funding Not reported.		for histological confirmation.	was assessed.	<table><tr><td>Disease considered resectable at laparoscopy</td><td>27</td><td>305</td></tr><tr><td></td><td>111</td><td>305</td></tr></table> Sensitivity‡ (95% CI): 75.7% (66.6 to 83.3) Specificity‡ (95% CI): 100% (98.8 to 100) Positive likelihood ratio‡ (95% CI): ∞ (not calculable) Negative likelihood ratio‡ (95% CI): 0.24 (0.18 to 0.34) Positive predictive value‡ (95% CI): 26.7% (22.5 to 31.2) Negative predictive value‡ (95% CI): 100% (not calculable) † calculated by the NGA technical team from data	introduced bias? Low risk Applicability: Is there concern that the included participants do not match the review question? Low risk Index tests Risk of bias: Were the index tests interpreted without knowledge of the reference standard? Yes If a threshold was used, was it pre-specified? N/A Could the conduct or interpretation of the index test have introduced bias? Low risk Applicability: Is there concern that the index test, its conduct or interpretation differ

				reported in the article using http://statpages.info/confint.html ‡ calculated by the NGA technical team from data reported in the article using https://www.medcalc.org/calc/diagnostic_test.php	from the review question? Low risk Reference standard Risk of bias: Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? No Could the reference standard, its conduct or interpretation have introduced bias? Low risk Applicability: Is there concern that the target condition as defined by the reference standard does not match the review question? Low risk

					Flow and timing Risk of bias: Was there an appropriate interval between index tests and reference standard? Yes Did all participants receive a reference standard? Yes Did participants receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the participant flow have introduced bias? Low risk
Full citation Heath, E. I., Kaufman, H. S., Talamini, M. A., Wu, T. T., Wheeler, J., Heitmiller, R. F., Kleinberg, L., Yang,	Sample size n = 59 Characteristics	Tests Diagnostic laparoscopy was performed, with careful attention to	Methods Biopsies taken at diagnostic laparoscopy	Results Change of treatment plan following diagnostic laparoscopy	Limitations Majority of participants with a change in treatment plan were actually

S. C., Olukayode, K., Forastiere, A. A., The role of laparoscopy in preoperative staging of esophageal cancer, Surgical EndoscopySurg Endosc, 14, 495-9, 2000 Ref Id 559013 Country/ies where the study was carried out USA Study type Prospective cohort study Aim of the study To evaluate the role of diagnostic laparoscopy for patients with esophageal cancer. Study dates March 1995 to October 1998. Source of funding Not reported.	Characteristics / Number of participants Gender Male: 50 Female: 9 Ethnicity White: 57 Black: 2 Age in years, median (range): 60 (24-76) Histopathology of tumour Squamous cell carcinoma: 7 Adenocarcinoma: 52 Location of tumour	common sites of distant spread. Hickman catheter placement and feeding jejunostomy tube placement were conducted at the same time.	were analysed by frozen section. Findings of distant metastasis precluded neoadjuvant therapy and oesophagectomy for cure. Pre-operative staging involved CT scan and endoscopic ultrasound	10/59 (17%, 95% CI† 8 to 29) (n = 4 diagnosed with gastric carcinoma instead of oesophageal carcinoma, and underwent gastrectomy, n = 2 diagnosed with gastric carcinoma instead of oesophageal carcinoma and underwent palliation, n = 4 identified with previously unsuspected metastatic disease). Procedure related morbidity 2/59 (3%, 95% CI† 0 to 12) (n = 1 small bowel perforation requiring laparotomy and small bowel resection, n = 1 intraoperative pulmonary oedema secondary to unexpected aortic valve stenosis). † calculated by the NGA technical team using http://statpages.info/confint.html	misdiagnosed with oesophageal cancer, and their primary cancer was gastric in origin. Not designed as a diagnostic accuracy study, therefore no reference standard included. Other information QUADAS 2 checklist Patient selection Risk of bias: Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes Could the selection of participants have

	Upper oesophagus: 0 Middle oesophagus: 3 Distal oesophagus: 56 Inclusion Criteria Biopsy proven oesophageal cancer. Under consideration for combined-method therapy (neoadjuvant therapy and oesophagectomy) Disease capable of being encompassed within a single radiotherapy port. Exclusion Criteria Poor performance status/medically unfit to undergo laparoscopy and subsequent oesophagectomy. Metastatic disease identified by spiral CT scan or endoscopic ultrasound.				introduced bias? Low risk Applicability: Is there concern that the included participants do not match the review question? Low risk Index tests Risk of bias: Were the index tests interpreted without knowledge of the reference standard? Yes If a threshold was used, was it pre-specified? N/A Could the conduct or interpretation of the index test have introduced bias? Low risk Applicability: Is there concern that the index test, its conduct or interpretation differ

					from the review question? Low risk Reference standard Risk of bias: Is the reference standard likely to correctly classify the target condition? N?A Were the reference standard results interpreted without knowledge of the results of the index test? N/A Could the reference standard, its conduct or interpretation have introduced bias? N/A Applicability: Is there concern that the target condition as defined by the reference standard does not match the review question? Low risk

					Flow and timing Risk of bias: Was there an appropriate interval between index tests and reference standard? N/A Did all participants receive a reference standard? N/A Did participants receive the same reference standard? N/A Were all patients included in the analysis? Yes Could the participant flow have introduced bias? Low risk
Full citation Hsu, P. K., Lin, K. H., Wang, S. J., Huang, C. S., Wu, Y. C., Hsu, W. H., Preoperative positron	Sample size n=76 Characteristics	Tests The preoperative staging workup included physical examination,	Methods Two pathologists individually examined	Results N stage vs SUV max of extra-tumour uptake with cutoff value of 4.9 . (Statistical analysis using the	Limitations QUADAS 2 checklist Patient selection

<table>
<tr>
<td>emission tomography/computed tomography predicts advanced lymph node metastasis in esophageal squamous cell carcinoma patients, World Journal of SurgeryWorld J Surg, 35, 1321-6, 2011

Ref Id

514238

Country/ies where the study was carried out

Taiwan

Study type

Retrospective cohort study

Aim of the study

To examine the role of positron emission tomography/computed tomography (PET/CT) in lymph node staging of patients with oesophageal squamous cell carcinoma

Study dates</td>
<td>Mean Age±SD = 61.7±10.9 years
Male % = 63/76 (83%)
All oesophageal carcinoma

Inclusion Criteria

Patients undergoing oesophagectomy (Patients without distant metastasis or definite evidence of extensive adjacent organ invasion)

Exclusion Criteria

Patients without PET/CT data

Patients undergoing neoadjuvant chemoradiation

Patients with histologies other than squamous cell carcinoma</td>
<td>laboratory tests, oesophagogastroduodenoscopy, flexible bronchoscopy, barium oesophagography, CT scan from the neck to the upper abdomen and whole body PET/CT.

PET-CT: The standeard uptake value (SUV) maximum was assessed for quantitative analysis of FDG uptake. All perioesophageal FDG-avid lesions, which represent FDG uptake by regional lymph nodes were regarded as 'extra-tumour uptake'. The number of PET abnormalities were defined as the number of all FDG-avidd</td>
<td>the pathological slides whereas two experienced nuclear medicine physicians independently performed all the measurements.</td>
<td>ROC curve identified an SUVmax of 4.9 as the value optimised the sensitivity and specificity for predicting N2/N3 classification (area under curve was 0.768, p=0.004) in patients with positive extra-tumour uptake
<table>
<tr><td>SUV</td><td>N0</td><td>N1</td><td>N2/N3</td><td>p</td></tr>
<tr><td><4.9</td><td>28</td><td>20</td><td>10</td><td>0.001</td></tr>
<tr><td>>4.90</td><td>3</td><td>4</td><td>11</td><td></td></tr>
</table>
N stage vs number of PET abnormalities
<table>
<tr><td>No of NPAs</td><td>N0</td><td>N1</td><td>N2/N3</td><td>p</td></tr>
<tr><td>1</td><td>19</td><td>8</td><td>6</td><td><0</td></tr>
<tr><td>2</td><td>9</td><td>12</td><td>2</td><td></td></tr>
<tr><td>≥3</td><td>3</td><td>4</td><td>13</td><td></td></tr>
</table>
</td>
<td>Risk of bias:

Was a consecutive or random sample of patients enrolled? Yes

Was a case-control design avoided? Yes

Did the study avoid inappropriate exclusions? Yes

Could the selection of participants have introduced bias? Low risk

Applicability:

Is there concern that the included participants do not match the review question? Low risk

Index tests

Risk of bias:

Were the index tests interpreted without knowledge</td>
</tr>
</table>

March 2007 to January 2010 Source of funding Not reported		abnormalities on PET/CT. Oesophagectomy: Most patients underwent triincisional appraoch (right thoracotomy, midline laparotomy and left cervicotomy or video-assisted thoracoscopic oesophagectomy. For patients with poor cardiopulmonary reserve, transhiatal approach was offered whereas left-sided thoracoabdominal approach was performed on surgeon's preference. Patients were staged using AJCC TNM staging system. N2 and N3 were grouped together as advanced			of the reference standard? Unclear If a threshold was used, was it pre-specified? No Could the conduct or interpretation of the index test have introduced bias? high risk Applicability: Is there concern that the index test, its conduct or interpretation differ from the review question? Low risk Reference standard Risk of bias: Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the

		lymph node metastases			results of the index test? Unclear Could the reference standard, its conduct or interpretation have introduced bias? Unclear risk Applicability: Is there concern that the target condition as defined by the reference standard does not match the review question? Low risk Flow and timing Risk of bias: Was there an appropriate interval between index tests and reference standard? Unclear Did all participants receive a reference standard? Yes Did participants receive the same

					reference standard? Yes Were all patients included in the analysis? Yes. Could the participant flow have introduced bias? Low risk Other information
Full citation Kaiser, G. M., Sotiropoulos, G. C., Fruhauf, N. R., Stavrou, G. A., Peitgen, K., Pottgen, C., Gerken, G., Paul, A., Broelsch, C. E., Value of staging laparoscopy for multimodal therapy planning in esophago-gastric cancer, International SurgeryInt Surg, 92, 128-32, 2007 Ref Id 559080	Sample size n = 125 Characteristics n = 98 male n = 27 female n = 70 oesophageal/gastric cardia cancer Median age for oesophageal cancer 57, range 42-70 n = 55 gastric cancer	Tests Laparoscopy was performed under general anaesthetic. Special attention was paid to the detection of liver metastases, peritoneal seeding and ascites. Tumour involvement was verified by biopsy and histological workup.	Methods Prior to laparoscopy, all patients underwent abdominal ultrasound, CT scanning, gastroscopy and endosonography of the upper GI tract.	Results Change in management following laparoscopy 28/125 (22%, 95% CI 15 to 31)† (n = 28 previously unsuspected distant metastasis identified at laparoscopy, change to palliative treatment strategy) Procedure related morbidity 0/125 (0%, 95% CI 0 to 3)† † calculated by the NGA technical team from data reported in the article	Limitations Other information QUADAS 2 checklist Patient selection Risk of bias: Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes

Country/ies where the study was carried out Germany Study type Retrospective cohort study Aim of the study To assess the impact of staging laparoscopy in locally advanced oesophago-gastric malignancy. Study dates Not reported Source of funding Not reported	Median age for gastric cancer 60 years, range 25-73 Inclusion Criteria Known oesophageal or gastric cancer Locally advanced disease Exclusion Criteria Not reported.			using http://statpages.info/confint.html	Did the study avoid inappropriate exclusions? Yes Could the selection of participants have introduced bias? Low risk Applicability: Is there concern that the included participants do not match the review question? Low risk Index tests Risk of bias: Were the index tests interpreted without knowledge of the reference standard? Yes If a threshold was used, was it pre-specified? N/A Could the conduct or interpretation of the index test have introduced bias? Low risk

					Applicability: Is there concern that the index test, its conduct or interpretation differ from the review question? Low risk Reference standard Risk of bias: Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? No Could the reference standard, its conduct or interpretation have introduced bias? Low risk Applicability:

					Is there concern that the target condition as defined by the reference standard does not match the review question? Low risk Flow and timing Risk of bias: Was there an appropriate interval between index tests and reference standard? Yes Did all participants receive a reference standard? Yes Did participants receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the participant flow have introduced bias? Low risk

<table>
<tr>
<td>Full citation

Krasna, M. J., Jiao, X., Mao, Y. S., Sonett, J., Gamliel, Z., Kwong, K., Burrows, W., Flowers, J. L., Greenwald, B., White, C., Thoracoscopy/laparoscopy in the staging of esophageal cancer: Maryland experience, Surgical Laparoscopy, Endoscopy & Percutaneous TechniquesSurg Laparosc Endosc Percutan Tech, 12, 213-8, 2002

Ref Id

514346

Country/ies where the study was carried out

USA

Study type

Prospective cohort study

Aim of the study</td>
<td>Sample size

n = 55

(underwent laparoscopy and eventual surgical resection, larger numbers included in full study)

Characteristics

n = 91 male

n = 20 female

Mean age 62 years (range 38-81)

n = 53 squamous cell carcinoma

n = 54 adenocarcinoma

n = 2 small cell carcinoma

n = 2 poorly differentiated carcinoma

Inclusion Criteria

Pathologically confirmed oesophageal cancer.

Age >18 years old

Performance status score 0-2</td>
<td>Tests

Patients underwent combined thoracoscopic and laparoscopic staging. For the purpose of this analysis the results of laparoscopy only are included.</td>
<td>Methods

Diagnostic accuracy of laparoscopy was compared to the final pathological staging, obtained either through laparoscopy or definitive resection.</td>
<td>Results

Detection of nodal metastasis

<table>
<tr><td></td><td>Nodal metastasis

identified on final staging</td><td>No nod metast

identifi on fina staging</td></tr>
<tr><td>Nodal metastasis

identified at laparoscopy</td><td>20</td><td>0</td></tr>
<tr><td>No nodal metastasis

identified at laparoscopy</td><td>2</td><td>33</td></tr>
</table>
</td>
<td>Limitations

QUADAS 2 checklist

Patient selection

Risk of bias:

Was a consecutive or random sample of patients enrolled? Yes

Was a case-control design avoided? Yes

Did the study avoid inappropriate exclusions? Yes

Could the selection of participants have introduced bias? Low risk

Applicability:

Is there concern that the included participants do not match the review question? Low risk</td>
</tr>
</table>

To evaluate the potential benefits of thoracoscopic/laparoscopic staging over conventional clinical staging for oesophageal cancer. Study dates 1991 to 1999. Source of funding Not reported.	Exclusion Criteria Previous chemo- or radiotherapy within the last 5 years.			<table><tr><td></td><td>22</td><td>33</td><td>3 5</td></tr></table> Sensitivity (95% CI)†: 90.9 (70.8 to 98.9) Specificity (95% CI)†: 100 (89.4 to 100) Positive likelihood ratio‡ (95% CI): ∞ (not calculable) Negative likelihood ratio‡ (95% CI): 0.09 (0.02 to 0.34) Positive predictive value (95% CI)†: 100% (not calculable) Negative predictive value (95% CI)†: 94.3% (81.5 to 98.4) † 95% confidence interval calculated by the NGA technical team from data reported in the article ‡ calculated by the NGA technical team from data reported in the article using https://www.medcalc.org/calc/diagnostic_test.php	Index tests Risk of bias: Were the index tests interpreted without knowledge of the reference standard? No - index test formed part of the reference standard where relevant If a threshold was used, was it pre-specified? N/A Could the conduct or interpretation of the index test have introduced bias? Low risk Applicability: Is there concern that the index test, its conduct or interpretation differ from the review question? Low risk Reference standard Risk of bias:

					Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? No Could the reference standard, its conduct or interpretation have introduced bias? Low risk Applicability: Is there concern that the target condition as defined by the reference standard does not match the review question? Low risk Flow and timing Risk of bias: Was there an appropriate interval

<table>
<tr>
<td></td>
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<td></td>
<td>between index tests and reference standard? Yes

Did all participants receive a reference standard? Yes

Did participants receive the same reference standard? Yes

Were all patients included in the analysis? No - some participants did not undergo laparoscopy, and/or surgical resection

Could the participant flow have introduced bias? Serious risk.</td>
</tr>
<tr>
<td>Full citation

Little, S. G., Rice, T. W., Bybel, B., Mason, D. P., Murthy, S. C., Falk, G. W., Rybicki, L. A., Blackstone, E. H., Is FDG-PET indicated for superficial</td>
<td>Sample size

n=58

Characteristics

All patients had adenocarcinoma.</td>
<td>Tests

Endoscopic ultrasound was performed in 53 patients. PET scanning was performed 50±52</td>
<td>Methods</td>
<td>Results
<table><tr><td></td><td>PET/CT(+)</td><td>PET/CT(-)</td><td></td></tr><tr><td>pTis</td><td>5</td><td>6</td><td>1</td></tr><tr><td>pT1</td><td>26</td><td>21</td><td>4</td></tr></table></td>
<td>Limitations

QUADAS 2 checklist

Patient selection

Risk of bias:</td>
</tr>
</table>

esophageal cancer?, European Journal of Cardio-Thoracic SurgeryEur J Cardiothorac Surg, 31, 791-6, 2007 Ref Id 559165 Country/ies where the study was carried out USA Study type Retrospective cohort study Aim of the study To evaluate fluorodeoxyglucose positron emission tomography (FDG-PET) in clinical staging of superficial oesophageal tumour Study dates June 2003 to August 2005 Source of funding Not reported	Inclusion Criteria Superficial adenocarcinoma of the oesophagus (pTis [high grade dysplasia] or pT1) undergoing oesophagectomy Preoperative FDG-PET scanning Exclusion Criteria	days before oesophagectomy. Fifty-three (91%) had fused computed tomography PET scans (PET/CT), and five (9%) had PET without CT. The PET/CT studies were reviewed by one of three experienced nuclear medicine physicians. All patients proceeded to surgery without indication chemoradiotherapy. 38 (66%) had transhilatal oesophagectomy whereas 20(34%) had thoracoabdominal oesophagectomy with two-field lymph node sampling		pTis - High-grade dysplasia; T1- tumour invasion up to outer half of submucosa PET and pN Sensitivity: 0% PPV: 0% NPV: 89% Specificity: 94% Accuracy: 84%	Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes Could the selection of participants have introduced bias? Low risk Applicability: Is there concern that the included participants do not match the review question? Low risk Index tests Risk of bias: Were the index tests interpreted without knowledge of the reference standard? Unclear

					If a threshold was used, was it pre-specified? Unclear Could the conduct or interpretation of the index test have introduced bias? Unclear risk Applicability: Is there concern that the index test, its conduct or interpretation differ from the review question? Low risk Reference standard Risk of bias: Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unclear

					Could the reference standard, its conduct or interpretation have introduced bias? Unclear risk Applicability: Is there concern that the target condition as defined by the reference standard does not match the review question? Low risk Flow and timing Risk of bias: Was there an appropriate interval between index tests and reference standard? No - the scan was performed an average of 50 days prior to oesophagectomy Did all participants receive a reference standard? Yes

<table>
<tr><td></td><td></td><td></td><td></td><td></td><td>Did participants receive the same reference standard? Yes

Were all patients included in the analysis? Yes

Could the participant flow have introduced bias? High risk

Other information</td></tr>
<tr><td>Full citation

Menon, K. V., Dehn, T. C., Multiport staging laparoscopy in esophageal and cardiac carcinoma, Diseases of the EsophagusDis Esophagus, 16, 295-300, 2003

Ref Id

559210

Country/ies where the study was carried out</td><td>Sample size

N = 133

Characteristics

n = 108 male

n = 25 female

Mean age 64 (range 21 to 82 years)

Inclusion Criteria

Histologically proven carcinoma of the oesophagus or cardia.</td><td>Tests

Laparoscopy was performed, with inspection of the abdominal cavity, omentum, surfaces of the small bowel and peritoneum, liver surface, macroscopic lymph nodes, coeliac axis, posterior wall of the stomach and lesser sac.</td><td>Methods

Findings from laparoscopy were compared to those at laparotomy and final histology.

Pre-operative staging involved CT scan.</td><td>Results

Detection of liver metastasis
<table><tr><td></td><td>Liver metastasis identified

at final staging</td><td>No liver metasta

s

at final staging</td></tr><tr><td>Liver metastasis identified</td><td>10</td><td>1</td></tr></table></td><td>Limitations

Note specificity less than 100% for liver metastasis, therefore laparoscopic staging presumably based on visual inspection of the abdomen alone, without histological confirmation (otherwise negative histology would have been included in laparoscopic</td></tr>
</table>

UK Study type Prospective cohort study Aim of the study To assess the utility of laparoscopy as a staging procedure for patients with carcinoma of the oesophagus and cardia. Study dates February 1993 to September 2000. Source of funding Not reported.	Under assessment for possible surgical resection. Exclusion Criteria Not reported.	Biopsies were taken under direct vision, and fluid for cytology was obtained by needle aspiration.		<table><tr><td>at laparoscopy</td><td></td><td></td></tr><tr><td>No liver metastasis identified at laparoscopy</td><td>0</td><td>99</td></tr><tr><td></td><td>10</td><td>100</td></tr></table> Sensitivity (95% CI)†: 100% (69.2 to 100) Specificity (95% CI)†: 99% (94.6 to 100) Positive likelihood ratio‡ (95% CI): 100 (14.22 to 702.99) Negative likelihood ratio‡ (95% CI): 0.00 (not calculable) Positive predictive value‡ (95% CI): 90.9% (58.7 to 98.6)	<table><tr><td>99</td></tr><tr><td>11</td></tr><tr><td>0</td></tr></table> staging, and sensitivity would have been 100%). Other information QUADAS 2 checklist Patient selection Risk of bias: Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes Could the selection of participants have introduced bias? Low risk Applicability: Is there concern that the included participants do not

<table>
<tr>
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<td></td>
<td>Negative predictive value‡ (95% CI): 100% (not calculable)

Detection of nodal metastasis
<table>
<tr><th></th><th>Nodal metastasis identified at final staging</th><th>No nodal metasis at final staging</th></tr>
<tr><td>Nodal metastasis identified at laparoscopy</td><td>47</td><td>9</td></tr>
<tr><td>No nodal metastasis identified at laparoscopy</td><td>10</td><td>42</td></tr>
</table>
</td>
<td>match the review question? Low risk

Index tests

Risk of bias:

Were the index tests interpreted without knowledge of the reference standard? Yes

If a threshold was used, was it pre-specified? N/A

Could the conduct or interpretation of the index test have introduced bias? Low risk

Applicability:

Is there concern that the index test, its conduct or interpretation differ from the review question? Low risk

Reference standard

Risk of bias:</td>
</tr>
</table>

				<table><tr><td></td><td>57</td><td>51</td><td>108</td></tr></table> Sensitivity (95% CI)†: 82.5% (70.1 to 91.3) Specificity (95% CI)†: 82.4% (69.1 to 91.6) Positive likelihood ratio‡ (95% CI): 4.67 (2.55 to 8.56) Negative likelihood ratio‡ (95% CI): 0.21 (0.12 to 0.38) Positive predictive value‡ (95% CI): 83.9% (74.0 to 90.5) Negative predictive value‡ (95% CI): 80.8% (70.2 to 88.2) Detection of peritoneal metastasis <table><tr><td></td><td>Peritoneal metastasis identified</td><td>No peritoneal metastasis at final staging</td></tr></table>	Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? No Could the reference standard, its conduct or interpretation have introduced bias? Low risk Applicability: Is there concern that the target condition as defined by the reference standard does not match the review question? Low risk Flow and timing Risk of bias: Was there an appropriate interval

					at final staging			between index tests and reference standard? Yes
				Peritoneal metastasis identified at laparoscopy	12	0	12	Did all participants receive a reference standard? Yes Did participants receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the participant flow have introduced bias? Low risk
				No peritoneal metastasis identified at laparoscopy	0	99	99	
					12	99	111	
				Sensitivity (95% CI)†: 100% (73.5 to 100) Specificity (95% CI)†: 100% (96.3 to 100)				

				Positive likelihood ratio‡ (95% CI): ∞ (not calculable) Negative likelihood ratio‡ (95% CI): 0.00 (not calculable) Positive predictive value‡ (95% CI): 100% (not calculable) Negative predictive value‡ (95% CI): 100% (not calculable) † 95% confidence interval calculated by the NGA technical team from data reported in the article using https://www.medcalc.org/calc/diagnostic_test.php ‡ point estimate and 95% confidence interval calculated by the NGA technical team from data reported in the article using https://www.medcalc.org/calc/diagnostic_test.php	
Full citation	Sample size	Tests	Methods	Results	Limitations

Mirza, A., Galloway, S., Laparoscopy, computerised tomography and fluorodeoxyglucose positron emission tomography in the management of gastric and gastro-oesophageal junction cancers, Surgical Endoscopy and Other Interventional Techniques, 30, 2690-2696, 2016 Ref Id 507933 Country/ies where the study was carried out UK Study type Retrospective cohort study Aim of the study To evaluate the utility of diagnostic laparoscopy, in comparison with CT and FDG-PET for patients with oesophago-gastric junction and gastric cancers.	n = 387 Characteristics n = 253 male n = 143 female Median age 61 years (range 39 to 86) Tumour site: n = 175 gastric n = 212 GOJ Differentiation n = 106 well differentiated n = 123 moderately differentiated n = 158 poorly differentiated Inclusion Criteria	Staging laparosopy was performed under general anaesthetic. A standard three port technique was used. The whole peritoneal cavity was examined, including pelvis, oesophageal hiatus, undersurface of the left lobe of the liver, anterior surface of the stomach, greater and lesser omentum. If ascitic fluid was identified, the sample was obtained for cytological examination, but peritoneal washings were not routinely taken. Any abnormal peritoneal nodule or abnormal tissue was biopsied.	Pre-operative imaging included staging CT scan for all participants. FDG-PET was also performed in 21% of gastric cancer and 56% of oesophageal cancer patients.	Change in management following laparoscopy 64/387 (17%, 95% CI 13 to 21)† (n = 54 unresectable disease, n = 10 downgraded from staging on CT scan and underwent curative resection or neoadjuvant treatment). Diagnostic accuracy N.B. insufficient data are reported to allow reconstruction of the 2x2 tables for diagnostic accuracy. Sensitivity and specificity are reported, and positive and negative likelihood ratios have bee calculated from these. Detection of T1/T2 disease Sensitivity: 85% Specificity: 92% Positive likelihood ratio‡: 10.63 Negative likelihood ratio‡: 0.16	N.B. sensitivity for laparoscopy reported as less then 100%, therefore presumably figures are calculated using visual inspection of the pelvis alone, and not histological assessment. Other information QUADAS 2 checklist Patient selection Risk of bias: Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes Could the selection of participants have

Study dates 1996 to 2013. Source of funding Not reported.	Confirmed histological diagnosis of malignancy GOJ or gastric cancer Exclusion Criteria Known metastatic disease Advanced co-morbidities (unfit for surgery).			Detection of T3 disease Sensitivity: 82% Specificity: 86% Positive likelihood ratio‡: 5.86 Negative likelihood ratio‡: 0.21 Detection of T4 disease Sensitivity: 84% Specificity: 89% Positive likelihood ratio‡: 7.64 Negative likelihood ratio‡: 0.18 Detection of N0 disease Sensitivity: 82% Specificity: 79% Positive likelihood ratio‡: 3.90	introduced bias? Low risk Applicability: Is there concern that the included participants do not match the review question? Low risk Index tests Risk of bias: Were the index tests interpreted without knowledge of the reference standard? Yes If a threshold was used, was it pre-specified? N/A Could the conduct or interpretation of the index test have introduced bias? Low risk Applicability: Is there concern that the index test, its conduct or interpretation differ

				Negative likelihood ratio‡: 0.23 Detection of N1 disease Sensitivity: 66% Specificity: 86% Positive likelihood ratio‡: 4.71 Negative likelihood ratio‡: 0.40 Detection of N2 disease Sensitivity: 89% Specificity: 89% Positive likelihood ratio‡: 8.09 Negative likelihood ratio‡: 0.12 Detection of metastatic disease Sensitivity: 83%	from the review question? Low risk Reference standard Risk of bias: Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? No Could the reference standard, its conduct or interpretation have introduced bias? Low risk Applicability: Is there concern that the target condition as defined by the reference standard does not match the review question? Low risk

				Specificity: 92% Positive likelihood ratio‡: 10.38 Negative likelihood ratio‡: 0.18 † 95% confidence interval calculated by the NGA technical team from data reported in the article using http://statpages.info/confint.html ‡ calculated by the NGA using data reported in the article.	Flow and timing Risk of bias: Was there an appropriate interval between index tests and reference standard? Yes Did all participants receive a reference standard? Yes Did participants receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the participant flow have introduced bias? Low risk
Full citation Molloy, R. G., McCourtney, J. S., Anderson, J. R., Laparoscopy in the	Sample size N = 244 Characteristics	Tests Laparoscopy was performed as a separate procedure under	Methods Findings at laparoscopy were compared to	Results Change in treatment plan 103/244 (42%, 95% CI 36 to 49%)[1]	Limitations Other information QUADAS 2 checklist

<table>
<tr>
<td>management of patients with cancer of the gastric cardia and oesophagus, British Journal of SurgeryBr J Surg, 82, 352-4, 1995

Ref Id

559225

Country/ies where the study was carried out

UK

Study type

Prospective cohort study

Aim of the study

To examine the value of laparoscopy in determining intra-abdominal status and suitability for resection.

Study dates

August 1984 to July 1992.

Source of funding

Not reported.</td>
<td>n = 165 male

n = 79 female

Mean age 66 years (range 30-49[sic])

n = 165 adenocarcinoma

n = 76 squamous cell carcinoma

n = 2 adenosquamous

n =1 carcinoid

Inclusion Criteria

Previously untreated, biopsy proven carcinoma of the oesophagus or gastric cardia.

Under consideration for resection

Exclusion Criteria

Evidence of metastatic disease.</td>
<td>general anasthesia. Percutaneous liver biopsy under direct vision was performed as clinically indicated.</td>
<td>final staging outcomes and treatment decisions.

Pre-operative staging included CT scan and ultrasound. Rigid bronchoscopy was performed in patients with lesions affectin the upper or middle third of the oesophagus.</td>
<td>(n = 103 participants avoided unnecessary laparotomy due to findings at laparoscopy)

Procedure related morbidity

11/244 (5%, 95% CI 2 to 8%)[1]

(n = 11 participants showed cardiovascular instability or slow functional recovery following laparoscopy, indicating unsuitability for further surgery)

Identification of hepatic metastasis
<table>
<tr><td></td><td>Hepatic metastasis on final staging</td><td>No hepatic metastasis on final staging</td></tr>
<tr><td>Hepatic metastasis</td><td>75</td><td>0</td></tr>
</table>
</td>
<td>Patient selection

Risk of bias:

Was a consecutive or random sample of patients enrolled? Yes

Was a case-control design avoided? Yes

Did the study avoid inappropriate exclusions? Yes

Could the selection of participants have introduced bias? Low risk

Applicability:

Is there concern that the included participants do not match the review question? Low risk

Index tests

Risk of bias:

Were the index tests interpreted without knowledge</td>
</tr>
</table>

				at laparoscopy No hepatic metastasis at laparoscopy 169 244 Sensitivity (95% CI)²: 96.2% (89.2 to 99.2) Specificity (95% CI)²: 100% (97.8 to 100) Positive likelihood ratio³ (95% CI): ∞ (not calculable) Negative likelihood ratio³ (95% CI): 0.04 (0.01 to 0.12) Positive predictive value³ (95% CI): 100% (not calculable) Negative predictive value³ (95% CI): 98.2% (94.8 to 99.4) 3 166 78 166 of the reference standard? Yes If a threshold was used, was it pre-specified? N/A Could the conduct or interpretation of the index test have introduced bias? Low risk Applicability: Is there concern that the index test, its conduct or interpretation differ from the review question? Low risk Reference standard Risk of bias: Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the

				[1] 95% CI calculated by the NGA technical team from data reported in the article using http://statpages.info/confint.html [2] 95% confidence interval calculated by the NGA technical team from data reported in the article using https://www.medcalc.org/calc/diagnostic_test.php [3] point estimate and 95% confidence interval calculated by the NGA technical team from data reported in the article using https://www.medcalc.org/calc/diagnostic_test.php	results of the index test? No Could the reference standard, its conduct or interpretation have introduced bias? Low risk Applicability: Is there concern that the target condition as defined by the reference standard does not match the review question? Low risk Flow and timing Risk of bias: Was there an appropriate interval between index tests and reference standard? Yes Did all participants receive a reference standard? Yes Did participants receive the same

					reference standard? Yes Were all patients included in the analysis? Yes Could the participant flow have introduced bias? Low risk
Full citation Munasinghe, A., Kazi, W., Taniere, P., Hallissey, M. T., Alderson, D., Tucker, O., The incremental benefit of two quadrant lavage for peritoneal cytology at staging laparoscopy for oesophagogastric adenocarcinoma, Surgical EndoscopySurg Endosc, 27, 4049-53, 2013 Ref Id 559241 Country/ies where the study was carried out UK	Sample size N = 316 Characteristics n = 242 male n = 74 female Mean age 67.9 years (standard deviation 11.9) Tumour location: n = 174 oesophageal/junctional n = 142 gastric Inclusion Criteria	Tests Staging laparoscopy was conducted with a standard three port technique. Samples of detectable ascites were aspirated for cytological evaluation. Peritoneal pelvic lavage was performed, followed by subphrenic lavage. The primary tumour was assessed where	Methods Initial diagnosis and staging were based on gastrointestinal endoscopy and biopsy, CT of the thorax, abdomen and pelvis, PET-CT and endoscopic ultrasound. The incremental value of	Results Change in management following laparoscopy 71/316 (22%, 95% CI 18 to 27)† (n = 28 visible peritoneal metastases, confirmed on biopsy, n = 43 positive cytology in the absence of overt peritoneal disease) Procedure related complications 1/316 (0.3%, 95% CI 0 to 2)† (n = 1 perioperative myocardial infarction)	Limitations Other information QUADAS 2 checklist Patient selection Risk of bias: Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes

Study type Retrospective cohort study Aim of the study To compare peritoneal lavage cytology from the subphrenic and pelvic spaces with that of the pelvis alone in patients with potentially resectable oesophagogastric adenocarcinoma. Study dates November 2006 to November 2010. Source of funding Not reported.	Histologically proven oesophageal, junctional or gastric adenocarcinoma. Exclusion Criteria Not reported.	possible. Biopsies were taken of suspicious lesions at the end of the procedure.	staging laparoscopy in addition to these procedures was assessed.	†calculated by the NGA technical team from data reported in the article using http://statpages.info/confint.html	Could the selection of participants have introduced bias? Low risk Applicability: Is there concern that the included participants do not match the review question? Low risk Index tests Risk of bias: Were the index tests interpreted without knowledge of the reference standard? Yes If a threshold was used, was it pre-specified? N/A Could the conduct or interpretation of the index test have introduced bias? Low risk Applicability:

					Is there concern that the index test, its conduct or interpretation differ from the review question? Low risk Reference standard Risk of bias: Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? No Could the reference standard, its conduct or interpretation have introduced bias? Low risk Applicability: Is there concern that the target condition as defined

					by the reference standard does not match the review question? Low risk Flow and timing Risk of bias: Was there an appropriate interval between index tests and reference standard? Yes Did all participants receive a reference standard? Yes Did participants receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the participant flow have introduced bias? Low risk
Full citation	Sample size	Tests	Methods	Results	Limitations

Nguyen, N. T., Roberts, P. F., Follette, D. M., Lau, D., Lee, J., Urayama, S., Wolfe, B. M., Goodnight, J. E., Evaluation of minimally invasive surgical staging for esophageal cancer, American Journal of SurgeryAm J Surg, 182, 702-6, 2001 Ref Id 559262 Country/ies where the study was carried out USA Study type Prospective cohort study Aim of the study To evaluate the role of minimally invasive surgical staging for patients with oesophageal cancer. Study dates December 1998 to February 2001. Source of funding	N = 33 Characteristics n = 24 female n = 9 male Tumour location: n = 26 distal oesophagus n = 6 mid oesophagus n = 1 proximal oesophagus Tumour histology n = 24 adenocarcinoma n = 9 squamous cell carcinoma Inclusion Criteria Known oesophageal carcinoma. Exclusion Criteria Not reported.	Minimally invasive surgical staging comprised laparoscopic staging, bronchoscopy, oesophagoscopy and laparoscopic ultrasonography of the liver.	Minimally invasive staging was performed before the surgical resection procedure to evaluate patients for enrollment into a neoadjuvant chemotherapy protocol. All participants had a preoperative CT scan of the chest and abdomen, and 27/33 had endoscopic ultrasonography.	N.B. results show change in management based on results of lapaorsocpy only, not full MIS strategy Change in management following laparoscopic staging 8/33 (24%, 95% CI 11 to 42%)† (n = 8 found to have unresectable disease on laparoscopy). N.B. a total of 12 patients had management altered following entire MIS procedure, but 3 of these were found during thoracoscopy, and 1 during laparoscopic ultrasound Procedure related morbidity 2/33 (6%, 95% CI 0 to 20)† n = 1 bladder perforation requiring conversion to laparotomy, n = 1 port site infection	Other information QUADAS 2 checklist Patient selection Risk of bias: Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes Could the selection of participants have introduced bias? Low risk Applicability: Is there concern that the included participants do not match the review question? Low risk Index tests

Not reported.				† calculated by the NGA technical team from data reported in the article using http://statpages.info/confint.html	Risk of bias: Were the index tests interpreted without knowledge of the reference standard? Yes If a threshold was used, was it pre-specified? N/A Could the conduct or interpretation of the index test have introduced bias? Low risk Applicability: Is there concern that the index test, its conduct or interpretation differ from the review question? Low risk Reference standard Risk of bias: Is the reference standard likely to correctly classify the target condition? Yes

					Were the reference standard results interpreted without knowledge of the results of the index test? No Could the reference standard, its conduct or interpretation have introduced bias? Low risk Applicability: Is there concern that the target condition as defined by the reference standard does not match the review question? Low risk Flow and timing Risk of bias: Was there an appropriate interval between index tests and reference standard? Yes

					Did all participants receive a reference standard? Yes Did participants receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the participant flow have introduced bias? Low risk
Full citation Nieveen Van Dijkum, E. J. M., De Wit, L. Th, Van Delden, O. M., Kruyt, P. M., Van Lanschot, J. J. B., Rauws, E. A. J., Obertop, H., Gouma, D. J., Staging laparoscopy and laparoscopic ultrasonography in more than 400 patients with upper gastrointestinal carcinoma, Journal of the American College of	Sample size N = 92 (N.B. additional patients were included in the study, but these participants had other malignancies, including hepatic, pancreatic or bile duct) Characteristics n = 68 male n = 24 female	Tests Laparoscopy was performed under general anaesthetic. Ultrasonography was used to examine the liver for intrahepatic metastases, to evaluate the pancreas and the portal and superior	Methods Preoperative staging included the following: ultrasonography of the neck, chest X-ray and ultrasonography combined with colour-	Results Change in management following laparoscopy 10/87 (11%, 95% CI 6 to 20)† (n = 10 participants who did not undergo laparotomy due to identification of metastatic disease at laparoscopy)	Limitations Participants included any oesophageal cancer when recruited before 1995 (n = 52). Preliminary data indicated that laparoscopy was of limited benefit for those with mid/upper oesophageal tumours, therefore

SurgeonsJ Am Coll Surg, 189, 459-465, 1999 Ref Id 559269 Country/ies where the study was carried out The Netherlands Study type Retrospective cohort study Aim of the study To assess the benefit of diagnostic laparoscopy for staging in patients with oesophageal, gastroesophageal junction and hepatopancreaticobiliary tumours. Study dates June 1992 and December 1996. Source of funding Not reported.	Mean age 62 years Tumour location: n = 56 oesophagus n = 36 gastroesophageal junction Inclusion Criteria Known oesophageal-gastric tumour Exclusion Criteria Insufficient laparoscopic examination (due to adhesions from previous surgery).	mesenteric vessels, and to examine the coeliac axis for lymph node metastasis. Biopsies of suspected metastatic lesions were taken under direct vision or ultrasound guidance.	Doppler of the abdomen. Endoscopic ultrasonography was conducted, and bronchoscopy for proximal tumours. Indirect laryngoscopy was also performed.	†calculated by the NGA technical team from data reported in the article using http://statpages.info/confint.html	participants recruited after 1995 had gastroesophageal junctional tumours only (n = 35). The avoidance of laparotomy was higher in the latter group (7/35) as compared to the former (3/52). Other information QUADAS 2 checklist Patient selection Risk of bias: Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes Could the selection of participants have

					introduced bias? Low risk Applicability: Is there concern that the included participants do not match the review question? High risk - included participants were of two groups - initially those with mid/upper oesophageal cancer were included, but these were excluded from later recruitment. Therefore the value of laparoscopy for junctional tumours may be underestimated (due to the inclusion of participants in whom laparoscopy yielded little information). Index tests Risk of bias:

					Were the index tests interpreted without knowledge of the reference standard? Yes If a threshold was used, was it pre-specified? N/A Could the conduct or interpretation of the index test have introduced bias? Low risk Applicability: Is there concern that the index test, its conduct or interpretation differ from the review question? Low risk Reference standard Risk of bias: Is the reference standard likely to correctly classify the target condition? Yes

					Were the reference standard results interpreted without knowledge of the results of the index test? No Could the reference standard, its conduct or interpretation have introduced bias? Low risk Applicability: Is there concern that the target condition as defined by the reference standard does not match the review question? Low risk Flow and timing Risk of bias: Was there an appropriate interval between index tests and reference standard? Yes

					Did all participants receive a reference standard? Yes Did participants receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the participant flow have introduced bias? Low risk
Full citation O'Brien, M. G., Fitzgerald, E. F., Lee, G., Crowley, M., Shanahan, F., O'Sullivan, G. C., A prospective comparison of laparoscopy and imaging in the staging of esophagogastric cancer before surgery, American Journal of GastroenterologyAm J Gastroenterol, 90, 2191-4, 1995	Sample size n=145 Characteristics Age: 65±10.3 yrs Male: 66% 21%SCC and 76% adenocarcinoma Site of adenocarcima tumour: stomach (57/110), GE junction (39/110) and distal oesophagus (14/110)	Tests Upper GI endoscopy and biopsy, and combined staging (abdominal ultrasound and CT of chest and abdomen) were performed on every patient. Laparoscope: A storze oblique	Methods "Of 186 presenting patients, 145 were recruited to the study." The study did not mention why they did not recruit the rest 41 patients.	Results Four of 145 patients who were negative for metastases refused surgery and were excluded from the analyses. Out of 141 included, 106 patients who were negative for disseminated disease by laparoscopic staging went on for surgical exploration. Among them, 98 patients received curative resection, 4 underwent palliative bypass and 4 were false negatives.	Limitations QUADAS 2 checklist Patient selection Risk of bias: Was a consecutive or random sample of patients enrolled? Yes

<table>
<tr>
<td>Ref Id

559294

Country/ies where the study was carried out

Ireland

Study type

Prospective cohort

Aim of the study

To carry out a prospective comparison of laparoscopy and combined imaging (CT and ultrasound) in the preoperative staging of distal oesophageal and gastric cancer in patients who were selected for surgery

Study dates

August 1989 and July 1994

Source of funding

Health Research Board of Ireland and the Cancer Research Appeal</td>
<td>Inclusion Criteria

All patients referred for treatment of carcinoma of distal oesophagus or stomach

Exclusion Criteria

Patients with clinically evident metastatic disease
Patients unfit for radical excisional surgery</td>
<td>viewing with a Wiest Laproflow Insufflator; was done under GA with intermittent positive pressure ventilation; was inserted subumbilically, if feasible. If indicated, biopsy were taken. Laparoscopy and scanning was done 2 weeks before the definitive surgery.

Standard test: histologically proven metastatic disease outside the potential field of resection</td>
<td>"The radiologist and laparoscopist were blinded to the results of their colleagues' investigations".</td>
<td>Of 35 patients with metastases, 7 patients underwent surgical palliation whereas 28 patients received non-surgical treatment.

Number of patients with metastases (outside the field of resection) being detected preopertively by laparoscopy/Total number of patients assessed

Stomach (AC): 16/57 (28%)
GEJ (AC): 8/39(22%)
Oesophagus (AC): 6/14 (43%)
SCC: 5/30 (17%)
Other: 0/5

At surgery, four more patients (AC stomach) were discovered to have metastases.

Staging of AC of Oesophagogastric region (n=106)
<table>
<tr><td></td><td>Sensitivi (%)</td><td>Specifici (%)</td></tr>
<tr><td>USG</td><td>8/30(27)</td><td>76/76(100)</td></tr>
</table>
</td>
<td>Was a case-control design avoided? Yes

Did the study avoid inappropriate exclusions? Yes

Could the selection of participants have introduced bias? Low risk

Applicability:

Is there concern that the included participants do not match the review question? Low risk

Index tests

Risk of bias:

Were the index tests interpreted without knowledge of the reference standard? Yes

If a threshold was used, was it pre-specified? N/A</td>
</tr>
</table>

				CT	11/30(37)	75/76(99)	Could the conduct or interpretation of the index test have introduced bias? Low risk Applicability: Is there concern that the index test, its conduct or interpretation differ from the review question? Low risk Reference standard Risk of bias: Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unclear Could the reference standard, its conduct or interpretation have
				Combined imaging	11/30(37)	75/76(99)	
				Laparoscopy	29/30(97)	72/76(95)	
				Laparoscopy+ biopsy	29/30(97)	76/76(100)	

					introduced bias? Low risk Applicability: Is there concern that the target condition as defined by the reference standard does not match the review question? Low risk Flow and timing Risk of bias: Was there an appropriate interval between index tests and reference standard? Yes Did all participants receive a reference standard? Yes Did participants receive the same reference standard? Yes Were all patients included in the analysis? Yes

<table>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Could the participant flow have introduced bias? Low risk

Other information</td>
</tr>
<tr>
<td>Full citation

Pech, O., Gunter, E., Dusemund, F., Origer, J., Lorenz, D., Ell, C., Accuracy of endoscopic ultrasound in preoperative staging of esophageal cancer: results from a referral center for early esophageal cancer, EndoscopyEndoscopy, 42, 456-61, 2010

Ref Id

545107

Country/ies where the study was carried out

Germany

Study type</td>
<td>Sample size

n=100

Characteristics

Mean age in years: 64.53 years Male %: 80%

Inclusion Criteria

Patients with confirmed early cancer in Barrett's oesophagus

Exclusion Criteria

Patients with prior CT for staging done by the referring physicians</td>
<td>Tests

All patients with proven cancer had intensive staging using endoscopic ultrasound (EUS) and helical CT of the chest and upper abdominal organs. They also underwent abdominal ultrasound examination to detect intraabdominal lesions. These patients were then categorised to 1) patients without any suspicious lymph nodes; 2) patients with</td>
<td>Methods</td>
<td>Results

Staging accuracy of correct T1m-category staging with miniprobe EUS
<table>
<tr><td></td><td>pT1m correct</td><td>pT1m n correct</td></tr>
<tr><td>EUS-+ve</td><td>39</td><td>13</td></tr>
<tr><td>EUS-ve</td><td>5</td><td>5</td></tr>
</table>
Staging accuracy of correct T1sm-category staging with miniprobe EUS
<table>
<tr><td></td><td>pTsm correct</td><td>pTsm n correct</td></tr>
<tr><td>EUS +ve</td><td>3</td><td>6</td></tr>
</table>
</td>
<td>Limitations

QUADAS 2 checklist

Patient selection

Risk of bias:

Was a consecutive or random sample of patients enrolled? Yes

Was a case-control design avoided? Yes

Did the study avoid inappropriate exclusions? Unclear

Could the selection of participants have</td>
</tr>
</table>

Prospective cohort study Aim of the study To evaluate computed tomography (CT) and endoscopic ultrasound (USG) as part of the regular staging protocol in oesophageal cancer in patients with early cancer of Barrett's oesophagus Study dates October 1999 to October 2001 Source of funding None		mediastinal or celiac lymph nodes > 1 cm in size or lymph nodes < 1 cm at the tumour level without suspicious EUS characteristics and 3) patients with lymph node > 1 cm at the tumour level or round and hypoechoic lymph nodes with sharp margins on EUS independent of size and location. The gold standard for assessing T category was histology (based on endoscopic resection or surgical specimens). When advanced carcinoma (>T1) was suspected after the staging process, patients were referred for surgery.		EUS - ve | 8 | 45 Staging accuracy of identifying T1 from T2 or T3 staging with miniprobe EUS | | pT1 | >pT1 | | EUS-T1 | 55 | 0 | | EUS>T1 | 0 | 7 | pT1m=mucosal carcinoma on histology; pT1sm=submucosal carcinoma on histology; pT2= carcinoma invading muscular layer on histology; pT3=carcinoma invading serosa on histology Out of 100 patients, 23 patients were scheduled for surgery. Eleven of them finally had surgery while others were unfit or declined the surgery. Five of them had mucosal invasion whereas	introduced bias? Unclear risk Applicability: Is there concern that the included participants do not match the review question? Low risk Index tests Risk of bias: Were the index tests interpreted without knowledge of the reference standard? Unclear If a threshold was used, was it pre-specified? N/A Could the conduct or interpretation of the index test have introduced bias? Unclear risk Applicability: Is there concern that the index test, its conduct or interpretation differ

<table>
<tr>
<td></td>
<td></td>
<td>Patients with suspected advanced cancer (>T1) were referred for surgery. If they were unfit or declined surgery and chemoradiotherapy, they were treated endoscopically with palliative intent. Patients with mucosal cancer received curative endoscopic resection. In patients with category 2 lymph nodes, the further procedure depended on the local tumour stage assessed using diagnostic endoscopic resection</td>
<td></td>
<td>six of them had malignancy on pathology (T2: n=4 and T3: n=2)

Lymph node staging EUS compared with pathology at surgical resection (n=11)
<table>
<tr><th></th><th>Ref+ve</th><th>Ref -ve</th></tr>
<tr><td>Index +ve</td><td>6</td><td>0</td></tr>
<tr><td>Index -ve</td><td>2</td><td>3</td></tr>
</table>
calculated by the NGA technical team from data reported in the article using https://www.medcalc.org/calc/diagnostic_test.php</td>
<td>from the review question? Low risk

Reference standard

Risk of bias:

Is the reference standard likely to correctly classify the target condition? Yes

Were the reference standard results interpreted without knowledge of the results of the index test? Unclear

Could the reference standard, its conduct or interpretation have introduced bias? Unclear risk

Applicability:

Is there concern that the target condition as defined by the reference standard does not match the review question? Low risk</td>
</tr>
</table>

					Flow and timing Risk of bias: Was there an appropriate interval between index tests and reference standard? Unclear Did all participants receive a reference standard? Yes with T staging but not N staging Did participants receive the same reference standard? Yes Were all patients included in the analysis? Yes. Could the participant flow have introduced bias? Unclear risk Other information
Full citation	Sample size	Tests	Methods	Results	Limitations

<table>
<tr>
<td>Pech, O., May, A., Gunter, E., Gossner, L., Ell, C., The impact of endoscopic ultrasound and computed tomography on the TNM staging of early cancer in Barrett's esophagus, American Journal of GastroenterologyAm J Gastroenterol, 101, 2223-2229, 2006

Ref Id

486403

Country/ies where the study was carried out

Germany

Study type

Prospective cohort study

Aim of the study

To investigate the staging accuracy of endoscopic ultrasound in oesophageal cancer

Study dates

February 2003 to December 2007</td>
<td>n=179

Characteristics

Mean age= 64.4 years
Male %= 79% (142/179)
Adenocarcinoma: SCC = 134:45

Inclusion Criteria

Patients with Barrett's adenocarcinoma or squamous cell carcinoma of the oesophagus who had received EUS staging at our department

Exclusion Criteria</td>
<td>All the investigations were done by two experienced endosonographers. Before endoscopic ultrasound (EUS), all of the patients had oesophagogastroscopy. Patients with stenotic lesions received bougienage and EUS was done 1 day later.

Lymph nodes were regarded as malignant if size≥10 mm, round shape, hypoechoic pattern and clearly visible borders. Moreover, abdominal and thoracic CT and abdominal ultrasound was done in all patients. Surgery was performed 2-</td>
<td></td>
<td>Diagnostic performance of EUS by T stage (%, 95%CI)

<table>
<tr><td></td><td>T1</td><td>T2</td><td>T</td></tr>
<tr><td>Sensitivity</td><td>82(73-89)</td><td>43(26-62)</td><td>8
9</td></tr>
<tr><td>Specificity</td><td>91(82-96)</td><td>85(78-90)</td><td>8
9</td></tr>
<tr><td>PPV</td><td>92(84-96)</td><td>37(22-55)</td><td>6
7</td></tr>
<tr><td>NPV</td><td>80(70-88)</td><td>88(82-93)</td><td>9
9</td></tr>
<tr><td>Accuracy</td><td colspan="3">74(66-80)</td></tr>
</table>

Diagnostic performance of EUS in N staging

<table>
<tr><td></td><td>pN0</td><td>pN1</td></tr>
<tr><td>EUS N0</td><td>82</td><td>20</td></tr>
<tr><td>EUS N1</td><td>29</td><td>48</td></tr>
</table>

<table>
<tr><td></td><td>%(95%CI)</td></tr>
</table>
</td>
<td>QUADAS 2 checklist

Patient selection

Risk of bias:

Was a consecutive or random sample of patients enrolled? Yes

Was a case-control design avoided? Yes

Did the study avoid inappropriate exclusions? No- the study excluded patients with curative endoscopic therapy, palliative endoscopic therapy and inclusion in other EUS study

Could the selection of participants have introduced bias? High risk

Applicability:

Is there concern that the included</td>
</tr>
</table>

Source of funding Not reported		4 weeks after staging. The study included only patients who underwent surgical treatment.		<table><tr><td>Sensitivity</td><td>71(58-81)</td></tr><tr><td>Specificity</td><td>74(65-82)</td></tr><tr><td>PPV</td><td>62(51-73)</td></tr><tr><td>NPV</td><td>80(71-87)</td></tr></table> calculated by the NGA technical team from data reported i the article using https://www.medcalc.org/calc/diagnostic_test.php	participants do not match the review question? Low risk Index tests Risk of bias: Were the index tests interpreted without knowledge of the reference standard? Unclear If a threshold was used, was it pre-specified? N/A Could the conduct or interpretation of the index test have introduced bias? Unclear risk Applicability: Is there concern that the index test, its conduct or interpretation differ from the review question? Low risk Reference standard Risk of bias:

					Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unclear Could the reference standard, its conduct or interpretation have introduced bias? Unclear risk Applicability: Is there concern that the target condition as defined by the reference standard does not match the review question? Low risk Flow and timing Risk of bias: Was there an appropriate interval

					between index tests and reference standard? Unclear Did all participants receive a reference standard? Yes Did participants receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the participant flow have introduced bias? Low risk Other information
Full citation Romijn, M. G., Van Overhagen, H., Spillenaar Bilgen, E. J., Ijzermans, J. N. M., Tilanus, H. W., Lameris, J. S., Laparoscopy and laparoscopic ultrasonography in staging	Sample size N = 60 Characteristics n = 54 male n = 6 female	Tests Combined laparoscopy and laparoscopic ultrasonography was performed under general anaesthesia.	Methods The number of additional metastases identified with these techniques was reported, as	Results N.B. results of laparoscopy only are reported here. Change in management plan following laparoscopy 5/60 (8%, 95% CI 3 to 18%)†	Limitations Other information QUADAS 2 checklist Patient selection Risk of bias:

of oesophageal and cardial carcinoma, British Journal of SurgeryBr J Surg, 85, 1010-1012, 1998 Ref Id 559410 Country/ies where the study was carried out The Netherlands Study type Prospective cohort study Aim of the study To assess the utility of laparoscopy and laparoscopic ultrasound in patients with oesophageal carcinoma. Study dates October 1993 to January 1996 Source of funding Not reported.	Mean age 61.7 years (range 43 to 79) n = 40 carcinoma of the oesophagus (including n = 15 squamous cell carcinoma and n = 25 adenocarcinoma) n = 20 adenocarcinoma of the gastric cardia Inclusion Criteria Biopsy proven carcinoma of the oesophagus or gastric cardia. Exclusion Criteria Metastasis identified on preoperative imaging (gastroscopy, bronchoscopy, ultrasonography of supraclavicular region and abdomen, CT scan of the chest and upper abdomen or endosonography).		was the sensitivity and specificity of laparoscopy and laparoscopic ultrasound to identify metastatic disease.	(n = 1 liver metastasis, n = 3 peritoneal metastasis, n = 1 omental metastasis) † calculated by the NGA technical team from data reported in the article, using http://statpages.info/confint.html	Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes Could the selection of participants have introduced bias? Low risk Applicability: Is there concern that the included participants do not match the review question? Low risk Index tests Risk of bias: Were the index tests interpreted without knowledge of the reference standard? Yes

					If a threshold was used, was it pre-specified? N/A Could the conduct or interpretation of the index test have introduced bias? Low risk Applicability: Is there concern that the index test, its conduct or interpretation differ from the review question? Low risk Reference standard Risk of bias: Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? No

					Could the reference standard, its conduct or interpretation have introduced bias? Low risk Applicability: Is there concern that the target condition as defined by the reference standard does not match the review question? Low risk Flow and timing Risk of bias: Was there an appropriate interval between index tests and reference standard? Yes Did all participants receive a reference standard? Yes Did participants receive the same reference standard? Yes

<table>
<tr><td></td><td></td><td></td><td></td><td></td><td>Were all patients included in the analysis? Yes

Could the participant flow have introduced bias? Low risk</td></tr>
<tr><td>Full citation

Salahudeen, H. M., Balan, A., Naik, K., Mirsadraee, S., Scarsbrook, A. F., Impact of the introduction of integrated PET-CT into the preoperative staging pathway of patients with potentially operable oesophageal carcinoma, Clinical RadiologyClin Radiol, 63, 765-73, 2008

Ref Id

514601

Country/ies where the study was carried out

UK</td><td>Sample size

n=25

Characteristics

Mean age (range): 62 (37-79) years
Male%: 17/25 (68%)
Adenocarcinoma: SCC: Mixed cell = 15/25 (60%): 8/25 (32%): 2/25 (8%)
Oesophagus: OGJ = 21/25(84%):4/25(16%)

Inclusion Criteria

de novo oesophageal or gastrtooesophageal junction (OGJ) malignancy who were potentially suitable for radical treatment and who underwent FDG PET-CT</td><td>Tests

PET-CT vs histology of the surgically resected tumour and lymph nodes

PET-CT was performed within 1 month following conventional imaging. The images were reviewed by experienced physician and radiologist.

Postoperative surgical histology was used as a</td><td>Methods</td><td>Results

PET-CT was not used for evaluating T staging of the tumour

Surgical resection with curative intent was carried out in 15 patients whereas the rest (n=10) had unresectable tumour or unfit for surgery. Ivor-Lewis oesophagectomy was performed in majority (n=12)

PET-CT vs histological staging (p=0.03)

<table><tr><td></td><td>PET-CT(+)</td><td>PET-CT(-)</td></tr></table></td><td>Limitations

QUADAS 2 checklist

Patient selection

Risk of bias:

Was a consecutive or random sample of patients enrolled? Yes

Was a case-control design avoided? Yes

Did the study avoid inappropriate exclusions? Unclear</td></tr>
</table>

Study type Retrospective cohort study Aim of the study To examine the role of positron emission tomography computed tompgraphy (PET-CT) in oesophageal carcinoma staging, in predicting prognosis and its influence on surgical management Study dates 1 September 2004 to 31 April 2007 Source of funding Not reported	Exclusion Criteria	reference standard for the presence (N1) or absence (N0) of local nodal disease. Note - EUS in the study was not considered for all patients so EUS was not included for the review		<table><tr><td>pN1</td><td>4</td><td>8</td><td>12</td></tr><tr><td>pN0</td><td>0</td><td>3</td><td>3</td></tr></table> Management outcome Number of patients who had altered management after PET-CT = 10/25 (40%) Five out of eight patients with active lesions on PET-CT were deemed inoperable whereas five patients with metabolically inactive PET-CT had altered management and had surgery with curative intent	Could the selection of participants have introduced bias? Unclear risk Applicability: Is there concern that the included participants do not match the review question? Low risk Index tests Risk of bias: Were the index tests interpreted without knowledge of the reference standard? Unclear If a threshold was used, was it pre-specified? Unclear Could the conduct or interpretation of the index test have introduced bias? Unclear risk Applicability:

					Is there concern that the index test, its conduct or interpretation differ from the review question? Low risk Reference standard Risk of bias: Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unclear Could the reference standard, its conduct or interpretation have introduced bias? Unclear risk Applicability: Is there concern that the target condition as defined

					by the reference standard does not match the review question? Low risk Flow and timing Risk of bias: Was there an appropriate interval between index tests and reference standard? Unclear Did all participants receive a reference standard? Yes Did participants receive the same reference standard? Yes Were all patients included in the analysis? No - only patients with histological results were included. Could the participant flow have introduced bias? High risk Other information

<table>
<tr>
<td>Full citation

Salminen, J. T., Farkkila, M. A., Ramo, O. J., Toikkanen, V., Simpanen, J., Nuutinen, H., Salo, J. A., Endoscopic ultrasonography in the preoperative staging of adenocarcinoma of the distal oesophagus and oesophagogastric junction, Scandinavian Journal of GastroenterologyScand J Gastroenterol, 34, 1178-82, 1999

Ref Id

559423

Country/ies where the study was carried out

Finland

Study type

Prospective cohort study

Aim of the study</td>
<td>Sample size

n=32

Characteristics

Median age (range): 58 (39-77) years
Male= 31/32 (98%)

Inclusion Criteria

Adenocarcinoma of the distal oesophagus or oesophagogastric junction without distant metastases

Exclusion Criteria</td>
<td>Tests

Olympus echoendoscope UM-20 was used and performed 1-2 weeks before surgery. The TNM staging was given prospectively without knowledge of the postoperative pathologic TNM staging. TNM stage of UICC for oesophageal carcinoma was used.
T1: mucosal and submucosal wall thickening
T2: invasion into muscularis propria
T3: invasion into adventitia
T4: invasion into other mediastinal organs

N0: no lymph node metastasis</td>
<td>Methods</td>
<td>Results

EUS T stage vs pathological T stage (pT)
<table><tr><td>pT</td><td>Correct T stage/ no of patients (Accuracy</td></tr><tr><td>pT1</td><td>1/7(14.3%)</td></tr><tr><td>pT2</td><td>2/5(40%)</td></tr><tr><td>pT3</td><td>18/20 (90%)</td></tr><tr><td>pT4</td><td>0</td></tr><tr><td>Total</td><td>21/32 (65.6%)</td></tr></table>EUS N stage vs pathological N stage (pN)
<table><tr><td>pN</td><td>Correct N stage/ no of patients(Accuracy</td></tr><tr><td>pN0</td><td>4/12(33.3%)</td></tr><tr><td>pN1</td><td>19/20(95%)</td></tr><tr><td>Total</td><td>23/32(71.9%)</td></tr></table></td>
<td>Limitations

QUADAS 2 checklist

Patient selection

Risk of bias:

Was a consecutive or random sample of patients enrolled? Yes

Was a case-control design avoided? Yes

Did the study avoid inappropriate exclusions? Unclear

Could the selection of participants have introduced bias? Unclear risk

Applicability:

Is there concern that the included participants do not match the review question? Low risk</td>
</tr>
</table>

To examine the role of endoscopic ultrasound in preoperative staging of adenocarcinoma of the distal oesophagus and oesophagogastric junction Study dates September 1994 to February 1999 Source of funding Finnish Foundation for Gastroenterolgoical research and grants from the Research Foundation of the Helsinki University Central Hospital		N1: metastasis in regional lymph nodes (mediastinal and perigastric nodes) M1a: metastasis to coeliac nodes M1b: other distant metastases Operative method: via transthoracic route by using left thoracoabdominal incision, right thoracotomy and laparotomy or right thoracotomy, laparotomy and cervicotomy. Radical en bloc resection was performed. The specimens were examined by senior pathologists.			Index tests Risk of bias: Were the index tests interpreted without knowledge of the reference standard? Yes If a threshold was used, was it pre-specified? Unclear Could the conduct or interpretation of the index test have introduced bias? Unclear risk Applicability: Is there concern that the index test, its conduct or interpretation differ from the review question? Low risk Reference standard Risk of bias: Is the reference standard likely to correctly classify the

					target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? Unclear Could the reference standard, its conduct or interpretation have introduced bias? Unclear risk Applicability: Is there concern that the target condition as defined by the reference standard does not match the review question? Low risk Flow and timing Risk of bias: Was there an appropriate interval between index tests and reference standard? Yes

					Did all participants receive a reference standard? Yes Did participants receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the participant flow have introduced bias? Low risk Other information
Full citation Sarela, A. I., Lefkowitz, R., Brennan, M. F., Karpeh, M. S., Selection of patients with gastric adenocarcinoma for laparoscopic staging, American Journal of SurgeryAm J Surg, 191, 134-138, 2006 Ref Id	Sample size n = 657 Characteristics n = 371 male n = 286 female n = 449 well differentiated tumour	Tests Laparoscopic staging was conducted in a standard manner. Laparoscopic ultrasound was performed at the discretion of the operating surgeon. The location and	Methods The detection of M1 disease by laparoscopy was compared to final surgical staging results.	Results Change in management plan following laparoscopy 151/657 (23%, 95% CI 20 to 26%)† (n = 151 identified with M1 disease by laparoscopy)	Limitations N.B. participants who underwent laparoscopy but then proceeded to neoadjuvant chemotherapy prior to surgical resection were excluded from the diagnostic accuracy calculations.

<table>
<tr>
<td>559425

Country/ies where the study was carried out

USA

Study type

Retrospective cohort study

Aim of the study

To identify patients in whom laparoscopy is not required for staging of gastric cancer.

Study dates

April 1993 to May 2002.

Source of funding

Not reported.</td>
<td>n = 208 poorly differentiated tumour

Inclusion Criteria

Had undergone laparoscopic staging of gastric adenocarcinoma.

Primary cancer judged to be more advanced that early gastric cancer.

Exclusion Criteria

Bleeding or gastric obstruction that required operation irrespective of disease stage

Definite evidence of M1 disease at radiological staging

Contraindication for gastrectomy

Received chemotherapy or radiation therapy prior to the first laparoscopy.

Incomplete clinical details.</td>
<td>extent of peritoneal disease was prospectively recorded. Biopsy of para-aortic nodes or other non-regional lymph nodes was only performed if clinically indicated. The diagnosis of M1 disease was confirmed by histopathology in all cases.</td>
<td>Pre-operative staging included CT abdomen and pelvis. Chest CT, MRI and endoscopic ultrasound were selectively used.</td>
<td>Detection of metastatic disease

(excludes 105 participants who proceeded to neoadjuvant chemotherapy prior to laparotomy)
<table>
<tr><th></th><th>Metastasis confirmed histologically

(following laparoscopy and/or laparotomy)</th><th>No metastasis on histolo</th></tr>
<tr><td>Metastasis identified at laparoscopy</td><td>151</td><td>0</td></tr>
<tr><td>No metastasis at laparoscopy</td><td>41</td><td>360</td></tr>
</table>
</td>
<td>Other information

QUADAS 2 checklist

Patient selection

Risk of bias:

Was a consecutive or random sample of patients enrolled? Yes

Was a case-control design avoided? Yes

Did the study avoid inappropriate exclusions? Yes

Could the selection of participants have introduced bias? Low risk

Applicability:

Is there concern that the included participants do not match the review question? Low risk

Index tests</td>
</tr>
</table>

				<table><tr><td></td><td>192</td><td>360</td><td>352</td></tr></table> Sensitivity‡ (95% CI): 78.7% (72.2 to 84.2) Specificity‡ (95% CI): 100% (99.0 to 100) Positive likelihood ratio‡ (95% CI): ∞ (not calculable) Negative likelihood ratio‡ (95% CI): 0.21 (0.16 to 0.28) Positive predictive value‡ (95% CI): 100% (not calculable) Negative predictive value‡ (95% CI): 89.8% (87 to 92) †calculated by the NGA technical team from data reported in the article using http://statpages.info/confint.html ‡calculated by the NGA technical team from data reported in the article	Risk of bias: Were the index tests interpreted without knowledge of the reference standard? Yes If a threshold was used, was it pre-specified? N/A Could the conduct or interpretation of the index test have introduced bias? Low risk Applicability: Is there concern that the index test, its conduct or interpretation differ from the review question? Low risk Reference standard Risk of bias: Is the reference standard likely to correctly classify the target condition? Yes

				using https://www.medcalc.org/calc/diagnostic_test.php	Were the reference standard results interpreted without knowledge of the results of the index test? No Could the reference standard, its conduct or interpretation have introduced bias? Low risk Applicability: Is there concern that the target condition as defined by the reference standard does not match the review question? Low risk Flow and timing Risk of bias: Was there an appropriate interval between index tests and reference standard? Yes Did all participants receive a reference

<table>
<tr><td></td><td></td><td></td><td></td><td></td><td>standard? No - some patients proceeded to neoadjuvant chemotherapy

Did participants receive the same reference standard? Yes

Were all patients included in the analysis? No - patients undergoing neoadjuvant treatment were excluded as metastatic disease could not be formally ascertained.

Could the participant flow have introduced bias? Low risk</td></tr>
<tr><td>Full citation

Staiger, W., Ronellenfitsch, U., Hofheinz, R. D., Strobel, P., Hahn, M., Post, S.,</td><td>Sample size

n=47

Characteristics</td><td>Tests

EUS was performed by using a rotating sector scan</td><td>Methods</td><td>Results<table><tr><td>Variable</td><td>pT1</td><td>pT2</td><td>pT3</td><td>pT4</td><td>A
C</td></tr></table></td><td>Limitations

QUADAS 2 checklist

Patient selection</td></tr>
</table>

<table>
<tr>
<td>Collet, P., Kahler, G., Schwarzbach, M., Endoscopic ultrasound in the pre-therapeutic staging of gastroesophageal adenocarcinoma: The diagnostic value in defining patients eligible for a neoadjuvant chemotherapy regimen, Wideochirurgia i Inne Techniki MaloinwazyjneWideochir, 5, 1-6, 2010

Ref Id

559470

Country/ies where the study was carried out

Germany

Study type

Prospective cohort study

Aim of the study

To assess the diagnostic value of endoscopic ultrasound for defining patients eligible for neoadjuvant chemotherapy</td>
<td>Inclusion Criteria

Patients who underwent elective resection with curative intention for primary adenocarcinoma of the stomach, gastrooesophageal junction and lower oesophagus
Patients who would have been eligible for neoadjuvant chemotherapy

Exclusion Criteria</td>
<td>echoendoscope
Surgical treatment for all patients was subtotal or total gastrectomy with D2-lymphadenectomy, transhiatal extended total gastrectomy or abdomino-thoracic resection of the oesophagus.
The results of the EUS staging were compared with histopathological results obtained from the surgical specimen which were considered gold standard.</td>
<td></td>
<td>
<table>
<tr><td>uT1</td><td>7</td><td>5</td><td>-</td><td>-</td><td>12</td></tr>
<tr><td>uT2</td><td>2</td><td>8</td><td>3</td><td>-</td><td>13</td></tr>
<tr><td>uT3</td><td>-</td><td>3</td><td>9</td><td>-</td><td>12</td></tr>
<tr><td>uT4</td><td>-</td><td>-</td><td>-</td><td>-</td><td>0</td></tr>
<tr><td>All cases</td><td>9</td><td>16</td><td>12</td><td>0</td><td>37</td></tr>
</table>
<table>
<tr><td>Variable</td><td>pN0</td><td>pN+</td><td>All cases</td></tr>
<tr><td>uN0</td><td>13</td><td>9</td><td>22</td></tr>
<tr><td>uN+</td><td>3</td><td>9</td><td>12</td></tr>
<tr><td>All cases</td><td>16</td><td>18</td><td>34</td></tr>
</table>
</td>
<td>Risk of bias:

Was a consecutive or random sample of patients enrolled? Yes

Was a case-control design avoided? Yes

Did the study avoid inappropriate exclusions? Yes

Could the selection of participants have introduced bias? Low risk

Applicability:

Is there concern that the included participants do not match the review question? Low risk

Index tests

Risk of bias:

Were the index tests interpreted without knowledge</td>
</tr>
</table>

Study dates January 2006 and June 2007 Source of funding Not reported					of the reference standard? Yes If a threshold was used, was it pre-specified? N/A Could the conduct or interpretation of the index test have introduced bias? Low risk Applicability: Is there concern that the index test, its conduct or interpretation differ from the review question? Low risk Reference standard Risk of bias: Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the

					results of the index test? Unclear Could the reference standard, its conduct or interpretation have introduced bias? Low risk Applicability: Is there concern that the target condition as defined by the reference standard does not match the review question? Low risk Flow and timing Risk of bias: Was there an appropriate interval between index tests and reference standard? Unclear Did all participants receive a reference standard? Yes Did participants receive the same

					reference standard? Yes Were all patients included in the analysis? No - one participant with T2 disease, and three lesions where invasion (mucosal or submucosal was unclear) were excluded. Could the participant flow have introduced bias? Unclear risk Other information
Full citation Strandby, R. B., Svendsen, L. B., Fallentin, E., Egeland, C., Achiam, M. P., The Multidisciplinary Team Conference's Decision on M-Staging in Patients with Gastric- and Gastroesophageal Cancer is not Accurate without Staging Laparoscopy,	Sample size n = 222 Characteristics n = 169 male n = 53 female Age:	Tests Staging laparoscopy was conducted under general anaesthesia. Careful inspection for any evidence of peritoneal carcinomatosis or liver metastasis was conducted.	Methods Pre-operative investigations included spirometry, upper endoscopy with biopsy, CT of the chest and abdomen	Results Gastric cancer Change of management plan 8/48 (17%, 95% CI 7 to 30)† (n = 8 peritoneal metastasis) Gastroesophageal junction/oesophageal cancer	Limitations Note that the majority of participants in the oesophageal cancer group (171/174) had gastroesophageal junction disease. Other information

Scandinavian Journal of Surgery, 105, 104-108, 2016 Ref Id 488240 Country/ies where the study was carried out Denmark Study type Retrospective cohort study Aim of the study To assess the contribution of staging laparoscopy in gastrooesophageal cancers. Study dates 2010 to 2012 Source of funding Not reported.	n = 9 aged <50 years n = 124 aged 50-70 years n = 89 aged >70 years Tumour site n = 174 oesophagus and gastroesophageal junction n = 48 gastric Histology: n = 196 adenocarcinoma n = 19 signet ring n =3 squamous cell n = 2 mixed n = 2 neuroendocrine Inclusion Criteria Patients discussed at the MDT for gastric or oesophageal carcinoma Considered to be operable and resectable	Intraoperative ultrasound was not performed. Suspicious lesions and any ascites were sent for histological/cytological confirmation of metastatic disease. For patients with a negative laparoscopy, neoadjuvant chemotherapy and subsequent resection of tumour were offered.	combined with ultrasound of the neck. 20 patients underwent PET-CT.	Change of management plan 13/174 (7%, 95% CI 4 to 12)† (n = 9 peritoneal metastasis, n = 4 liver metastasis) †calculated by the NGA technical team from data reported in the article using http://statpages.info/confint.html	QUADAS 2 checklist Patient selection Risk of bias: Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes Could the selection of participants have introduced bias? Low risk Applicability: Is there concern that the included participants do not match the review question? Low risk Index tests Risk of bias:

	Information on laparoscopy results available Exclusion Criteria Suspicion of metastatic disease on pre-operative imaging.				Were the index tests interpreted without knowledge of the reference standard? Yes If a threshold was used, was it pre-specified? N/A Could the conduct or interpretation of the index test have introduced bias? Low risk Applicability: Is there concern that the index test, its conduct or interpretation differ from the review question? Low risk Reference standard Risk of bias: Is the reference standard likely to correctly classify the target condition? Yes

					Were the reference standard results interpreted without knowledge of the results of the index test? No Could the reference standard, its conduct or interpretation have introduced bias? Low risk Applicability: Is there concern that the target condition as defined by the reference standard does not match the review question? Low risk Flow and timing Risk of bias: Was there an appropriate interval between index tests and reference standard? Yes

<table>
<tr><td></td><td></td><td></td><td></td><td></td><td>Did all participants receive a reference standard? Yes

Did participants receive the same reference standard? Yes

Were all patients included in the analysis? Yes

Could the participant flow have introduced bias? Low risk</td></tr>
<tr><td>Full citation

Vilgrain, V., Mompoint, D., Palazzo, L., Menu, Y., Gayet, B., Ollier, P., Nahum, H., Fekete, F., Staging of esophageal carcinoma: comparison of results with endoscopic sonography and CT, AJR. American Journal of RoentgenologyAJR Am J Roentgenol, 155, 277-81, 1990</td><td>Sample size

n=32

Characteristics

Median age (range): 58 years (39-77)
Male %: 97% (31/32)

Inclusion Criteria

Patients with adenocarcinoma of the distal oesophagus or oesophagogastric junctional</td><td>Tests

Olympus echoendoscope was used and endoscopic ultrasound (EUS) was performed 1-2 weeks before surgery and TNM staging were given prospectively without knowledge</td><td>Methods</td><td>Results
<table><tr><td></td><td>correct T/ number of patients (accuracy%)</td></tr><tr><td>pT1</td><td>1/7(14.3)</td></tr><tr><td>pT2</td><td>2/5(40)</td></tr><tr><td>pT3</td><td>18/20(90)</td></tr><tr><td>pT4</td><td>0/0</td></tr></table></td><td>Limitations

QUADAS 2 checklist

Patient selection

Risk of bias:

Was a consecutive or random sample of patients enrolled? Yes</td></tr>
</table>

Ref Id 559556 Country/ies where the study was carried out Finland Study type Prospective cohort study Aim of the study To evaluate the accuracy of endoscopic ultrasound in adenocarcinoma of the oesophagus and oesophgogastric junctional cancer Study dates September 1994 and February 1999 Source of funding The Finnish Foundation for gastroenterological research and grants from the Research Foundation (EVO) of the Helsinki University Central Hospital	cancer without distant metastases Exclusion Criteria	of pathologic TNM staging. EUS Staging criteria: mucosal and submucosal wall thickening; T2 = infiltrates muscularis propria; T3=infiltrates into the adventitia; T4=tumour invasion into other mediastinal structures Operative method applied: transthoracic route by left thoracoabdominal incision, right thoracotomy and laparotomy or right thoracotomy, laparotomy and cervicotomy. Patients with subtotal resection of the oesophagus and stomach (n=19); patients with subtotal		Total 21/32(65.6) CorrectN/ number of patients (accuracy%) pN0 4/12(33.3) pN1 19/20(95) Total 23/32(71.9)	Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes Could the selection of participants have introduced bias? Low risk Applicability: Is there concern that the included participants do not match the review question? Low risk Index tests Risk of bias: Were the index tests interpreted without knowledge of the reference standard? Yes If a threshold was used, was it pre-specified? N/A

		resection of the oesophagus and total gastrectomy (n=13). Pathology: all specimens stained with HE and PAF staining. pTNM stage was given according to UICC handbook			Could the conduct or interpretation of the index test have introduced bias? Low risk Applicability: Is there concern that the index test, its conduct or interpretation differ from the review question? Low risk Reference standard Risk of bias: Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? unclear Could the reference standard, its conduct or interpretation have

					introduced bias? Unclear risk Applicability: Is there concern that the target condition as defined by the reference standard does not match the review question? Low risk Flow and timing Risk of bias: Was there an appropriate interval between index tests and reference standard? Yes Did all participants receive a reference standard? Yes Did participants receive the same reference standard? Yes Were all patients included in the analysis? Yes

<table>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Could the participant flow have introduced bias? Low risk

Other information</td>
</tr>
<tr>
<td>Full citation

Wilkiemeyer, M. B., Bieligk, S. C., Ashfaq, R., Jones, D. B., Rege, R. V., Fleming, J. B., Laparoscopy alone is superior to peritoneal cytology in staging gastric and esophageal carcinoma, Surgical EndoscopySurg Endosc, 18, 852-6, 2004

Ref Id

559586

Country/ies where the study was carried out

USA

Study type

Prospective cohort study</td>
<td>Sample size

n = 40

Characteristics

n = 32 male

n = 9 female

Median age at diagnosis 62.5 years

n = 31 gastric cancer

n = 10 oesophageal cancer

Inclusion Criteria

Gastric or lower oesophageal carcinoma

Planned operative resection

Exclusion Criteria</td>
<td>Tests

Staging laparoscopy was conducted under general anaesthesia. The peritoneum, liver, pouch of Douglas, root of mesentery, caudate lobe and lesser sac were examined. Suspicious lesions were biopsied for histological confirmation of metastasis.</td>
<td>Methods

Pre-operative staging is not reported.

All patients without evidence of metastatic disease underwent laparotomy with exploration and resection.

Identification of metastatic disease by laparoscopy was</td>
<td>Results

Detection of intra-abdominal metastasis

<table>
<tr><td></td><td>Metastatic disease confirmed</td><td>Confirmation of no metasta</td></tr>
<tr><td>Metastasis identified at laparoscopy</td><td>22</td><td>0</td></tr>
<tr><td>No metastasis identified</td><td>0</td><td>18</td></tr>
</table>
</td>
<td>Limitations

Other information

QUADAS 2 checklist

Patient selection

Risk of bias:

Was a consecutive or random sample of patients enrolled? unclear

Was a case-control design avoided? Yes

Did the study avoid inappropriate exclusions? Yes

Could the selection of participants have</td>
</tr>
</table>

Aim of the study To assess the additional benefit of peritoneal washings to staging of oesophageal and gastric malignancies. Study dates Not reported. Source of funding The Society of American Gastrointestinal Endoscopic Surgeons.	Inability to complete laparoscopy		compared to final staging of intra-abdominal metastasis by laparotomy.	<table><tr><td>at laparoscopy</td><td></td><td></td></tr><tr><td></td><td>22</td><td>18</td></tr></table> Sensitivity (95% CI)†: 100% (84.6 to 100) Specificity (95% CI)†: 100% (81.5 to 100) Positive likelihood ratio (95% CI): ∞ (not calculable) Negative likelihood ratio (95% CI): 0.00 (not calculable) Positive predictive value (95% CI)†: 100% (not calculable) Negative predictive value (95% CI)†: 100% (not calculable) † 95% confidence interval calculated by the NGA technical from data reported in the article	4 0	introduced bias? Low risk Applicability: Is there concern that the included participants do not match the review question? Low risk Index tests Risk of bias: Were the index tests interpreted without knowledge of the reference standard? Yes If a threshold was used, was it pre-specified? N/A Could the conduct or interpretation of the index test have introduced bias? Low risk Applicability: Is there concern that the index test, its conduct or interpretation differ

				using https://www.medcalc.org/calc/diagnostic_test.php ‡ point estimate and 95% confidence interval calculated by the NGA technical team from data reported in the article using https://www.medcalc.org/calc/diagnostic_test.php	from the review question? Low risk Reference standard Risk of bias: Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index test? No Could the reference standard, its conduct or interpretation have introduced bias? Low risk Applicability: Is there concern that the target condition as defined by the reference standard does not match the review question? Low risk

					Flow and timing Risk of bias: Was there an appropriate interval between index tests and reference standard? Yes Did all participants receive a reference standard? Yes Did participants receive the same reference standard? Yes Were all patients included in the analysis? Yes Could the participant flow have introduced bias? Low risk
Full citation Yau, K. K., Siu, W. T., Cheung, H. Y., Li, A. C., Yang, G. P., Li, M. K., Immediate preoperative	Sample size N = 63 Characteristics	Tests Laparoscopic staging was performed immediately prior	Methods The number of unexpected metastases	Results Change in management following laparoscopy	Limitations Other information QUADAS 2 checklist

laparoscopic staging for squamous cell carcinoma of the esophagus, Surgical EndoscopySurg Endosc, 20, 307-10, 2006 Ref Id 545511 Country/ies where the study was carried out Hong Kong Study type Retrospective cohort study Aim of the study To evaluate the efficacy of laparoscopic staging for the management of squamous cell carcinoma of the mid and distal oesophagus. Study dates January 1998 to January 2004. Source of funding Not reported.	(not reported for full cohort, only for patients who underwent resection, of whom n = 47 male, n = 7 female, median age 66 years) Inclusion Criteria Histologically confirmed squamous cell carcinoma of the oesophagus. Operative treatment. Exclusion Criteria Not reported.	to laparotomy and resection. The peritoneal cavity and pelvis were examined, and biopsies of suspicious lesions were taken for frozen section.	identified at laparoscopy was recorded. Pre-operative staging included barium swallow, CT chest and abdomen, endoscopy, bronchoscopy and endoscopic ultrasonography (from 2000 onwards).	7/63 (11%, 95% CI 5 to 22%)† (n = 5 abdominal metastases, n = 2 other medical conditions that precluded oesophagectomy) † calculated by the NGA technical team from data reported in the article using http://statpages.info/confint.html	Patient selection Risk of bias: Was a consecutive or random sample of patients enrolled? Yes Was a case-control design avoided? Yes Did the study avoid inappropriate exclusions? Yes Could the selection of participants have introduced bias? Low risk Applicability: Is there concern that the included participants do not match the review question? Low risk Index tests Risk of bias: Were the index tests interpreted without knowledge

					of the reference standard? Yes If a threshold was used, was it pre-specified? N/A Could the conduct or interpretation of the index test have introduced bias? Low risk Applicability: Is there concern that the index test, its conduct or interpretation differ from the review question? Low risk Reference standard Risk of bias: Is the reference standard likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the

					results of the index test? No Could the reference standard, its conduct or interpretation have introduced bias? Low risk Applicability: Is there concern that the target condition as defined by the reference standard does not match the review question? Low risk Flow and timing Risk of bias: Was there an appropriate interval between index tests and reference standard? Yes Did all participants receive a reference standard? Yes Did participants receive the same

					reference standard? Yes Were all patients included in the analysis? Yes Could the participant flow have introduced bias? Low risk

1

2

F.63 HER2 testing in adenocarcinoma

4 **Which people with adenocarcinoma of the stomach and oesophagus should have their tumours HER2 tested?**

5 No evidence was available for this review.

F.76 T1N0 oesophageal cancer

7 **What is the optimal management of T1N0 oesophageal cancer?**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Shimizu, Y., Tsukagoshi, H., Fujita, M., Hosokawa, M., Kato, M., Asaka, M., Long-term outcome after endoscopic	**Sample size** Extended EMR group n=26 Surgical resection group n=44	**Interventions** Endoscopic mucosal resection or surgical resection	**Details** **Surgical resection group** Patients underwent esophagectomy with lymph node dissection at our hospital **(including the 8 patients who underwent esophagectomy after EMR).** All resection specimens from the	**Results** **Overall 5 year survival** HR: 1.59 [0.49-5.14] favours surgical resection	**Limitations** Non-randomized **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
mucosal resection in patients with esophageal squamous cell carcinoma invading the muscularis mucosae or deeper, Gastrointestinal EndoscopyGastrointest Endosc, 56, 387-90, 2002 **Ref Id** 475064 **Country/ies where the study was carried out** Japan **Study type** Comparative observational study **Aim of the study** To prospectively evaluate long-term outcome after EMR in patients with squamous cell esophageal carcinomas invading the muscularis mucosae or deeper as compared with a similar group of patients who underwent surgical resection	**Characteristics** All patients had squamous cell carcinoma of the esophagus Extended EMR group mean age: 68.4 (SD 7.8) M:F 25:1 Surgical resection group mean age: 62.9 (SD 7.7) M:F 40:4 **Inclusion criteria** EMR group Patients with squamous cell esophageal carcinoma invading the muscularis mucosae or upper submucosa were enrolled in the study for EMR if: (1) increased operative risk because of concurrent illness; OR (2) presence of another nonesophageal advanced cancer; OR (3) age greater than 75 years; OR (4) refusal to undergo open surgery despite explanation of the risk of cancer metastasis.		esophagus were cut into longitudinal slices 2 to 5 mm in width and embedded in paraffin. Each slice was stained with hematoxylin-eosin and examined microscopically. The depth of cancer invasion was classified according to the criteria proposed by the Japanese Society for Esophageal Diseases. All specimens were reviewed by a single pathologist blinded to the clinical characteristics of the patients. **EMR** Endoscopic examination and EUS (including use of a high-frequency catheter probe) were performed in all patients to evaluate depth of cancer invasion. Together with CT, EUS was also used to identify lymph node metastases. Lymph nodes more than 5 mm in shortest dimension that were spherical and had distinct borders on EUS, and those more than 10 mm in shortest dimension. After treatment, all patients were monitored to detect local or distant recurrence every 3 to 6 months during the first year after treatment and annually thereafter. Follow-up evaluations included upper endoscopy, CT of the chest and upper abdomen, and percutaneous US of the neck and upper abdomen. EUS was also performed if clinically indicated. Endpoints were:		Calculations for survival HR were done using the HR calculator based on Tieney 2007 methodology

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>Study dates
June 1992 - March 2000

Source of funding
None listed</td>
<td>Surgical resection group
Patients with esophageal carcinoma invading the muscularis mucosae or the upper third of the submucosa

Exclusion criteria
Patients with evidence of lymph node metastasis were excluded.</td>
<td></td>
<td>Overall survival and cause-specific survival: calculated from the date of EMR or surgical resection. Overall survival included deaths from any cause. Survival curves were plotted according to the Kaplan-Meier method. The significance of differences in survival was assessed by the logrank test. Differences in frequency distribution were tested with the chi-square test, and quantitative data were examined with two-tailed t test. A p value < 0.05 was considered to indicate statistical significance.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full citation

Takahashi, H., Arimura, Y., Masao, H., Okahara, S., Tanuma, T., Kodaira, J., Kagaya, H., Shimizu, Y., Hokari, K., Tsukagoshi, H., Shinomura, Y., Fujita, M., Endoscopic submucosal dissection is superior to conventional endoscopic resection as a curative treatment for early squamous cell carcinoma of the esophagus, Gastrointestinal EndoscopyGastrointest</td>
<td>Sample size
EMR n=184
ESD n=116

Characteristics
EMR
Mean age: 66.4±8.0
M:F 9.2:1
Mean size of cancer: 20±11
ESD
Mean age: 67.1±8.6
M:F 7.4:1
Mean size of cancer: 30±16

Inclusion criteria</td>
<td>Interventions
EMR or ESD</td>
<td>Details
Of the 184 EMR procedures, 167 were performed from 1994 to 2003, whereas the remaining 17 EMR and all ESD procedures were performed from March 2004 to July 2007.
Statistics
A chi-square test was used for nominal or ordinal variables, and the exact P value based on the Pearson statistic or the Monte Carlo method was applied.
We used a t test for scale variables and considered P< 0.05 to be significant in a 2-tailed test.
Cumulative disease-free survival rates and overall survival rates were calculated by the Kaplan-Meier method along with the log-rank test.</td>
<td>Results
<table>
<tr><td></td><td colspan="2">EMR</td><td colspan="2">ESD</td></tr>
<tr><td>Outcome</td><td>n</td><td>N</td><td>n</td><td>N</td></tr>
<tr><td>Pathological margins free</td><td>144</td><td>184</td><td>113</td><td>116</td></tr>
<tr><td>Perforation</td><td>3</td><td>184</td><td>3</td><td>116</td></tr>
<tr><td>Stenosis</td><td>17</td><td>184</td><td>20</td><td>116</td></tr>
</table>
Cumulative disease-free survival rate
HR: 0.45 [0.27-0.78] favours ESD
Pathological margins free
RR: 0.12 (0.04-0.04)</td>
<td>Limitations
Calculations for survival HR were done using the HR calculator based on Tieney 2007 methodology.

RR calculated by technical team

Other information</td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Endosc, 72, 255-264, 2010 **Ref Id** 492989 **Country/ies where the study was carried out** Japan **Study type** Retrospective cohort study **Aim of the study** To analyze the long-term clinicopathologic outcomes including the local recurrence rates in a large series of patients with SCCE who underwent conventional EMR or ESD **Study dates** March 1994 - July 2007 **Source of funding** None listed	The pathologic depth of squamous cell cancer invasion in the resected specimens was confined to the mucosal layer and was graded from m1 (carcinoma in situ) to m3 (limited to the muscularis mucosa) were prospectively included in the database Patients had confirmed SCCE by biopsy under chromoendoscopy with the Lugol dye-spray method. **Exclusion criteria** Patients to be treated by surgery, chemoradiotherapy, and/or radiotherapy; patients who had previous or adjuvant treatment, adenocarcinoma of the esophagus, or submucosal invasion; and patients dropped from the follow-up program for any reason			**Perforation** RR: 1.59 (0.33-7.73) **Stenosis** RR: 1.87 (1.02-3.41)	

F.82 Surgical treatment of oesophageal cancer

What is the most effective operative approach for the surgical treatment of oesophageal cancer?

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>Full citation

Biere, S. S., van Berge Henegouwen, M. I., Maas, K. W., Bonavina, L., Rosman, C., Garcia, J. R., Gisbertz, S. S., Klinkenbijl, J. H., Hollmann, M. W., de Lange, E. S., Bonjer, H. J., van der Peet, D. L., Cuesta, M. A., Minimally invasive versus open oesophagectomy for patients with oesophageal cancer: a multicentre, open-label, randomised controlled trial, LancetLancet, 379, 1887-92, 2012

Ref Id

470845

Country/ies where the study was carried out

Netherlands, Spain, Italy</td>
<td>Sample size
n=115; Open = 56 vs Minimally invasive= 59

Characteristics
<table>
<tr><th></th><th>Open (n=56)</th><th>MIO (n=59)</th></tr>
<tr><td>Age (years, range)</td><td>62 (42-75)</td><td>62 (34-75)</td></tr>
<tr><td>Female</td><td>10</td><td>16</td></tr>
<tr><td>Tumour location</td><td></td><td></td></tr>
<tr><td>Upper third</td><td>3</td><td>1</td></tr>
<tr><td>Middle third</td><td>22</td><td>26</td></tr>
</table>
</td>
<td>Interventions
Both arms: Neoadjuvant treatment: weekly 50 mg/m² paclitaxel plus carboplatin and concurrent radiotherapy (41·4 Gy in 23 fractions for 5 days per week). Surgery was planned 6–8 weeks after neoadjuvant treatment. Open oesophagectomy: right thoracotomy, midline laparotomy, and cervical incision. No cervical incision was used for patients with an intrathoracic anastomosis. Minimally invasive oesophagectomy: right thoracoscopy, upper abdominal laparoscopy, and cervical incision. After surgery, all patients were admitted to the intensive-care unit for stabilisation and detubation, and were discharged the next day to a general surgical ward</td>
<td>Details
Method of randomization: computer generated. Stratified by centre. Exclusion after randomization: none Lost to follow-up: none Method of allocation concealment: not reported Intention-to-treat analysis: yes Description of sample size calculation: yes Blinding: no blinding Duration of follow-up: 3-years</td>
<td>Results
Postoperative complication:

1. Anastomotic leakage Open: 4/56 (7%) MIO: 7/59 (12%)
2. Pulmonary complications (mediastinitis, empyema, chylous leakage needing reoperation, and hiatal herniation) Open: 2/56 MIO: 2/59</td>
<td>Limitations
Random sequence generation: low risk Allocation concealment: unclear risk Blinding (performance bias): low risk Blinding of outcome assessment (detection bias): high risk Incomplete outcome data (attrition bias): low risk Selective reporting: low risk Other bias: low risk</td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type multicentre open-label randomised controlled trial **Aim of the study** To assess whether minimally invasive oesophagectomy reduces morbidity compared with open oesophagectomy. **Study dates** June 2009 to March 2011 **Source of funding** Digestive Surgery Foundation of the Unit of Digestive Surgery of the VU University Medical Centre	**Lower third** 31 32 **Neoadjuvant chemotherapy** 4 5 **Neoadjuvant chemoradiotherapy** 52 54 **Inclusion criteria** • Aged 18-75 years • WHO performance score ≤ 2 • Resectable oesophageal cancer of intrathoracic oesophagus and gastro-oesophageal junction **Exclusion criteria** · Cervical oesophageal cancer ·	or medium-care unit. Enteral feeding day 1 after surgery via percutaneous jejunostomy.		3. Intraoperative blood loss (ml) (Median and IQR) Open: 475 (50 - 3000) MIO: 200 (20 - 1200) 4. EORTC Global health score QoL (0 to 100; higher score, better well-being) Open: 51 (21; 44 to 58) MIO:61 (18; 56 to 67); p=0.020 5. Length of operation (min) (Median and IQR) Open: 299 (66 - 570) MIO: 329 (90 - 559)	**Other information** Additional follow-up data was taken from: 1. Maas, K. W., Cuesta, M. A., van Berge Henegouwen, M. I., Roig, J., Bonavina, L., Rosman, C., Gisbertz, S. S., Biere, S. S., van der Peet, D. L., Klinkenbijl, J. H., Hollmann, M. W., de Lange, E. S., Bonjer, H. J., Quality of Life and Late Complications After Minimally Invasive Compared to Open

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				6. Resection margin - R0 (>1 mm from a resection margin) Open: 47/56 MIO: 54/59 7. Resection margin - R1 Open: 5/56 MIO: 1/59 8. Number of lymph nodes resected (Median and IQR) Open: 21 (7-47) MIO: 20 (3-44) 9. 30-day mortality Open: 0/56 MIO: 1/59 3-year follow-up:	Esophagectomy: Results of a Randomized Trial, World Journal of SurgeryWorld J Surg, 39, 1986-93, 2015 2. Straatman, J., van der Wielen, N., Cuesta, M. A., Daams, F., Roig Garcia, J., Bonavina, L., Rosman, C., van Berge Henegouwen, M. I., Gisbertz, S. S., van der Peet, D. L., Minimally Invasive Versus Open Esophageal Resection: Three-year Follow-up of the Previously Reported

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				1. Survival i) number of death/recurrence Open: 36/56 MIO: 37/59, p=0.602 HR with 95%CI (open vs MIO) = 0.89 (0.56 to 1.4) ii) number of death ~ Open: 36 - 35 (8 local recurrence and 27 metastasis) = 1 MIO: 37 - 29 (7 local recurrence and 22 metastasis) = 8 2. 3-year overall survival	Randomized Controlled Trial: the TIME Trial, Annals of Surgery., 09, 2017

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				rate= HR (95%CI) = 0.961 (0.585 to 1.579) Open: 41.2% (27.5 to 54.9) MIO: 42.9%(30.4 to 55.4), p=0.633 3. 3-year disease free survival rate = HR (95% CI) = 0.946 (0.585 to 1.531) Open: 37.3% (23.5% to 49%) MIO: 42.9 %(28.6% to 55.4%); p=0.602	

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>Full citation

Chou, S. H., Chuang, H. Y., Huang, M. F., Lee, C. H., Yau, H. M., A prospective comparison of transthoracic and transhiatal resection for esophageal carcinoma in Asians, Hepato-GastroenterologyHepatogastroenterology, 56, 707-10, 2009

Ref Id

470901

Country/ies where the study was carried out

Taiwan

Study type
randomised controlled trial

Aim of the study
To compare transhiatal and transthoracic resection of oesophageal cancer in Asians</td>
<td>Sample size
n= 87; Transthoracic (TT) =47 vs Transhiatal (TH) = 40

Characteristics
<table>
<tr><th></th><th>TT (n=47)</th><th>TH (n=40)</th></tr>
<tr><td>Age (years)</td><td>54.8+/-10.3</td><td>59.1 +/- 11.1</td></tr>
<tr><td>Female sex</td><td>3</td><td>2</td></tr>
<tr><td>Location of tumour</td><td></td><td></td></tr>
<tr><td>Middle third</td><td>41</td><td>32</td></tr>
<tr><td>Lower third</td><td>6</td><td>8</td></tr>
</table>
</td>
<td>Interventions
Transthoracic: three-stage technique – laparotomy, left oblique cervical incision and right thoractotomy Transhiatal: laparotomy and cervical oesophagogastrostomy.
Feeding jejunostomy was routine for both arms</td>
<td>Details
Method of randomization: ‘patients were randomly allocated and operated on by either TTE or THE approach in turns, according to the schedule. I.e. if the previous patient had been treated with TTE the next would be operated with THE and so on’.
Exclusion after randomization: none
Lost to follow-up: none
Method of allocation concealment: not reported
Intention-to-treat analysis: no</td>
<td>Results

1. Anastomotic leakage
TT:
TH:
2. Intraoperative blood loss
TT:
TH:
3. Length of operation (min)
TT:
TH:
4. Pneumonia
TT:
TH:</td>
<td>Limitations
Random sequence generation: high risk
Allocation concealment: high risk
Blinding (performance bias): low risk
Blinding of outcome assessment (detection bias): low risk
Incomplete outcome data (attrition bias): low risk
Selective reporting: low risk
Other bias: low risk

Other information</td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates January 2003-December 2006 **Source of funding** not reported	**Inclusion criteria** • Stage II and III resectable oesophageal cancer **Exclusion criteria** • Upper third and T4 cancer were excluded		Description of sample size calculation: no Blinding: not possible Duration of follow-up: 2 years		
Full citation Chu, K. M., Law, S. Y., Fok, M., Wong, J., A prospective randomized comparison of transhiatal and transthoracic resection for lower-third esophageal carcinoma, American Journal of SurgeryAm J Surg, 174, 320-4, 1997 **Ref Id** 470903	**Sample size** n=39; 19 patients in transthoracic (TT) versus 20 patients in transhiatal (TH) **Characteristics** **Patient characteristics:**	**Interventions** Open transhiatal (n=20) vs open abdominal right-side chest transthoracic (n=19) approach to oesophagectomy	**Details** Method of randomization: not reported Exclusion after randomization: none Lost to follow-up: none Method of allocation concealment: none Intention-to-	**Results** 19 TT versus 20 TH 1. Anastomotic leak TT: 1/19 TH: 0/20 2. Intraoperative blood loss (ml) TT: 671±47 TH: 724±58	**Limitations** Random sequence generation: unclear risk Allocation concealment: unclear risk Blinding (performance bias): low risk Blinding of outcome assessment

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>Country/ies where the study was carried out
Hong Kong
Study type
randomised controlled trial
Aim of the study
To compare transhiatal and transthoracic resection of a oesophageal cancer
Study dates
March 1990 – November 1994
Source of funding
not reported</td>
<td>
<table>
<tr><th></th><th>TH (n=20)</th><th>TT (n=19)</th></tr>
<tr><td>Female sex</td><td>2</td><td>2</td></tr>
<tr><td>Age</td><td>60.7 +/- 1.8</td><td>63.9 +/- 1.1</td></tr>
<tr><td>Pre-operative staging</td><td></td><td></td></tr>
<tr><td>Early</td><td>4</td><td>2</td></tr>
<tr><td>Moderately/locally advanced</td><td>16</td><td>17</td></tr>
<tr><td>Median survival</td><td>16</td><td>13.5</td></tr>
<tr><td>Mean follow-up</td><td>13.7 +/- 3.4</td><td>15.8 +/- 3.0</td></tr>
</table>
Inclusion criteria
</td>
<td></td>
<td>treat analysis: yes
Description of sample size calculation: no
Blinding: not reported
Duration of follow-up</td>
<td>3. Length of operation (min)
TT: 210±7
TH: 174±6
4. Pneumonia
TT: 0/19
TH: 2/20
5. Recurrence
TT: 6/19
TH: 4/20
6. 30-day mortality
TT: 0
TH:0
7. Hospital stay
TT: 27±5
TH: 18±2.2</td>
<td>(detection bias): low risk
Incomplete outcome data (attrition bias): low risk
Selective reporting: low risk Other bias: low risk
Other information</td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	• Newly diagnosed oesophageal cancer **Exclusion criteria** • Carcinoma of lower third of oesophagus • Previous radiotherapy or chemotherapy				
Full citation Goldminc, M., Maddern, G., Prise, E., Meunier, B., Campion, J. P., Launois, B., Oesophagectomy by a transhiatal approach or thoracotomy: a prospective randomized trial, The British journal of surgery, 80, 367-70, 1993 **Ref Id** 470968	**Sample size** n=67 ; transhiatal = 32 versus thoracotomy = 35 **Characteristics** Age (mean): 57.4 years Male = 64/67 (96%) Occlusive stenosis on endoscopy = 11/67 (16%) Tumour location Upper/Middle/Lower = 2/37/28 Three patients originally randomized to the	**Interventions** The operative technique of transhiatal oesophagectomy was similar to that described by Orringer and Sloan3, while patients undergoing thoracotomy were treated using the method already published from this centre. All patients had a feeding jejunostomy inserted during the operation.	**Details** Randomisation method was not described in details.	**Results** 1. Pulmonary infection Transthoracic: 7/16 Transhiatal: 6/18 2. Anastomotic leakage Transthoracic: 3/16 Transhiatal: 2/18	**Limitations** Random sequence generation: Unclear risk Allocation concealment: unclear risk Blinding (performance bias): unclear risk Blinding of outcome assessment

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out France **Study type** A prospective randomized trial **Aim of the study** To compare the transhiatal approach with thoracotomy among people undergoing oesophagectomy for oesophaegal carcinoma in a prospective randomised study **Study dates** February 1988 and May 1991 **Source of funding** Not reported	transhiatal approach were converted to a right thoracotomy because it was not possible to remove the tumour safely by the former route. **Inclusion criteria** • Age <70 year • Squamous cell carcinoma of the oesophagus • Karnofsky score >60 or WHO performance status <2 • Life expectancy estimated >3 months • No previous treatment for cancer • Acceptance of the trial and randomization by the patient **Exclusion criteria**			3. Thoracic bleeding Transthoracic: 1/16 Transhiatal: 0/18 4. Jejunostomy leak Transthoracic: 0/16 Transhiatal: 1/18 5. Median operating time (hr) (Median and IQR) Transthoracic: 6 (3.5 to 9.5) Transhiatal: 4 (3 to 8) 6. Median transfusion (units) (Median and IQR) Transthoracic: 2.3 (0 to 8)	(detection bias): unclear risk Incomplete outcome data (attrition bias): high risk Selective reporting: low risk Other bias: low risk **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	• Carcinoma of the cervical oesophagus • Malignant oesophagotracheal fistula or tracheal mucosal involvement • Preoperative evidence of extraoesophageal spread (liver metastases, subclavicular node or recurrent laryngeal nerve paralysis) • Weight loss 15% of initial weight • Past history of cancer (except carcinoma of the skin or cervix treated curatively and ear, nose and throat cancer treated without evidence of recurrence for at least 5 years			Transhiatal: 2.3 (1 to 10) 7. Hospital death (up to day 80) Transthoracic: 3/35 Transhiatal: 2/32 8. Stay in intensive care unit (days) (Median and IQR) Transthoracic: 8.6 (2 to 60) Transhiatal: 9.2 (2 to 45) 9. Hospital stay (days) (Median and IQR) Transthoracic: 8.6 (2 to 60) Transhiatal: 9.2 (2 to 45) 10. number of death at	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	• Renal insufficiency (serum creatinine 120 pmol/l) or liver insufficiency (prothrombin time <: 6O%, transaminases up >threefold) • chronic pulmonary or cardiac insufficiencies • Uncontrolled sepsis • WBCs <2 x 109/1 or platelets <120 x 109/1 • Radiotherapy or chemotherapy receivedin another institution for treatment of oesophageal carcinoma • Follow-up not possible			follow-up (2 months) Transthoracic: 22 Transhiatal: 16 ROC curve = survival rate at 36 months Transthoracic: 18% Transhiatal: 30%	
Full citation Guo, M., Xie, B., Sun, X., Hu, M., Yang, Q., Lei, Y., A	**Sample size** n=221; 111 patients in MIO/VATS group versus	**Interventions** Video assisted thoracoscopy combined with laparoscopy and a neck incision (n=111) vs	**Details** Method of randomization: not reported	**Results** 1. Anastomotic leak	**Limitations** • Random

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>comparative study of the therapeutic effect in two protocols: Video-assisted thoracic surgery combined with laparoscopy versus right open transthoracic esophagectomy for esophageal cancer management, Chinese-German Journal of Clinical Oncology, 12, P68-P71, 2013

Ref Id

470975

Country/ies where the study was carried out

China

Study type
randomised controlled trial

Aim of the study
To evaluate the best intra-thoracoscopic surgery technique between video-assisted thoracic surgery (VATS) combined with laparoscopy and right open</td>
<td>110 patients in open oesophagectomy

Characteristics
<table>
<tr><th></th><th>Open (n=110)</th><th>MIO (n=111)</th></tr>
<tr><td>Female</td><td>38</td><td>43</td></tr>
<tr><td>Age (years, range)</td><td>60.8 (40-78)</td><td>57.3 (42-75)</td></tr>
<tr><td>Tumour location</td><td></td><td></td></tr>
<tr><td>Upper third</td><td>7</td><td>13</td></tr>
<tr><td>Middle third</td><td>76</td><td>78</td></tr>
<tr><td>Lower third</td><td>27</td><td>20</td></tr>
<tr><td>TNM Stage</td><td></td><td></td></tr>
</table>
</td>
<td>traditional open right transthoracic oesophagectomy (n=110)
Postoperative care: ICU observation for several days, nasogastric suction tube sited through anastomosis until a water-soluble contrast swallow. Enteral nutrition provided via a jejunostomy 2 days after surgery.</td>
<td>Exclusion after randomization: none
Lost to follow-up: none
Method of allocation concealment: none
Intention-to-treat analysis: not reported
Description of sample size calculation: no
Blinding: not reported/not possible
Duration of follow-up: 3-years</td>
<td>MIO: 1
open: 2
2. Pulmonary complications
MIO: 3
open: 9
3. Intraoperative blood loss (ml)
MIO: 219.7 ± 194.4
open: 590.0 ± 324.4
4. Operative time (min)
MIO: 272.3±57.9
open: 218.7±91
5. Retrieved lymph nodes
MIO: 24.3 ± 21.0
Open: 19.2 ± 12.5</td>
<td>sequence generation: unclear risk
• Allocation concealment: unclear risk
• Blinding (performance bias): low risk
• Blinding of outcome assessment (detection bias): low risk
• Incomplete outcom</td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
transthoracic oesophagectomy in oesophageal cancer. **Study dates** November 2006 to May 2008 **Source of funding** Not reported	**T1-T2N0M0** 31 24 **T3N0M0** 5 7 **T2-3N1M0** 74 80 **Inclusion criteria** Patients with oesophageal cancer **Exclusion criteria** Not reported				e data (attrition bias): unclear risk • Selective reporting: low risk Other bias: low risk **Other information**
Full citation Hulscher, J. B., Sandick, J. W., Boer, A. G., Wijnhoven, B. P., Tijssen, J. G., Fockens, P., Stalmeier, P. F., Kate, F. J., Dekken, H., Obertop, H., Tilanus, H. W., Lanschot, J. J., Extended transthoracic resection compared with	**Sample size** n=217; Transthoracic (TT)=106 versus Transhiatal (TH)=111 **Characteristics**	**Interventions** Transhiatal: dissection of oesophagus under direct vision through the widened diaphragmatic hiatus. Esophagogastrostomy was performed in the neck via a right-sided incision, without cervical lymphadenectomy.	**Details** • Method of randomization: stratified by hospital and	**Results** 1. Anastomotic leak TT: 18/114 TH: 15/106 2. Overall survival at 5-years follow-up	**Limitations** • Random sequence generation: unclear risk

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>limited transhiatal resection for adenocarcinoma of the esophagus, The New England journal of medicine, 347, 1662-9, 2002

Ref Id

471022

Country/ies where the study was carried out

Netherlands

Study type
randomised controlled trial

Aim of the study
To study whether transthoracic oesophagectomy with extended en bloc lymphadenectomy sufficiently improves outcomes compared to transhiatal oesophagectomy

Study dates
April 1994 to February 2000</td>
<td>
<table>
<tr><th></th><th>TH (n=106)</th><th>TT (n=111)</th></tr>
<tr><td>Age (years, range)</td><td>69 (23-79)</td><td>64 (35-78)</td></tr>
<tr><td>Sex (female)</td><td>14</td><td>17</td></tr>
<tr><td>Oesophageal tumour</td><td>87</td><td>93</td></tr>
<tr><td>Gastric cardia tumour</td><td>19</td><td>21</td></tr>
<tr><td>TNM Stage</td><td></td><td></td></tr>
<tr><td>0</td><td>2</td><td>2</td></tr>
<tr><td>I</td><td>10</td><td>15</td></tr>
<tr><td>IIa/IIb</td><td>18/10</td><td>10/7</td></tr>
<tr><td>III</td><td>47</td><td>60</td></tr>
<tr><td>IV</td><td>7</td><td>17</td></tr>
</table>
</td>
<td>Transthoracic: Posterolateral thoracotomy and mid-line laparotomy with left-sided cervical oesophagogastrostomy.</td>
<td>tumour site.
• No blocking was used within strata.
• Exclusion after randomization: none
• Lost to follow-up: none
• Method of allocation concealment: not reported
• Intention-to-treat analysis: yes
• Description of sample</td>
<td>i) number of death
TT: 71/110
TH: 68/95
ii) 5-year overall survival difference: 20% (95%CI 3% to 37%, p=0.02)
TT: 39%
TH: 19%
TH vs TT : HR(95% CI) = 1.14 (0.73, 1.79)
3. Number of lymph node resected
TT: 31±14 (n=111)
TH: 16±9 (n=94)
4. R0 resection margin
TT: 79/111
TH: 68/94</td>
<td>• Allocation concealment: unclear risk
• Blinding (performance bias): low risk
• Blinding of outcome assessment (detection bias): low risk
• Incomplete outcome data (attrition bias): low risk
• Selective</td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding Dutch Health Care Insurance Funds Council	**Inclusion criteria** • Adults (18 years and older) with adenocarcinoma of mid-to-distal oesophagus or adenocarcinoma of the gastric cardia involving the distal oesophagus with no evidence of lymph node involvement or metastases **Exclusion criteria** • Neoadjuvant chemotherapy		size calculation: yes • Blinding: not possible • Median follow-up: 4.7 (range: 2.5-8.3)	5. R1 resection margin TT: 28/111 TH: 23/94 6. R2 resection margin TT: 4/111 TH: 1/94 7. Recurrence TT: 59/110 TH: 59/95 8. Progression-free survival i) 5-year progression free survival difference: 41% (95%CI 24% to 58%, p=0.02) TT: 64% TH: 23% TH vs TT: HR (95%CI)	reporting: low risk Other bias: low risk **Other information** Additional data taken from 1. de Boer, A. G., van Lanschot, J. J., van Sandick, J. W., Hulscher, J. B., Stalmeier, P. F., de Haes, J. C., Tilanus, H. W., Obertop, H., Sprangers, M. A., Quality of life after transhiatal compared with extended transthoracic

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				= 1.17 (0.75,1.84)	resection for adenocarcinoma of the esophagus, Journal of Clinical Oncology J Clin Oncol, 22, 4202-8, 2004 2. Omloo, J. M., Lagarde, S. M., Hulscher, J. B., Reitsma, J. B., Fockens, P., Dekken, H., Kate, F. J., Obertop, H., Tilanus, H. W., Lanschot, J. J., Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the mid/distal esophagus:

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>five-year survival of a randomized clinical trial, Annals of Surgery Ann Surg, 246, 992-1000; discussion 1000-1, 2007</td></tr>
<tr><td>Full citation

Jacobi, C. A., Zieren, H. U., Muller, J. M., Pichlmaier, H., Surgical therapy of esophageal carcinoma: the influence of surgical approach and esophageal resection on cardiopulmonary function, European Journal of Cardio-Thoracic SurgeryEur J Cardiothorac Surg, 11, 32-7, 1997

Ref Id

471040

Country/ies where the study was carried out</td><td>Sample size
n=32; 16 TT vs 16 TH

Characteristics<table><tr><th></th><th>TH (n=16)</th><th>TT (n=16)</th></tr><tr><td>Age (years, range)</td><td>54 (38-67)</td><td>55 (43-72)</td></tr><tr><td>Thoracic lesion</td><td>14</td><td>14</td></tr></table></td><td>Interventions
Blunt transhiatal oesophageal dissection with cervical oesophagogastrostomy compared to transthoracic en-bloc resection with cervical oesophagogastrostomy</td><td>Details
Method of randomization: stratified according to the hospital and tumour site (oesophagus or gastric cardia).</td><td>Results
Transhiatal (TH) blunt resection vs Transthoracic (TT) en-bloc resection
Pulmonary complications
TT: 8/16
TH: 4/16
30-day mortality
TT: 1/16
TH: 1/16
Time of operation (min)</td><td>Limitations
Random sequence generation: low risk
Allocation concealment: unclear risk
Blinding (perfor</td></tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Netherlands **Study type** randomised controlled trial **Aim of the study** To compare blunt transhiatal esophagectomy and transthoracic en-bloc esophagectomy **Study dates** January 1992 to April 1995 **Source of funding** none declared	**Abdominal lesion** 2 2 **Stage I** 1 2 **Stage IIa/IIb** 2/5 2/4 **Stage III** 6 7 **Stage IV** 2 1 **Inclusion criteria** • Aged ≤ 75 years • Oesophageal cancer suitable for curative resection **Exclusion criteria** • Cervical oesophageal cancer or evidence of extra-		• No blocking used within strata. • Exclusion after randomization: none • Lost to follow-up: none • Method of allocation concealment: not reported • Intention-to-treat analysis: not reported • Description of sample size	(median and range) TT: 330 (260 - 430) TH: 190 (145 - 230) 4. Blood loss (ml) (median and range) TT: 2270 (730 to 2800) TH: 1000 (450 to 1600) 5. Postoperative hospitalisation (days) (median and range) TT: 21 (9 to 38) TH: 23 (9 to 30)	mance bias): low risk • Blinding of outcome assessment (detection bias): low risk • Incomplete outcome data (attrition bias): low risk • Selective reporting: low risk • Other bias: high risk (low

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	oesophageal spread of disease		calculation: yes • Blinding: not reported Duration of follow-up: until July 2002. • Median follow-up: 4.7 years.		sample size) **Other information**
Full citation Mariette, C., Meunier, B., Pezet, D., Dalban, C., Collet, D., Thomas, P. A., Brigand, C., Perniceni, T., Carrere, N., Bonnetain, F., Piessen, G., Hybrid minimally invasive versus open oesophagectomy for patients with oesophageal cancer: A multicenter, open-label, randomized phase III controlled trial, the MIRO trial,	**Sample size** n= 207; Hybrid=103 vs Open=104 **Characteristics** No baseline data provided **Inclusion criteria**	**Interventions** Hybrid minimally invasive oesophagectomy: a laparoscopic gastric mobilisation followed by an open thoracotomy. Open oesophagectomy: open gastric mobilisation through a midline laparotomy followed by an open thoracotomy.	**Details** • Method of randomization: stratified block randomisation (blocks of 4)	**Results** 1. Pulmonary complication Hybrid: 18/103 Open: 31/104 2. Major post-operative complication	**Limitations** (data extracted from conference abstract and published study protocol) • Random sequence generat

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Journal of Clinical Oncology. Conference, 33, 2015 **Ref Id** 471215 **Country/ies where the study was carried out** not reported likely French **Study type** randomised controlled multi-centre phase III trial- the MIRO trial **Aim of the study** To assessed whether hybrid minimally invasive oesophagectomy reduces morbidity compared with open. **Study dates** October 2009 to April 2012 **Source of funding**	• Squamous or adenocarcinoma of middle or lower oesophagus or junctional Siewert's type I tumour staged I, II or III (T1, T2, T3, N0 or N1, M0) before any treatment; • patients who are undergoing or not undergoing neoadjuvant radiotherapy and/or chemotherapy; • tumours deemed to be resectable with a curative intent · • 18 - 75 years of age; · • patients with WHO status performance of 0, 1 or 2; • patients who can undergo one of the surgical modalities to be investigated		• Exclusion after randomization: none reported • Lost to follow-up: none • Method of allocation concealment: envelops and blinded allocation • Intention-to-treat analysis: not reported • Description of sample size calculation: yes	Hybrid: 37/103 Open: 67/104 3. 30-day mortality Hybrid: 5/103 Open: 5/104	ion: low risk • Allocation concealment: low risk • Blinding (performance bias): low risk • Blinding of outcome assessment (detection bias): low risk • Incomplete outcome data (attrition bias): low risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Programme Hospitalier de Recherche Clinique from the French National Cancer Institute (INCA):	**Exclusion criteria** • contraindications for surgery related to patient status, disease extension or operative technique. • disease-associated exclusion criteria are (i) another histological subtype of OC besides SCC or ADC, (ii) tumours located at the pharyngoesophageal junction, the cervical oesophagus, the upper third of the oesophagus, or the oesophagogastric junction (types 2 or 3 of the Siewert's classification), (iii) distant metastases, including peritoneal carcinomatosis or metastasis to the		• Blinding: not possible • Duration of follow-up: 3-years		• Selective reporting: low risk Other bias: low risk **Other information** Additional information taken from 1. Briez, N., Piessen, G., Bonnetain, F., Brigand, C., Carrere, N., Collet, D., Doddoli, C., Flamein, R., Mabrut, J. Y., Meunier, B., Msika, S., Perniceni, T., Peschaud, F., Prudhomme, M., Triboulet,

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	supra-clavicular and celiac lymph nodes, (iv) recurrent nerve palsy, (v) tumoural involvement of adjacent mediastinal structures. • status, disease extension or operative technique. • patient-associated exclusion criteria are patients with the following features: (i) PaO2 < 60 mmHg, (ii) Pa CO2 > 45 mmHg, (iii) FEV1 < 1000 ml/sec, (iv) cirrhosis, (v) myocardial infarction or evolutive coronary artery disease, (vi) Leriche-Fontaine at stage II or more peripheral arterial occlusive disease, (vii) weight loss exceeding 15%, (viii) the presence of another malignant				J. P., Mariette, C. Open versus laparoscopically-assisted oesophagectomy for cancer: a multicentre randomised controlled phase III trial - the MIRO trial. BMC Cancer. (2011) 11:310

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr><td></td><td>tumour within the last 5 years or a synchronous malignant tumour, and (ix) any other simultaneous experimental treatment</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Full citation

van Sandick, J. W., Gisbertz, S. S., ten Berge, I. J., Boermeester, M. A., van der Pouw Kraan, T. C., Out, T. A., Obertop, H., van Lanschot, J. J., Immune responses and prediction of major infection in patients undergoing transhiatal or transthoracic esophagectomy for cancer, Annals of SurgeryAnn Surg, 237, 35-43, 2003

Ref Id

471464

Country/ies where the study was carried out</td><td>Sample size
n=20: Transthoracic (TT) =10 vs Transhiatal (TH)=10

Characteristics
<table><tr><th></th><th>TH (n=10</th><th>TT (n=10)</th></tr><tr><td>Age (years, range)</td><td>64 (46-78)</td><td>64 (45-78)</td></tr><tr><td>Female sex</td><td>1</td><td>1</td></tr></table>
Inclusion criteria</td><td>Interventions
Subtotal esophagectomy with proximal gastrectomy was performed in 10 patients by a transhiatal approach without thoracotomy (THE) and in 10 patients via a right-sided thoracotomy followed by a laparotomy in combination with a two-field lymph node dissection (TTE/Ivor-Lewis). In all patients, a narrow gastric tube was constructed and gastrointestinal continuity was restored by a cervical anastomosis</td><td>Details

• Method of randomization: not reported
• Exclusion after randomization: nine due to protocol deviations
• Lost to follow-</td><td>Results

1. Intraoperative blood loss (L)
TT: 1.2 (0.5 to 2.6)
TH: 1.0 (0.3 to 1.7)
2. Length of operation (hrs)
TT: 6.5 (5.0 to 9.3)
TH: 3.5(1.8 to 4.2)
3. Hospital stay (days)
TT: 23 (13 to 105)</td><td>Limitations

• Random sequence generation: unclear risk
• Allocation concealment: unclear risk
• Blinding (performance</td></tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Germany **Study type** randomised controlled trial **Aim of the study** To investigate alterations in immune responses after transhiatal versus transthoracic esophageal resection and to evaluate the role of preoperative immune functions in predicting postoperative infectious complications **Study dates** June 1997 to June 1998 **Source of funding** not reported	• Adenocarcinoma of the oesophagus suitable for curative resection · • ≥18 years of age • Invasive adenocarcinoma of the middle or distal esophagus or EGJ, • locally resectable disease without distant metastases on preoperative investigation **Exclusion criteria** • Chemotherapy, irradiation, or immunotherapy before or after surgery		up: not reported • Method of allocation concealment: not reported • Intention-to-treat analysis: no • Description of sample size calculation: no • Blinding: not reported • Mean duration of follow-up: 12 months	TH: 16(11 to 64)	bias): unclear risk • Blinding of outcome assessment (detection bias): unclear risk • Incomplete outcome data (attrition bias): low risk • Selective reporting: low risk • Other bias: high risk (low

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			(8-36 months)		sample size) **Other information**

1

F.92 Lymph node dissection in oesophageal and gastric cancer

3 **Does the extent of lymph node dissection influence outcomes in adults with oesophageal and gastric cancer?**

Full citation	Participant characteristics	Limitations
Mocellin, S., McCulloch, P., Kazi, H., Gama-Rodrigues, J. J., Yuan, Y. H., Nitti, D., Extent of lymph node dissection for adenocarcinoma of the stomach, Cochrane Database of Systematic Reviews, 2015	Patients undergoing surgery for resectable primary (non-metastatic) adenocarcinoma of the stomach. **Study Inclusion criteria** RCTs comparing D1, D2, D3 of lymphadenectomy for primary non-metastatic resectable gastric cancer reported survival data. For a study to be eligible, the full text of the article describing that study had to report time-to-event data on at least one of the chosen primary outcomes (i.e., OS, DSS and DFS). **Interventions** •D1 type lymphadenectomy: only lymph nodes adherent to the stomach (also known as perigastric lymph nodes) are removed during surgery.	**Quality of the systematic review** ROBIS Score: Study eligibility criteria: low risk Identification and selection of studies: low risk Data collection and study

Ref Id: 449258 **Study type:** Cochrane Systematic Review **Aim of the study:** Does more extended lymphadenectomy lead to a survival advantage for patients undergoing surgery for gastric carcinoma? To compare the effectiveness of the three different types of lymphadenectomy (i.e., D1, D2 and D3) in patients with primary (non-metastatic) resectable adenocarcinoma of the stomach, according to the evidence from available RCTs. **This review contains 8 RCTs (n=2515):**	•D2 type lymphadenectomy: in addition to perigastric lymph nodes, lymph nodes located along the three branches of the coeliac axis (i.e., left gastric artery, splenic artery and hepatic artery) are removed during surgery. •D3 type lymphadenectomy: in addition to lymph nodes harvested in D1 and D2 type lymphadenectomy, lymph nodes located around the aorta (also known as periaortic lymph nodes) are removed during surgery .	appraisal: unclear risk (no information about efforts to minimise error in data collection and risk of bias assessments) Synthesis and findings: high risk (between study variability in operative procedure: pancreatectomy and splenectomy not accounted for in analysis) Risk of bias in the review: High risk

Gastrectomy with D1 vs D2 Lymphadenectomy

*All data extracted from Cochrane review except for baseline characteristics data which was extracted from individual studies

<table>
<tr>
<td>Cuschieri 1999

UK MRC Trial</td>
<td>Participant Characteristics Number randomly assigned: 400 (D2 = 200, D1 = 200)

Age (mean): 66 years

Sex (M/F): 270/130

Inclusion criteria: patients with resectable primary non-metastatic gastric carcinoma

Equivalence of baseline characteristics: age and stage distribution similar for both groups.

Methods:

Method of randomization: patients randomized centrally by use of random permuted

blocks

Exclusion after randomization: none

Lost to follow-up: 4%

Method of allocation concealment: unreported

Intention-to-treat analysis: yes

Description of sample size calculation: yes (expected number = 400)</td>
<td>Baseline Characteristics:
<table>
<tr><td></td><td>D1 (200)</td><td>D2 (200)</td></tr>
<tr><td>Splenectomy</td><td>54</td><td>18</td></tr>
<tr><td>Pancreatosplenectomy</td><td>8</td><td>113</td></tr>
<tr><td>T1</td><td>48</td><td>40</td></tr>
<tr><td>T2</td><td>63</td><td>69</td></tr>
<tr><td>T3</td><td>84</td><td>86</td></tr>
<tr><td>Unknown T status</td><td>5</td><td>5</td></tr>
<tr><td>N0</td><td>69</td><td>78</td></tr>
<tr><td>N1</td><td>76</td><td>61</td></tr>
<tr><td>N2</td><td>39</td><td>53</td></tr>
<tr><td>Unknown N status</td><td>16</td><td>8</td></tr>
<tr><td>Distal gastrectomy</td><td>88</td><td>91</td></tr>
</table></td>
<td>Cochrane Risk of Study Bias Assessment:

Random sequence generation: low risk

Allocation concealment: unclear risk (unreported)

Blinding (performance bias): unclear – reported for participants, but not possible for surgeons

Blinding of outcome assessment (detection bias): unclear (unreported)

Incomplete outcome data (attrition bias): low risk

Selective reporting: low risk

Other bias: low risk</td>
</tr>
</table>

<table>
<tr><td></td><td></td><td><table><tr><td>Total gastrectomy</td><td>110</td><td>108</td></tr></table></td><td></td></tr>
<tr><td>Degiuli 2014 (D1 vs D2)

Italian Gastric Cancer Study Group</td><td>Participant Characteristics:

Number randomly assigned: 267 (D2 = 134, D1 = 133)

Age (mean): 63 years

Sex (M/F): 131/136

Inclusion criteria: patients with resectable primary non-metastatic gastric carcinoma

Equivalence of baseline characteristics: age and stage distribution similar for both groups

Median follow-up: 8.8 years

Number of patients enrolled did not reach the calculated sample size due to slow accrual

Methods

Method of randomization: sequence generated by a random-number table

Exclusion after randomization: none

Lost to follow-up: 9 (D2), 5 (D1)

Method of allocation concealment: unreported</td><td>Baseline Characteristics:<table><tr><td></td><td>D1 (133)</td><td>D2 (134)</td></tr><tr><td>Total gastrectomy</td><td>35</td><td>31</td></tr><tr><td>Distal gastrectomy</td><td>98</td><td>103</td></tr><tr><td>Splenectomy</td><td>9</td><td>12</td></tr><tr><td>Distal pancreatectomy and splenectomy</td><td>2</td><td>2</td></tr><tr><td>T1</td><td>49</td><td>39</td></tr><tr><td>T2</td><td>42</td><td>55</td></tr><tr><td>T3</td><td>40</td><td>37</td></tr><tr><td>Unknown Tstage</td><td>2</td><td>3</td></tr></table></td><td>Cochrane Risk of Study Bias Assessment:

Random sequence generation: low risk

Allocation concealment: unclear risk (unreported)

Blinding (performance bias): unclear – reported for participants, but not possible for surgeons

Blinding of outcome assessment (detection bias): low risk

Incomplete outcome data (attrition bias): low risk

Selective reporting: low risk

Other bias: low risk</td></tr>
</table>

<table>
<tr>
<td></td>
<td>Intention-to-treat analysis: yes

Description of sample size calculation: yes (expected number: 320)</td>
<td>
<table>
<tr><td>N0</td><td>63</td><td>57</td></tr>
<tr><td>N+</td><td>68</td><td>74</td></tr>
<tr><td>Unknown nodal status</td><td>2</td><td>3</td></tr>
</table>
</td>
<td></td>
</tr>
<tr>
<td>Robertson 1994 (D1 vs D2

Hong Kong</td>
<td>Participant Characteristics:

Number randomly assigned: 54 (D1 = 25, D2 = 29)

Age (mean): 59 years

Sex (M/F): 42/12

Inclusion criteria: patients with resectable primary non-metastatic gastric carcinoma

Equivalence of baseline characteristics: age and sex distribution similar for both groups

Median follow-up: 2.2 years

Methods

Method of randomization: “by opening a numbered, sealed envelope containing the treatment option. The treatment options were determined by random numbers generated on a personal computer.”

Exclusion after randomization: none

Lost to follow-up: none</td>
<td>Baseline Characteristics
<table>
<tr><td></td><td>D1 (25)</td><td>D2 (29)</td></tr>
<tr><td>T1N0</td><td>8</td><td>8</td></tr>
<tr><td>T1N1</td><td>2</td><td>1</td></tr>
<tr><td>T2N0</td><td>5</td><td>3</td></tr>
<tr><td>T2N1</td><td>2</td><td>4</td></tr>
<tr><td>T2N2</td><td>0</td><td>1</td></tr>
<tr><td>T3N0</td><td>1</td><td>2</td></tr>
<tr><td>T3N1</td><td>6</td><td>5</td></tr>
<tr><td>T3N2</td><td>1</td><td>3</td></tr>
<tr><td>T4N0</td><td>0</td><td>1</td></tr>
<tr><td>T4N2</td><td>0</td><td>1</td></tr>
</table>
</td>
<td>Cochrane Risk of Study Bias Assessment:

Random sequence generation: unclear risk (unreported)

Allocation concealment: unclear risk (unreported)

Blinding (performance bias): unclear – reported for participants, but not possible for surgeons

Blinding of outcome assessment (detection bias): unclear risk (unreported)

Incomplete outcome data (attrition bias): low risk

Selective reporting: low risk

Other bias: unclear risk (Sample size is insufficient for achieving an adequate statistical power given a clinically meaningful expected survival difference between study arms)</td>
</tr>
</table>

<table>
<tr>
<td></td>
<td>Method of allocation concealment: unreported

Intention-to-treat analysis: yes

Description of sample size calculation: unreported (unlikely it was performed due to

the small number of patients enrolled, insufficient for achieving an adequate statistical

power given a clinically meaningful expected survival difference between study arms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Songun 2010 (D1 vs D2)

Dutch Gastric Cancer Trial</td>
<td>Participant Characteristics:

Number randomly assigned: 523 (D2 = 483, D1 = 513)

Age < 70 years: 33%

Sex (M/F): 401/310

Inclusion criteria: patients with resectable primary non-metastatic gastric carcinoma

Equivalence of baseline characteristics: age, sex and stage distribution similar for both groups

Median follow-up: 15.2 years

Methods:

Method of randomization: “The sequence of randomisation was in blocks of six with stratification according to the participating centre.” Exclusion after randomization: D1 =</td>
<td>Baseline Characteristics:
<table>
<tr><td></td><td>D1 (380)</td><td>D2 (331)</td></tr>
<tr><td>T1</td><td>98</td><td>85</td></tr>
<tr><td>T2</td><td>181</td><td>152</td></tr>
<tr><td>T3</td><td>94</td><td>82</td></tr>
<tr><td>N0</td><td>171</td><td>144</td></tr>
<tr><td>N1</td><td>138</td><td>113</td></tr>
<tr><td>N2</td><td>50</td><td>47</td></tr>
<tr><td>N3</td><td>21</td><td>27</td></tr>
<tr><td>Total gastrectomy</td><td>115</td><td>126</td></tr>
</table>
</td>
<td>Cochrane Risk of Study Bias Assessment:

Random sequence generation: low risk

Allocation concealment: low risk

Blinding (performance bias): low risk

Blinding of outcome assessment (detection bias): low risk

Incomplete outcome data (attrition bias): low risk

Selective reporting: low risk

Other bias: unclear risk (It is unclear whether the number of patients excluded after randomization had any impact on the trial outcomes)</td>
</tr>
</table>

<table>
<tr>
<td></td>
<td>133 (metastatic disease); D2 = 152 (metastatic disease)

Lost to follow-up: one method of allocation concealment: “The sequence of randomisation was in blocks of six with stratification according to the participating centre.”

Intention-to-treat analysis: yes

Description of sample size calculation: reported (expected number: 1062)</td>
<td>
<table>
<tr><td>Partial gastrectomy</td><td>265</td><td>205</td></tr>
<tr><td>Splenectomy</td><td>41</td><td>124</td></tr>
<tr><td>Resection of tail of pancreas</td><td>10</td><td>98</td></tr>
</table>
</td>
<td></td>
</tr>
<tr>
<td>Wu 2006 (D1 vs D2)

Taiwan</td>
<td>Participant Characteristics:

Number randomly assigned: 221 (D2 = 111, D1 = 110)

Age (mean): 67 years

Sex (M/F): 170/51

Inclusion criteria: patients with resectable primary non-metastatic gastric carcinoma

Equivalence of baseline characteristics: age, sex, tumor location and comorbidity similar for both groups

Median follow-up: 7.9 years

Methods:

Method of randomization: “Eligible patients were randomized by means of permuted block randomization”</td>
<td>Baseline Characteristics:
<table>
<tr><td></td><td>D1 (110)</td><td>D2 (111)</td></tr>
<tr><td>T1</td><td>23</td><td>29</td></tr>
<tr><td>T2</td><td>26</td><td>20</td></tr>
<tr><td>T3</td><td>56</td><td>59</td></tr>
<tr><td>T4</td><td>5</td><td>3</td></tr>
<tr><td>N0</td><td>39</td><td>44</td></tr>
<tr><td>N1</td><td>54</td><td>43</td></tr>
<tr><td>N2</td><td>14</td><td>18</td></tr>
<tr><td>N3</td><td>3</td><td>6</td></tr>
</table>
</td>
<td>Cochrane Risk of Study Bias Assessment:

Random sequence generation: low risk

Allocation concealment: low risk

Blinding (performance bias): low risk

Blinding of outcome assessment (detection bias): unclear risk

Incomplete outcome data (attrition bias): low risk

Selective reporting: low risk

Other bias: low risk</td>
</tr>
</table>

<table>
<tr>
<td></td>
<td>Exclusion after randomization: none

Lost to follow-up: none

Method of allocation concealment: “Eligible patients were randomized by means of permuted block randomization.”

Intention-to-treat analysis: yes

Description of sample size calculation: reported (expected number: 150)</td>
<td>
<table>
<tr><td>Total gastrectomy</td><td>30</td><td>23</td></tr>
<tr><td>Subtotal gastrectomy</td><td>80</td><td>88</td></tr>
<tr><td>Distal Pancreatosplenectomy</td><td>1</td><td>13</td></tr>
<tr><td>Splenectomy</td><td>3</td><td>1</td></tr>
</table>
</td>
<td></td>
</tr>
<tr>
<td colspan="4">Gastrectomy with D2 vs D3 Lymphadenectomy

*All data extracted from Cochrane review except for baseline characteristics data which was extracted from individual studies</td>
</tr>
<tr>
<td>Sasako 2008 (D2 vs D3)

Japan Clinical Oncology Group</td>
<td>Participant Characteristics:

Number randomly assigned: 523 (D3 = 260, D2 = 263)

Age (mean): 60 years

Sex (M/F): 359/164

Inclusion criteria: patients with resectable primary non-metastatic gastric carcinoma

Equivalence of baseline characteristics: age, sex and stage distribution similar for both

groups

Median follow-up: 5.7 years</td>
<td>Baseline Characteristics:
<table>
<tr><td></td><td>D2 (263)</td><td>D3 (260)</td></tr>
<tr><td>T1</td><td>9</td><td>14</td></tr>
<tr><td>T2a</td><td>46</td><td>37</td></tr>
<tr><td>T2b</td><td>79</td><td>95</td></tr>
<tr><td>T3</td><td>121</td><td>109</td></tr>
<tr><td>T4</td><td>8</td><td>5</td></tr>
</table>
</td>
<td>Cochrane Risk of Study Bias Assessment:

Random sequence generation: low risk

Allocation concealment: low risk

Blinding (performance bias):Low risk

Blinding of outcome assessment (detection bias): low risk

Incomplete outcome data (attrition bias): low risk

Selective reporting: low risk

Other bias: low risk</td>
</tr>
</table>

<table>
<tr>
<td></td>
<td>Methods:

Method of randomization: “the surgeon contacted the [data center] by telephone to receive a randomly generated assignment”

Exclusion after randomization: none

Lost to follow-up: none

Method of allocation concealment: “the surgeon contacted the [data center] by telephone to receive a randomly generated assignment”

Intention-to-treat analysis: yes

Description of sample size calculation: reported (expected number: 412)</td>
<td><table>
<tr><td>Positive nodes</td><td>184</td><td>164</td></tr>
</table></td>
<td></td>
</tr>
<tr>
<td>Maeta 1999 (D2 vs D3)

Japan</td>
<td>Participant Characteristics:

Number randomly assigned: 70 (D3 = 35, D2 = 35)

Age (mean): 60 years

Sex (M/F): 41/29

Inclusion criteria: patients with resectable primary non-metastatic gastric carcinoma

Equivalence of baseline characteristics: age and stage distribution similar for both groups

Median follow-up: 2.3 years

Methods:</td>
<td>Baseline Characteristics:<table>
<tr><td></td><td>D2 (35)</td><td>D3 (35)</td></tr>
<tr><td>Depth of invasion

Muscularis propria, subserosa</td><td>2</td><td>6</td></tr>
<tr><td>Serosa</td><td>30</td><td>27</td></tr>
<tr><td>Adjacent structures</td><td>3</td><td>2</td></tr>
</table></td>
<td>Cochrane Risk of Study Bias Assessment:

Random sequence generation: unclear risk (unreported)

Allocation concealment: unclear risk (unreported)

Blinding (performance bias): unclear risk (unreported for participants only, blinding not possible for surgeons)

Blinding of outcome assessment (detection bias): unclear risk (unreported)

Incomplete outcome data (attrition bias): low risk</td>
</tr>
</table>

<table>
<tr>
<td></td>
<td>Method of randomization: unreported

Exclusion after randomization: unreported

Lost to follow-up: none

Method of allocation concealment: unreported

Intention-to-treat analysis: yes

Description of sample size calculation: unreported (unlikely it was performed due to the small number of patients enrolled, insufficient for achieving an adequate statistical power given a clinically meaningful expected survival difference between study arms)</td>
<td><table>
<tr><td>Lymph node involvement</td><td>20</td><td>23</td></tr>
</table></td>
<td>Selective reporting: low risk

Other bias: high risk (Sample size is insufficient for achieving an adequate statistical power given a clinically meaningful expected survival difference between study arms. Moreover, the description of the methods is quite scarce leaving room for doubt about the soundness of the design and conduct of the trial)</td>
</tr>
<tr>
<td>Yonemura 2008 (D2 vs D3)

East Asia Surgical Oncology Group (Japan)</td>
<td>Participant Characteristics:

Number randomly assigned: 269 (D2 = 135, D3 = 134)

Age (mean): 63 years

Sex (M/F): 181/88

Inclusion criteria: patients with resectable primary non-metastatic gastric carcinoma

Equivalence of baseline characteristics: age, sex, and type of gastrectomy similar for both

Median follow-up: 5 years

Methods:</td>
<td>Baseline Characteristics:

<table>
<tr><td></td><td>D2</td><td>D3</td></tr>
<tr><td>Female</td><td>45</td><td>43</td></tr>
<tr><td>Age (median, range in years)</td><td>63.8 (9.7)</td><td>62.5 (10.2)</td></tr>
<tr><td>T1</td><td>2</td><td>5</td></tr>
<tr><td>T2</td><td>61</td><td>56</td></tr>
</table></td>
<td>Cochrane Risk of Study Bias Assessment:

Random sequence generation: low risk

Allocation concealment: unclear risk

Blinding (performance bias): low risk

Blinding of outcome assessment (detection bias): low risk

Incomplete outcome data (attrition bias): low risk

Selective reporting: low risk

Other bias: low risk</td>
</tr>
</table>

	Method of randomization: “After the final assessment of eligibility, patients were enrolled randomly by a computer algorithm” Exclusion after randomization: none Lost to follow-up: none Method of allocation concealment: “After the final assessment of eligibility, patients were enrolled randomly by a computer algorithm” Intention-to-treat analysis: yes Description of sample size calculation: reported (expected number: 227)	T3	58	56		
		T4	14	17		
		N0	37	35		
		N1	41	43		
		N2	50	39		
		N3	7	5		
		N4	0	12		
		Pancreatectomy	20	35		
		Splenectomy	53	71		
		Total gastrectomy	79	75		
		Subtotal gastrectomy	55	57		
		Proximal	1	2		
Full citation Jiang, L., Yang, K. H., Chen, Y., Guan, Q. L., Zhao, P., Tian, J. H., Wang, Q., Systematic	**Study characteristics** **Inclusion criteria:** Histologically or cytologically confirmed gastric cancer, prospective RCT comparing D1 with D2 dissection, and available data on relevant outcomes. If more than one					**Limitations** **<u>Quality of the systematic review</u>** ROBIS Score: Study eligibility criteria: low risk

review and meta-analysis of the effectiveness and safety of extended lymphadenectomy in patients with resectable gastric cancer, British Journal of SurgeryBr J Surg, 101, 595-604, 2014 **Ref Id:** 449212 **Study type:** Systematic Review 8 RCTs: n=2044 (D1, 1042; D2, 1002): Dent et al.16 Cuschieri et al. (MRC trial)12,19 Wu et al.20,21 Bonenkamp et al.22 Hartgrink 11 Robertson et al. (Hong Kong trial)23	publication of a single trial existed, only the publication with the most complete data was included unless the relevant outcomes were published only in earlier versions. **Interventions** D1 and D2 dissection Subgroup analysis: D2 gastrectomy with spleen and pancreas preservation.	Identification and selection of studies: low risk Data collection and study appraisal: low risk Synthesis and findings: low risk Risk of bias in the review: Low risk

Li et al. (Chinese study)32 Degiuli et al.15v **Aim of the study: T**o evaluate the effectiveness and safety of extended lymphadenectomy in patients with resectable gastric cancer. **Study dates: 1988 and 2010** **Source of funding** Fundamental Research Funds for the Central Universities			
D1 vs D2			
Li 2007 (publication written in Chinese, data extracted from Jiang 2014) **Study dates: 1989-2001**	D1:108 D2:109 Median age: D1: 48.1 (30-72) D2: 47.7 (36-77)		**Risk of Bias assessment (from Jiang 2014, but no explanations given for high risk rating):** Random sequence generation: unclear risk Allocation concealment: unclear risk

<table>
<tr>
<td></td>
<td></td>
<td></td>
<td>Blinding (performance bias): unclear risk

Blinding of outcome assessment (detection bias): unclear risk

Incomplete outcome data (attrition bias): unclear risk

Selective reporting: unclear risk

Other bias: unclear risk</td>
</tr>
<tr>
<td>Full citation:

Dent, D. M., Madden, M. V., Price, S. K., Randomized comparison of R1 and R2 gastrectomy for gastric carcinoma, British Journal of SurgeryBr J Surg, 75, 110-2, 1988

Ref Id:449189

Country: South Africa

Study type: Randomised controlled trial</td>
<td>Participant Characteristics:

Sample size: n=43 (D1=22, D2=21)

Inclusion criteria: Patients were eligible if at laparotomy the surgeon assess that the Japanese clinical stage was T1-3, N0-1 with some perigrastric N2 nodes and M0.

Exclusion criteria: older than 75 years, previous or coexisiting malignancy disease, coexisting non-malignany disease with made prolonged follow-up unlikely or if they came from a remote area.

Randomisation method: sealed envelopes containing computer generated sets of numbers.

Length of Follow-up: 5 years</td>
<td>Baseline characteristics*:
<table>
<tr><td></td><td>D1 (22)</td><td>D2 (21)</td></tr>
<tr><td>Age:</td><td>45 (8.9)</td><td>55.8 (11.4)</td></tr>
<tr><td>Female</td><td>10</td><td>6</td></tr>
<tr><td>Subtotal gastrectomy</td><td>18</td><td>19</td></tr>
<tr><td>Total gastrectomy</td><td>4</td><td>2</td></tr>
<tr><td>T1</td><td>6</td><td>7</td></tr>
<tr><td>T2</td><td>5</td><td>5</td></tr>
<tr><td>T3</td><td>11</td><td>9</td></tr>
</table>
</td>
<td>Risk of Bias assessment (from Jiang, but no explanations given for high risk rating):

Random sequence generation: low risk

Allocation concealment: low risk

Blinding (performance bias): unclear risk

Blinding of outcome assessment (detection bias): low risk

Incomplete outcome data (attrition bias): high risk

Selective reporting: high risk

Other bias: unclear risk</td>
</tr>
</table>

Aim of the study: To assess whether R2 radical gastrectomy for localised and potentially curable gastric carcinoma may be superior to gastrectomy without lymphadenectomy. **Study dates:** 1982-1986 **Source of funding:** no information All data extracted from Jiang 2014 unless indicated with *, which denotes data extracted from original publication.	Median follow-up 3.1 years **Methods:** **Interventions:** R1: N1 nodes on gastric wall removed and staging biopsies taken from abnormal nodes, coeliac, common hepatic and hepatic nodes. R2 performed as described by Kajitani. Lymphadenectomy performed in the infra- and supraduodenal areas along the hepatic, common hepatic, coeliac and splenic arteries. No effort was made to screen for recurrence, patients were investigated appropriately when signs and symptoms suggestive of recurrence developed. Method of randomization: Yes Exclusion after randomization: unreported Lost to follow-up: not reported Method of allocation concealment: Yes Intention-to-treat analysis: unreported		

<table>
<tr><td></td><td>Description of sample size calculation: unreported</td><td></td><td></td></tr>
<tr><td>Full citation

Kulig, J., Popiela, T., Kolodziejczyk, P., Sierzega, M., Szczepanik, A., Polish Gastric Cancer Study, Group, Standard D2 versus extended D2 (D2+) lymphadenectomy for gastric cancer: an interim safety analysis of a multicenter, randomized, clinical trial, 193, 10-5, 2007

Ref Id

451936

Country/ies where the study was carried out:

Polish Gastric Cancer Study Group

Study type: Randomised controlled trial</td><td>Participant characteristics

Sample size: n=275. (D2: 141. D2+PAND (D3): 134)

Inclusion criteria:

All patients who qualified for gastric resection for gastric cancer. Entry criteria before laparotomy included histologically proven gastric adenocarcinoma (assumed depth of infiltration T1–T3 according to the American Joint Committee on Cancer (AJCC) classification), age older than 18 years, and informed consent.

Exclusion criteria:

Disseminated tumours, cancer of the gastric stump, synchronous or metachronous malignancy, any serious disorder of the cardiocirculatory or respiratory system (American Society of Anesthesiologists), and renal or hepatic failure. Patients with tumors macroscopically infiltrating surrounding organs (T4 according to the AJCC classification), gross metastasis in para-aortic lymph nodes, and those with macroscopically noncurative resection were excluded from the trial intraoperatively.

Interventions: D2 vs D2+para-aortic node removal</td><td>Baseline characteristics:
<table><tr><td></td><td>D2 (n=141)</td><td>D3 (n=134)</td></tr><tr><td>Sex (Female)</td><td>56</td><td>51</td></tr><tr><td>Median age (years, range)</td><td>56 (31-81)</td><td>54 (34-77)</td></tr><tr><td>Depth of disease</td><td></td><td></td></tr><tr><td>T1</td><td>33</td><td>24</td></tr><tr><td>T2</td><td>31</td><td>30</td></tr><tr><td>T3</td><td>77</td><td>80</td></tr><tr><td>N0</td><td>50</td><td>56</td></tr><tr><td>N1</td><td>37</td><td>39</td></tr><tr><td>N2</td><td>33</td><td>26</td></tr><tr><td>N3</td><td>21</td><td>13</td></tr><tr><td>Total gastrectomy</td><td>92</td><td>95</td></tr></table></td><td>Limitations

Random sequence generation: low risk

Allocation concealment: low risk

Blinding (performance bias): unclear risk

Blinding of outcome assessment (detection bias): unclear risk

Incomplete outcome data (attrition bias): low risk

Selective reporting: low risk

Other bias: low risk</td></tr>
</table>

Randomised Controlled trial **Aim of the study:** To evaluate the possible benefits of extended D2 (D2+) lymphadenectomy after potentially curative resection of gastric cancer **Study dates:** May 1999 and December 2003 **Source of funding: Polish state committee for scientific research**	Splenectomy was routinely performed for tumour located in the upper-third of the stomach, and resection of the tail of pancreas was optional. D2: dissection of lymph node groups 1 to 12. Modified slightly depending on the location of the tumour. D2+: group 1-12 lymph nodes with additional removal of para-aortic lymph nodes (nodes 16a2, from the upper margin of the celiac trunk to the lower margin of the left renal vein, and 16b1 from the lower margin of the left renal vein to the upper margin of the inferior mesenteric artery)) All patients received perioperative prophylactic antibiotics. Patients with positive lymph nodes received different regimens of adjuvant chemotherapy as part of other RCTs. **Methods:** **Method of randomization:** Because of technical reasons randomization was performed separately for each participating center, so stratification by study center was planned in the final analysis to control possible bias. After laparotomy, patients who met the eligibility criteria were assigned to either of the treatment groups according to a computer-generated randomization list. No blocking or stratification was used. **Exclusion after randomization:** none	Distal gastrectomy	41	29	
		Proximal subtotal gastrectomy	8	10	
		Splenectomy	53	54	
		Pancreatic tail resection	12	7	

<table>
<tr><td></td><td>Lost to follow-up: none reported

Method of allocation concealment: Patients were assigned to either of the treatment groups according to a computer-generated randomization list.

Intention-to-treat analysis: yes

Description of sample size calculation: reported. Expected 230 randomised to each arm</td><td></td><td></td></tr>
<tr><td colspan="4">Oesophageal Cancer</td></tr>
<tr><td>Full citation:

Kato, H., Watanabe, H., Tachimori, Y., Iizuka, T., Evaluation of neck lymph node dissection for thoracic esophageal carcinoma, Ann Thorac SurgThe Annals of thoracic surgery, 51, 931-5, 1991

Ref Id: 451935

Country: Japan</td><td>Participant Characteristics:

Sample size: n=150 (3 field: 77, 2 field: 73)

Inclusion criteria: thoracic oesophageal cancer undergoing oesophagectomy with good surgical status.

13 people in Group A and 16 in Group B received postoperative radiation therapy, 5 and 9 of whom respectively had residual disease. 21 and 12 patients in groups A and B had postoperative adjuvant chemotherapy with two doses of IV cisplatin and vindesine. 3 and 5 in Groups A and B received combination radiotherapy and chemotherapy (IV cisplatin and 5FU). 40 patients received no adjuvant therapy.

Length of follow-up 5 years

Methods:</td><td>Baseline Characteristics:<table><tr><td></td><td>3 field (n=77)</td><td>2 field (n=73)</td></tr><tr><td>Age</td><td>60.5 (8.9)</td><td>64.5 (10)</td></tr><tr><td>Female</td><td>6</td><td>7</td></tr><tr><td>Tumour location (upper/middle /lower)</td><td>7/42/28</td><td>6/52/15</td></tr><tr><td>Tis</td><td>3</td><td>2</td></tr><tr><td>T1</td><td>22</td><td>24</td></tr><tr><td>T2</td><td>21</td><td>13</td></tr></table></td><td>Risk of Bias assessment:

Random sequence generation: unclear risk

Allocation concealment: unclear risk

Blinding (performance bias): unclear risk

Blinding of outcome assessment (detection bias): low risk

Incomplete outcome data (attrition bias): low risk (median length of follow-up not reported)

Selective reporting: low risk

Other bias: low risk</td></tr>
</table>

<table>
<tr>
<td>Study type: Randomised controlled trial

Aim of the study: not stated

Study dates 1985-1989

Source of funding: not stated</td>
<td>Intervention: oesophagectomy through right thoracotomy (5th intercostal space) and laparotomy.

Group A (3 field): standard radical operation with neck lymph node dissection.

Group B (2 field): standard radical lymph node dissection without neck lymph node dissection.

Method of randomization: unreported

Exclusion after randomization: unreported

Lost to follow-up: not reported

Method of allocation concealment: unreported

Intention-to-treat analysis: unreported

Description of sample size calculation: unreported</td>
<td>
<table>
<tr><td>T3</td><td>23</td><td>25</td></tr>
<tr><td>T4</td><td>8</td><td>9</td></tr>
<tr><td>N+</td><td>43</td><td>46</td></tr>
<tr><td>M+</td><td>18</td><td>15</td></tr>
</table>
</td>
<td></td>
</tr>
<tr>
<td>Full citation:

Nishihira, T., Hirayama, K., Mori, S., A prospective randomized trial of extended cervical and superior mediastinal</td>
<td>Participant Characteristics

Sample Size: n=62 (3 field: 32, 2-field: 30)

Squamous cell carcinoma only

Inclusion criteria: invasive esophageal carcinoma, excluding stage 0, and T4 or M1 tumors that were unlikely to be treated with</td>
<td>Baseline Characteristics:
<table>
<tr><td></td><td>Extended lymphadenectomy (3 field) (n=32)</td><td>Conventional lymphadenectomy (2 field) (n=30)</td></tr>
</table>
</td>
<td>Risk of Bias assessment

Random sequence generation: unclear risk (method of randomisation not described)

Allocation concealment: low risk

Blinding (performance bias):low risk</td>
</tr>
</table>

<table>
<tr>
<td>lymphadenectomy for carcinoma of the thoracic esophagus, 175, 47-51, 1998

Ref Id: 451938

Aim of Study: To evaluate the significance of and problems associated with extended lymphadenectomy.

Study type: Randomised controlled study

Country: Japan

Study dates: 1987-1993

Source of funding: not stated

*Note: Intervention may not strictly follow definition of 3-Field and 2-Field in protocol and other studies</td>
<td>curative resection. Patients under 70 years of age were included, and there were strict inclusion criteria as to organ function of the lung, heart, kidney, and liver.

Follow-up: No median follow-up reported. 5-year survival data reported.

Methods:

Patients were randomly assigned by a double-blind method to either the extended lymphadenectomy or conventional lymphadenectomy group.

Postoperatively, double-blind random assignment was again used to assign patients to groups receiving either radiochemotherapy or chemotherapy alone (aggressive cancer chemotherapy) as the postoperative adjuvant therapy.

Intervention:

3-Field: mediastinal and cervical lymph node removal.

2-Field*: abdominal and partial mediastinal lymph node removal only.

Method of randomization: unreported

Exclusion after randomization: unreported

Lost to follow-up: not reported</td>
<td>
<table>
<tr><td>Age</td><td>58.8 (5.2)</td><td>58.2 (8.1)</td></tr>
<tr><td>Female</td><td>6</td><td>4</td></tr>
<tr><td>T1</td><td>4</td><td>6</td></tr>
<tr><td>T2</td><td>27</td><td>22</td></tr>
<tr><td>T3</td><td>1</td><td>2</td></tr>
<tr><td>N0</td><td>14</td><td>12</td></tr>
<tr><td>N1</td><td>12</td><td>13</td></tr>
<tr><td>Upper oesophageal tumour</td><td>1</td><td>0</td></tr>
<tr><td>Middle oesophageal tumour</td><td>20</td><td>23</td></tr>
<tr><td>Lower oesophageal tumour</td><td>11</td><td>7</td></tr>
</table>
</td>
<td>Blinding of outcome assessment (detection bias): low risk

Incomplete outcome data (attrition bias): low risk

Selective reporting: low risk

Other bias: small sample size</td>
</tr>
</table>

<table>
<tr><td></td><td>Method of allocation concealment: Yes

Intention-to-treat analysis: unreported

Description of sample size calculation: unreported</td><td></td><td></td></tr>
<tr><td>Full citation:

Tabira, Y., Kitamura, N., Yoshioka, M., Tanaka, M., Nakano, K., Toyota, N., Mori, T., Significance of three-field lymphadenectomy for carcinoma of the thoracic esophagus based on depth of tumor infiltration, lymph nodal involvement and survival rate, Journal of Cardiovascular Surgery, 40, 737-740, 1999

Ref Id: 449300

Country: Japan</td><td>Participant characteristics:

Sample size: n=152 (3-field: 66. 2-field: 86)

Inclusion criteria: Consecutive patients who underwent curative oesophagectomy for carcinoma of the thoracic oesophagus invading to submucosa (pT1), muscularis propria (pT2), adventitia (pT3) and adjacent tissues (pT4).

Exclusion criteria: not described

Patients younger than 75 years and no comorbid disease underwent 3-field lymphadenectomy.

Duration of follow-up: 150 months

Mean follow-up: 46.5 months

Intervention:

3-Field lymphadenectomy: bilateral neck dissection, perigastric, left gastric artery nodes removed.</td><td>Baseline characteristics:

142 squamous cell carcinoma

2 adenosquamous cell carcinoma

1 adenocarcinoma

<table><tr><td></td><td>3-Field</td><td>2-Field</td></tr><tr><td>Age (mean, sd)</td><td>61 (8)</td><td>66 (10)</td></tr><tr><td>Female (not clearly recorded)</td><td>11</td><td>14</td></tr><tr><td>T1/T2/T3/T4</td><td>15/9/39/3</td><td>26/19/38/3</td></tr><tr><td>N0/N+</td><td>12/44 (?missing data)</td><td>39/47</td></tr><tr><td>M+</td><td>21</td><td>9</td></tr></table></td><td>Bias due to selection of participants: no information

Bias due to confounding: Critical (younger and potentially fitter patients allocated to more invasive surgery compared to less invasive and confounding not controlled for in analysis). Attempted to stratify results by disease severity

Bias in classification of interventions: low risk of bias

Bias due to departures from intended interventions: not reported

Bias due to missing data: low risk

Bias in measures of outcomes: low risk

Bias in selection of the reported result: low risk

Overall bias: moderate</td></tr>
</table>

<table>
<tr>
<td>Study type: prospective observational study

Aim of the study: To examine the significance of three-filed lymphadenectomy for carcinoma of the thoracic oesophagus.

Study dates: 1983-1996

Source of funding: not stated</td>
<td>2-Field: perigastric and left gastric artery nodes removed. Neck nodes not removed</td>
<td><table>
<tr><td>5 year survival</td><td>43.8%</td><td>30.2%</td></tr>
</table></td>
<td></td>
</tr>
<tr>
<td>Full citation

Kato, H., Lymph node dissection for thoracic esophageal carcinoma. Two- and 3-field lymph node dissection, Ann Chir GynaecolAnnales chirurgiae et gynaecologiae, 84, 193-9, 1995

Ref Id: 451934</td>
<td>Participant Characteristics:

Sample size: n=310 (2-field: 410, 3-field: 100)

Inclusion criteria: Patients with thoracic oesophageal cancer who underwent oesophagectomy by right thoracotomy and laparotomy.

Exclusion criteria:

Patients with microscopically confirmed residual tumour after surgery.

Methods:

From 1962-1981 410 participants with thoracic oesophageal carcinoma underwent oesophagectomy and conventional 2-Field</td>
<td>Baseline Characteristics:<table>
<tr><td></td><td>2 Field (n=410)</td><td>3-Field (n=100)</td></tr>
<tr><td>Mean Age (years)</td><td>61.5</td><td>61.9</td></tr>
<tr><td>Female</td><td>66</td><td>10</td></tr>
<tr><td>Tumour location</td><td></td><td></td></tr>
<tr><td>Upper thoracic</td><td>18</td><td>5</td></tr>
</table></td>
<td>Risk of Bias assessment

Bias due to selection of participants: serious risk

Bias due to confounding: critical (no control for potential confounders particularly since difference procedures were performed in different time frames, also no reference to adjuvant therapy)

Bias in classification of interventions: serious

Bias due to departures from intended interventions: low risk</td>
</tr>
</table>

<table>
<tr>
<td>Country: Japan

Study type: retrospective observational study

Aim of the study: To evaluate the effect of lymph node dissection on the survival of patients with thoracic oesophageal carcinoma.

Study dates: 1962-1993

Source of funding: not reported

Note: The study includes 120 and 64 patients who underwent ‘extended’ and ‘super-extended 2-field’ nodal dissection respectively, which refers to partial neck node dissection. These have not been included in the analysis here.</td>
<td>dissection. Between 1985 and 1993, 100 patients underwent 3-Field lymphadenectomy.

Intervention:

2-Field dissection: dissection of lymph nodes in mediastinum and abdomen.

3-Field: dissection of cervical lymph nodes in addition to abdominal and mediastinal nodes.</td>
<td>
<table>
<tr><td>Mid-thoracic</td><td>255</td><td>52</td></tr>
<tr><td>Lower-thoracic</td><td>137</td><td>43</td></tr>
<tr><td>Tis</td><td>1</td><td>1</td></tr>
<tr><td>T1</td><td>34</td><td>29</td></tr>
<tr><td>T2</td><td>101</td><td>17</td></tr>
<tr><td>T3</td><td>255</td><td>49</td></tr>
<tr><td>T4</td><td>13</td><td>4</td></tr>
<tr><td>Unknown</td><td>6</td><td>0</td></tr>
<tr><td>Squamous cell carcinoma</td><td>368</td><td>93</td></tr>
<tr><td>Adenocarcinoma</td><td>5</td><td>1</td></tr>
<tr><td>Adenosquamous carcinoma</td><td>5</td><td>1</td></tr>
<tr><td>undifferentiated</td><td>20</td><td>0</td></tr>
<tr><td>carcinosarcoma</td><td>7</td><td>4</td></tr>
</table>
</td>
<td>Bias due to missing data: low risk

Bias in measures of outcomes: moderate risk

Bias in selection of the reported result: low risk

Overall bias: serious</td>
</tr>
</table>

		other	5	1	

F.10 Localised oesophageal and gastro-oesophageal junctional adenocarcinoma

What is the optimal choice of chemotherapy or chemoradiotherapy in relation to surgical treatment for people with localised oesophageal and gastro-oesophageal junctional cancer?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Surgical resection with or without preoperative chemotherapy in oesophageal cancer: a randomised controlled trial, Lancet (London, England), 359, 1727-33, 2002 **Ref Id** 516163 **Country/ies where the study was carried out** UK	**Sample size** N=802 **Characteristics** Median age= 63 (range 30-84) 605 M/ 197 F Histology: SCC %: 31 AC: 533 Undifferentiated:21 Unknown: 1 **Inclusion criteria** previously untreated cancer of the oesophagus	**Interventions** See Kidane SR.	**Details** OEO2 recruited 802 patients, 400 on CS and 402 on S. The nature of the first recurrence event and cause of death are detailed. Statistics Overall survival was calculated from the date of random assignment to date of death from any cause and surviving patients were censored at the	**Results** **Disease-free Survival** Higher in CS group than S HR 0.75 (95% CI: 0.63-0.89), P=0.0014 Total disease-free at 5 years: CS: 9/400 S: 7/402	**Limitations** Preoperative RT offered to some patients. 9% of patient in each arm received pre-op RT. **Cochrane risk of bias tool** Selection bias random sequence generation: unclear allocation concealment: randomization by telephone call to clinical trials unit Performance bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type RCT **Aim of the study** We aimed to assess the effects of preoperative chemotherapy on survival, dysphagia, and performance status in patients with esophageal cancer undergoing resection. **Study dates** Between March, 1992, and June, 1998 **Source of funding** The trial was funded by the British Medical Research Council	that was judged resectable microscopically confirmed as squamous carcinoma, adenocarcinoma, or undifferentiated carcinoma. tumours of the upper, middle, or lower third of the oesophagus and of the cardia **Exclusion criteria** no additional		date they were last known to be alive. Disease-free survival was calculated from a landmark time of 6 months from random assignment to allow for the difference in timing of surgery between the two groups. In this analysis, events including macroscopically incomplete resection, local and distant recurrence, and death arising within the first 6 months after random assignment were regarded as events at this landmark time. Survival curves are presented by the Kaplan-Meier method and treatment comparisons are by the log-rank test. The consistency of treatment effect across subgroups was		blinding: unclear but unlikely due to obvious differences between treatments Detection bias blinding: unclear but unlikely due to obvious differences between treatments Attrition bias outcome data complete Reporting bias outcomes stated in aim reported Overall assessment: unclear risk of bias due to inadequate reporting of randomization and blinding. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			assessed using 2 tests for heterogeneity.		Author= MRC (Medical Research Council)
Full citation Ancona, E, Ruol, A, Santi, S, Merigliano, S, Sileni, Vc, Koussis, H, Zaninotto, G, Bonavina, L, Peracchia, A, Only pathologic complete response to neoadjuvant chemotherapy improves significantly the long term survival of patients with resectable esophageal squamous cell carcinoma: final report of a randomized, controlled trial of preoperative	**Sample size** N= 434 **Characteristics** S group 38 M/ 9 F Mean age= 58 +/- 9.3 Tumour stage IIA: 31 IIB: 6 III: 11 CS group 38 M/ 9 F Mean age= 58 +/- 9.7 Tumour stage	**Interventions** See Kidane SR	**Details** This randomized, controlled trial compared patients with clinically resectable esophageal epidermoid carcinoma who underwent surgery alone (Arm A) with those who received preoperative chemotherapy (Arm B). Overall survival and the prognostic impact of major response to chemotherapy were analyzed. Forty-eight patients were enrolled in each arm. **Statistics** Statistical analyses were performed using the SAS statistical	**Results** **Tumour regression** After chemotherapy Complete response: 6/47 Major response: 13/47	**Limitations** **Cochrane risk of bias tool** Selection bias random sequence generation: random permuted blocks allocation scheme using the Moses-Oakford algorithm allocation concealment: unclear Performance bias blinding: unclear but unlikely due to obvious difference between treatments Detection bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
chemotherapy versus surgery alone, Cancer, 91, 2165-74, 2001 **Ref Id** 516179 **Country/ies where the study was carried out** Italy **Study type** RCT **Aim of the study** The primary objective of this single-center, randomized controlled trial was to analyze the overall prognostic impact of preoperative chemotherapy compared with surgery alone.	IIA: 32 IIB: 4 III: 12 **Inclusion criteria** clinically resectable squamous cell carcinoma of the esophagus (Stage IIA, IIB, and III; i.e., T2–T3 N0 M0 and T1–T3 N1 M0); ages 18–70 years; adequate cardiac, hepatic, renal, and bone marrow reserve; tolerate both the planned chemotherapy regimen and the surgical procedure. **Exclusion criteria** previously undergone treatment for the esophageal carcinoma		package (SAS Institute, Cary, NC). Differences between groups were assessed with the Pearson chi-square test, Fisher exact test, Mann–Whitney test, or Student *t* test, as indicated. All statistical comparisons were made with two-tailed tests, and *P* values , 0.05 were reported as significant. Survival was measured from the date of randomization to the date of death or last follow-up. Survival rates and standard errors were calculated with the Kaplan–Meier method, including deaths from all causes. All patients had a minimum follow-up of 3 months.		blinding: unclear but unlikely due to obvious difference between treatments Attrition bias outcome date complete Reporting bias outcomes stated in the objective were reported Overall assessment: UNLCEAR risk of bias due not inadequate reporting of allocation concealment, and blinding. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates 1992 until 1997 **Source of funding** Supported in part by a grant from the CNR (project ACRO 012809).	previous or concomitant primary malignancies. the presence of distant lymph node metastasis (i.e., M1 Lym, Stage IV) excluded patient eligibility				
Full citation Ando, N, Iizuka, T, Ide, H, Ishida, K, Shinoda, M, Nishimaki, T, Takiyama, W, Watanabe, H, Isono, K, Aoyama, N, Makuuchi, H, Tanaka, O, Yamana, H, Ikeuchi, S, Kabuto, T, Nagai, K, Shimada, Y, Kinjo, Y, Fukuda, H, Surgery plus chemotherapy compared with	**Sample size** n=242 **Characteristics** Male= 218/242 Age mean(range) in years = 59 (40 - 76) N0 tumour = 44/242 **Inclusion criteria** Histologically proven squamous cell carcinoma of the thoracic oesophagus no microscopic residual tumour (R0)	**Interventions** Chemotherapy - cisplatin 80 mg/m^2 for 2 hours on day 1 and flourourcil 800 mg/m^2 on day 1 to 5. Two couses of chemotherapy was separated by 3-weeks interval. Surgery - oesophagectomy via right thoracotomy in both arms. 2 patients in Sx+CT underwent left thoractomy. Two-field lymphadenectomy was perform in 61 patients in Sx arm and 46 patients in Sx+CT arm. Three-field	**Details** The primary end point was disease-free survival. The secondary end point were overall survival and toxicities. The study was planned to include 290 patients over 5-year to detect 13% improvement in 5-year disease free survival with one sided alpha of 0.05 and 0.80.	**Results** 242 patients entered the study at 17 institutions, allocating 122 patients in surgery (Sx) arm and 120 patients in surgery followed by chemotherapy (Sx+CT) arm. In Sx+CT arm, 29 patients did not fully complete planned postoperative CT because of toxicity or patients refusal.	**Limitations** **Cochrane risk of bias tool** Selection bias random sequence generation: Unclear allocation concealment: unclear Performance bias blinding: unclear Detection bias blinding: unclear

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
surgery alone for localized squamous cell carcinoma of the thoracic esophagus: a Japan Clinical Oncology Group Study--JCOG9204, Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 21, 4592-6, 2003 **Ref Id** 516180 **Country/ies where the study was carried out** Japan **Study type** Multicenter prospective randomised phase III study **Aim of the study**	Pathologic stage IIA **Exclusion criteria** if the patient had an additional synchronous or metachronous cancer	lymphadenectomy was performed in 61 patients in Sx arm and 74 patients in Sx+CT arm.		Disease free survival Sx+CT(n=120) vs Sx (n=122) = HR (95% CI): 0.75 (0.51 to 1.03) (Adjusted for age, sex, performance status, tumor location, pathologic T-stage, intramural metastatsis, pathologic N-stage, pathologic M-stage, and extent of lymphadenopathy) . Unadjusted HR: 0.73 (0.51 to 1.03)	Attrition bias Unreported loss of follow-up - unclear Reporting bias outcomes stated in method session reported Overall assessment: unclear risk of bias due to inadequate reporting of randomization and blinding. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
To determine whether postoperative adjuvant chemotherapy improves outcome in patients with oesophageal squamous cell carcinoma undergoing radical surgery **Study dates** July 1992 to January 1997 **Source of funding** Grant-in-Aid for Cancer Research from the Ministry of Health, Labour and Welfare of Japan and from the Second Term Comprehensive 10 year Strategy for Cancer Control					

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Ando, N, Kato, H, Igaki, H, Shinoda, M, Ozawa, S, Shimizu, H, Nakamura, T, Yabusaki, H, Aoyama, N, Kurita, A, Ikeda, K, Kanda, T, Tsujinaka, T, Nakamura, K, Fukuda, H, A randomized trial comparing postoperative adjuvant chemotherapy with cisplatin and 5-fluorouracil versus preoperative chemotherapy for localized advanced squamous cell carcinoma of the thoracic esophagus (JCOG9907), Annals of Surgical Oncology, 19, 68-74, 2012	**Sample size** n=330; 166 were assigned to postoperative chemotherapy (Sx+CT) and 164 patients to preoperative chemotherapy (CT+Sx). 162 patients in Sx+CT and 159 patients in CT+Sx arms underwent surgery. 166 patients in the former and 164 patients in the latter were included in the efficacy analysis. 95 patients in Sx+CT group and 159 patients in CT+Sx group were used for safety analysis of chemotherapy whereas 162 patients in Sx+CT group and 154 patients in CT+Sx group were used for safety analysis of surgery./ **Characteristics** Age in median (range) years: 61 (34 - 75) Male = 197/330 N0 tumour = 112/330	**Interventions** Surgery - total or subtotal thoracic oesophagectomy and regional lymphadenectomy with curative intent through right or left thoracotomy with resection of regional lymph nodes including perigastric nodes. Dissectin of distant lymph nodes were optional. Chemotherapy (CT): cisplatin(80 mg/m^2) for 2 hours on day 1 and 5 fluorouracil (800 mg/m^2) on day 1 to 5, repeated twice every 3 weeks. In Sx+CT arm, the surgery was followed by chemotherapy after 2 to 10 weeks and chmeotherapy was followed by surgery within 5 weeks in CT+Sx arm. Among patients in Sx+CT arm, CT was not provided postoperatively in patients with node-negative status.	**Details** The patients were randomised at the Japan Clinical Oncology Group (JCOG) Data center. The primary end point was progression-free survival and the secondary end points were overall survival, chemotherapy toxicities, operative morbidities and mortality, response rate in CT+Sx group and complete resection rate. A recruitment of 330 randomised patients was designed to detect about 13% improvment in progression-free survival with one sided alpha of 0.05 and power of 0.80.	**Results** 24 institutions participated. **Analysed 'n'** Sx+CT: 166 CT+Sx: 164 **R0 resection rate** Sx+CT: 91% CT+Sx: 96% **Overall survival** CT+Sx vs Sx+CT: HR(95%CI) = 0.73 (0.54 to 0.99); p=0.04 Pro**gression free survival** CT+Sx vs Sx+CT: HR(95%CI) = 0.84(0.63-1.11); p=0.22 **Median blood loss** Sx+CT: 446 ml (65 - 2839) CT+Sx: 450 ml (68 - 2715)	**Limitations** **Cochrane risk of bias tool** Selection bias random sequence generation: Unclear allocation concealment: unclear Performance bias blinding: unclear Detection bias blinding: unclear Attrition bias low risk Reporting bias outcomes stated in method session reported Overall assessment: unclear risk of bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref Id 516182 **Country/ies where the study was carried out** Japan **Study type** Randomised controlled trial **Aim of the study** To examine the survival outcomes of preoperative chemotherapy using cisplatin plus 5-fluoracil in comparison with post-operative chemotherapy in patients with locally advanced oesophageal squamous cell carcinoma **Study dates**	**Inclusion criteria** Histologically proven squamous cell carcinoma of the thoracic oesophagus clinical stage II or III excluding T4 disease (UICC tumour, node, metastasis system (TNM) classification) resectable disease **Exclusion criteria**	In CT+Sx arm, patients were not given a second course of chemotherapy before surgery even if the initial response to the first course chemotherapy was progressive.		**Treatment-related mortality** Sx+CT: 2/162 CT+Sx: 1/153 **Treatment related morbidity** 1) Anastomotic leakage Sx+CT: 24/162 CT+Sx: 19/153 2) Wound infection Sx+CT: 20/162 CT+Sx: 16/153 3) Pulmonary Sx+CT: 21/162 CT+Sx: 24/153 4) Cardiovascular (Intraoperative) Sx+CT: 3/162 CT+Sx: 4/153	due to inadequate reporting of randomization and blinding. **Other information** Additional information from Hirao, M., Ando, N.,Tsujinaka, T., et al. (2011) Influence of preoperative chemotherapy for advanced thoracic oesophageal squamous cell carcinoma on perioperative complications. British Journal of Surgery. 98: 1735-1741

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
May 2000 to May 2006 **Source of funding** Grant-in-aid for Cancer Research from the Ministry of Health, Labour and Welfare of Japan					
Full citation Apinop, C, Puttisak, P, Preecha, N, A prospective study of combined therapy in esophageal cancer, Hepato-gastroenterology, 41, 391-3, 1994 **Ref Id** 516186 **Country/ies where the study was carried out** Thailand	**Sample size** n=69 CRT followed by surgery = 35 Surgery alone =34 **Characteristics** Mean age in years: 59.7 Male %: 78.3 **Inclusion criteria** Biopsy-proven previously untreated locoregional squamous-cell carcinoma	**Interventions** Please find details in Kumagai 2014 SR. CRT followed by surgery versus Surgery alone	**Details** Surgery was performed approximately 4 weeks after the last day of CT if there was no distant metastatic disease in CRT plus surgery group whereas the treatment plan for surgery group started the second week after admission. Survival percentages were determined using Kaplan-Meier product limit method, in which only tumour-related	**Results** **Overall Survival at 1 years** CRT+S: 49% (n=35) S alone: 39% (n=34) **Overall survival at 5-years** CRT + S: 24% (n=35) S alone: 10% (n=34)	**Limitations** **Cochrane risk of bias tool** Selection bias random sequence generation: unclear allocation concealment: unclear Performance bias blinding: unclear Detection bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type RCT **Aim of the study** To report on the results of prospective randomised clinical trial of combined therpy and surgery alone **Study dates** January 1986 to December 1992 **Source of funding** NR	of the middle or distal esophagus Physically capable of undergoing subsequent surgery Normal FBC, electrolytes and creatinine **Exclusion criteria** Patients with concomitant second primary lesions		death was considered as failure.		blinding: unclear Attrition bias No loss of follow up Reporting bias The complete response was mentioned in the method session but not reported. Overall assessment: UNLCEAR risk of bias due to inadequate reporting of randomisation, allocation concealment, and blinding. **Other information**
Full citation Bosset, Jf, Gignoux, M, Triboulet, Jp, Tiret, E, Mantion, G,	**Sample size** n= 282 **Characteristics**	**Interventions** Details can be found in Kumagai 2014.	**Details** With 80% power, one-sided type I error of 0.05, the study had enough power to detect	**Results** **T0 stage tumour after curative resection**	**Limitations** **Cochrane risk of bias tool** Selection bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Elias, D, Lozach, P, Ollier, Jc, Pavy, Jj, Mercier, M, Sahmoud, T, Chemoradiotherapy followed by surgery compared with surgery alone in squamous-cell cancer of the esophagus, The New England journal of medicine, 337, 161-7, 1997 **Ref Id** 516214 **Country/ies where the study was carried out** France **Study type** Multi-centre RCT **Aim of the study** To initiate a prospective, multicenter,	Age (mean) in years: 56.7 Male %: 93.3 Node +ve tumour %: 23 **Inclusion criteria** Invasive SCC ECOG performance status of 0 to 2 <70years Resectable tumour Participants with T1N0, T1N1, T2N0, T2N1, T3N0 **Exclusion criteria** if participants had lost more than 15 percent of their body weight if they had previously undergone treatment for this disease or any other cancer except basal cell-carcinoma of the skin Tumour located within the first 4 cm of the		an improvement in five-year survival from 15 percent in S alone gorup to 25 % in CRT +S group.	CRT+S: 29/112 S alone: 0/94 **Disease free survival (longer in CRT + S group)** HR (95% CI): 0.6 (0.4 to 0.9) P= 0.003 **Overall Survival** S alone: 95 events/ 139 HR= 1.0 (95% CI= 0.7-1.5), P= 0.78 by log rank test **Tumour regression grade** in combined-treatment group Complete pathological response: 29/112 Major pathological response: 20/112	random sequence generation: unclear allocation concealment: unclear Performance bias blinding: unclear Detection bias blinding: unclear Attrition bias No loss of data Reporting bias outcomes stated in aim reported Overall assessment: unclear risk of bias due to inadequate reporting of randomization and blinding **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
randomised tiral comparing preoperative CRT followed by surgery with surgery alone. The main endpoint was overall survival. Secondary endpoint were disease free survival and survival free of local disease or distant metastatses. **Study dates** January 1989 to June 1995 **Source of funding** Grant from Ligue Departmental de Lutte contre le Cancer du Doubs, France	esophagus, metastases in cervical lymph nodes, evidence of invasion of the bronchus on bronchoscopy, and tumour classified as T3N1, T4N0 or T4N1				
Full citation	**Sample size** n=75	**Interventions**	**Details**	**Results**	**Limitations**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Burmeister, Bh, Thomas, Jm, Burmeister, Ea, Walpole, Et, Harvey, Ja, Thomson, Db, Barbour, Ap, Gotley, Dc, Smithers, Bm, Is concurrent radiation therapy required in patients receiving preoperative chemotherapy for adenocarcinoma of the oesophagus? A randomised phase II trial, European journal of cancer (Oxford, England : 1990), 47, 354-60, 2011 **Ref Id** 516221 **Country/ies where the study was carried out** Australia	**Characteristics** Age median (range) in years: 61 (36-75) Male %: 66/75 (87%) Nodal involvement: 16/75 (21%) **Inclusion criteria** Histologically confirmed invasive adenocarcinoma of the thoracic oesophagus or gastro-oesophageal junction; Disease limited to the oesophagus or gastro-oesophageal junction and regional lymph nodes (cT2-3, cN0-1) and fit for resection **Exclusion criteria** Prior treatment with radiation therapy or chemotherapy	Chemotherapy followed by surgery (CT+S) = 36 versus Chemoradiotherapy followed by surgery (CRT+S) = 39 Chemotherapy: 2 cycles - cisplatin 80 mg/m^2 on day 1 followed by a 96 hour infusion of 5 fluouracil(5 FU) 1000 mg/ m^2/d. The 2nd cycle started on day 21. In CRT group, the second cycle started together with radiation with the dose of 5FU reduced to 800 mg/m^2/d. Radiotherapy: 35 Gy given in 15 fractions over 3 weeks Surgery: resection of the primary tumor with enbloc resection of lymph nodes through Ivor-lewis or 3-stage thoracoscopic approach	The consent patients (n=75) were randomised to 36 CT+S and 39 CRT+S groups. 21 patients in CT+S arm and 23 patients in CRT+S arm received CT per protocol. 33 patients in either group underwent surgery. Intention to treatment analysis was applied.	**Treatment-related morbidity** 1) Anastomotic leak CT+S: 2/36 CRT+S: 2/39 2) Wound infection CT+S: 1/36 CRT+S: 5/39 3) Cardiac problems CT+S: 6/36 CRT+S: 7/39 **30-days postoperative mortality** CT+S: 0/36 CRT+S: 0/39 **R0 resection rate** CT+S: 29/36 CRT+S: 33/39	**Cochrane risk of bias tool** Selection bias random sequence generation: low risk allocation concealment: unclear Performance bias blinding: unclear Detection bias blinding: unclear Attrition bias ITT analysis Reporting bias outcomes stated in method sessions reported Overall assessment: unclear risk of bias due to inadequate reporting of

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type Randomised controlled trial **Aim of the study** To compare the preoperative chemotherapy and chemoradiotherapy for resectable adenocarcinoma of the oesophagus and gastro-oesophageal junction **Study dates** November 2000 until December 2006 **Source of funding** None				**Tumor regression grade (TRG)** 1) complete pathological response (pCR) (no viable tumour seen on any of the sections of the primary lesions and within lymph nodes): CT+S: 0/36 CRT+S: 5/39 2) <10% viable cells CT+S: 3/36 CRT+S: 7/39 3) Macroscopic CT+S: 30/36 CRT+S: 21/39 4) Residual disease CT+S: 3/36 CRT+S: 6/39 5) Major response (pCR + <10% viable cells) CT+S: 3/36 CRT+S: 12/39	allocation concealment and blinding. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Hagen, P, Hulshof, Mc, Lanschot, Jj, Steyerberg, Ew, Berge, Henegouwen Mi, Wijnhoven, Bp, Richel, Dj, Nieuwenhuijzen, Ga, Hospers, Ga, Bonenkamp, Jj, Cuesta, Ma, Blaisse, Rj, Busch, Or, Kate, Fj, Creemers, Gj, Punt, Cj, Plukker, Jt, Verheul, Hm, Spillenaar, Bilgen Ej, Dekken, H, Sangen, Mj, Rozema, T, Biermann, K, Beukema, Jc, Piet, Ah, Rij, Cm, Reinders, Jg, Tilanus, Hw, Gaast, A, Preoperative chemoradiotherapy	**Sample size** n= 368 **Characteristics** Age: Median: 60 years Gender: Male: 78% Tumour type: SCC: 23% Tumor staging: T2 and above 98% +ve lymph node 65% N1 116/178 CRT+S versus 120/188 S alone **Inclusion criteria** 18-75 years of age, WHO performance status ≤2 Participants withHistologically confirmed, potentially curable squamous-cell carcinoma, adenocarcinoma or large-	**Interventions** Please find in Kumagai 2014 SR.	**Details** 368 underwent randomisation. 180 and 188 were assigned to CRT+S and S alone respectively. 178 in CRT+S and 188 in S gourp were included in ITT analysis. A resection was not possible in 7 in CRT+S and 25 in S alone group because of the primary tumour or lymph nodes were identified as unresectable during surgery. CRT+S: 7 participants did not receive any CRT (5 because of disease progression before commencing therapy and 2 because of declination). A total of 162 (91%) received the full treatment	**Results** **Survival at 60 months** CRT+S: 28/178 S alone: 17/188 *At 84.1 median follow-up, Median overall survival* *CRT +S: 49.4 months(95% CI 32.1 to 65.1)* *S alone: 24 months(95%CI 14.2 to 33.7)* *HR 0.657 (0.495-0.871), P=0.003* **Survival at 60 months among SCC group** CRT+S: 8/41 S alone: 4/43	**Limitations** **Cochrane risk of bias tool** Selection bias random sequence generation: unclear allocation concealment: unclear Performance bias blinding: unclear but the baseline characters (age, gender, tumor type, locations and staging) were similar between the two groups Detection bias blinding: unclear Attrition bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
for esophageal or junctional cancer, The New England journal of medicine, 366, 2074-84, 2012 **Ref Id** 516290 **Country/ies where the study was carried out** Netherlands **Study type** RCT **Aim of the study** To compare neoadjuvant chemoradiotherapy followed by surgery with surgery alone in patients with potentially curable esophageal or esophagogastric junction carcinoma. **Study dates**	cell undifferentiated carcinoma of the esophagus or esophagogastric junction (i.e., tumour involving both the cardia and the eosphagus on endoscopy) The upper border of tumor had to be at least 3cm below the upper esophageal sphincter. Only patients with tumours of clinical stage T1N1 or T2-3 N0-1 and no clinical evidence of metastatic spread Patients with adequate haematologic, renal, hepatic and pulmonary function as well as no history of other cancer or previous radiotherapy or chemotherapy **Exclusion criteria** Participants with proximal gastric tumours with minimal invasion of the esophagus		regimen of five cycles of chemotherpy and 164 (92%) received the full dose of radiotherapy. 2 participants (1%) received a higher dose of RT (45 and 54 Gy). The most common reason for not completing treatment was low platelet count.	*HR 0.453 (95% CI: 0.243-0.844), P= 0.011* **Survival at 60 months among AC group** CRT+S: 18/134 S alone: 10/141 *HR 0.732 (95% CI: 0.524-0.998), P=0.049* **R0 Resection achieved** CRT+S group: 148/161 S group: 111/161 **Tumour regression grade** Complete response: 47/161	ITT analysis Reporting bias High: One of the interested outcomes (quality of life) in the protocol was not reported in the study. Overall assessment: unclear risk of bias due to inadequate reporting of randomization and blinding. **Other information** Data were also taken from: Shapiro, J., Lanschot, J.J.B.v., Hulshof, M.C., et al. (2015) Neoadjuvant chemoradiotherapy plus surgery alone for esophageal or junctional cancer (CROSS): long term

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
March 2004 to December 2008 **Source of funding** Dutch Cancer Foundation	Lenght of tumor >8cm or width of tumor >5 cm			(AC: 28/121, SCC: 18/37) **Disease-Free Progression (extracted from Shapiro, 2015)** CRT+S: 14/178 S alone: 6/188 *HR 0.64 (95%CI: 0.49-0.82), P=0.000217* **Disease-free Progression amo ng SCC group** CRT+S: 5/41 S alone: 1/43 *HR 0.48 (95% CI: 0.28-0.82), P= 0.006* **Disease-free Progression amo ng AC group**	results of randomised controlled trial. Lancet. 16

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				CRT+S: 9/134 S alone: 5/141 *HR 0.69 (95% CI: 0.52-0.92), P=0.010*	
Full citation Kidane, Biniam, Coughlin, Shaun, Vogt, Kelly, Malthaner, Richard, Preoperative chemotherapy for resectable thoracic esophageal cancer, Cochrane Database of Systematic Reviews, 2015 **Ref Id** 516340 **Country/ies where the study was carried out** Canada	**Sample size** A total of 13 randomised controlled trials (RCTs) were included (Number of trials (N)=13; number of participants (n)=2362), of which 10 RCTs were relevant for the review. **Characteristics** Trials were identified by searching the Cochrane Central Register of Controlled trials (CENTRAL), MEDLINE (1966 to 2013), EMBASE (1988 to 2013) and CANCERLIT (1993 to 2013). The search was limited to RCTs. The	**Interventions** Ancona 2001 CT+S: Cisplatin 100 mg/m^2 x 1 D x 2-3 cycles + 5-FU 1000 mg/m^2 x 1 D x 2-3 cycles post-op chemotherapy and radiation for residual disease S: right thoractomy, abdomen, left neck with gastric tranposition, 2-field lymph nodes+ postop chemotherapy and radiation for residual disease Baba 2000	**Details** Studies were selected by two independent reviewers. Standardized data extraction form was used to summarise the trials. The quality was assessed by the Jaded (1996) criteria and scored independently by 2 reviewers. Any discrepancies were resolved by consensus. Missing data for included trials were sought. Heterogeneity of trial results were detected by formal statistical testing. The review manager with	**Results** Survival K=10; n=2122; HR(Random, 95% CI: 0.88 [0.80, 0.96]) Complete resection rate (R0) K=9; n=2135; RR (M-H, Random, 95% CI: 1.11[1.03, 1.19]) Treatment morbidity: Anastomotic leaks K=8; n=1501; RR (M-H, Random,	**Limitations** ROBIS tool for bias risk assessment in systematic reviews: Study Eligibility Criteria Did the review adhere to pre-defined objectives and eligibility criteria? Y Were the eligibility criteria appropriate for the review question? Y Were the eligibility criteria unambiguous? Y

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type Systematic review and Meta-analysis **Aim of the study** To determine the role of preoperative chemotherapy in the treatment of patients with resectable thoracic oesophageal carcinoma **Study dates** The search was updated in October 2013. **Source of funding** None	primary outcomes was overall survival after randomization. **Ancona 2001** Italy, n=96; 100% squamous cell cancer (SCC); Resectable T2,3; N0,1; No metastases **Baba 2000** Japan, n=42; 100%SCC; Upper, middle and lower oesophageal tumors; No metastases **Boonstra 2011** Netherlands multicenter, n=169; T1-3, N, M0; Upper, middle and lower oesophageal tumors **Kelsen 1998** North America multicancer; n=467; 44% SCC and 51% Adenocarcinoma; Operable; Stage I, II and III	CT+S: Cisplatin 70 mg/m^2 x 1D x 2 cycles + 5-FU 700 mg/m^2 x 5 Ds x 2 cycles + Leucovorin 20 mg/m^2 x 5 Ds x 2 cycles S: right thoracotomy, laparotomy, neck incision, gastric or colon interposition with 2-field or 3-field node dissections Boonstra 2011 CT+S: Cycle 1 (Cisplatin 80 mg/m^2 IV over 4 hours on day 1 of each cycle; Etoposide 100 mg/m^2 IV over 2 hours on days 1 and 2 of each cycle; Etoposide 200 mg/m^2 PO on days 3 and 5 of each cycle), Cycle 2 (as above, repeated on week 4) 2 additional cycles was given for responders; immediate referal to surgery if no responders or those with severe side effects S: oesophagectomy (right thoracotomy, transhiatal	random effect models was used to synthesize the data. Sensitivity analyses 2(study quality, publication bias, histologic subtypes, types of chemotherpeutic agents, years of publication, tumor location) were carried out to determine whether conclusions were changed when different trials were included in the analysis.	95% CI: 0.92[0.62, 1.37]) Treatment morbidity: Cardiac complications K=5; n=1314; RR (M-H, Random, 95% CI: 1.03[0.69, 1.55]) Treatment morbidity: Infectious complication K=5; n=1184; RR (M-H, Random, 95% CI: 0.65[0.41, 1.02]) Treatment morbidity: Pulmonary complication K=8; n=1501; RR (M-H, Random, 95% CI: 1.10[0.76, 1.61])	Were all the restrictions on eligibility criteria based on study characteristics appropriate? Y Were any restrictions in eligibility criteria based on sources of information available? Y Concern regarding specification of study eligibility criteria: Low Identification and Selection of Studies Did the search include an appropriate range of databases/electronic sources for published and unpublished reports? Y

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Law 1997 Hong Kong, n=147; 100%SCC, resectable, no metastases **Maipang 1994** Thailand, n=46; 100% SCC, Stage I, II and III, distal 2/3 oesophagus, no cervical lesions **MRC Allum 2009** UK, n=802; 31% SCC, 66% Adenocarcinoma, 3% undifferentiated; Upper, middle and lower oesophagus **Nygaard 1992** Scandinavia, multicentre; n=106; 100% SCC; T1-2, Nx, M0, >21 cm from incisors, no metastases **Schlag 1992** Germany, n=46; 100% SCC; Stage I, II and III; no metastases	oesophagectomy, enbloc resection of tumor and adjacent lymph nodes Kelsen 1998 CT+S: Cisplatin 100 mg/m^2 x 1D x 3 cycles + 5FU 1000 mg/m^{2}x 5Ds x 3 cycles (if responder , postop cisplatin 75 mg/m^2+ 5FU 1000 mg/m^2 x 2 cycles) + radiation if positive margins S: Abdominothoracic or thoracoabdominocervical or transhiatal with gastric or colon interposition) + radiation if positive margins Law 1997 CT+S: Cisplatin 100 mg/m^2 x 1D x 2 cycles + 5-FU 500 mg/m^2 x 5Ds x 2 cycles S: Abdominothoracic or transhiatal with gastric interposition and removal of adjacent nodes Maipang 1994		Postoperative mortality K=10; n=2196; RR (M-H, Random, 95% CI: 0.93[0.68, 1.28]) Quality of life (dysphagia at 1-year postop) K=1; 28% in CT+S vs 27% in S alone	Were the methods additional to database searching used to identify relevant reports? Y Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible? Y Were restrictions based on date, publication format or language appropriate? Y Were efforts made to minimise error in selection of studies? Y Concern regarding methods used to identify or select studies: LOW Data Collection and Study Appraisal

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Ychou 2011 France, multicenter (28) n=169 but 122/169 from one center; Resectable adenocarcinoma of lower third of the oesophagus or GEJ or stomach (only 25% and 24% in each arm had non-GEJ stomach cancer) **Inclusion criteria** Participants consisted of patients with localised potentially resectable thoracic oesophageal carcinoma. Trials that compared chemotherapy before surgery (oesophagectomy) versus surgical resection alone were included. **Exclusion criteria** Trials including patients with carcinoma of the cervical oesophagus were excluded. Studies which were excluded if other treatment modalities (e.g.	CT+S: Cisplatin 100 mg/m^2 x 1D x 2 cycles + vinblastine 3 mg/m^2 x 4Ds x 2 cycles + bleomycin 10 mg/m^2 x 5Ds x 2 cycles S: Laparotomy; right thoractomy with gastric or colon interposition MRC Allum 2009 Radiation: pre-op external beam radiation was given irrespective of randomisation (25-32.5 Gy in 10 fractions) CT+S: Cisplatin 80 mg/m^2 x 1D x 2 cycles + 5-FU 1000 mg/m^2 x 4 Ds x 2cycles S: oesophagectomy Nygaard 1992 CT+S: Cisplatin 20 mg/m^2 x 5Ds x 2 cycles + Bleomycin 10mg/m^2 x 5Ds x 2 cycles S: laparotomy and right thoracotomy with stomach interposition			Were efforts made to minimise error in data collection? Y were sufficient study characteristics available? Y Were all relevant study results collected for use and synthesis? Y Was risk of bias formally assessed using appropriate criteria? Y Were efforts made to minimise error in risk of bias assessment? Y Concern: LOW Synthesis and Findings Did the synthesis include all studies it should? Y

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	radiotherapy, hyperthermia) were used.	Schlag 1992a CT+S: Cisplatin 20 mg/m^2 for 5 days for 3 cycles + 5 FU 1000 mg/m^2 for 5 days for 3 cycles if responder after 1st cycle S: Abdominothoracic or thoracoabdominocervical with gastric or colon interposition + 2-field lymph node resection Ychou 2011 CT+S: 2-3 cycles of FU 800 mg/m^2/d as IV infusion for 5 consecutive days and cisplatin 100 mg/m^2 as 1-hour infusion, every 28 days (3-4 postop cycles were administered if good tolerance and no evidence of progressive disease after preoperative chemotherapy) S: Enbloc resection of tumour and extended lymphadenectomy (D2 recommended)			Were all pre-defined analyses reported and departures explained? Y Was the synthesis appropriate given the nature and similarity in the research questions? Y Was heterogeneity minimal or addressed? Y Were the findings robust as demonstrated though funnel plot or sensitivity analysis? Y Were biases in primary studies minimal or addressed in the synthesis? Y Concern= LOW

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					Risk of bias in the review Did the interpretation of findings address all the concerns identifies in 1-4? Y Was the relevance of identified studies to the review's research question appropriately considered? Y Did the reviewers avoid emphasizing results on the basis of their statistical significance? Y Risk of bias= LOW **Other information**
Full citation Klevebro, F, Dobeln, Ga, Wang,	**Sample size** n=181	**Interventions**	**Details** All participants being randomised were	**Results** **90-day mortality**	**Limitations** **Cochrane risk of bias tool**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
N, Johnsen, G, Jacobsen, A-B, Friesland, S, Hatlevoll, I, Glenjen, Ni, Lind, P, Tsai, Ja, Lundell, L, Nilsson, M, A randomized clinical trial of neoadjuvant chemotherapy versus neoadjuvant chemoradiotherapy for cancer of the oesophagus or gastro-oesophageal junction, Annals of Oncology, 27, 660-7, 2016 **Ref Id** 516343 **Country/ies where the study was carried out** Norway and Sweden **Study type** RCT	(CT+S=91 versus CRT+S=90) **Characteristics** Age (median): 63 Male %: 83 N0 tumour %: 37 SCC %: 28 Adenocarcinoma %: 73 **Inclusion criteria** Patients with histologically confirmed SCC or AC of the esophagus or GOJ (including Siewert type I and II) who were eligible for curative treatment with surgical resection were enrolled. Clinical tumour stage; T1-3, any N (with the exception of T1N0) Cervical cancers were required to be resectable without laryngectomy	Chemotherapy (CT): 3 cycles of cisplatin, 100 mg/m^2 day 1 and fluorouracil 750 mg/m^2/24 hr, days 1-5. Each cycle lasted 21 days Radiotherapy (RT); 40Gy (2 Gy/day in 20 fractions, 5 days a week) with chemotherapy cycles 2 and 3 (concurrent) Surgery (Sx): Ivour Lewis procedure or McKeown procedure (if middle and upper thirds of oesophagus) Comparison: CT followed by Sx versus CRT followed by Sx	included in analysis. The sample size was based on the intention of showing a difference in the primary end point of 15% between treatment arms with a power of 80% which required 172 patients.	CT+Sx: 2/91 CRT+Sx: 5/90 **Treatment-related morbidity (Any complication)** CT+Sx: 35/91 CRT+Sx: 42/90 **Treatment-related morbidity (Anastomotic leakage)** CT+Sx: 7/91 CRT+Sx: 10/90 **Treatment-related morbidity (Cardiovascular complication)** CT+Sx: 4/91 CRT+Sx: 7/90 **R0 resection** Total: CT+Sx: 58/91 CRT+Sx: 68/90	Selection bias random sequence generation: unclear allocation concealment: unclear Performance bias blinding: unclear Detection bias blinding: All surgical specimens were reviewed by an expert pathologist who was blinded to randomisation Attrition bias No loss of follow-up data Reporting bias outcomes stated in aim reported Overall assessment: unclear risk of bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study Phase II ranodmised trial comparing the rate of histological complete response after nCRT with that after nCT. Overall survival, number of lymph node metastases R0-resection rate, progression-free survival, and site of recurrence were evaluated as secondary end points **Study dates** 2006-2013 **Source of funding** Swedish Society of Medicine, the Swedish Cancer Society, The Cancer Research	**Exclusion criteria** None			**3-year overall survival** Total: CT+Sx: 45/91 CRT+Sx: 42/90 HR (95%CI) with ITT analysis: 1.11 (0.74 - 1.67) adjusted for ECOG performance status, histological type, clinical T stage and N stage (p=0.77) **Progression-free survival** Total CT+Sx: 40/91 CRT+Sx: 40/90 **Tumor regression grade** 1) TRG1 (Histological complete response): 7/91 in CT+S vs 22/90 in	due to inadequate reporting of randomization and blinding. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Foundations of Radiumhemmet, and the Stockholm County Council				CRT+S 2) TRG2 (1-10% tumour cells): 5/91 in CT+S vs 19/90 in CRT+S 3) TRG 3(>10-50% tumour cells): 5/91 in CT+S vs 14/90 in CRT+S 4) TRG 4 (>50% tumour cells): 61/91 in CT+S vs 23/90 in CRT+S	
Full citation Kumagai, K, Rouvelas, I, Tsai, Ja, Mariosa, D, Klevebro, F, Lindblad, M, Ye, W, Lundell, L, Nilsson, M, Meta-analysis of postoperative morbidity and perioperative mortality in patients receiving	**Sample size** Studies= 23 14 relevant studies comparing CRT followed by surgery (CRT +S)vs S alone (post 1990) **Characteristics** All patients T0-3 N0-1 tumour stage. No major differences in other patient characteristics.	**Interventions** See Characteristics for intervention details.	**Details** Database Search Medline, Cochrane Database and Embase were search for studies published up to March 2013. Manual searching of reference lists to further identify potentially relevant studies. Data	**Results** **CRT+S vs S** **30-day mortality** N=3 (SCC=1; AC and SCC=1, unknown= 1) SCC --> RR(95% CI): 1.29 (0.46, 3.63)	**Limitations** ROBIS tool for bias risk assessment in systematic reviews: Study Eligibility Criteria Did the review adhere to pre-defined objectives and eligibility criteria? Y

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal and gastro-oesophageal junctional cancers (Provisional abstract), British Journal of Surgery, 101, 321-338, 2014 **Ref Id** 516352 **Country/ies where the study was carried out** Sweden **Study type** Systematic review of RCTs **Aim of the study** To systematically review and complete a meta-analysis to compare the survival of	**CRT+S vs S** **Apinop 1994** (n=69) SCC only CRT+S: Cis 100 mg/m^2 on days 1 and 29; FU 1000 mg/m^2 per day on days 1-4 and 29-32 AND 40Gy, 2Gy per fraction over 4 weeks (concurrent) **Le Prise 1994** (n=86) SCC only CRT+S: Cis 100mg/m^2 on days 1 and 21; FU 600 mg/m^2 per day on days 2-5 and 22-25 AND 20Gy in 10 fractions over 12 days (sequential) **Bosset 1997** (n=297) SCC only CRT+S: Cis 80 mg/m^2 0-2 days before each course of radiotherapy AND 37 Gy, 3.7Gy per fraction in two 1-week courses, separated by 2 weeks (sequential)		Data was extracted by author with discrepancies dealt with by discussion with other authors. Bias Assessment Jadad's score was used to evaluate the risk of bias in individual studies. Analysis Stata was used to analyse data and a random-effects model was used to estimate RRs and CIs. Higgins statistic was used to assess heterogeneity. Sensitivity analysis was performed.	AC and SCC --> RR(95% CI): 0.89 (0.24, 3.24) Nygaard 1992: CRT+S: 8/47 S: 5/38 van Hagen 2012 CRT+S: 4/168 S: 5/186 Bagheri 2012: CRT +S: 1/20 S: 1/20 **Total Postoperative Mortality** N=12 (SCC=6; AC and SCC=4, AC= 1, unknown=1)	Were the eligibility criteria appropriate for the review question? Y Were the eligibility criteria unambiguous? Y Were all the restrictions on eligibility criteria based on study characteristics appropriate? PY Were any restrictions in eligibility criteria based on sources of information available? Y Concern regarding specification of study eligibility criteria: Low Identification and Selection of Studies

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
neoadjuvant chemotherapy versus chemoradiotherapy for esophageal cancer. **Study dates** RCTs range 1992-2012 **Source of funding** No funding reported.	**Urba 2001** (n=100) SCC and AC CRT+S: Cis 20 mg/m2 on days 1-5 and 17-21; FU 300 mg/m^2 on days 1-21; vinblastine 1 mg/m^2 on days 1-4 and 17-20 AND 45 Gy, 1.5 Gy per fraction over 3 weeks (concurrent) **Lee 2004** (n=101) SCC only CRT+S: Cis 60 mg/m^2 on days 1 and 22; FU 1000mg/m^2 per day on days 2-5 AND 45.6 Gy, 1.2 Gy per fraction over 28 days (concurrent) **Burmeister 2005** (n=256) SCC and AC CRT+S: Cis 80 mg/m^2 on day 1; FU 800 mg/m^2 per day on days 1-4 AND 35 Gy in 15 fractions over 3 weeks (concurrent) **Natsugoe 2006** (n=45) SCC only			SCC --> RR(95% CI): 1.95(1.06, 3.60) AC and SCC --> RR(95% CI): 0.79(0.39, 1.61) Nygaard 1992: CRT+S: 8/47 S: 5/38 LePrise 1994: CRTS: 3/35 S: 3/42 Bosset 1997: CRTS: 17/138 S: 5/137 Lee 2004: CRTS: 1/35 S: 1/48 Natsugoe 2006: CRTS: 1/20	Did the search include an appropriate range of databases/electronic sources for published and unpublished reports? PY Were the methods additional to database searching used to identify relevant reports? Y Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible? Y Were restrictions based on date, publication format or language appropriate? PY Were efforts made to minimise error in

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	CRT+S: Cis 7 mg days 1-5, 8-12, 15-19 and 22-26; FU 350 mg/day on days 1-28 AND 40 Gy, 2 Gy per fraction over 4 weeks (concurrent) **Nygaard 1992** CRT+S: Cis 20 mg/m^2 on days 1-5 and 15-19; bleomycin 5 mg/m^2 on days 1-5 and 15-19 AND 35 Gy, 1.75 Gy per fraction over 4 weeks (sequential) **Tepper 2008** (n=56) SCC and AC CRT+S: Cis 60 mg/m^2 days 1 and 29; FU 1000 mg/m^2 per day on days 1-4 and 29-32 AND 50.4 Gy, 1.8 Gy per fraction over 5.6 weeks (concurrent) **van Hagen 2012** (n=368) SCC and AC CRT+S: 5 weeks concurrent chemotherpy;			S: 0/23 Walsh 1996 CRTS: 4/51 S: 2/55 Urba 2000 CRTS: 1/47 S: 2/50 Burmeister 2005 CRTS: 5/112 S: 6/123 Tepper 2008 CRTS: 0/26 S: 1/26 van Hagen 2012 CRT+S: 6/168 S: 8/186 Bagheri 2012: CRT +S: 1/20	selection of studies? Y Concern regarding methods used to identify or select studies: Low Data Collection and Study Appraisal Were efforts made to minimise error in data collection? PY were sufficient study characteristics available? Y Were all relevant study results collected for use and synthesis? Y Was risk of bias formally assessed using appropriate criteria? Y Were efforts made to minimise error in risk of bias assessment? NI

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	carboplatin area under curve 2 mg per ml per min and paclitaxel 50 mg/m^2 on day 1 weekly AND 41.4 Gy, 1.8 Gy per fraction over 4.6 weeks (concurrent) **Bagheri 2012 (**n= 40) Unknown tumour type (AC or SCC) CRT: "cis and FU based", 40 Gy over 4 weeks (Concurrent) Walsh 1996 (n=113) AC CRT: cis 75 mg/m^2 on days 7 and 42, FU 15 mg/kg on days 1-5 and 36-40, 40 Gy in 15 fractions over 3 weeks (concurrent) **Nygaard 1992** n= 217 SCC only CT: cisplatin 20 mg/m^2 on days 1-5 and 15-19; bleomycin 5 mg/m^2 on days 1-5 and 15-19			S: 1/20 **Treatment-related Mortality** N=11 (SCC=7; AC and SCC=4) SCC --> RR(95% CI): 1.97 (1.07, 3.64) AC and SCC --> RR(95% CI): 0.85 (0.43, 1.71) Apinop 1994 CRTS: 5/35 S: 5/34 LePrise 1994: CRTS: 3/39 S: 3/42 Bosset 1997: CRTS: 18/142 S: 5/137	Concern: Unclear Synthesis and Findings Did the synthesis include all studies it should? Y Were all pre-defined analyses reported and departures explained? Y Was the synthesis appropriate given the nature and similarity in the research questions? Y Was heterogeneity minimal or addressed? Y Were the findings robust as demonstrated though funnel plot or sensitivity analysis? Y

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	RT: 35 Gy, 1.75 Gy per fr over 4 weeks (sequential) **Cao 2009** n= 473 SCC only CT: cisplatin 20 mg/m^2 on days 1-5; 5FU 500mg/m^2 per day on days 1-5; ,mitomycin 10 mg/m^2 per day on day 1 RT: 40 Gy, 2 Gy per fr over 4 weeks (concurrent) **Lv 2010** (n=238) SCC CT: cis 20 mg/m^2 on days 1-3 and 22-24, paclitaxel 135 mg/m^2 starting on days 1 and 22 of RT RT: 40 Gy, 2 Gy per fraction over 4 weeks (concurrent) **Inclusion criteria** RCTs			Lee 2004: CRTS: 2/51 S: 1/48 Natsugoe 2006: CRTS: 1/22 S: 0/23 Lv 2010: CRTS: 3/80 S: 0/80 Walsh 1996 CRTS: 5/57 S: 2/55 Urba 2000 CRTS: 1/49 S: 2/50 Burmeister 2005 CRTS: 5/125 S: 6/123	Were biases in primary studies minimal or addressed in the synthesis? Y Concern= LOW Risk of bias in the review Did the interpretation of findings address all the concerns identifies in 1-4? Y Was the relevance of identified studies to the review's research question appropriately considered? Y Did the reviewers avoid emphasizing results on the basis of their statistical significance? Y Risk of bias= LOW

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	compared postoperative morbidity/mortality after neoadjuvant chemotherapy or neoadjuvant chemoradiotherapy **Exclusion criteria** full texts not available in English			Tepper 2008 CRTS: 1/28 S: 1/26 van Hagen 2012 CRT+S: 7/171 S: 8/186 Bagheri 2012: CRT +S: 1/20 S: 1/20	**Other information** Long-term survival not included as an outcome.
Full citation Law, S, Fok, M, Chow, S, Chu, Km, Wong, J, Preoperative chemotherapy versus surgical therapy alone for squamous cell carcinoma of the esophagus: a prospective	**Sample size** N= 147 **Characteristics** 125 male/ 22 female Mean age= 63.5 years **Inclusion criteria** histologic evidence of squamous cell carcinoma	**Interventions** **CT** Cisplatin 100 mg/m^2 day 1 and 5 FU 500 mg/m^2/day days 1-5 Cycle repeated on days 22-26 Surgery performed on day 42	**Details** A prospective randomized trial was undertaken in 147 patients: 74 received preoperative chemotherapy comprising cisplatin and 5-fluorouracil and 73 had surgical therapy alone. End points were	**Results** **Tumour response** complete pathologic response: 4/60 complete clinical remission: 4/60 partial response: 27/60	**Limitations** No serious limitations. **Cochrane risk of bias tool** Selection bias random sequence generation: unclear

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
randomized trial, The Journal of thoracic and cardiovascular surgery, 114, 210-7, 1997 **Ref Id** 516361 **Country/ies where the study was carried out** Hong Kong **Study type** RCT **Aim of the study** This study investigated the role of preoperative chemotherapy in squamous cell cancer of the esophagus. **Study dates**	thoracic tumour site **Exclusion criteria** nonregional lymph node metastases distant metastases tumour infiltration to trachea or bronchi inadequate renal, bone marrow function history of cancer in last 5 years	**Surgery** Abdominal and right thoracotomy incisions with a mediastinal lymphadenectomy.	cancer and therapy-related deaths. Statistics Differences between groups were determined by Students t test, fishers exact test, chi-squared test, Mann-Whitney U test where appropriate. Survival data was analysed with Wilcoxon test. SPSS package used.	no response: 25/60 (60 represents those assessed for tumour response after chemotherapy)	allocation concealment: unclear Performance bias blinding: unclear but unlikely due to obvious difference between treatments Detection bias blinding: unclear but unlikely due to obvious difference between treatments Attrition bias outcome date complete Reporting bias outcomes stated in the objective were reported Overall assessment: UNLCEAR risk of bias due not

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
December 1989 to January 1995 **Source of funding** NR					inadequate reporting of allocation concealment, randomization process and blinding. **Other information**
Full citation Lv, J, Cao, Xf, Zhu, B, Ji, L, Tao, L, Wang, Dd, Long-term efficacy of perioperative chemoradiotherapy on esophageal squamous cell carcinoma, World Journal of Gastroenterology, 16, 1649-54, 2010 **Ref Id** 516390 **Country/ies where the study was carried out**	**Sample size** n=160 **Characteristics** Age (≥60 years) %: 56 Male %: 64 **Inclusion criteria** Stage II to III thoracic esophageal SCC (diagnosed by endoscopic biopsy and histopathology diagnosed by endoscopic biopsy and histopathology) Stage II: thickness exceeded 5mm but no invasion of the	**Interventions** CRT+S: 80 S+CRT: 80 S alone: 80	**Details** The primary endpoint of the study was Progression free survival and the secondary was overall survival.	**Results** **Radical resection (n)** CRT+S: 76/80 S+CRT: 61/78 S alone: 64/80 **10 year progression free survival** CRT+S: 18.1% (15/80) S+CRT: 17.8% (14/78) S alone: 6.2% (5/80) **10 year overall survival (pvalue**	**Limitations** **Cochrane risk of bias tool** Selection bias random sequence generation: Computer generated allocation concealment: unclear Performance bias blinding: unclear Detection bias blinding: unclear

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
China **Study type** 3-armed study (CRT followed by Sx versus Sx followed by CRT vs Sx alone) **Aim of the study** To investigate the role of perioperative CRT in the treatment of locally advanced thoracic oesophageal SCC. **Study dates** January 1997 and June 2004 **Source of funding** NR	mediastinum or distant metastasis Stage III: invaded the adjacent mediastinal structure **Exclusion criteria** NR			**compared to successive above)_** CRT+S: 24.5% (20/80)(p=0.0051) S+CRT: 24.4% (19/78)(p=0.50) S alone: 12.5% (10/80)(p=-0.02) **Treatment-related death** CRT+S: 3/80 S+CRT: 0/78 S alone: 0/80	Attrition bias No loss of data Reporting bias outcomes stated in aim reported Overall assessment: unclear risk of bias due to inadequate reporting of randomization and blinding. **Other information**
Full citation	**Sample size** n=195	**Interventions**	**Details**	**Results**	**Limitations**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Mariette, C, Dahan, L, Mornex, F, Maillard, E, Thomas, Pa, Meunier, B, Boige, V, Pezet, D, Robb, Wb, Brun-Ly, V, Bosset, Jf, Mabrut, Jy, Triboulet, Jp, Bedenne, L, Seitz, Jf, Surgery alone versus chemoradiotherapy followed by surgery for stage I and II esophageal cancer: final analysis of randomized controlled phase III trial FFCD 9901, Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 32, 2416-22, 2014 **Ref Id** 516397	CRT plus surgery = 98 Surgery alone = 97 **Characteristics** Age (years) median and range : 57.8 years, (36.9 to 76.4) Male %: 85.6 SCC %: 70.3 N0 %: 72.3 **Inclusion criteria** Patients age < 75 years, judged suitable for curative resection with untreated stage I or II (T1 or T2, N0 or N1 and T3N0, M0) thoracic esophageal adenocarcinoma or squamous cell carcinoma,as assessed by CT and Endoscopic USG Capable of receiving either treatment with WHO performance status of 0 or 1	Chemoradiotherapy (CRT) (Concurrent): 2 cycles of fluorouracil and cisplatin (FU 800 mg/m^2 per 24 hours from days 1 to 4 and 29 to 32; Cisplatin [75 mg/m^2 by infusion on day 1 or 2 and again on day 29 or 30] or [15 mg/m^2 from days 1 to 5 and 29 to 33] and a total dose of 45 Gy in 25 fractions (5 fractions per week) over 5 weeks Surgery: performed 4 to 6 weeks after completion of NRCT in group CRT and within 4 weeks of random assignment in group S	Eligible patients were randomly assigned to receive either NCRT followed by surgery or surgery alone group in 1:1. Patients were stratified according to centre, histology, disease stage (I v IIA v IIB) and tumour location (above or below carina). Out of 98 being assigned to CRT and surgery, 84 patients completed 2 cycles of chemotherapy. Three patients with non-resectable primary tumour were removed from the analysis and finally, 81 patients were inclued in the analysis. There were no treatment-related deaths before surgery. Out of 97 being assigned to	**Disease-free survival (DFS)** HR (95% CI) CRT +S vs S alone: 0.92 (0.66 to 1.30) CRT+S: 14/98 S alone: 7/96 **Overall Survival** HR (95% CI)= 0.99 (0.69-1.30) CRT+S: 15/98 S: 11/96 **Overall survival at 8 years** CRT+S: 15/98 Sx alone: 11/96 **30-day postoperative mortality** CRT+S: 6/81 Sx alone: 1/89	**Cochrane risk of bias tool** Selection bias random sequence generation: "centrally with a minimization technique" allocation concealment: unclear Performance bias blinding: unclear Detection bias blinding: unclear There is no difference in baseline characters between the two groups Attrition bias High risk Reporting bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out French **Study type** Multi-centre RCT **Aim of the study** To assess whether neoadjuvant chemoradiotherapy improves outcomes for patients with stage I or II locally advanced esophageal cancer. The primary endpoint was overall survival. Secondary end points included disease-free survival (DFS), in-hospital postoperative mortality and morbidity and identification of	**Exclusion criteria** Weight loss > 10% at baseline and respiratory, liver or cardiac insufficiency Patients with a previously treated malignancy, evidence of supraclavicular or celiac nodes, a multifocal tumour, tumour with a proximal limit < 19 cm from the incisor teeth or Evidence of invasion of the tracheobronchial tree		Surgery alone, 91 patients underwent surgery whereas six patients did not undergo sugery for metastaes on exploration(n=3) or liver cirrhosis discovered at surgery (n=1) or unavailable data (n=2). Two patients with unresectable tumour were subsequently removed and finally, 89 patients were inclued in analysis.	**In-hospital postoperative mortality** CRT+S: 9/81 S alone: 3/89 **HR for death of SCC subgroup** CRT+S: 42/67 S alone: 46/70 **R0 resection** CRT+S: 76/81 S alone: 82/89 **Tumour Regression Grade (extracted from Robb 2015)** Data available for 76/81 treated with CRT. Complete pathological response: 27/76 Complete tumoural response: 33/76	outcomes stated in aim reported Overall assessment: unclear risk of bias due to inadequate reporting **Other information** Tumour regression grade extracted from Robb 2015

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
prognostic factors for OS. **Study dates** June 2000 to June 2009 **Source of funding** French National Cancer Institute and Lile University Hospital				Good treatment response (TRG 1-2)= 56/76 Poor treatment response (TRG 3-5)= 20/76	
Full citation Natsugoe, S, Okumura, H, Matsumoto, M, Uchikado, Y, Setoyama, T, Yokomakura, N, Ishigami, S, Owaki, T, Aikou, T, Randomized controlled study on preoperative chemoradiotherapy followed by surgery versus surgery	**Sample size** N= 45 (CRT+S: 22, S group: 23) **Characteristics** No significant differences in TNM staging were identified between the CRT and Surgery groups.	**Interventions** See Kumagai SR for intervention details.	**Details** Tumor extension was evaluated by esophagography, esophagoscopy, endoscopic ultrasonography, ultrasonography, and computed tomography of the neck, chest and abdomen.	**Results** **Tumour regression** No change: 8/22 Partial response: 12/22 (Response in remaining 2 not reported) **5-year survival**	**Limitations** **Cochrane risk of bias tool** Selection bias random sequence generation: stratified block randomization (unclear how random sequence was generated) allocation concealment: unclear

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
alone for esophageal squamous cell cancer in a single institution, Diseases of the esophagus : official journal of the International Society for Diseases of the Esophagus / I.S.D.E, 19, 468-72, 2006 **Ref Id** 516417 **Country/ies where the study was carried out** Japan **Study type** RCT **Aim of the study** The purpose of the present study was	Additional baseline characteristics not reported. **Inclusion criteria** (i) invasive squamous cell carcinoma of the esophagus without visceral organ metastasis or tracheobronchial fistula; (ii) possibility of complete resection through a right thoracic approach; (iii) age < 70 years without synchronous or metachronous malignancy in other organs; (iv) Karnofsky performance status ≥90%; (v) normal function of the heart, lung, liver and kidney; (vi) normal blood biochemistry.		Bronchoscopy and bronchscopic ultrasonography were performed for patients in whom tracheobronchial invasion was highly suspected. After agreement, patients were randomly assigned to the CRT or Surgery group using the stratified blocked randomization method. Stratification factors were: age ≥65 years versus < 65 years; tumor diameter, ≥6 cm versus < 6 cm on esophagography; and presence versus absence of lymph node metastasis. End-points comprised the survival of patients.	CRT group: 12/20 Surgery group: 10/23 log-rank P= 0.58	Performance bias blinding: unclear but unlikely due to obvious difference between treatments Detection bias blinding: unclear but unlikely due to obvious difference between treatments Attrition bias unclear Reporting bias unclear, outcomes of interest not reported in the objectives Overall assessment: UNCLEAR risk of bias due to inadequate reporting of allocation concealment, randomization

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
to compare the clinical results between preoperative chemoradiotherapy followed by surgery (CRT group) and surgery alone (Surgery group) by a randomized controlled study. **Study dates** January 1997 to December 2001 **Source of funding** NR	**Exclusion criteria** No additional				process and blinding. **Other information** 2 patients in CRT group did not go on to surgery due to discovery of bone metastasis.
Full citation	**Sample size**	**Interventions**	**Details**	**Results**	**Limitations**
Schlag, Pm, Randomized trial of preoperative	n= 46	See Kidane SR	With ∝=0.05 and 80% power, 57 patients in each group was	**Tumour response to preoperative chemotherapy**	**Cochrane risk of bias tool**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
chemotherapy for squamous cell cancer of the esophagus. The Chirurgische Arbeitsgemeinschaft Fuer Onkologie der Deutschen Gesellschaft Fuer Chirurgie Study Group, Archives of surgery (Chicago, Ill. : 1960), 127, 1446-50, 1992 **Ref Id** 516483 **Country/ies where the study was carried out** Germany **Study type** RCT **Aim of the study** To test the efficacy of of preoperative chemotherapy for	Chemotherapy followed by surgery = 22 versus Surgery alone = 24 **Characteristics** Age (median) years = 56.8 Male %: 89 There was no relevant differences between the groups in age, sex, tumour length or tumour location. **Inclusion criteria** Histologically confirmed squamous cell carcinoma of the oesophagus, potentially curable by surgery alone No evidence of distant metastases by computed tomographic scan of chest and abdomen and liver ultrasound No tumour infiltration or fistula to the trachea Age under 68 years		required to detect an increase in resectability rate from 60% to 80%. The study discontinued after one year for the following reasons: 1) if the treatment-related mortality rate in the surgery and chemotherapy group was significantly higher than in the patients treated with surgery alone group; 2) if the probability of healthy survival in one therapy group was smaller than in the other group. There was one protocol violation (a patient unable to undergo chemotherapy after randmisation) and one patient unavailable to follow-up.	N=21 Not classifiable: 2 Disease progression: 4 Stable disease: 4 Minor response: 3 Major response: 7 Complete pathological response: 1	Selection bias random sequence generation: unclear allocation concealment: unclear Performance bias blinding: unclear Detection bias blinding: unclear Attrition bias one out of 22 patient in C+S group violated protocol. Reporting bias outcomes stated in the objective were reported Overall assessment: UNLCEAR risk of bias due not inadequate reporting

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
squamous cell carcinoma of the esophagus Note - Non-randomised participants were excluded from this review. (31 out of 77 eligible participants) **Study dates** NR **Source of funding** NR	No previous chemotherapy or radiotherapy Karnofsky performance status above 70% Normal FBC, liver and pulmonary function tests Patients agreed for randomisation **Exclusion criteria** No additional.				of randomisation, allocation concealment, and blinding. **Other information**
Full citation Ychou, M, Boige, V, Pignon, Jp, Conroy, T, Bouché, O, Lebreton, G, Ducourtieux, M, Bedenne, L, Fabre, Jm, Saint-Aubert, B, Genève, J, Lasser, P, Rougier,	**Sample size** n=224 **Characteristics** Median age (range) in years = 63 (36-75) Male%= 84%	**Interventions** Chemotherapy (CT) comprised two or three preoperative cycles of FU 800mg/m^2/d as continuous intervenous infusion for 5 consecutive days (day 1 to 5) and cisplatin 100 mg/m^2 as a 1-hour infusion, every 28 days and 3 to 4	**Details** Patients were randomly assigned through the centralised randomisation system. Random assignment was stratified according to centre, WHO performance status (0 v 1), and site of tumor	**Results** Out of 113 patients randomly assigned to CT+Sx group, 109 patients (97%) received preoperative CT. Surgery was performed in 109 patients (96.5%) of	**Limitations** **Cochrane risk of bias tool** Selection bias random sequence generation: unclear allocation concealment:

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
P, Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial, Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 29, 1715-21, 2011 **Ref Id** 516566 **Country/ies where the study was carried out** France **Study type** Open-label randomized phase III trial	**Inclusion criteria** Patients were eligible if they had histologically proven adenocarcinoma of the lower third of of the oesophagus or GEJ or stomach that was judged suitable for curative resection. **Exclusion criteria** Patients were excluded if they had in situ carcinoma, histology other than adenocarcinoma, prior chemotherapy or radiotherapy.	postoperative cycles in case of good tolerance and no evidence of progressive disease after preoperative chemotherapy for a total of 6 cycles. The dose of FU was reduced (75% of the dose) in case of grade 3 or 4 neutropenia or thrombocytopenia, grade 3 diarrhoea or grade 2/3 mucositis. Surgery (Sx) was planned within 4 weeks after random assignment in the surgery group and 4 to 6 weeks after completion of the last cycle of chemotherapy in the CT+Sx group. Surgery consisted in a complete excision of the tumour with an extended lymphadenectomy (D2 recommended).	(non-GEJ stomach, GEJ, oesophagus) with the use of a minimization procedure. Sample size calculation was based on two-sided log-rank test: 250 patients (178 deaths) were required to detect an increase in 5-year survival from 20% in the surgery group to 35% in the preoperative chemotherapy plus surgery group, with 80% power and 5% type I error. The primary endpoint was overall survival after randomisation and secondary end point were disease-free survival. R0 resection rate and safety.	the CT+Sx group. The reason for not performing were progressive disease for four patients and toxic death for one patient. Of 109 patients receiving pre-operative CT, 54 patients (50%) received post-operative CT. Of 111 patients randomly assigned to Sx group, 110 (99%) underwent surgery. **Overall survival** n= 109 in CT+S vs n=110 in Sx CT+S vs S: HR for death (95% CI) 0.69 (0.5 to 0.95; p=0.02) death rate: 71/113 in CT+S vs 85/111 in S	randomisation assigned through data centre Performance bias blinding: unclear but unlikely due to obvious difference between treatments Detection bias blinding: unclear but unlikely due to obvious difference between treatments Attrition bias outcome date complete Reporting bias outcomes stated in the objective were reported Overall assessment: UNLCEAR risk of bias due not inadequate reporting

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study To compare surgical resection with or without perioperative chemotherapy using 5-fluouracil and cisplatin in patients with resectable gastroesophageal adenocarcinoma in terms of survival, curative resection rate, and tolerance **Study dates** November 1995 to December 2003 **Source of funding** Jean Geneve				**Disease free survival** n= 109 in CT+S vs n=110 in Sx CT+S vs S: HR for recurrence or death (95% CI) 0.65 (0.48 to 0.89; p=0.003) recurrence rate: 63/113 in CT+S vs 71/111 in S group **Treatment-related morbidity** 1)Postoperative morbidity: n=28/109 in CT+S vs n=21/110 in S group 2) 41/109 patients who received CT experienced at least grade 3 to 4 toxicity under preoperative chemotherapy **Treatment-related mortality**	of randomization process and blinding. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				n=5/109 in CT+S vs n=5/110 in S group **R0 resection rate** n=95/109 in CT+S vs n=81/110 in S group	
Full citation Bass, G. A., Furlong, H., O'Sullivan, K. E., Hennessy, T. P. J., Walsh, T. N., Chemoradiotherapy, with adjuvant surgery for local control, confers a durable survival advantage in adenocarcinoma and squamous cell carcinoma of the oesophagus, European Journal of Cancer, 50, 1065-1075, 2014	**Sample size** N= 211 MMT: 104 Surgery: 107 **Characteristics** AC group N= 113 83 male/30 female Median age= 65 SCC group N=98 50 male/48 female	**Interventions** Chemotherapy Two cycles of 5-fluorouracil and cisplatin were administered during treatment weeks 1 and 6. On days1–5 of each cycle, patients received an infusion of fluorouracil (15 mg/kg of body weight/day) over a period of 16 h. Cisplatin (75 mg/m^2 of body surface area) was infused over 8 h on day 7.	**Details** Between 1990 and 1997, two RCTs were undertaken on 211 patients. Patients with AC (n = 113) or SCC (n = 98) were separately-randomised to identical protocols of MMT or surgical monotherapy. Statistical analysis Statistical analyses were performed with using the statistical	**Results** **Tumour grade response:** Complete tumour response in MMT group: AC trial: 13/58 SCC trial: 12/46 **Mean overall survival time** MMT= 88, S= 104	**Limitations** **Cochrane risk of bias tool** Selection bias random sequence generation: unclear allocation concealment: unclear Performance bias blinding: unclear but unlikely due to obvious difference between treatments

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref Id 476994 **Country/ies where the study was carried out** Ireland **Study type** RCT **Aim of the study** Long-term results of two simultaneous randomised controlled trials (RCTs) comparing neo-adjuvant chemo-radiotherapy and surgery (MMT) with surgical monotherapy were examined, and the response of adenocarcinoma (AC) and squamous cell carcinoma	Approx. median age= 66 **Inclusion criteria** - Biopsy-proven adenocarcinoma (AC) or squamous cell carcinoma (SCC) of the oesophagus - Age less than 76 years - Leucocyte count of greater than 3500/mm3 - Platelet count of greater than 100,000/mm3 - Serum creatinine concentration below 1.4 mg/dL (124 micromol/L) - cT0–4N0–2M0 disease - Eastern Cooperative Oncology Group (ECOG) performance status of 0–2 **Exclusion criteria**	Radiation therapy Concurrent external-beam radiation therapy was commenced on day 1 of the first cycle of chemotherapy and administered on days 1–5, 8–12 and 15–19. Tumour extent was defined endoscopically and radiologically and the treatment fields extended 2–3 cm and 5 cm beyond the radial and longitudinal margins, respectively. Prior to 1994, all patients were treated with parallel-opposed fields (anterio-posterior and posterioanterior) with a mid-plane dose of 40 Gy in 15 fractions. This was then modified to a more conformal three-field	package PASW version 200 for Windows (IBM Corp., Chicago, IL). Continuous variables were expressed as mean ± standard error of the mean and were compared using a two-sample t-test. Categorical variables were compared using a chi-squared test, with Fisher's exact test used where appropriate. Survival probabilities for clinical, pathological and treatment variables were estimated using the Kaplan–Meier method and pair-wise comparisons were made using the log–rank test. The effect of treatment modality (neoadjuvant chemotherapy and external-beam radiation	MMT mean (SEM, range)= 63.8 (8.25, 47.6-80.6) Surgery mean (SEM, range)= 23.48 (3.76, 16.1-30.9) Subgroup: SCC MMT mean (SEM, range)= 48.8 (10.92, 27.4-70.21) Surgery mean (SEM, range)= 22.09 (5.62, 11.06-33.1) Subgroup: AC MMT mean (SEM, range)= 75.65 (11.74, 52.6-98.7) Surgery mean (SEM, range)= 22.97 (3.94, 15.25-30.89)	Detection bias blinding: unclear but unlikely due to obvious difference between treatments Attrition bias outcome data complete Reporting bias outcomes stated in the objective were reported Overall assessment: UNCLEAR risk of bias due to inadequate reporting of allocation concealment, randomization process and blinding. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
(SCC) to identical regimens compared. **Study dates** 1990 and 1997 **Source of funding** No external funding was sought or received in relation to this manuscript.	- Excluding cervical oesophagus requiring laryngectomy - Age greater than 77 years - Leukopaenia - Thrombocytopenia - Renal failure - Patients with evidence of distant metastases - Previous chemotherapy or radiotherapy, previous malignancy (excluding skin cancer)	approach (anterior, left-posterior and right-posterior oblique fields). Using a computerised treatment-planning system (AECL/Theratronics Therplan), without heterogeneity corrections, a dose of 40 Gy in 15 fractions was delivered to the treatment volume. Fractions were delivered by mega-voltage therapy units with 4- or 8-MV photons (Cobalt model SEM100, Fairy Engineering, Phillips model SL75–5 and Dynaray model 10, Radiation Dynamics, respectively).	therapy followed by surgical resection versus surgical monotherapy), tumour histology, size and stage, clinical tumour response to neo-adjuvant therapy and the presence of positive lymph-nodes on survival outcomes were examined using logistic regression, and optimal cut-offs were determined using the maximal chi-squared method. P values of less than 0.05 were considered statistically significant. Prior to each trial, Freedman's log-rank method was used to estimate the sample size required to detect a 20% improvement in overall survival at 2 years over baseline. The baseline overall	**In-hospital mortality** AC trial: 7/113 MMT group: 5/58 Surgery group: 2/55 SCC trial: 17/98 MMT: 9/46 Surgery: 8/52 **Number alive at end of trial (p<0.001)** AC trial: (p<0.001) MMT: 12/58 Surgery: 2/55 SCC trial: (p=0.036)	AC trial also published as Walsh 1996.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
		Surgery The patients assigned to surgical monotherapy had neither pre-operative chemotherapy nor radiation therapy. Surgery was performed approximately 1 week following randomisation (compared with 8–10 weeks in the multi-modal group), and was delayed if the leucocyte count was less than 2500/mm^3 or platelet count was less than 100,000/mm^3. Five operative approaches were employed (laparotomy and leftotomy, lewis-tanner, transhiatal, three stage, abdominal).	survival following surgery at our institution at the commencement of the study was 23% and 15% for resectable oesophageal AC and SCC, respectively; thus, with an alpha error of 5% and a power of 80%, the number of patients required to demonstrate a significant survival difference was estimated at 190 patients in the AC trial and 166 patients in the SCC trial.	MMT: 5/46 Surgery: 2/52	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Kelsen, D. P., Ginsberg, R., Pajak, T. F., Sheahan, D. G., Gunderson, L., Mortimer, J., Estes, N., Haller, D. G., Ajani, J., Kocha, W., Minsky, B. D., Roth, J. A., Chemotherapy followed by surgery compared with surgery alone for localized esophageal cancer, New England Journal of MedicineN Engl J Med, 339, 1979-84, 1998 **Ref Id** 474687	**Sample size** n= 467 (CS= 233, S= 234) **Characteristics** 370 male/70 female median age =~ 61.5 years **Inclusion criteria** presence of confirmed epidermoid cancer or adenocarcinoma of the esophagus, including the gastroesophageal junction, with or without metastases in local lymph nodes and clinically limited to the locoregional area (tumor stage 1, 2, or 3; any nodal stage; and no metastasis [M0] in the tumor–node–metastasis [TNM]	**Interventions** See Kidane SR.	**Details** Preoperative chemotherapy for patients randomly assigned to the chemotherapy group included three cycles of cisplatin and fluorouracil. Surgery was performed two to four weeks after the completion of the third cycle; patients also received two additional cycles of chemotherapy after the operation. Patients randomly assigned to the immediate-surgery group underwent the same surgical procedure.	**Results** **Tumour regression:** complete response: 7% partial response: 12% **Disease-free survival** log-rank P=0.50 DFS at 3-years CS group: 30/213 S group: 20/227 DFS at 5-years CS group: 11/213 S group: 11/227	**Limitations** **Cochrane risk of bias tool** Selection bias random sequence generation: Zelen method with stratification allocation concealment: unclear Performance bias blinding: unclear but unlikely due to obvious difference between treatments Detection bias blinding: unclear but unlikely due to obvious difference between treatments Attrition bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out USA and Canada **Study type** RCT **Aim of the study** We performed a multi-institutional randomized trial comparing preoperative chemotherapy followed by surgery with surgery alone for patients with local and operable esophageal cancer. **Study dates**	classification; carcinoma stage, 1 to 3). All patients were at least 18 years of age; had adequate hepatic, renal, and bone marrow reserve; could tolerate the planned surgical procedure. **Exclusion criteria** cervical esophageal tumors (upper border, <18 cm from the incisor teeth) or supraclavicular or other distant metastases (T4 tumors) if they had previously undergone treatment or had previously had another primary cancer		The main end point was overall survival.		outcome data complete Reporting bias outcomes stated in the objective were reported Overall assessment: UNCLEAR risk of bias due to inadequate reporting of allocation concealment, and blinding. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
August 1990 until December 1995 **Source of funding** Supported in part by grants (CA 21661, CA 32115, and CA 37422) from the National Cancer Institute.					
Full citation Le Prise, E., Etienne, P. L., Meunier, B., Maddern, G., Ben Hassel, M., Gedouin, D., Boutin, D., Campion, J. P., Launois, B., A randomized study	**Sample size** n= 86 **Characteristics** Median age(years) and range: 56 (32 to 69) Male %: 93 **Inclusion criteria**	**Interventions** Details can be found in Kumagai 2014 SR. CRT +S: 39 S alone:47	**Details** A sample of 150 patients was planned, so that an improvement in 2-year survival rate from 10% to 30% could be detected with type I error of 0.05. The study was ended at 104 patients which were considered for	**Results** **T0 stage after resection** CRT +S: 5/39 S alone: 1/47 **Disease free survival (median in months)**	**Limitations** **Cochrane risk of bias tool** Selection bias random sequence generation: unclear allocation concealment: unclear

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
of chemotherapy, radiation therapy, and surgery versus surgery for localized squamous cell carcinoma of the esophagus, CancerCancer, 73, 1779-1784, 1994 **Ref Id** 474749 **Country/ies where the study was carried out** France **Study type** RCT **Aim of the study** To evaluate the contribution of sequential preoperative chemotherapy and radiation therapy to the treatment of	Histologically proven SCC esophagus <70years WHO status <2 Estimated survival time of > 3 months No previous treatment of cancer Informed consent **Exclusion criteria** Loss of body weight >15% normal Tracheosophageal fistula or histologic proof of tracheobronchial invasion Metastatic deposits in other viscera Supraclavicular lymph node involvement Paralysis of the recurrent laryngeal nerve		randomisation. Out of 104, 18 was found to be unsuitable. Finally, 86 were randomised and included in analysis (statistical power 0.7).	CRT+S: 7.6 months S alone: 5 months **Survival at 3-years follow-up** CRT+S: 19.2% S alone: 13.8% **Tumour regression grade:** complete remission: 11/39 tumour response greater than 50%: 12/39	Performance bias blinding: unclear Detection bias blinding: unclear Attrition bias High as the study stopped recruitment without fulfilling the initial sample size. Reporting bias outcomes stated in aim reported Overall assessment: unclear risk of bias due to inadequate reporting of randomization and blinding **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
localised SCC of esophagus **Study dates** January 1988 to April 1991 **Source of funding** NR	History of cancer except skin cancers or CIS cervix or respiratory or GI without evidence of recurrence for at least 5 years				
Full citation Lee, J. L., Park, S. I., Kim, S. B., Jung, H. Y., Lee, G. H., Kim, J. H., Song, H. Y., Cho, K. J., Kim, W. K., Lee, J. S., Kim, S. H., Min, Y. I., A single institutional phase III trial of preoperative chemotherapy with hyperfractionation radiotherapy plus surgery versus surgery alone for resectable	**Sample size** n=101 **Characteristics** Median age, years (range) 63 (39 - 75) Gender: male ; 92% ECOG perfomance 0/1 : 5/96 (out of 101 total participants) node +ve tumour %: 64 **Inclusion criteria**	**Interventions** Please find in Kumagai 2014 for details CRT+S= 51 S alone = 50	**Details** Survival time was calculated from the date of randomisation to the date of death due to any cause. Event free survival was definded as the time from the date of randomisation to the date of first observation of disease progression or relapse or death due to any cause. The survival anlalysis was performed by the	**Results** **Number going to R0 resection among those going for surgery:** CRT +S: 35/35 S alone: 42/48 **Survival rates at 2-years** CRT+S: 55% S alone: 57% P=0.69 by log rank test	**Limitations** **Cochrane risk of bias tool** Selection bias --> Unclear risk random sequence generation: unclear allocation concealment: unclear Performance bias --> Unclear risk blinding: unclear

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
esophageal squamous cell carcinoma, Annals of OncologyAnn Oncol, 15, 947-54, 2004 **Ref Id** 474752 **Country/ies where the study was carried out** Korea **Study type** RCT **Aim of the study** A prospective phase III study of concurrent CRT followed by surgery (CRT+S) versu surgery alone for patients with resectable SCC. The primary endpoint was overall survival.	Previously untreated, biopsy proven invasive SCC of the esophagus clinically resectable esophageal carcinoma (IIA, IIB and III; T2-3N0M0 and T1-3N1M0) according to American Joint Committee on Cancer Classification ≥18 years Eastern Cooperative Oncology Group (ECOG) performance status ≥2 Adequate bone marrow reserve consisting of WBC count of >3500 cells/ul and a platelet count of >100000/ul Adequate renal function with serum creatinine level of <1.5 mg/dl bilirubin <1.5 mg/l no history of prior malignancy excluding		actuarial Kaplan-Meier method and differences between the curves were analysed using the log-rank test. Sample size calcualation: needed 190 patients to dtect improvement in median survival from 15 to 22 months , corresponding to an increase in the 2-year survival rate from 30% to 50% (Hazard ratio 0.625) 80% power and α of 0.05.	**Event free interval at 2 years** CRT+S: 49% S alone: 51% P=0.93 by log-rank test **Tumour regression grade** Assessed in 47 patients Complete response: 11 Partial response: 33 Stable disease: 2 Disease progression: 1	Detection bias ---> unclear blinding: unclear Attrition bias --> Low risk No loss of data Reporting bias --> Low risk outcomes stated in aim reported Overall assessment: unclear risk of bias due to inadequate reporting of randomization and blinding. **Other information** 21 patients who underwent esophagectomy after CRT received post-op chemotherapy.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Secondary endpoints were event-free survival, pathological response to CRT and pattern of failure. **Study dates** March 1999 to May 2002 **Source of funding** NR	surgically cured basal cell carcinoma of the skin **Exclusion criteria** - if the primary tumour was located in the cervical esophagus (upper border, <18 cm from the incisor teeth) or if there were cervical or coeliac lymph node involvement or evidence of distant metastasis or if they had previously undergone treatment for esophageal carcinoma				
Full citation Rajabi Mashhadi, M., Bagheri, R., Abdollahi, A., Ghamari, M. J., Shahidsales, S., Salehi, M., Shahkaram, R., Majidi, M. R., Sheibani, S., The Effect of	**Sample size** n=100 Comparison: CRT followed by surgery (n=50) versus Surgery alone (n=50) **Characteristics** Age (mean) in years: 55 Male % = 53	**Interventions** Chemoradiotherapy (CRT): Cisplatin followed by 50 Gy radiation. The radiation consisted of 4000 cGy and on the first and final days of radiotherapy, patients received chemotherapy with cisplatin (20 mg/m^2) and 5-fluorouracil (5FU)	**Details** Preoperative staging was performed in all patients including a laboratory examination, endoscopic ultrasound scan and a computed tomography scan of the thorax and upper abdomen, as well as	**Results** **30-day mortality** CRT followed by surgery: 4/50 Surgery alone: 3/50	**Limitations** **Cochrane risk of bias tool** Selection bias random sequence generation: Computer-generated random numbers

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Neoadjuvant Therapy on Early Complications of Esophageal Cancer Surgery, Iranian journal of otorhinolaryngology Iran, 27, 279-84, 2015 **Ref Id** 474987 **Country/ies where the study was carried out** Iran **Study type** RCT **Aim of the study** To evaluate early post-operative side effects of oesophagectomy among two groups of patients: those undergoing surgery followed by	SCC % = 72 **Inclusion criteria** Lower oesophageal cancer General condition suitable for cancer as well as lack of previous cardiac, pulmonary, or renal problems No contraindication to neoadjuvant treatment lack of distant macroscopic metastases **Exclusion criteria** Cervical, upper and middle-part oesophageal cancer No desire for surgery following neoadjuvant chemoradiotherapy (NACR) Intolerance to surgery after receiving NACR	(700 mg/m^2/infusion over 24 hours). Surgery: Transhiatal oesophagectomy	abdominal sonography and barium swallow.		allocation concealment: unclear Performance bias blinding: unclear Detection bias blinding: unclear Attrition bias No loss of follow up data Reporting bias Outcomes stated in method session (e.g. resectability of the tumour) was not reported Overall assessment: unclear risk of bias due to inadequate reporting of methodology **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
neoadjuvant chemoradiotherapy (NACR) and those undergoing surgery with no NACR **Study dates** 2009 and 2011 **Source of funding** NR	acute malnutrition (albumin<2.5g/dl) macrometastases (Stage 4) and serious complication during surgery such as airway damage or intense bleeding				
Full citation Tachibana, M., Yoshimura, H., Kinugasa, S., Shibakita, M., Dhar, D. K., Ueda, S., Fujii, T., Nagasue, N., Postoperative chemotherapy vs chemoradiotherapy for thoracic esophageal cancer: a prospective randomized clinical trial, European Journal of Surgical	**Sample size** n=45 **Characteristics** The 45 patients were randomised one month after surgery to postoperative chemotherapy (Sx+CT, n=23) and postoperative chemoradiotherapy (Sx+CRT, n=22). Age < 60 years = 12/45 Male = 41/45 N0 tumour = 11/45	**Interventions** Chemotherapy: Cisplatin (50 mg/m^2) was given on day 1 and 15 and 5-fluorouracil (300 mg/m^2) was given daily for 5 weeks. Radiotherapy: 45-50 Gy radiotherapy (RT) was given to tumour bed with at least 2 cm margin. the dose was 2 Gy/day five times per week for 4-5 weeks/	**Details** The patients were regularly followed up at the outpatient department monthly interval until fifth year.	**Results** Death Sx+CT: 10/23 Sx+CRT: 10/22 Overall survival: p=0.97	**Limitations** **Cochrane risk of bias tool** Selection bias random sequence generation: unclear allocation concealment: unclear Performance bias blinding: unclear Detection bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
OncologyEur J Surg Oncol, 29, 580-7, 2003 **Ref Id** 475129 **Country/ies where the study was carried out** Japan **Study type** Randomised controlled trial **Aim of the study** To compare postoperative chemotherapy alone and chemoradiotherapy after curative resection for squamous cell carcinoma of thoracic oesophagus **Study dates**	**Inclusion criteria** Patients with primary squamous cell carcinoma of the oesophagus R0 oesophagectomy all patients underwent a right thoracic subtotal oesophagectomy along with a three-field lymph node dissection **Exclusion criteria** Patients who received preoperative radio/chemotherapy Patients with superficial tumours on resection without lymph node metastases and postoperative complications Patients who received miscellaneous postoperative adjuvant treatments off protocol				blinding: unclear Attrition bias No loss of data Reporting bias outcomes stated in aim reported Overall assessment: unclear risk of bias due to inadequate reporting of randomization and blinding **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
November 1991 to December 2000 **Source of funding** Not reported					
Full citation Tepper, J., Krasna, M. J., Niedzwiecki, D., Hollis, D., Reed, C. E., Goldberg, R., Kiel, K., Willett, C., Sugarbaker, D., Mayer, R., Phase III trial of trimodality therapy with cisplatin, fluorouracil, radiotherapy, and surgery compared with surgery alone for esophageal cancer: CALGB 9781, Journal of Clinical OncologyJ Clin Oncol, 26, 1086-92, 2008	**Sample size** N= 56 (trimodality therapy= 30, surgery alone= 26) **Characteristics** 91 % male median age= 60.7 75% AC/ 25% SCC **Inclusion criteria** Tumors had to be considered surgically resectable (T1-3, NX),	**Interventions** See Kumagai SR for intervention details.	**Details** Definition of Response A complete pathologic response was defined as no gross or microscopic tumor in the surgical specimen using light microscopy, but not immunohistochemical stains (primary and nodes). A partial pathologic response was defined as shrinkage in tumor size compared with the original esophagogastroduodenoscopy. This was subclassified as macroscopic (evident at	**Results** **Overall Survival** Median follow-up was 6 years (5.8 years after surgery alone and 6.1 years after trimodality therapy) with 57.5 and 109.9 person-years followed for the surgery alone and trimodality treatment arms, respectively. Median OS was 4.48 (95% CI, 2.4 years to not estimable) v 1.79 years (95% CI,	**Limitations** **Cochrane risk of bias tool** Selection bias random sequence generation: unclear allocation concealment: unclear Performance bias blinding: unclear but unlikely due to obvious difference between treatments Detection bias blinding: unclear but unlikely due to

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref Id 475149 **Country/ies where the study was carried out** USA **Study type** RCT **Aim of the study** The primary treatment modality for patients with carcinoma of the esophagus or gastroesophageal junction has been surgery, although primary radiation therapy with concurrent chemotherapy produces similar results. As both have curative	including regional thoracic lymph node (N1) metastases Patients with histologically documented untreated squamous cell carcinoma or adenocarcinoma of the thoracic esophagus (below 20 cm) or gastroesophageal junction and with less than 2 cm distal spread into the gastric cardia were eligible. There could be no evidence of distant metastatic disease by history and physical examination; upper endoscopy with biopsy, computed tomography (CT) of the chest and upper abdomen, and pulmonary function studies were all required. Bone scan was required for alkaline phosphatase more than 3× the institutional normal value.		time of surgery) or microscopic (evident only at pathology review) residual disease. An increase in ≥ 25% of the product of perpendicular diameters at the indicator lesion, or the appearance of new lesions, was defined as progressive disease. Stable disease was defined as not qualifying as a partial or complete pathologic response or progressive disease. Resections were defined as curative (R0) when all gross disease was removed with negative margins. Incomplete resection (R1) was defined as residual gross disease or positive surgical margins (tumor ≤ 1 mm from any margin). Statistical Methods	1.41 to 2.59 years) in favor of trimodality therapy. The 95% CI estimate of the OS hazard ratio is 1.46 to 5.69 (log rank P=0.002). Five-year OS was 39% (95% CI, 21% to 57%) v 16% (95% CI, 5% to 33%) for trimodality therapy versus surgery alone. **Progression-free survival** Median PFS was 3.47 years (95% CI, 1.31 to 4.76 years) among patients treated with preoperative chemoradiotherapy versus 1.01 years (95% CI,	obvious difference between treatments Attrition bias outcome data complete Reporting bias outcomes stated in the objective were reported Overall assessment: UNCLEAR risk of bias due to inadequate reporting of allocation concealment, randomization process and blinding. **Other information** Trial fell very short of target sample size.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
potential, there has been great interest in the use of trimodality therapy. To this end, we compared survival, response, and patterns of failure of trimodality therapy to esophagectomy alone in patients with nonmetastatic esophageal cancer. **Study dates** October 1997 and March 2000 **Source of funding** Supported by the Cancer and Leukemia Group B, North Central Cancer Treatment Group, Eastern Cooperative Oncology Group,	Bronchoscopy was required if the primary tumor was adjacent to the trachea or left main stem bronchus. Patients were required to have granulocyte counts ≥1,800/mL, platelet count ≥00,000/mL, and a creatinine clearance ≥50 mL/min. Esophageal ultrasound (EUS) and preresection staging by thoracoscopy (ts) and laparoscopy/minilaparotomy (ls), including biopsy of celiac axis and lesser curvature, were recommended. **Exclusion criteria** Patients could not have previously received		The primary objective of this study was to determine whether trimodality therapy improves overall survival (OS) when compared to surgery alone. Secondary end points included response, local and distant control rates, and progression-free survival (PFS). A target sample of 475 eligible patients was to be randomly assigned with equal probability to each treatment arm. The targeted sample size was inflated to 500 patients to account for ineligibility.	0.22 to 1.46 years) among patients treated with surgery alone. The 95% CI estimate of the PFS hazard ratio is 1.37 to 5.32 (log rank P=0.007). Five-year PFS was 28% (95% CI, 12% to 47%) and 15% (95% CI, 4% to 33%) for trimodality therapy versus surgery alone. **Tumour response:** Available for 25 patients Complete response: 10/25 Partial response: 10/25	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
and Radiation Therapy Oncology Group.	chemotherapy or radiation therapy for this tumor or any radiation therapy that would overlap the radiation fields required for this malignancy. Patients with previous malignancies were eligible if more than 5 years had elapsed from diagnosis without evidence of tumor recurrence. There could be no other serious illness that would limit survival to less than 2 years, or psychiatric condition that would prevent compliance with treatment or informed consent. Patients with uncontrolled or severe cardiovascular disease, pulmonary disease, or active infections were excluded, as were pregnant patients.			Stable disease: 2/25 Disease progression: 2/25 (1 patient not assessable)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Zhao, Q., Li, Y., Wang, J., Zhang, J., Qiao, X., Tan, B., Tian, Y., Shi, G., Xu, Q., Li, R., Liu, Y., Yang, P., Concurrent Neoadjuvant Chemoradiotherapy for Siewert II and III Adenocarcinoma at Gastroesophageal Junction, American Journal of the Medical SciencesAm J Med Sci, 349, 472-6, 2015 **Ref Id** 475274 **Country/ies where the study was carried out** China(ii) **Study type**	**Sample size** N= 76 CRT+ S: 36 S: 40 **Characteristics** CRT group: 32 men/ 4 women Median age: 61 S group: 32 men/8 women Median age: 57 **Inclusion criteria** (1) confirmation, by gastroscopy and CT, of Siewert II or III adenocarcinoma of the gastroesophageal junction with a presurgery tumor long diameter of #8 cm;	**Interventions** Chemotherapy Regimen The following XELOX regimen was used. Capecitabine was administered 1,000 mg/m^2 twice daily for 14 days (days 1–14), and oxaliplatin was given intravenously 130 mg/m^2 on day 1 for 2 cycles. Two chemotherapy cycles were administered before surgery and 6 cycles after. Radiotherapy Regimen Concurrent CT-based 3-dimensional conformal radiotherapy was delivered by a linear accelerator as multiple shaped beams of 6 to 20 MV X-rays in 5 daily fractions of 1.8 Gy per week for 5 weeks (total dose: 45 Gy). The biologically effective dose, calculated using the linear-	**Details** Pathological Analysis Pathological examinations included detecting tumor; invasion depth; number of metastatic lymph nodes; surgical margins; human epidermal growth factor receptor-2 HER-2 expression and tumor regression grade (TRG). Tumor regression grades were defined as follows: grade 0 (complete remission) is no cancer cells. Grade 1 (partial remission) is single cells or small groups of cancer cells. Grade 2 (low efficacy) is residual cancer outgrown by fibrosis. Grade 3 (poor efficacy) is minimal or no	**Results** **R0 resection rates:** CRTS group: 36/36 S group: 32/40 **Tumour grade response:** Pathological complete RR: 6/36 pathological RR (grade 0 or 1): 26/36	**Limitations** **Cochrane risk of bias tool**Selection bias random sequence generation: unclear allocation concealment: unclear Performance bias blinding: unclear but unlikely due to obvious difference between treatments Detection bias blinding: unclear but unlikely due to obvious difference between treatments Attrition bias outcome data complete Reporting bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
RCT **Aim of the study** This study was conducted to investigate the efficacy and safety of using a concurrent neoadjuvant chemoradiotherapy (a XELOX regimen) to treat adenocarcinoma of the gastroesophageal junction. **Study dates** August 2012 and August 2013 **Source of funding**	(2) presurgery classification as progressive gastric cancer (T3/4, N+, M0) using the American Joint Committee on Cancer (American Joint Committee on Cancer, AJCC) 2010 patient classification with no evidence of metastasis to the liver, lung, brain, bone or other organs; (3) no prior antitumor therapy; (4) no contraindications for chemotherapy or surgery; (5) a Karnofsky Performance Status (KPS) score of .60 and an Eastern Cooperative Oncology Group (ECOG) score of 0 to 2 and (6) informed consent obtained before enrollment. **Exclusion criteria**	quadratic formalism and an a/b ratio of 10 for early responding-tissues (tumor), was 51.1 Gy. According to tolerance of different patients, the chosen dosage ranged from 50 to 52 Gy. Radiation targets included the entire adenocarcinoma of gastroesophageal junction, any perigastric extension and lymph nodes (gastric, celiac, porta hepatis, gastroduodenal, splenic-suprapancreatic and retropancreatic-duodenal), with adequate margins. The distal margins of the esophagus (3–5 cm) were included when the tumor involved the gastroesophageal junction. Surgery	treatment effect and extensive residual cancer cells. Statistical Analysis Statistical analysis was performed using SPSS version 19.0 software. Quantitative data comparisons were made using the x2 test. Qualitative data were expressed as the mean 6 SD and compared using the t test. A P value< 0.05 was considered statistically significant.		outcomes stated in the objective were reported Overall assessment: UNCLEAR risk of bias due to inadequate reporting of allocation concealment, randomization process and blinding. **Other information** No critical outcomes reported.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Supported by Chinese Gastrointestinal Oncology Group Gastric Cancer Research Fund (20120101016).	No additional reported.	Surgical treatment consisted of either (1) proximal subtotal gastrectomy or (2) total gastrectomy and a subsequent extended lymph node dissection (D2 resection).			
Full citation Zhao, Y., Dai, Z., Min, W., Sui, X., Kang, H., Zhang, Y., Ren, H., Wang, X., Perioperative versus Preoperative Chemotherapy with Surgery in Patients with Resectable Squamous Cell Carcinoma of Esophagus: A Phase III Randomized Trial, Journal of Thoracic	**Sample size** n=346 (175 in perioperative chemotherapy (S + CT) vs 171 in preoperative chemotherapy (Sx)) **Characteristics** Median age: 59 (range 23 - 90) years Female %: 14.2 **Inclusion criteria**	**Interventions** Both groups had surgery and two preoperative cycles of PCF and S+CT had two additional postoperative cycles of PCF. PCF: Each 3 week cycle consisted of paclitaxcel IV infusion (100 mg/m^2 on D1), Cisplatin (60 mg/m^2) IV on day 1 and 5 and 5-FU (700 mg/m^2) from day 1-5	**Details** Patients in the trial were stratified on the basis of clinical characteristics, including age, sex, WHO performancek body weight loss, site and maximum diameter of tumor. Eligible patients with resectable SCC oesophagus were randomly assigned. The trial was designed to detect an absolute increase in the survival	**Results** Overall survival (HR for death) S+CT vs S: 0.79 (0.59 - 0.95; p<0.001) number of survivals at 5 years: S+CT = 27/173 S = 12/170	**Limitations** **ochrane risk of bias tool** Selection bias random sequence generation: unclear allocation concealment: unclear Performance bias blinding: unclear

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Oncology, 10, 1349-1356, 2015 **Ref Id** 475276 **Country/ies where the study was carried out** China(i) **Study type** Randomised controlled trial (RCT) **Aim of the study** To examine whether perioperative paclitaxel, cisplatin and 5-fluorouracil (PCF) could improve the outcomes of resectable squamous cell carcinoma of oesophagus comparing with	Patients with histopathologically proven squamous cell carcinoma (SCC) of oesophagus suitable for curative resection; The disease was limited to primary and regional nodes Operative candidate **Exclusion criteria**	Surgery was scheduled within 2-4 weeks after completion of the second cycle of preoperative chemotherapy in the two groups. Oesophagectomy was done through left thoracotomy/transhiatal/Lewis-Ivor approach depending on the site of the tumour Postoperative chemotherapy was initiated within 5 weeks after surgery. S+CT: 175 being randomised, 172 received pre-operative PCF; 161 underwent surgery; 131 started post-operative PCF. S: 171 being randomised, 169 received pre-operative PCF: 159 proceeded to surgery. Apart from those withdrawing the consent after randomisation (2 in S+CT and 1 in S groups);	of 15% in the perioperative chemotherapy group, with a two-sided α level of 5% and a statistical power of 80%, given the enrollment of 350 patients over a period of 3 years and approximately 170 deaths. Overall survival was calculated from randomisation to death from any cause.	Relapse free interval (HR for relapse) S+CT vs S: 0.62 (0.49 - 0.73; p<0.001) number of relapse free survivals at 5 years: S+CT = 22/173 S = 10/170	Detection bias blinding: unclear Attrition bias No loss of follow up Reporting bias All the outcomes mentioned in the method session were reported. Overall assessment: UNLCEAR risk of bias due to inadequate reporting of randomisation, allocation concealment, and blinding. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
those receiving preoperative PCF **Study dates** January 2005 to April 2007 **Source of funding** National Natural Science Foundation of China and the Fundamental Research Funds for the Central Universities		all the participants were included in the analysis.			
Full citation Burmeister, B. H., Smithers, B. M., Gebski, V., Fitzgerald, L., Simes, R. J., Devitt, P., Ackland, S., Gotley, D. C., Joseph, D., Millar, J., North, J., Walpole, E. T., Denham, J. W.,	**Sample size** n=256 **Characteristics** Age (years): ~ 61.5 Gender: Male %: 82 SCC %: 37 +ve regional node %: 15.5 **Inclusion criteria**	**Interventions** Please find in Kumagai 2014 SR	**Details** The primary endpoints was progression-free survival from date of randomisation. Of 129 and 128 participants allocated to CRT plus S and S alone respectively, 105 in the former and 110 in the latter received the	**Results** **Progression-free survival (HR (95% CI))** All patients CRT+S: 13/128, S alone: 9/128 P= 0.32	**Limitations** **Cochrane risk of bias tool** Selection bias --> Low risk random sequence generation: central telephone randomisation in

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Surgery alone versus chemoradiotherapy followed by surgery for resectable cancer of the oesophagus: a randomised controlled phase III trial, Lancet OncologyLancet Oncol, 6, 659-668, 2005 **Ref Id** 494320 **Country/ies where the study was carried out** Australia, New Zealand, Singapore **Study type** Multicentre RCT **Aim of the study** To assess whether downstaging of the tumour as a result	Histologically confirmed invasive cancer of the thoracic esophagus Restricted to esophagus and regional lymph nodes (clinical T1 to 3, N 0-1 disease) with resectable nodes to be removed as part of the planned surgical procedure (participants with involvement of gastric cardia confined to the lower third of the esophagus were also eligible if the tumour was mainly in the esophagus) Participants with no previous radiotherapy or chemotherapy ECOG (Eastern Cooperative Oncology Group) performance status of the patients had to be 0 or 1 Normal FBC and serum biochemistry		allocated treatment. After randomisation, 1 participant from CRT plus S (SCC in situ on biopsy) was found to be ineligible and excluded from the analysis. Analyses were done by ITT (n=128 in each group). Sample size calculations were made on the basis of a projected 3-year progression-free survival of 35% for patients assigned chemoradiotherapy and of 20% for those assigned to surgery alone.With an overall two-sided significance level of 5% and a stiatiscal power of 80% to detect a difference of 15% in 3-year progression-free survival, 4 years' accrual, and 4 years' follow-up, the calculated sample size	HR 0.82 (0.61-1.10) SCC only CRT plus S by S alone: 0.47 (0.25-0.86), p=0.014 SCC only : CRT plus S: 7/45 versus S alone: 4/50 Non-SCC only HR 1.02 (0.72-1.44), P=0.92 CRT+s: 5/ 78, S alone: 6/83 **Overall survival (HR (95% CI))** All patients CRT+S: 15/128, S alone: 10/128 P= 0.57	block of four --> low risk allocation concealment: yes to all central staff --> low risk Performance bias --> Unclear/Low risk blinding: research staff and investigators blinded but not patients Detection bias --> Low risk blinding of research staff Attrition bias --> Low risk ITT analysis Reporting bias --> Low outcomes stated in the method session reported except quality of life which

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
of chemoradiotherapy improved progression-free survival and overall survival after surgery. **Study dates** Nov 1994 to Sep 2000 **Source of funding** National Health and Medical Research Council of Australia (NHMRC)	Creatinine clearance > 1.0 mL/s (Gault and Cockcroft formula) and > 0.83mL/s by direct measurement Note - Participants with any malignant disease other than non-melanomatous skin cancer or cervical carcinoma in situ were eligible if there had been no recurrence for at least 5 years before randomisation **Exclusion criteria** - Patients with tumours localised to the cervical esophagus and those with involvement of the coeliac nodes		was 230 patients. Planned interimi analysis were performed to exclude major differences in outcomes between groups. Progression-free and overall survival were estimated withh the Kaplan-Meier method and groups were compared by use of the log-rank test. Age, tumour location and tumour grade were included in the multivariate anslaysis. The Cox proportional models was used oto define diffences in survival between groups and subgroups.	HR 0.89 (0.67-1.19) SCC only CRT plus S by S alone: 0.69(0.42-1.15), p=0.16 SCC only: CRT plus S: 8/45 S alone: 4/50 Non-SCC only HR 1.04 (0.74-1.48), P=0.81 CRT+S: 5/78, S alone: 6/83 **R0 resection** RCT+S group: 103/128 S only group: 76/128	the authors mentioned to be reported elsewhere Overall assessment: Low risk of bias **Other information** QoL outcomes to be reported separately.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Tumour regression grade Complete response: 21/73* Partial response: 49/73* * 73 of 128 patients assigned to CRT underwent pre-operative staging by endoscopy	

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F.11 Gastric Cancer

What is the optimal choice of chemotherapy of chemoradiotherapy in relation to surgical treatment for gastric cancer?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Bamias, A, Karina, M, Papakostas, P, Kostopoulos, I, Bobos, M, Vourli, G, Samantas, E, Christodoulou, Ch, Pentheroudakis, G, Pectasides, D, Dimopoulos, Ma, Fountzilas, G, A randomized phase III study of adjuvant platinum/docetaxel chemotherapy with or without radiation therapy in patients with gastric cancer, Cancer Chemotherapy and Pharmacology, 65, 1009-21, 2010 **Ref Id** 539203 **Country/ies where the study was carried out**	**Sample size** N= 143 **Characteristics** Arm A (CT) Median age (range)= 62 (41–79) 27 % female Arm B (CRT) Median age (range)= 63 (32–75) 33% female There were no significant differences in major characteristics between the two treatment groups, with the exception of histological subtype (*P* = 0.007).	**Interventions** Patients were randomized to one of the following regimens: (1) Six cycles of docetaxel with cisplatin (group A) and (2) Six cycles of docetaxel with cisplatin and RT (group B). After the first 45 patients (22 group A, 23 group B), the protocol was amended due to excessive nausea and vomiting and cisplatin was substituted by carboplatin. CT The doses of the chemotherapeutic agents used were 75 mg m¡2 docetaxel in 250 mL saline administered over a 1-h period; 75 mg m¡2	**Details** Statistical Analysis In order to identify the factors that had a significant effect on patients' OS and DFS, multivariate Cox regression analysis was performed. Variables included were age, number of involved nodes (0–7 vs. 8–15 vs>15), stage (T1/T2 vs. T3/T4), grade, histological subtype (intestinal vs. diffuse vs. mixed/unclassified), and randomization group. Statistical tests were two-sided and were performed to a	**Results** Overall Survival* Group A= 34 events, Group B= 40 events HR (95% CI)= 1.20 (0.75-1.91), P=0.448 Disease-free survival* Group A= 37 events, Group B= 43 events HR (95% CI)= 1.04 (0.66-1.63), P=0.879 *adjusted for lymph noder involvement and T stage (unadjusted not reported) Grade 3-4 Toxicities Anemia	**Limitations** **Cochrane risk of bias tool** Selection bias • random sequence generation: unclear • allocation concealment: unclear, centrally randomized but concealment not described Performance bias • blinding: unclear but unlikely due to obvious difference between treatments Detection bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Greece **Study type** RCT **Aim of the study** We compared the efficacy of a docetaxel and platinum adjuvant chemotherapy regimen, in patients with high-risk gastric cancer, with that of the same chemotherapy plus radiation therapy (RT). **Study dates** April 2002 and April 2005 **Source of funding**	**Inclusion criteria** Patients with histologically confirmed gastric adenocarcinoma (including adenocarcinoma of the gastroesophageal junction) were included in the study. Patients were eligible for post-operative adjuvant therapy if: disease was absent from the peritoneal cavity and other distant organs, negative surgical margins were obtained, had serosal infiltration (pT3 based on American Joint Committee on Cancer criteria [19]) or infiltrated lymph nodes; they had performance status 2 or lower according to the Eastern Cooperative Oncology Group criteria; they had no history of other malignancy except basal cell or squamous cell carcinoma of the skin; were	cisplatin in 500 mL saline administered over a 1-h period or carboplatin to an area under the curve (AUC) of 5 in 500 mL saline or 5% dextrose administered over a 1-h period; treatment was administered every 3 weeks for six cycles. RT Radiation therapy (RT) was administered 3–4 weeks after the third chemotherapy cycle. RT was planned with dedicated computed tomography (CT) and a three-dimensional planning system. It was delivered with linear accelerators with nominal energy of 6 and/or 18 MV, through parallel-opposed AP-PA Welds. RT consisted of fractionated external irradiation at a dose of	significance level of 0.05. Results of this study were presented according to reporting recommendations for tumor marker prognostic studies.	Group A: 1/70 Group B: 1/71 Neutropenia (non-febrile) Group A: 8/70 Group B: 12/71 Febrile Neutropenia Group A: 6/70 Group B: 5/71 Thrombocytopenia Group A: 1/70 Group B: 3/71 Nausea/Vomiting Group A: 1/70 Group B: 3/71 Stomatitis Group A: 0/70 Group B: 1/71 Diarrhea Group A: 5/70 Group B: 3/71 Infection Group A: 0/70 Group B: 1/71 Peripheral Neuropathy Group A: 1/70 Group B: 0/71 Fatigue Group A: 1/70	• blinding: unclear but unlikely due to obvious difference between treatments Attrition bias • outcome data complete Reporting bias • outcomes stated in the objective were reported Overall assessment: UNCLEAR risk of bias due to inadequate reporting of allocation concealment, randomization process and blinding. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Supported in part by a HeCOG Research Grant: RD/2	at least 18 years of age; had no evidence of cardiac failure; had absolute neutrophil count >1,500 L¡1, platelet count >100,000 mL¡1, normal serum bilirubin, alanine transaminase and aspartate transaminase <2 times the upper limit of normal, and calculated creatinine clearance >60 mL min¡1; and were of satisfactory nutritional status (weight increase following gastrectomy or minimum intake of 1,500 kcal day¡1). **Exclusion criteria** No additional criteria reported	1.8 Gy per fraction given once daily 5 days per week (Monday through Friday) over a period of 5 weeks, for a total dose of 45 Gy.		Group B: 0/71 Allergic reaction Group A: 1/70 Group B: 0/71	
Full citation Bang, Yj, Kim, Yw, Yang, Hk, Chung, Hc, Park, Yk, Lee, Kh, Lee,	**Sample size** N= 1035 **Characteristics**	**Interventions** D2 gastrectomy within 6 weeks prior to randomisation CT group	**Details** Assessment by MRI or abdominal CT every 6 months during the first 3	**Results** Disease free survival *	**Limitations** **Cochrane risk of bias tool** Selection bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Kw, Kim, Yh, Noh, Si, Cho, Jy, Mok, Yj, Kim, Yh, Ji, J, Yeh, Ts, Button, P, Sirzén, F, Noh, Sh, Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial, Lancet (London, England), 379, 315-21, 2012 **Ref Id** 539204 **Country/ies where the study was carried out** Korea and China **Study type** RCT **Aim of the study** To investigate the effect on disease-free survival of adjuvant	<u>Surgery only group:</u> mean age (SD)= 55.8 (11.6) 70% male <u>Chemotherapy group:</u> mean age (SD)= 56.1 (11.1) 72% male **Inclusion criteria** • 18 years and older • histologically confirmed gastric adenocarcinoma • T stage II-IIIb • no evidence of metastatic disease • D2 surgery • achieved R0 resection • KPS score >70% • adequate hepatic, renal and haematological function	8 3-week cycles of oral capeticitabine (1000 mg/m2 twice daily on days 1-14 of each cycle) plus intravenous oxaliplatin (130 mg/m2 on day 1 of each cycles).	years and yearly thereafter. Adverse events were graded by the National Cancer Institute's Common Terminology Criteria for Adverse Events. <u>Statistical Analysis</u> Time to endpoint calculations by Kaplan-Meier survival methods and two-sided log rank test. Interim analysis was preplanned.	HR (95%CI)= 0.58 (0.47-0.72), P<0.0001 Chemotherapy group: 139 events Surgery group: 203 events <u>Overall survival</u> * HR (95% CI)= 0.66 (0.51-0.85), p=0.0015 Chemotherapy group: 103 events Surgery group: 141 events * extracted from Noh, 2014 <u>Adverse events, grade III or IV</u> Any event surgery group: 30/478 chemo group: 279/496 Nausea surgery group: 0/478 chemo group: 39/496	• random sequence generation: computerized random permuted blocks • allocation concealment: centralized allocation Performance bias • blinding: high risk Detection bias • blinding: high risk Attrition bias • outcome data complete Reporting bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
chemotherapy with capecitabine plus oxaliplatin after D2 gastrectomy compared with D2 gastrectomy only in patients with stage II-IIIB gastric cancer. **Study dates** June 2006- June 2009 **Source of funding** Sponsored by Hoffman-La Roche and Sanofi-Aventis.	**Exclusion criteria** - previous chemotherapy, radiotherapy or immunotherapy for gastric cancer			Neutropenia surgery group: 1/478 chemo group: 107/496 Decreased appetite surgery group: 1/478 chemo group: 23/496 Peripheral neuropathy surgery group: 0/478 chemo group: 12/496 Diarrhoea surgery group: 1/478 chemo group: 9/496 Vomiting surgery group: 0/478 chemo group: 37/496 Fatigue surgery group: 0/478	• outcomes stated in the objective were reported Overall assessment: Low risk of bias due to adequate allocation concealment and randomization process. Lack of blinding likely not an issue as all outcomes objectively measures. **Other information** Additional study report (Noh, 2014) extracted under this title. Noh, 2014 also includes detailed adjusted analysis of OS and DFS. AKA CLASSIC trial.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				chemo group: 23/496 Thrombocytopenia surgery group: 0/478 chemo group: 40/496 Hand-foot syndrome surgery group: 0/478 chemo group: 5/496 Asthenia surgery group: 0/478 chemo group: 10/496 Abdominal pain surgery group: 2/478 chemo group: 8/496 Constipation surgery group: 0/478 chemo group: 1/496 Dizziness surgery group: 0/478	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				chemo group: 3/496 Stomatitis surgery group: 0/478 chemo group: 3/496 Weight loss surgery group: 2/478 chemo group: 1/496 Peripheral sensory neuropathy surgery group: 0/478 chemo group: 3/496	
Full citation Bouché, O, Ychou, M, Burtin, P, Bedenne, L, Ducreux, M, Lebreton, G, Baulieux, J, Nordlinger, B, Martin, C, Seitz, Jf, Tigaud, Jm, Echinard, E, Stremsdoerfer, N, Milan,	**Sample size** n=278 randomised and 260 included were included in analyses. (127 in postCT group vs 133 in surgery alone group) no significant difference between patients ineligible from postCT to surgery alone.(ITT	**Interventions** Eomparison: post-chemotherapy versus surgery alone Surgery: total or subtotal gastrectomy with curative intent and en bloc resection of the tumour with negative margins	**Details** The primary outcome was OS(date of randomisation to date of death from any cause or the date of the last follow-up).	**Results** <u>Treatment-related mortality</u> Surgery alone group: 1/133 (1 post-op pulmonary embolism) Chemo group: 2/127 (1 post-op	**Limitations** **<u>Cochrane risk of bias tool</u>** Selection bias • random sequence generation: low

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
C, Rougier, P, Adjuvant chemotherapy with 5-fluorouracil and cisplatin compared with surgery alone for gastric cancer: 7-year results of the FFCD randomized phase III trial (8801), Annals of oncology : official journal of the European Society for Medical Oncology, 16, 1488-97, 2005 **Ref Id** 539219 **Country/ies where the study was carried out** France **Study type** multicenter, prospective, randomized, controlled phase III trial (randomisation stratified by institution and tumour site)	analyses was performed on 260 patients) **Characteristics** 64 centres in France Age median(SE): 61(0.9) Male %=71.5% Macroscopic type:Infiltrative=111(42.7%), exophytic=147(56.5%) amd unknown=2(0/8%) Histology: well differentiated=124(47.7), poorly differentiated=62(23.9%), signet ring cell=63(24.2%), other=11(4.2%) pT3/4=201(77.3%) **Inclusion criteria** • istologically confirmed adenocarcinoma of the stomach or gastro-oesophageal junction:	Chemotherapy: 2 stage post-operative chemotherapy: IV 5FU 800 mg/m2 per day in continuous infusion for 5 days initiated not later than 14 days after surgery and the 2nd stage began 4 weeks later in the absence of WHO grade 4 toxicity, with four cycles of FUP (5-day continuous infusion of 5FU 1g/m2 per day combined with cisplatin 100 mg/m2 IV ove 1 hr on day 2) regime. repeeated the cycle FUP every 4 weeks. And, appropriate precaution and management was taken for signs of toxicity. Follow-up: 3 months interval for 2 years, then 6 months intervals for 3 years and yearly thereafter;	Secondary end points were disease-free survival (date of randomisation to the date of first occurence of a neoplastic event (relapse or second malignancy)) or the date of death from any cause)and safety. 200 patients in each arm over 5 years recruitment with 2-years follow-up were planned to provide 80% power to detect the difference between 5-year OS of 40% in the surgery alone arm and 55% in the chemotherapy arm [HR 0.65] with type I error of 0.05. The convariates included in multivariate	pulmonary embolism, 1 neutropenic sepsis)	• allocation concealment: unclear, centrally randomized but concealment not described Performance bias • blinding: unclear Detection bias • blinding: unclear Attrition bias • ITT analysis Reporting bias • outcomes stated in the objective were reported Overall assessment: UNCLEAR risk of bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study To evaluate the efficacy of adjuvant chemotherapy after resection for gastric cancer **Study dates** April 1989 and December 1997 **Source of funding** not reported	• complete resection of the neoplasm defined as resection of all tumour with no distant metastasis • no post-operative complications • early registration with treatment beginning before 14 days after surgery **Exclusion criteria** • linitis plastica • concurrent active malignancy		analyses were: age, gender and all clinical variables significant at p<0.15. adjustments were performed for the centers, the tumour site and the type of treatment. The enrollment was stopped after a median followup of 7 years and the posthoc power was 47%^.		due to inadequate reporting of allocation concealment and blinding. **Other information** Included in Cochrane M-A. See Diaz-Nieto for additional details and results.
Full citation Chipponi, J, Huguier, M, Pezet, D, Basso, N, Hay, Jm, Quandalle, P, Jaeck, D, Fagniez, Pl, Gainant, A, Randomized trial of adjuvant chemotherapy after	**Sample size** n=205 (104 in surgery and 101 in post CT group) **Characteristics** Mean age: 61 years (63 in surgery alone vs 59 in post CT group, statically	**Interventions** Comparison: Post-CT vs surgery alone Surgery: D1 or D2 resection Chemotherapy: 5-day course of leucovorin through IV bolus injection followed by infusion of	**Details** The primary end point survival as the time of operation to death. The others were side effects of the chemotherapy.	**Results** <u>Treatment-related mortality</u> Surgery group: 0/103 Surgery + chemo group: 4/93 There were 4 deaths as the	**Limitations** **<u>Cochrane risk of bias tool</u>** Selection bias • random sequence generation: low

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
curative resection for gastric cancer, American Journal of SurgeryAm J Surg, 187, 440-5, 2004 **Ref Id** 539238 **Country/ies where the study was carried out** France **Study type** RCT **Aim of the study** To evaluate the efficacy of adjuvant chemotherapy on survival after resection for gastric cancer **Study dates** October 1989 to September 1997	significant different) Male%=129(65.8%) LN+=163(83%) **Inclusion criteria** • patients with histologically proven gastric adenocarcinoma • patients with lymph node involvement or serosal involvement • patients who underwent curative resection • patients with adjacent tissues invasion amenable to an en-bloc resection **Exclusion criteria** • prior other malignancy, chemotherapy or	5FU(375 mg/m2 daily in 1L saline over 2 hours) followed by infusion of CDDP (15 mg/m2 daily in 250 mL saline over 1 hour). another 1L saline infused over 1 hour after CDDP. Cycles were repeated every 21 days. In the absence of GI, renal or haematological toxicity, daily dose of 5FU increased by 25 mg/m2/day at each cycle(maximum daily dose 500 mg/m2/day). Appropriate precaution and management were undertaken for toxicity.	200 patients in each group was required (90% power, type I error 0.05) to detect 5-year survival rate of 35% and an improvement of survival to 50%. Treatment was randomly assigned after the eligibility of the patient to participate in the study. Randomisation was done by a centralised random permuted block technique. ITT analyses was done for survival analyses. Median follow up time was 101 months (43-140)	result of chemotherapy toxicity, 1 from hemotological aplasia, 1 from both hematological and digestive toxicity, 1 from cardiovascular collapse, and 1 at home from unknown cause.	• allocation concealment: unclear, centrally randomized but concealment not described Performance bias • blinding: unclear Detection bias • blinding: unclear Attrition bias • outcome data complete Reporting bias • outcomes stated in the objective were reported

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding Not reported	radiotherapy and contraindicated to chemotherapy				Overall assessment: UNCLEAR risk of bias due to inadequate reporting of allocation concealment and blinding. **Other information** Included in Cochrane M-A. See Diaz-Nieto for additional details.
Full citation Schuhmacher, C, Schlag, P, Lordick, F, Hohenberger, W, Heise, J, Haag, C, Gretschel, S, Mauer, Me, Lutz, M, Siewert, Jr, Neoadjuvant chemotherapy versus surgery alone for locally advanced adenocarcinoma of the stomach and cardia: Randomized EORTC phase III trial #40954	**Sample size** N=144 **Characteristics** median age= 57 (26-70) 69.4% male 93.8% T3, 6.3% T4 71.5% WHO status 0; 28.% WHO status 1 **Inclusion criteria**	**Interventions** Surgery: Resection of the gastric tumor was performed within 14 days after random assignment in patients randomly assigned to surgery alone and within 4 weeks after the last day of chemotherapy in patients receiving chemotherapy. Resection consisted of a	**Details** Follow-up • Specimens classified according to fifth UICC TNM system • Reduction of tumour size assessed with	**Results** <u>Overall survival</u> CT+ surgery group: 32 events/ 72 Surgery alone group: 35 events/ 72 HR (95% CI)= 0.84 (0.52 to 1.35), P=0.466	**Limitations** **<u>Cochrane risk of bias tool</u>** Selection bias • random sequence generation: unclear- details not provided • allocation concealment: unclear- details not provided

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
[abstract no. 4510], Journal of Clinical OncologyJ Clin Oncol, 27, 204, 2009 **Ref Id** 539498 **Country/ies where the study was carried out** Europe **Study type** RCT **Aim of the study** We examined the value of purely preoperative chemotherapy in a phase III trial with strict preoperative staging and surgical resection guidelines. **Study dates**	Study inclusion criteria were: • age 18 to 70 years (amended to 75 years in 2003); • WHOperformance status 0 to 1; • histologically proven adenocarcinoma of the stomach or the esophagogastric junction (AEG II and III); • T3 or T4 tumor based on endoscopic ultrasound; • no evidence of distant metastases or disease considered nonresectable by EUS, computed tomography (CT) and extended diagnostic laparoscopy;	subtotal or gastrectomy with extension depending on the location of the primary tumor with either a D1 lymphadenectomy (for perigastric nodes at lesser and greater curvature; seven patients) or, preferably, a D2 lymphadenctomy (for regional lymph nodes outside the perigastric area; 130 patients). CT: Chemotherapy started within 7 days of random assignment and consisted of two 48-day cycles of cisplatin 50 mg/m2 intravenous (IV) over 1 hour with hydration on days 1, 15, and 29, followed by d-L-folinic acid 500 mg/m2 IV over 2 hours and fluorouracil 2,000 mg/m2 continuous IV infusion over hours on days 1, 8, 15, 22, 29, and 36.1	endoscopy and CT • Toxicity and adverse events assessed using National Cancer Institute Common Toxicity Criteria grading version 2.0 • Patients followed by CT scan at 3, 6, 9, 12, 18, 24 months and yearly thereafter. Statistics Statistical analysis was performed on all randomly assigned patients	<u>Disease-free survival</u> CT+ surgery group: 40 events/ 72 Surgery alone group: 44 events/ 72 HR (95% CI)= 0.76 (0.49 to 1.16), P=0.20 <u>Operative Complications</u> Any complication (patients with at least one) CT +Surgery group: 19/70 Surgery alone group: 11/68 Bleeding CT +Surgery group: 3/70 Surgery alone group: 1/68 Transfusion CT +Surgery group: 10/70	Performance bias • blinding: unclear but unlikely due to obvious difference between treatments Detection bias • blinding: unclear but unlikely due to obvious difference between treatments Attrition bias • outcome data complete Reporting bias • outcomes stated in the objective were reported

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
July 1999 and February 2004 **Source of funding** Supported by Grants No. 5U10-CA11488-29 through 5U10 CA11488-38 from the National Cancer Institute (Bethesda, MD) and by a donation from the Fe´de´ration Belge Contre le Cancer from Belgium through the EORTC Charitable Trust. Its content is solely the responsibility of the authors and does not necessarily reflect the official views of the National Cancer Institute.	• no prior gastric surgery; no previous chemotherapy or radiotherapy; no uncontrolled infectious or cardiac disease; • adequate renal function; • and no previous or other current cancer except for curatively treated nonmelanoma skin cancer or carcinoma in situ of the cervix. **Exclusion criteria** No additional eligibility criteria.		on an intent-to-treat basis. Overall survival and progression-free survival were calculated from random assignment. Survival curves were estimated by the Kaplan-Meier technique. Durations of survival were compared between the arms using a two-sided log-rank test. To adjust for confounding factors, the Cox proportional hazard model with retrospective stratification was used. Stratification factors included institution, primary tumor extension (cT3 or cT4), tumor location (upper third of the	Surgery alone group: 4/68 Anastomotic Leak CT +Surgery group: 3/70 Surgery alone group: 2/68 Duodenal stump leakage CT +Surgery group: 1/70 Surgery alone group: 0/68 Peritonitis CT +Surgery group: 2/70 Surgery alone group: 1/68 Fistula CT +Surgery group: 3/70 Surgery alone group: 5/68 Septicemia CT +Surgery group: 5/70 Surgery alone group: 2/68 Retention CT +Surgery group: 0/70	Overall assessment: UNCLEAR risk of bias due to inadequate reporting of allocation concealment, randomization process and blinding. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			stomach including the cardiac middle and lower third), sex, and histologic subtype (intestinal *v* nonintestinal).	Surgery alone group: 1/68 Wound infection CT +Surgery group: 2/70 Surgery alone group: 1/68 Abscess CT +Surgery group: 4/70 Surgery alone group: 4/68 Intestinal occlusion CT +Surgery group: 1/70 Surgery alone group: 1/68 <u>Death resulting from post-op complications</u> CT +Surgery group: 3/70 Surgery alone group: 1/68 <u>R0 resection</u> CT + surgery group: 59/72	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Surgery group: 48/72	
Full citation Yu, C. H., Yu, R., Zhu, W. G., Song, Y. Q., Li, T., Intensity-modulated radiotherapy combined with chemotherapy for the treatment of gastric cancer patients after standard D1/D2 surgery, Journal of Cancer Research and Clinical Oncology, 138, 255-259, 2012 **Ref Id** 540180 **Country/ies where the study was carried out** China **Study type** RCT	**Sample size** N= 68 **Characteristics** Mean age= 56-57 43 male/25 female Pathological type= adenocarcinoma **Inclusion criteria** (1) the subjects must agree to participate in the study and sign an informed consent form; (2) men or women who were 18–70 years old; (3) the presence of gastric cancer with a pathological stage T3/T4 and/or N?	**Interventions** CT: All patients underwent chemotherapy that consisted of 425 mg/m2 5-FU and 25 mg/m2 LV for one cycle prior to the concurrent radiotherapy. Chemotherapy was also given within the first 4 days and last 3 days during the chemoradiotherapy period (400 mg/m2 5-FU and 25 mg/m2 LV) and after chemoradiotherapy (two cycles of 425 mg/m2 5-FU and 25 mg/m2 LV). In the single chemotherapy group, 425 mg/m2 5-FU and 25 mg/m2 LV were given for five cycles.	**Details** Sixty-eight untreated gastric cancer patients (T3/T4 and/or N?) were enrolled. After surgery, they were randomized into two groups: the CCRT group and the single chemotherapy group. Radiotherapy patients were treated according to the Intergroup 0116 guidelines. The chemotherapy consisted of continuously administered 5-fluorouracil (5-FU) and tetrahydrofolic acid (LV). The CCRT began 28	**Results** <u>Overall Survival</u> One-, two-, and three-year survival rates were, 85.9, 73.4, and 67.7% in the CCRT group and 68.0, 50.0, and 44.1% in the single chemotherapy group (v2 = 4.367, P = 0.037). HR calculated by NGA technical team*: HR (95% CI)= 0.47 (0.23-0.96) <u>Disease-free Survival</u> The corresponding disease-free survival rates were 73.5, 64.7, and 55.8% in the	**Limitations** **<u>Cochrane risk of bias tool</u>** Selection bias • random sequence generation: unclear • allocation concealment: unclear Performance bias • blinding: unclear but unlikely due to obvious difference between treatments Detection bias • blinding: unclear but unlikely due

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study The purpose of the current study is to evaluate the efficacy and complications of concurrent chemoradiotherapy (CCRT) for the treatment of gastric cancer patients after D1/D2 surgery. **Study dates** NR **Source of funding** NR	gastric adenocarcinoma, as prove through histology; (4) previously untreated and with no prior history of cancer, chemotherapy, or radiotherapy; and (5) laboratory tests at baseline are as follows: haemoglobin (Hb) C 110 g/L, WBC C 3.5 9 109/L, platelet C 100 9 109/L, hepatic and renal function \1.25 times normal upper limit, and blood glucose in normal range **Exclusion criteria** No additional criteria reported.	RT: All the patients received therapy 3–4 weeks after surgery. In the CCRT group, intensity-modulated radiotherapy was applied, and the radiation scope was determined based on the intraoperative situation and the silver-clip labels, as well as the NCCN guidelines. The target areas consisted of the tumor bed, the stroma, and the draining lymph nodes. The therapeutic machine was a Siemens ONCOR Lineal Accelerator, and CMS treatment planning system was used. The radiation limits of sensitive tissues were as follows: 60%\30 Gy for the liver, \45 Gy for the spinal cord, an average dosage of\10 Gy and the	days after the first cycle of chemotherapy, and chemotherapy was given within the first four and last three days during theCCRT period, at a radiation dosage of 45 Gy/25 f, i.e., 1.8 Gy 5 times per week. Two cycles of the same chemotherapy were administrated 1 month after the radiotherapy. Five cycles of 5-FU and LV were applied to CG. Statistics Survival time was defined as the duration from definitive diagnosis until death. SPSS 13.0 software was used for data management. The	CCRT group and 61.8, 38.2, and 29.4% in the single chemotherapy group (v2 = 5.297, P = 0.021) HR calculated by NGA technical team*: HR (95% CI)= 0.48 (0.25-0.89) *Method described by Tierney 2007 <u>Adverse Reactions- Grade III or IV</u> Anorexia CCRT group: 3/34 Chemotherapy group: 2/34 Nausea and vomiting CCRT group: 5/34 Chemotherapy group: 3/34 HB decrease	to obvious difference between treatments Attrition bias • outcome data complete Reporting bias • Unclear- outcomes of interest were not defined in the objectives Overall assessment: High risk of bias due to inadequate reporting of allocation concealment, randomization process and blinding. Very limited details on methodology. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
		volume treated with 20 Gy\20% for the kidneys, and 1/3\50 Gy for heart. The dosage for the lungs and the left ventricle was reduced as much as possible. The dosage for the target area was 45 Gy/28.	data were compared using a v2 test. Survival analysis was performed using the Kaplan–Meier method using a log-rank test. P\0.05 was considered statistically significant.	CCRT group: 3/34 Chemotherapy group: 1/34 Neutrocytopenia CCRT group: 9/34 Chemotherapy group: 6/34 Thrombocytopenia CCRT group: 5/34 Chemotherapy group: 3/34 Abdominal pain CCRT group: 1/34 Chemotherapy group: 1/34 Diarrhoea CCRT group: 0/34 Chemotherapy group: 0/34 ALT increase CCRT group: 0/34	Limited detail, short report.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Chemotherapy group: 0/34 Liver enzyme increase CCRT group: 0/34 Chemotherapy group: 0/34	
Full citation Cunningham, D., Allum, W. H., Stenning, S. P., Thompson, J. N., Van De Velde, C. J. H., Nicolson, M., Scarffe, J. H., Lofts, F. J., Falk, S. J., Iveson, T. J., Smith, D. B., Langley, R. E., Verma, M., Weeden, S.,	**Sample size** N= 503 **Characteristics** Median age= 62 396 male: 107 female Site: 73.9% stomach; 14.5% lower oesophagus; 11.5% GEJ	**Interventions** Patients were randomly assigned to either perioperative chemotherapy and surgical resection (the perioperative-chemotherapy group) or to surgical resection	**Details** Surgeons were asked to document the extent of dissection and to state whether the procedure was likely to be curative. The	**Results** **<u>Overall survival</u>** HR= 0.75; 95 percent confidence interval, 0.60 to 0.93; P = 0.009	**Limitations** **<u>Cochrane risk of bias tool</u>** Selection bias • random sequence generation: unclear- not described

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Yu, J. C., Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer, New England Journal of MedicineN Engl J Med, 355, 11-20, 2006 **Ref Id** 485419 **Country/ies where the study was carried out** UK and others **Study type** RCT **Aim of the study** We assessed whether the addition of a perioperative regimen of ECF to surgery improves outcomes among patients with	**Inclusion criteria** Patients of any age who had a World Health Organization (WHO) performance status of 0 or 1 were eligible if they had histologically proven adenocarcinoma of the stomach or lower third of the esophagus that was considered to be stage II (through the submucosa) or higher, with no evidence of distant metastases, or locally advanced inoperable disease, as evaluated by computed tomography, chest radiography, ultrasonography, or laparoscopy.13 The original trial design included patients with gastric carcinomas only, but on the basis of the increased incidence of tumors of the	alone (the surgery group). CT Chemotherapy was administered for three cycles preoperatively and three cycles postoperatively. Each 3-week cycle consisted of epirubicin (50 mg per square meter of body-surface area) by intravenous bolus on day 1, cisplatin (60 mg per square meter) intravenously with hydration on day 1, and fluorouracil (200 mg per square meter) daily for 21 days by continuous intravenous infusion with the use of a double-lumen Hickman catheter and a portable infusion pump. Surgery	resection was judged curative, either absolutely or relatively, if all macroscopic and microscopic disease seemed to have been removed. All resected specimens were examined at local pathology laboratories according to a standard protocol that used the tumor–node–metastasis (TNM) classification. Statistics Kaplan–Meier curves for progression-free and overall survival were compared with the use of the log-rank test on an intention-to-treat basis. Hazard	(favours perioperative chemo) **Progression-free survival** HR= 0.66; 95 percent confidence interval, 0.53 to 0.81; P<0.001 (favours perioperative chemo) **Adverse events, Grade III or IV** Reported for pre-op chemo and post-op chemo only Not reported for both group. **Extent of resection according to surgeon** (surrogate	• allocation concealment: centralized allocation Performance bias • blinding: unclear but unlikely due to obvious difference between treatments Detection bias • blinding: unclear but unlikely due to obvious difference between treatments Attrition bias • outcome data complete Reporting bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
potentially curable gastric cancer. **Study dates** July 1994 and April 2002 **Source of funding** Not reported	esophagogastric junction, eligibility criteria were extended in 1999 to include adenocarcinomas of the lower third of the esophagus. **Exclusion criteria** Patients were excluded if they had previously received cytotoxic chemotherapy or radiotherapy, had uncontrolled cardiac disease, or had creatinine clearance of 60 ml per minute or less.	Surgery was scheduled to take place within six weeks after randomization in the surgery group and three to six weeks after completion of the third cycle of chemotherapy in the perioperative chemotherapy group. Postoperative chemotherapy was to be initiated 6 to 12 weeks after surgery. In radical total gastrectomy, the whole stomach was removed, with the proximal line of division through the distal esophagus, and the distal line of division through the proximal duodenum. The resection also included the greater and lesser omenta and any other organs involved by extension of the primary growth (e.g.,	ratios were calculated with the use of a Cox regression model including treatment alone (primary analysis) and after adjustment for baseline stratification factors. Categorical data were compared with the use of chi-square tests, with a test for trend over ordered categories (e.g., T stage). Tumor measurements were compared with the use of nonparametric Mann–Whitney tests. All tests were two-sided and unadjusted for multiple comparisons.	outcome for R0 resection) Curative resection perioperative-chemotherapy group: 169/244 surgery group: 166/250	• outcomes stated in the objective were reported Overall assessment: UNCLEAR risk of bias due to inadequate reporting of randomization process and blinding. **Other information** Aka MAGIC trial

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
		pancreas, spleen, mesocolon, colon, or left lobe of liver). The procedure for a radical subtotal distal gastrectomy was the same, but a small, viable gastric remnant was left intact. In both procedures, the resection lines had to be at least 3 cm from the edge of the macroscopic tumor.	The trial was overseen by an independent datamonitoring committee that met five times (approximately annually) to review accrual, safety, and efficacy data.		
Full citation Di Costanzo, F., Gasperoni, S., Manzione, L., Bisagni, G., Labianca, R., Bravi, S., Cortesi, E., Carlini, P., Bracci, R., Tomao,	**Sample size** n=258(130 to postCT group vs 128 to surgery alone group) **Characteristics**	**Interventions** Comparison: Surgery vs Post-CT Surgery: total or subtotal gastrectomy with negative resection	**Details** randomisation was centrally managed and done by computer-generated permuted-block	**Results** Treatment-related mortality Follow-up group: 0/128 Chemotherapy group: 1/130	**Limitations** **Cochrane risk of bias tool** Selection bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
S., Messerini, L., Arcangeli, A., Torri, V., Bilancia, D., Floriani, I., Tonato, M., Adjuvant chemotherapy in completely resected gastric cancer: A randomized phase III trial conducted by GOIRC, Journal of the National Cancer InstituteJ Natl Cancer Inst, 100, 388-398, 2008 **Ref Id** 485473 **Country/ies where the study was carried out** Italy **Study type** multicenter randomised open-label phase III trial **Aim of the study** To evaluate in an adjuvant setting the efficacy of PELF	Median age =59 years Male%=157(61%) T3/T4%=124(48.6%) **Inclusion criteria** • Histologically proven gastric cancer • radical resection of tumour not more than 8 weeks before the date of random assignment with no evidence of residual disease as determined by staging exams, gastric cancers of stages IB, II, IIIA-B or IV (T4N2M0) • no previous malignancies other than superficial skin cancer or in situ cervical carcinoma	margins with at least D1 lymphadenectomy CT: cisplatin (40 mg/m2 IV for 30 min infusion on day 1 and 5), epirubicin (30 mg/m2 by IV bolous injection on day 1 and 5), L-leucovorin (100 mg/m2 by IV injection on day 1-4) and 5FU (300 mg/m2 by IV bolus on day 1-4). cycle repeated at 21-day interval.	randomisation lists stratified by institution, stage (IB or II or III or IV) and tumour site (upper third vs middle or inferior third of stomach)	(due to cardiovascular complications and electrolytic imbalance after grade 4 vomiting)	• random sequence generation: low • allocation concealment: unclear Performance bias • blinding: no but depends on outcome assessment Detection bias • blinding: no but depends on outcome assessment Attrition bias • outcome data complete Reporting bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
(cisplatin, epirubicin, 5-FU and leucovorin) compared with surgery alone overall survival and disease-free survival **Study dates** January 1995 to September 2000 **Source of funding** National Council of Research - Clinical Application of Oncological Research; Italian association of Cancer Research	**Exclusion criteria**				• outcomes stated in the objective were reported Overall assessment: UNCLEAR risk of bias due to inadequate reporting of allocation concealment and blinding. **Other information** See Diaz-Nieto Cochrane review for additional results and details.
Full citation Macdonald, J. S., Smalley, S. R., Benedetti, J., Hundahl, S. A., Estes, N. C., Stemmermann, G. N., Haller, D. G., Ajani, J.	**Sample size** N=556 **Characteristics** Median age= 59-60 71-72% male	**Interventions** After undergoing gastrectomy, patients were randomly assigned to surgery alone or to the postoperative combination of fluorouracil plus	**Details** Follow-up Follow-up of both groups occurred at three-month intervals for two years, then at six-month intervals for	**Results** **<u>Overall Survival</u>** The difference in overall survival was significant (P=0.005 by a two-sided log-rank test). A total of 169	**Limitations** **<u>Cochrane risk of bias tool</u>** Selection bias • random sequence generation:

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
A., Gunderson, L. L., Milburn Jessup, J., Martenson, J. A., Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction, New England Journal of MedicineN Engl J Med, 345, 725-730, 2001 **Ref Id** 486132 **Country/ies where the study was carried out** US **Study type** RCT **Aim of the study** We investigated the effect of surgery plus postoperative (adjuvant) chemoradiotherapy on	**Inclusion criteria** The eligibility criteria included histologically confirmed adenocarcinoma of the stomach or gastroesophageal junction; complete resection of the neoplasm, defined as resection performed with curative intent and resulting in resection of all tumor with the margins of the resection testing negative for carcinoma; a classification of the resected adenocarcinoma of the stomach or gastroesophageal junction as stage IB through IVM0 according to the 1988 staging criteria of the American Joint Commission on Cancer15; a performance status of 2 or lower according to the criteria of the Southwest Oncology Group; adequate function of major organs (indicated by a creatinine	leucovorin and local–regional radiation. The regimen of fluorouracil and leucovorin was developed by the North Central Cancer Treatment Group16 and was administered before and after radiation. Chemotherapy (fluorouracil, 425 mg per square meter of body-surface area per day, and leucovorin, 20 mg per square meter per day, for 5 days) was initiated on day 1 and was followed by chemoradiotherapy beginning 28 days after the start of the initial cycle of chemotherapy. Chemoradiotherapy consisted of 4500 cGy of radiation at 180 cGy per day, five days per week for five weeks, with fluorouracil (400 mg per square meter per day) and leucovorin (20 mg	three years, and yearly thereafter. Follow-up consisted of physical examination, a complete blood count, liver-function testing, chest radiography, and CT scanning as clinically indicated. The site and date of the first relapse and the date of death, if the patient died, were recorded. Statistics The two stratification factors, the T stage (three levels) and the N stage (three levels), were included as covariates in the Cox regression analysis.20 The examination of other potential	of the 281 patients in the chemoradiotherapy group and 197 of the 275 patients in the surgery-only group died during the follow-up period. The hazard ratio for death in the surgery-only group, as compared with the chemoradiotherapy group, was 1.35 (95 percent confidence interval, 1.09 to 1.66; P=0.005). **Relapse-free Survival** This difference in relapse-free survival was significant (P<0.001 by a two-sided log-rank test). A total of 174 of the 281 patients	unclear- not described • allocation concealment: unclear- not described Performance bias • blinding: unclear but unlikely due to obvious difference between treatments Detection bias • blinding: unclear but unlikely due to obvious difference between treatments Attrition bias • outcome data complete Reporting bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
the survival of patients with resectable adenocarcinoma of the stomach or gastroesophageal junction. **Study dates** August 1, 1991, and July 15, 1998 **Source of funding** Supported in part by the following Public Health Service Cooperative Agreement grants from the National Cancer Institute: CA38926, CA-32102, CA35176, CA96429, CA15488, CA21661, CA25224, CA22433, CA04919, CA46441, CA20319, CA58348, CA46113, CA27057, CA- 45450, CA58882, CA46368, CA63844, CA04920, CA37981, CA58686,	concentration no more than 25 percent higher than the upper limit of normal; a hemogram within the normal limits; a bilirubin concentration no more than 50 percent higher than the upper limit of normal; a serum aspartate aminotransferase concentration no more than five times the upper limit of normal; and an alkaline phosphatase concentration no more than five times the upper limit of normal); a caloric intake greater than 1500 kcal per day by oral or enterostomal alimentation; registration between 20 and 41 days after surgery, with treatment beginning within 7 working days after registration; and the provision of written informed consent according to institutional and federal guidelines.	per square meter per day) on the first four and the last three days of radiotherapy. One month after the completion of radiotherapy, two five-day cycles of fluorouracil (425 mg per square meter per day) plus leucovorin (20 mg per square meter per day) were given one month apart. The dose of fluorouracil was reduced in patients who had grade 3 or 4 toxic effects. The 4500 cGy of radiation was delivered in 25 fractions, five days per week, to the tumor bed, to the regional nodes, and 2 cm beyond the proximal and distal margins of resection.	covariates (age, race, the extent [D level] of the dissection, and the location of the primary tumor) yielded no significant effects, and these variables were not included in the analysis. All eligible patients were included in the analyses of survival and relapse-free survival according to the intention-to-treat principle. The sites of relapse were classified as follows: the relapse was coded as local if tumor was detected in the surgical anastomosis, residual stomach, or gastric bed, as regional if tumor	in the chemoradiotherapy group and 206 of the 275 patients in the surgery-only group died or had a relapse during the follow-up period. The hazard ratio for relapse in the surgery-only group, as compared with the chemoradiotherapy group, was 1.52 (95 percent confidence interval, 1.23 to 1.86; P<0.001). **Adverse events, Grade 3/4 toxic effect** Reported only for the 273 in the CRT group not for the surgery only group Reported as N (%) Hematologic 148 (54)	• outcomes stated in the objective were reported Overall assessment: UNCLEAR risk of bias due to inadequate reporting of allocation concealment, randomization process and blinding. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
CA12644, CA42777, CA58416, CA46136, CA74647, CA76447, CA45- 461, CA45807, CA45377, CA58723, CA35176, CA63845, CA16385, CA52654, CA58415, CA35281, CA35192, CA76448, CA35261, CA67- 663, CA46282, CA12213, and CA31946.	**Exclusion criteria** No additional eligibility criteria.		was detected in the peritoneal cavity (including the liver, intraabdominal lymph nodes, and peritoneum), and as distant if the metastases were outside the peritoneal cavity. All eligible patients in the chemoradiotherapy group who rece	Gastrointestinal 89 (33) Influenza-like 25 (9) Infection 16 (6) Neurologic 12 (4) Cardiovascular 11 (4) Pain 9 (3) Metabolic 5 (2) Hepatic 4 (1) Lung-related 3 (1) Death 3 (1)	
Full citation Verheij, M., Jansen, E. P. M., Cats, A., V. an Grieken N.C.T, Aaronson, N. K., Boot, H., Lind, P. A., Kranenbarg, E. M. K., Nordsmark, M., Putter, H., Trip, A. K., V. an Sandick J.W, Sikorska, K., V. an Tinteren H, Van De Velde, C. J. H., A multicenter	**Sample size** n= 788(393 CT; 395 CRT) **Characteristics** Baseline characteristics were well balanced with 70% males and a median age of 61 years. 84% completed 3 cycles before surgery.	**Interventions** Neo-adjuvant CT was prescribed in both arms and consisted of 3 courses of epirubicin, cisplatin/oxaliplatin and capecitabine (ECC/EOC). Post-CT: received another 3 courses of ECC/EOC postoperatively Post-CRT: 45 Gy in 25 fractions combined with	**Details** Primary endpoint is OS; secondary endpoints are: disease free survival, toxicity profile and quality of life.	**Results** In the CT arm 46% and in the CRT arm 55% completed treatment according to protocol. After a median follow-up of 50 months, 405 patients have died. 5-year survival: CT: 41.3%	**Limitations** The quality assessment was based on conference abstract publication with support of protocol **Cochrane risk of bias tool** Selection bias • random sequence generation:

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
randomized phase III trial of neo-adjuvant chemotherapy followed by surgery and chemotherapy or by surgery and chemoradiotherapy in resectable gastric cancer: First results from the CRITICS study, Journal of Clinical OncologyJ Clin Oncol, 34, no pagination, 2016 **Ref Id** 486877 **Country/ies where the study was carried out** Netherlands, Sweden and Denmark **Study type** randomized phase III multicenter study **Aim of the study** To investigate whether chemoradiotherapy after	**Inclusion criteria** Patients with stage Ib-IVa resectable gastric cancer **Exclusion criteria**	weekly cisplatin and daily capecitabine		CRT: 40.9% (n=0.99) Haematological toxicity (grade 3 or higher) CT:44% CRT: 34%(p=0.01) GI toxicity (grade 3 or higher) CT: 37% CRT: 42%	unclear (did not even details in protocol) • allocation concealment: unclear Performance bias • blinding: unclear Detection bias • blinding: unclear Attrition bias • Unclear Reporting bias • outcomes stated in the objective were not reported: High risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
neo-adjuvant chemotherapy and adequate (D2) surgery leads to improved overall survival (OS) in comparison with postoperative chemotherapy **Study dates** January 2007 and April 2015 **Source of funding** Dutch Cancer Society (Data management) Roche Netherlands (Unrestricted Educational Grant)					Overall assessment: UNCLEAR/HIGH risk of bias due to inadequate reporting of allocation concealment, randomization process and blinding. **Other information**
Full citation Diaz-Nieto, R., Orti-Rodriguez, R., Winslet, M., Post-surgical chemotherapy versus surgery alone for	**Sample size** No of studies= 4 N= 878 **Characteristics**	**Interventions** Bouche 2005 Post-surgical chemo: 5-FU r500 mg/m2 + cisplatin 100 mg/m2 Chipponi 2004	**Details** Search methods	**Results** **Overall Survival** Bouche 2005 Surgery alone= 133, post-op chemo= 127,	**Limitations** Risk of bias of SR assessed using ROBIS checklist: Study Eligibility Criteria 1.Did the review adhere to pre-defined

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
resectable gastric cancer, Cochrane Database of Systematic ReviewsCochrane Database Syst Rev, 9, CD008415, 2013 **Ref Id** 489936 **Country/ies where the study was carried out** Multiple **Study type** Cochrane systematic review of RCTs **Aim of the study** To determine whether post-surgical chemotherapy should be used routinely in resectable gastric cancer. **Study dates** Search up to July 2013	Bouche 2005 Country= France N= 278 mean age= 61 Chipponi 2004 Country= France N= 205 mean age= 61 Di Costanzo 2008 Country= Italy N= 258 mean age= 59.0 Neri 2001 Country: Italy. Sample size: 137. Females: 39. Mean age: 63.0. **Inclusion criteria** Bouche 2005 • gastric adenocarcinoma • R0 Chipponi 2004 - resected gastric adenocarcinoma with no	Post-surgical chemo: leucovorin 200 mg/m2 + 5Fu 375 mg/m2 + cisplatin Di Costanzo 2008 post-surgical chemo: cisplatin 40 mg/m2 + leucovorin 100 mg/m2 + 5FU 300 mg/m2 Neri 2001 post-surgical chemo: Epidoxirubicin 75mg/m² + Leucovorin 200mg/m² + 5-FU 450mg/m²	We searched the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library*, MEDLINE, EMBASE, and Science Citation Index Expanded (July 2013). Selection criteria Randomised controlled trials (RCT) comparing post-surgical chemotherapy versus surgery alone for resectable gastric cancer. Data collection and analysis Two authors independently assessed trials for inclusion and	log(HR)= -0.3, (SE)= 0.16 Chipponi 2004 Surgery alone= 103, post-op chemo= 93, log(HR)= -0.01, (SE)= 0.17 Di Costanzo 2008 Surgery alone= 128, post-op chemo= 130, log(HR)= -0.11, (SE)= 0.17 Neri 2001 Surgery alone= 68, post-op chemo= 69, log(HR)= -0.42, (SE)= 0.14 **Disease-free Survival** Bouche 2005 Surgery alone= 133, post-op	objectives and eligibility criteria? Y 2.Were the eligibility criteria appropriate for the review question? Y 3.Were the eligibility criteria unambiguous? Y 4.Were all the restrictions on eligibility criteria based on study characteristics appropriate? Y 5.Were any restrictions in eligibility criteria based on sources of information available? Y 6.Concern regarding specification of study eligibility criteria: Low Identification and Selection of Studies 1.Did the search include an appropriate range of databases/electronic sources for published and unpublished reports? Y 2.Were the methods additional to database searching used to

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding	macroscopic margin involvement Di Costanzo 2008 • • resected gastric adenocarcinoma Neri 2001 - gastric adenocarcinoma **Exclusion criteria** Bouche 2005 • WHO performance status > 2 • linitis plastica • previous concurrent malignancy • previous chemo-radiotherapy • metastatic disease • contraindication to surgery or chemo Chipponi 2004 • previous malignancy		independently extracted the data.We analysed the data with both the fixedeffect and the random-effects models using the RevMan analysis software. We calculated the hazard ratio (HR) with 95% confidence interval (CI) based on intention-to-treat or available case analysis.	chemo= 127, log(HR)= -0.36, (SE)= 0.16 Chipponi 2004 NR Di Costanzo 2008 Surgery alone= 128, post-op chemo= 130, log(HR)= -0.08, (SE)= 0.17 Neri 2001 NR **Adverse Effects** Bouche 2005 Surgery alone= 133, post-op chemo= 127 Nausea and vomiting Surgery group= NR Post-op chemo group= 57	identify relevant reports? Y 3.Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible? PY 4.Were restrictions based on date, publication format or language appropriate? PY 5.Were efforts made to minimise error in selection of studies? Y 6.Concern regarding methods used to identify or select studies: LOW Data Collection and Study Appraisal 1.Were efforts made to minimise error in data collection? Y 2.were sufficient study characteristics available? Y 3.Were all relevant study results collected for use and synthesis? Y

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	• > 75 years old • previous chemo-radiotherapy • metastatic disease • contraindication for surgery or chemotherapy <u>Di Costanzo 2008</u> ->75 years old. -Performance Status >2. -Previous malignancy. -Previous chemo-radiotherapy. -Metastatic disease. -Contraindication for surgery or chemotherapy. <u>Neri 2001</u> -Karnofsky index < 60.			<u>Chipponi 2004</u> Surgery alone= 103, post-op chemo= 93 Aneamia surgery group= NR post-op chemo group= 10 Leukopenia surgery group= NR post-op chemo group= 24 Thrombopenia surgery group= NR post-op chemo group= 13 Nausea and vomiting surgery group= NR post-op chemo group= 29 <u>Di Costanzo 2008</u> Surgery alone= 128, post-op chemo= 130	4.Was risk of bias formally assessed using appropriate criteria? Y 5.Were efforts made to minimise error in risk of bias assessment? Y 6.Concern: LOW Synthesis and Findings 1.Did the synthesis include all studies it should? Y 2.Were all pre-defined analyses reported and departures explained? Y 3.Was the synthesis appropriate given the nature and similarity in the research questions? Y 4.Was heterogeneity minimal or addressed? Y 5.Were the findings robust as demonstrated though funnel plot or sensitivity analysis? Y 6.Were biases in primary studies minimal or addressed in the synthesis? Y

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	-Metastatic disease. -Contraindication for surgery or chemotherapy.			Aneamia surgery group= NR post-op chemo group= 4 Leukopenia surgery group= NR post-op chemo group= 24 Thrombopenia surgery group= NR post-op chemo group= 5 Nausea and vomiting surgery group= NR post-op chemo group= 25 Neri 2001 Surgery alone= 68, post-op chemo= 69 Aneamia surgery group= NR post-op chemo group= 3	7.Concern= LOW Risk of bias in the review 1.Did the interpretation of findings address all the concerns identifies in 1-4? Y 2.Was the relevance of identified studies to the review's research question appropriately considered? Y 3.Did the reviewers avoid emphasizing results on the basis of their statistical significance? Y 4. Risk of bias= LOW Risk of bias of individual studies extracted from the SR: Bouche 2005 Random sequence generation: unclear risk Allocation concealment (selection bias): Unclear risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Leukopenia surgery group= NR post-op chemo group= 6 Thrombopenia surgery group= NR post-op chemo group= 2 Nausea and vomiting surgery group= NR post-op chemo group= 44	Blinding (performance bias and detection bias): High risk Incomplete outcome data (attrition bias): Unclear risk Selective reporting (reporting bias): Low risk Other bias: Low risk (Adequate base balance) Chipponi 2004 Random sequence generation: low risk Allocation concealment (selection bias): Unclear risk Blinding (performance bias and detection bias): High risk Incomplete outcome data (attrition bias): Unclear risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					Selective reporting (reporting bias): Low risk Other bias: high risk (early stopping bias) Di Costanzo 2008 Random sequence generation: unclear risk Allocation concealment (selection bias): Unclear risk Blinding (performance bias and detection bias): High risk Incomplete outcome data (attrition bias): high risk Selective reporting (reporting bias): Low risk Other bias: Low risk (Adequate base balance) Neri 2001 Random sequence generation: unclear risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					Allocation concealment (selection bias): Unclear risk Blinding (performance bias and detection bias): High risk Incomplete outcome data (attrition bias): unclear risk Selective reporting (reporting bias): Low risk Other bias: unclear risk **Other information** The following studies included in the Cochrane review did not meet the review protocol: Allum 1989- outside date range

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					Bajetta 2002- etoposide not in protocol Bonfanti 1988- outside date range Chou 1994- ftorafur not in protocol Cirera 1999- tegafur and mitcomycin not in protocol Coombes 1990- mitomycin not in protocol De Vitta 2007- etoposide not in protocol Douglas 1982- outside date range Engstrom 1985- outside date range Fielding 1983- outside date range Fujimoto 1977- outside date range Grau 1993- mitomycin not in protocol Hallissey 1994- mitomycin not in protocol Higgins 1983- outside date range

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					Huguier 1980- outside date range Kim 1992- mitomycin not in protocol Krook 1991- doxorubicin not in protocol Kulig 2010- doxorubicin not in protocol Lise 1995- doxorubicin and mitomycin not in protocol Macdonald 1995- doxorubicin not in protocol Nakajima 1999- tegafur and mitomycin not in protocol Nashimoto 2003- mitomycin not in protocol Nitti 2006- chemo regime not in protocol Ochiai 1983- outside date range Popiela 1982- outside date range Sakuramoto 2007- tegafur not in protocol Tentes 2006- chemo regime not in protocol

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Imano, M., Itoh, T., Satou, T., Sogo, Y., Hirai, H., Kato, H., Yasuda, A., Peng, Y. F., Shinkai, M., Yasuda, T., Imamoto, H., Okuno, K., Shiozaki, H., Ohyanagi, H., Prospective randomized trial of short-term neoadjuvant chemotherapy for advanced gastric cancer, European Journal of Surgical OncologyEur J Surg Oncol, 36, 963-8, 2010 **Ref Id** 487385 **Country/ies where the study was carried out** Japan	**Sample size** N=63 **Characteristics** 41 male: 22 female mean age= 58.4-61.5 years **Inclusion criteria** All patients had to have histologically proven and clinical resectable gastric cancer, and had to be younger than 75 years of age. Patients were also required to have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 1 or better and to fulfill the following criteria: WBC count 4000/mL hemoglobin	**Interventions** All eligible patients were randomized to four groups: Group F, 16 cases who received a single administration of 5-fluorouracil (5-FU); Group C, 15 cases who received a single administration of cis-diamminedichloroplatinum (CDDP; cisplatin); Group FC, 16 cases who received both 5-FU and CDDP; and a Control group, 16 cases who did not receive chemotherapy. CT We administered 5-FU (330 mg/m2/24 h) by continuous intravenous	**Details** Statistics Data are shown as mean standard error. Statistical differences were assessed by t-test and chi-square test. The survival was estimated by KaplaneMeier methods and the comparison of curves was made using the long-rank test. A difference of $P < 0.05$ was considered significant.	**Results** **Overall survival** No differences between groups. Data reported graphically and narratively only (no figures reported). **Operative complications** Anastomotic leakage Control group: 0/16 F group: 0/16 C group: 0/15 FC group: 0/16 Surgical site infection Control group: 0/16 F group: 0/16 C group: 1/15 FC group: 0/16	**Limitations** **Cochrane risk of bias tool** Selection bias • random sequence generation: unclear- not described • allocation concealment: low risk Performance bias • blinding: unclear but unlikely due to obvious difference between treatments Detection bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type RCT **Aim of the study** We performed short-term neoadjuvant chemotherapy (s-NAC) to examine whether anticancer drugs can change the proliferative ability of cancer cells in gastric cancer patients. **Study dates** 1992 and 2002 **Source of funding** None reported	9.5 g/dL, platelets 100,000/mL, AST and ALT within three times the upper limit, bilirubin 2.0 mg/dL, serum blood urea nitrogen 25 mg/dL, creatinine 1.5 mg/dL, and a creatinine clearance 50 mL/min. **Exclusion criteria** Patients with serious complications and active carcinoma at other sites were excluded.	administration for 72 h starting from 80 h before operation. CDDP (6 mg/m2/each time) was administered three times before the operation for 30 min at 68 h, 44 h, and 20 h in each case. In brief, 5-Fu administration finished 8 h and CDDP administration finished 19.5 h before starting of operation. Surgery The surgical procedure was either total gastrectomy for proximal tumors or subtotal gastrectomy when the primary tumor was located distally in the stomach, with a 5 cm safe margin. In all cases an en-bloc D2 lymph node dissection was		Post-op pneumonia Control group: 1/16 F group: 0/16 C group: 0/15 FC group: 0/16	• blinding: unclear but unlikely due to obvious difference between treatments Attrition bias • outcome data complete Reporting bias • outcomes stated in the objective were reported Overall assessment: UNCLEAR risk of bias due to inadequate reporting of randomization process and blinding. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
		performed according to the JRSGC guidelines			
Full citation Miyashiro, I., Furukawa, H., Sasako, M., Yamamoto, S., Nashimoto, A., Nakajima, T., Kinoshita, T., Kobayashi, O., Arai, K., Gastric Cancer Surgical Study Group in the Japan Clinical Oncology, Group, Randomized clinical trial of adjuvant chemotherapy with intraperitoneal and intravenous cisplatin followed by oral fluorouracil (UFT) in serosa-positive gastric cancer versus curative resection alone: final results of the Japan Clinical Oncology Group	**Sample size** n=268(135 in adjuvant CT vs 133 in surgery alone) **Characteristics** Median age: 57 (23-73) years in surgery alone vs 59 (33-75) in Surgery +CT (p=0.043) Male%= 182 (68%) T3/T4%=176(66%) Histology: Papillary=3; Well differenitated=22; Moderately differentiated=68; Poorly differetiated=136; Mucinous=11; Signet ring cell=26 **Inclusion criteria**	**Interventions** CT ; intraperitoneal cisplatin (70mg/m2) soon after abdominal closure; IV cisplatin (70 mg/m2) on post op day 14; IV 5FU (700 mg.m2\) on postop days 14-16 and UFT (267 mg/m2) starting 4 weeks after surgery for 12 months. IP cisplatin (70 mg/m2) also given via drainage tube.	**Details** Patients were randomised with minimization method and stratified by instiution T or N category when found eligible at surgery. The primary end point was Overall survival (date of randomisation to date of death or censored at the date of last follow-up). Relapse-free interval (from date of randomisation to date of first observation of relapse or date of death from any	**Results** **Grade 3-4 leukopenia** Surgery:0/127 Surgery+CT: 4/129	**Limitations** **Cochrane risk of bias tool** Selection bias • random sequence generation: low • allocation concealment: unclear, centrally randomized but concealment not described Performance bias • blinding: unclear but unlikely Detection bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
trial JCOG9206-2, Gastric CancerGastric Cancer, 14, 212-8, 2011 **Ref Id** 487579 **Country/ies where the study was carried out** Japan **Study type** multicenter prospective randomised controlled phase III clinical trial **Aim of the study** To evaluate the survival benefit of adjuvant chemotherapy after curative resection in serosa-positive gastric cancer, a multicenter phase III clinial trial **Study dates** January 1993 to March 1998	• macroscopically complete operation • histologically proven gastric adenocarcinoma • macroscopically serosa-positive T3-4 with no metastases to level 3-4 lymph node stations • no previous treatment for gastric cancer • negative peritoneal cytology • adequate organ function assessed by lab studies **Exclusion criteria** • patients who underwent any chemotherapy or radiotherapy • those with synchronous or		caure) and site of recurrence were also collected. 140 patients in each arm was required (80% power) to detect 15% differece in 5-year OS rate between surgery group (40%) and CT arm (55%)		• blinding: unclear but unlikely Attrition bias • outcome data complete Reporting bias • outcomes stated in the objective were reported Overall assessment: UNCLEAR risk of bias due to inadequate reporting of allocation concealment and blinding. **Other information** Data being extracted in Yan 2007 SR

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding grants for Cancer Reserch and the Second-term Comprehensive 10-year strategy for cancer control	metachronous cancer of other organs				
Full citation Wu, A. W., Xu, G. W., Wang, H. Y., Ji, J. F., Tang, J. L., Neoadjuvant chemotherapy versus none for resectable gastric cancer, Cochrane Database of Systematic ReviewsCochrane Database Syst Rev, 2007 **Ref Id** 476577 **Country/ies where the study was carried out**	**Sample size** No of studies= 3 N= **Characteristics** Kobayashi 2000 resectable gastric cancer, 65 male, 26 female Wang 2000 resectable gastric cardia cancer, 23 male, 7 female **Inclusion criteria** Of the SR:	**Interventions** Kobayashi 2000 5'-DFUR 610mg/m2 Wang 2000 FPLC 20 ml bid po	**Details** Search strategy Electronic databases including Cochrane Library, MEDLINE, EMBASE, CancerLit, Chinese Biomedical Literature Database (CBMDISC) and ongoing clinical trials as well as	**Results** **Death at the end of follow-up** Kobayashi 2000 NAC: 34/91 control: 29/80 Wang 2000 NAC: 18/30 control: 23/30 **R0 resection** Kobayashi 2000 NAC: 74/91 control: 66/80 **Grade II-IV toxicity** Kobayashi 2000 NAC: 5/27 control: 0/1	**Limitations** Risk of bias of SR assessed using ROBIS checklist: Study Eligibility Criteria 1.Did the review adhere to pre-defined objectives and eligibility criteria? Y 2.Were the eligibility criteria appropriate for the review question? Y 3.Were the eligibility criteria unambiguous? Y 4.Were all the restrictions on eligibility criteria based on study characteristics appropriate? Y

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Multiple **Study type** Cochrane SR of RCTs. **Aim of the study** To evaluate the effect of neoadjuvant chemotherapy versus none for patients with resectable gastric cancer in terms of efficacy and toxicity. **Study dates** Search up to June 2005 **Source of funding**	All randomized controlled trials were considered for inclusion. It is not possible to do placebo controlled or blinded in a study comparing neoadjuvant treatment to no neoadjuvant treatment. The control group consisted of gastric cancer patients undergoing surgical resection without preoperative chemotherapy or radiotherapy. For this review, abstracts or unpublished data were included. If there was sufficient information on study designs, geographic location of the studies, characteristics of participants including TNM stage and interventions and outcomes, the final results were confirmed by contacting the study's first author. Trials that related solely to the gastroesophageal junction were excluded.		handsearching of conference proceedings, were searched to retrieve relevant data. Selection criteria Randomized controlled clinical trials of neoadjuvant chemotherapy on resectable gastric cancer. Data collection and analysis We identified a total of 36 published citations or meeting abstracts. Thirty-two items were excluded. Of the four remaining studies, three stated random allocation but the method of		5.Were any restrictions in eligibility criteria based on sources of information available? Y 6.Concern regarding specification of study eligibility criteria: Low Identification and Selection of Studies 1.Did the search include an appropriate range of databases/electronic sources for published and unpublished reports? Y 2.Were the methods additional to database searching used to identify relevant reports? Y 3.Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible? PY 4.Were restrictions based on date, publication format or language appropriate? PY

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Exclusion criteria Of the SR: Studies enrolling oesophageal carcinoma patients and stage IV with M1 and recurrent cancer patients were excluded except where definite results from gastric cancer subgroups conforming to the inclusion criteria were given.		randomization was unclear. Two of these employed allocation concealment by sealed envelope which was controlled by an independent party. None of the trials was double blind. All trials presented a detailed description of the number of withdrawals, dropouts and losses to follow-up.		5.Were efforts made to minimise error in selection of studies? Y 6.Concern regarding methods used to identify or select studies: LOW Data Collection and Study Appraisal 1.Were efforts made to minimise error in data collection? Y 2.were sufficient study characteristics available? Y 3.Were all relevant study results collected for use and synthesis? Y 4.Was risk of bias formally assessed using appropriate criteria? Y 5.Were efforts made to minimise error in risk of bias assessment? Y 6.Concern: LOW Synthesis and Findings 1.Did the synthesis include all studies it should? Y

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					2.Were all pre-defined analyses reported and departures explained? Y 3.Was the synthesis appropriate given the nature and similarity in the research questions? Y 4.Was heterogeneity minimal or addressed? Y 5.Were the findings robust as demonstrated though funnel plot or sensitivity analysis? Y 6.Were biases in primary studies minimal or addressed in the synthesis? Y 7.Concern= LOW Risk of bias in the review 1.Did the interpretation of findings address all the concerns identifies in 1-4? Y 2.Was the relevance of identified studies to the review's research

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					question appropriately considered? Y 3.Did the reviewers avoid emphasizing results on the basis of their statistical significance? Y 4. Risk of bias= LOW Risk of bias of individual studies extracted from the Cochrane SR: Kobayashi 2000 Random allocation- unclear Allocation concealment- low risk Blinding- high risk Wang 2000 Random allocation- unclear Allocation concealment- high risk Blinding- high risk **Other information** The following studies were not relevant to review question:

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					Nio 2004- chemo outside protocol Hartgrink 2004- methotrexate not included in protocol
Full citation Zhou, M. L., Kang, M., Li, G. C., Guo, X. M., Zhang, Z., Postoperative chemoradiotherapy versus chemotherapy for R0 resected gastric cancer with D2 lymph node dissection: an up-to-date meta-analysis, World Journal of Surgical OncologyWorld J Surg Oncol, 14, 209, 2016 **Ref Id** 516832 **Country/ies where the study was carried out** multiple	**Sample size** No of studies= 4 N= 960 **Characteristics** Kwon 2010 N= 61 mean age= 49-56 44 male/ 17 female Kim 2010 N= 90 mean age= NR 59 male/ 31 female Zhu 2012 N= 351 mean age= 56-59 261 male/ 90 female Lee 2012 (ARTIST trial)	**Interventions** Kwon 2010 CRT: FP/RT CT: FP Details extracted from Kwon 2010 RCT: Arm A patients received one cycle of FP chemotherapy (5-FU 1000 mg/m2 continuous infusion on day 1–5, cisplatin 60 mg/m2 on day 1) followed by regional radiotherapy with capecitabine beginning 28 days after the beginning of the initial cycle of chemotherapy. Four weeks after the completion of radiotherapy, the patients received three additional cycles of the FP regimen	**Details** We conducted a systematic review of randomized controlled trials (RCTs), extracted data of survival and toxicities, and pooled data to evaluate the efficacy and toxicities of CRT compared with chemotherapy (CT) after D2 lymphadenectomy	**Results** **Disease-free survival** Kwon 2010 N=61 Log HR= -0.56, SE= 0.46, HR (95% CI)= 0.57 (0.23-1.41) Kim 2010 N=90 Log HR= -0.36, SE= 0.31, HR (95% CI)= 0.70 (0.38-1.28) Zhu 2012 N=351 Log HR= -0.3, SE= 0.14, HR (95% CI)= 0.74 (0.56-0.97) Lee 2012 (ARTIST trial)	**Limitations** Quality assessment of SR using ROBIS checklist: Study Eligibility Criteria 1.Did the review adhere to pre-defined objectives and eligibility criteria? PY- limited detail on eligibility criteria 2.Were the eligibility criteria appropriate for the review question? Y 3.Were the eligibility criteria unambiguous? NI 4.Were all the restrictions on eligibility criteria based on study characteristics appropriate? NI

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type SR of RCTs **Aim of the study** This meta-analysis aims to provide more evidence on the role of postoperative chemoradiotherapy (CRT) for gastric cancer (GC) patients in Asian countries where D2 lymphadenectomy is prevalent. **Study dates** Search up to July 2015. **Source of funding** none.	N= 458 mean age= 56 295 male/ 162 female **Inclusion criteria** Inclusion criteria of the SR: All RCTs that compared CRT with CT in postoperative treatment for R0 resected GC with D2 lymphadenectomy were included in this meta-analysis. **Exclusion criteria** Exclusion criteria of the SR: preoperative CT or CRT is not allowed	every 3 weeks. A total dose of 4500 cGy in 25 fractions over 5 weeks was delivered to the target volume including the gastric bed, anastomosis, stump, and regional lymph node areas. Arm B patients received 6 cycles of FP every 3 weeks. Kim 2010 CRT: FL/RT CT: FL Details extracted from Kim 2010 RCT: In the CT arm, patients received 5 cycles of the FL regimen (fluorouracil 425 mg/m2 and leucovorin 20 mg/m2, for 5 days with a 4-week interval) from 3 to 7 weeks after surgery. In the CRT arm, patients received 1 cycle of FL (fluorouracil 425 mg/m2		N=458 Log HR= -0.3, SE= 0.18, HR (95% CI)= 0.74 (0.52-1.05) **Overall survival** Kwon 2010 N=61 Log HR= -0.11, SE= 0.43, HR (95% CI)= 0.90 (0.39-2.08) Kim 2010 N=90 Log HR= -0.14, SE= 0.33, HR (95% CI)= 0.87 (0.46-1.66) Zhu 2012 N=351 Log HR= -0.21, SE= 0.14, HR (95% CI)= 0.81 (0.62-1.07) Lee 2012 (ARTIST trial) N=458 Log HR= 0.12, SE= 0.19,	5.Were any restrictions in eligibility criteria based on sources of information available? Y 6.Concern regarding specification of study eligibility criteria: Unclear Identification and Selection of Studies 1.Did the search include an appropriate range of databases/electronic sources for published and unpublished reports? Y 2.Were the methods additional to database searching used to identify relevant reports? Y 3.Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible? PY 4.Were restrictions based on date, publication format or language appropriate? PY

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
		and leucovorin 20 mg/m2, for 5 days), then RT (45 Gy of radiation at 1.8 Gy per day, 5 days per week) with 2 cycles of FL (fluorouracil 400 mg/m2 and leucovorin 20 mg/m2, for the first 4 days of the first week of RTand for the first 3 days of the fifth week of RT) after the start of the first cycle of FL, followed by the 2 additional cycles of FL (fluorouracil 425 mg/m2 and leucovorin 20 mg/m2, for 5 days with 4-week intervals) at 3 weeks after completion of RT. Zhu 2012 CRT: FL/IMRT CT: FL Lee 2012 (ARTIST trial) CRT: XP/XRT/XP CT: XP Details extracted from Lee 2012 RCT: In the chemotherapy arm, patients received six		HR (95% CI)= 1.13 (0.78-1.64) **Adverse Events, Grade III or IV** Nausea/Vomiting Kwon 2010 CRT: 2/31 CT: 4/30 Zhu 2012 CRT: 8/186 CT: 0/165 Lee 2012 (ARTIST trial) CRT: 35/230 CT: 32/228 Diarrhoea Kwon 2010 CRT: 1/31 CT: 0/30 Zhu 2012 CRT: 3/186 CT: 0/165 Lee 2012 (ARTIST trial) CRT: 2/230 CT: 5/228 Neutropenia Kwon 2010 CRT: 15/31	5.Were efforts made to minimise error in selection of studies? Y 6.Concern regarding methods used to identify or select studies: LOW Data Collection and Study Appraisal 1.Were efforts made to minimise error in data collection? Y 2.were sufficient study characteristics available? Y 3.Were all relevant study results collected for use and synthesis? Y 4.Was risk of bias formally assessed using appropriate criteria? Y 5.Were efforts made to minimise error in risk of bias assessment? Y 6.Concern: LOW Synthesis and Findings 1.Did the synthesis include all studies it should? Y

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
		cycles of the XP regimen (capecitabine 1,000 mg/m2 twice daily on days 1 to 14 cisplatin 60 mg/m2 on day 1 every 3 weeks). Patients assigned to the XP/XRT/XP arm received two cycles of XP (capecitabine 1,000 mg/m2 twice daily n days 1 to 14; cisplatin 60 mg/m2 on day 1 every 3 weeks), then XRT (45 Gy of radiation at 1.8 Gy per day, 5 days per week, for 5 weeks with continuous capecitabine 825 mg/m2 twice daily during radiotherapy), followed by two additional cycles of XP (capecitabine 1,000 mg/m2 twice daily on days 1 to 14; cisplatin 60 mg/m2 on day 1 every 3 weeks).		CT: 5/30 Zhu 2012 CRT: 14/186 CT: 12/165 Lee 2012 (ARTIST trial) CRT: 110/230 CT: 92/228 Anemia Kwon 2010 CRT: 4/31 CT: 5/30 Zhu 2012 CRT: 0/186 CT: 0/165 Lee 2012 (ARTIST trial) CRT: 1/230 CT: 4/228 Thrombocytopenia Zhu 2012 CRT: 0/186 CT: 0/165 Lee 2012 (ARTIST trial) CRT: 2/230 CT: 0/228	2.Were all pre-defined analyses reported and departures explained? Y 3.Was the synthesis appropriate given the nature and similarity in the research questions? Y 4.Was heterogeneity minimal or addressed? Y 5.Were the findings robust as demonstrated though funnel plot or sensitivity analysis? Y 6.Were biases in primary studies minimal or addressed in the synthesis? Y 7.Concern= LOW Risk of bias in the review 1.Did the interpretation of findings address all the concerns identifies in 1-4? Y 2.Was the relevance of identified studies to the review's research

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					question appropriately considered? Y 3.Did the reviewers avoid emphasizing results on the basis of their statistical significance? Y 4. Risk of bias= LOW Quality of individual studies extracted from the SR: Kwon 2010 random sequence generation: unclear risk of bias allocation concealment: unclear risk of bias blinding: low risk of bias incomplete outcome data: low risk of bias selective reporting: low risk of bias other: low risk of bias Kim 2010 random sequence generation: unclear risk of bias allocation concealment: unclear risk of bias blinding: low risk of bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					incomplete outcome data: low risk of bias selective reporting: high risk of bias (no details on toxicities) other: low risk of bias Zhu 2012 random sequence generation: unclear risk of bias allocation concealment: unclear risk of bias blinding: low risk of bias incomplete outcome data: low risk of bias selective reporting: low risk of bias other: low risk of bias Lee 2012 (ARTIST trial) random sequence generation: unclear risk of bias allocation concealment: unclear risk of bias blinding: low risk of bias incomplete outcome data: low risk of bias selective reporting: low risk of bias other: low risk of bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					Other information
Full citation Feingold, P. L., Kwong, M. L. M., Davis, J. L., Rudloff, U., Adjuvant intraperitoneal chemotherapy for the treatment of gastric cancer at risk for peritoneal carcinomatosis: A systematic review, Journal of Surgical OncologyJ Surg Oncol, 115, 192-201, 2017 **Ref Id** 589137 **Country/ies where the study was carried out** USA **Study type** Systematic review	**Sample size** Number of studies included: 9 N = 1583 **Characteristics** <u>Fujimoto 1999</u> N = 141 Stage I-III: n = 120 Stage IV: n = 21 <u>Fujimura 1994</u> N = 58 Stage I-III: n = 40 Stage IV: n = 18 <u>Hamazoe 1994</u> N = 82 Stage I-III: n = 71 Stage IV: n = 11 <u>Ikeguchi 1995</u> N = 174 Stage I-III: n = 140 Stage IV: n = 34	**Interventions** <u>Fujimoto 1999</u> Intervention: surgery plus adjuvant heated intraperitoneal Mitomycin c 10µg/ml in 3-4L Comparator: surgery plus systemic chemotherapy (not otherwise specified) <u>Fujimura 1994</u> Intervention: surgery plus 300mg cisplatin and mitomycin c as either heated or normothermic intraperitoneal chemotherapy (2 subgroups) Comparator: surgery alone <u>Hamazoe 1994</u> Intervention: surgery plus heated intraperitoneal mitomycin c 10µg/ml Comparator: surgery alone	**Details** A systematic search of the literature was conducted using Pubmed and Cochrane databases for articles published between 1st January 1960 and 31st August 2015. Articles considering the use of intraperitoneal chemotherapy for gastric cancer were considered for inclusion. Titles and abstracts were screened for eligibility by two researchers, according to the exclusion criteria listed.	**Results** **<u>Overall survival</u>** <u>Fujimoto 1999</u> 2 year survival: 88% for hyperthermic IP chemo group versus 77% for surgery plus systemic chemo 4 year survival: 76% for hyperthermic IP chemo group versus 58% for surgery plus systemic chemo 8 year survival: 62% for hyperthermic IP chemo group versus 49% for surgery plus systemic chemo <u>Fujimura 1994</u>	**Limitations** Risk of bias of SR assessed using ROBIS checklist: <u>Study Eligibility Criteria</u> 1.Did the review adhere to pre-defined objectives and eligibility criteria? PY 2.Were the eligibility criteria appropriate for the review question? Y 3.Were the eligibility criteria unambiguous? N - inclusion criteria are not fully described 4.Were all the restrictions on eligibility criteria based on study characteristics appropriate? Y 5.Were any restrictions in eligibility criteria based on sources of information available? Y

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study To evaluate the use of adjuvant intraperitoneal chemotherapy in patients with resectable gastric cancer. **Study dates** Inclusion dates for searches: 1/1/1960 to 31/8/2015 **Source of funding** Not reported	Kang 2014 N = 521 Stage I-III: n = 431 Stage IV: n = 90 Miyashiro 2011 N = 268 Stage I-III: n = 266 Stage IV: n = 2 Shimoyama 1999 N = 87 Stage I-III: n = 85 Stage IV: n = 2 Takahashi 1995 N = 113 (stage not reported) Yonemura 2001 N = 139 Stage I-III: n = 102 Stage IV: n = 37 **Inclusion criteria** Not reported.	Ikeguchi 1995 Intervention: surgery plus heated intraperitoneal mitomycin c 80-100mg/m², plus systemic chemotherapy (IV mitomycin c 10mg on day 7 and 14, oral 1-(2-tetrahydrofuryl)-5-fluorouracil/uracil (1:4) [UFT] 600mg per day from day 14 to 6 months) Comparator: surgery plus systemic chemotherapy (IV mitomycin 10mg on day 0, 7 and 14, oral UFT 600mg per day from day 14 to 6 months) Kang 2014 Intervention: surgery plus normothermic intraperitoneal cisplatin 100mg in 1L x 2 hr, plus systemic chemotherapy (IV mitomycin c, oral doxifludridine, IV cisplatin) Comparator: surgery plus systemic chemotherapy	Data extracted from included articles comprised: author, date, number of participants, stage of disease, type of intraperitoneal chemotherapy administered, toxicity, follow up, outcome data, disease-free survival, overall survival and peritoneal recurrence-free survival. Study arms with the most frequently reported outcome measures (such as five-year survival) were selected and compared using pooled odds ratios with random effects models.	1 year survival: 95% hyperthermic IP chemo; 81% normothermic IP chemo; 43% surgery alone 2 year survival: 89% hyperthermic IP chemo; 75% normothermic IP chemo; 23% surgery alone 3 year survival: 68% hyperthermic IP chemo; 51% normothermic IP chemo; 23% surgery alone Hamazoe 1994 5 year survival: 64.3% hyperthermic IP chemo versus 52.5% for surgery alone Median overall survival: 77 months for hyperthermic IP chemo group	6.Concern regarding specification of study eligibility criteria: Low Identification and Selection of Studies 1.Did the search include an appropriate range of databases/electronic sources for published and unpublished reports? PY 2.Were the methods additional to database searching used to identify relevant reports? Y 3.Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible? PY 4.Were restrictions based on date, publication format or language appropriate? Y 5.Were efforts made to minimise error in selection of studies? Y

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Exclusion criteria Exclusion criteria for articles in the review Non-English language publication Study designs other than RCTs (for the purposes of this evidence review) Participants with established carcinomatosis, or articles focused on other malignancies (ovarian or appendiceal) No report of patient outcome data Studies including more than 50% of patients with established peritoneal carcinomatosis Preclinical or phase 1 studies, or conference abstracts Use of a non-chemotherapeutic IP agent such as immune or radiation therapy Use of neoadjuvant systemic chemotherapy (n.b. specific inclusion/exclusion criteria	(IV mitomycin c, oral doxifludridine and mitomycin c) Miyashiro 2011 Intervention: surgery plus normothermic cisplatin 70mg/m² x 2 hr Comparator: surgery plus IV cisplatin 70mg/m² on day 14, 5 fluorouracil 700mg/m² daily from day 14-16, oral UFT daily from 4 weeks to 12 months. Shimoyama 1999 Intervention: surgery plus normothermic intraperitoneal mitomycin c 10mg, plus systemic chemotherapy (IV cisplatin and UFT) Comparator: surgery plus IV cisplatin and UFT Takahashi 1995 Intervention: surgery plus normothermic intraperitoneal mitomycin c 50mg in 100ml, and		versus 66 months for surgery alone Ikeguchi 1995 5 year survival: 51% hyperthermic IP chemo group versus 46% surgery alone Kang 2014 3 year survival: 71% for normothermic IP chemo group versus 60% for surgery plus systemic chemo group 5 year survival: 59% for normothermic IP chemo group versus 50% for surgery plus systemic chemo group Miyashiro 2011 5 year survival: 62.0% for	6.Concern regarding methods used to identify or select studies: LOW Data Collection and Study Appraisal 1.Were efforts made to minimise error in data collection? PY 2.were sufficient study characteristics available? Y 3.Were all relevant study results collected for use and synthesis? Y 4.Was risk of bias formally assessed using appropriate criteria? N 5.Were efforts made to minimise error in risk of bias assessment? N/A 6.Concern: HIGH Synthesis and Findings 1.Did the synthesis include all studies it should? Y 2.Were all pre-defined analyses reported and

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	for the individual studies are not reported).	activate carbon particles 375mg x 3hr Comparator: surgery alone Yonemura 2001 Intervention: surgery plus normothermic or heated intraperitoneal mitomycin c 30mg and cisplatin 300mg (2 groups) Comparator: surgery alone		normothermic IP chemo versus 60.9% for surgery plus systemic chemo group Shimoyama 1999 1 year survival: 94% for normothermic IP chemo group (diffuse type) versus 81% for surgery and systemic chemotherapy (diffuse type) 4 year survival: 73% for normothermic IP chemo group versus 32% (diffuse type) for surgery and systemic chemotherapy (diffuse type) Takahashi 1995 2 year survival: 66% for	departures explained? PY 3.Was the synthesis appropriate given the nature and similarity in the research questions? Y 4.Was heterogeneity minimal or addressed? Y 5.Were the findings robust as demonstrated though funnel plot or sensitivity analysis? N/A 6.Were biases in primary studies minimal or addressed in the synthesis? N 7.Concern= LOW Risk of bias in the review 1.Did the interpretation of findings address all the concerns identifies in 1-4? Y 2.Was the relevance of identified studies to the review's research question appropriately considered? Y

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				normothermic IP chemo group versus 35% for surgery alone 3 year survival: 66% normothermic IP chemo group versus 20% for surgery alone Yonemura 2001 5 year survival: 61% for hyperthermic IP chemo group; 44% normothermic IP chemo group; 42% surgery alone **Disease free survival** Miyashiro 2011 5 year disease free survival: 57.5% for normothermic IP chemo group versus 55.6% for surgery plus systemic chemo group	3.Did the reviewers avoid emphasizing results on the basis of their statistical significance? Y 4. Risk of bias= LOW **Other information** The following studies included in this systematic review did not meet the review protocol or provide sufficient details for this evidence report: Atiq 1993: non-comparative study Hirose 1999: case control study Jones 1994: non-comparative study Kaibara 1989: published outside of date criteria Koga 1988: published outside of date criteria Rosen 1998: the outcomes were reported in median only

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					Sautner 1995: post-operative intraperitoneal chemotherapy Topuz 2002: non-comparative study Yu 2001: post-operative intraperitoneal chemotherapy
Full citation Kodera, Y., Takahashi, N., Yoshikawa, T., Takiguchi, N., Fujitani, K., Ito, Y., Miyamoto, K., Takayama, O., Imano, M., Kobayashi, D., Miyashita, Y., Morita, S., Sakamoto, J., Feasibility of weekly intraperitoneal versus intravenous paclitaxel therapy delivered from the day of radical surgery for gastric cancer: a preliminary safety analysis of the INPACT study, a randomized controlled trial, Gastric	**Sample size** n=86 **Characteristics** Age median (range)= ~67 (26-86) years Male %= 60/83 Large type 3/4 = 64/83 Total gastrectomy % = 58/83 R0 resection= 20/39 in IPC vs 26/44 in IVC **Inclusion criteria** • Patients with resectable advanced gastric	**Interventions** Surgery: total or partial gastrectomy with D2 lymph node dissection Intraperitoneal chemotherapy (IPC): 60 mg/m2 paclitaxel on postop day 1, 15, 22, 29, 43, 50 and 57; dissolved in 1L saline Intravenous chemotherapy (IVC); 80 mg/m2 paclitaxcel on postop day 1, 15, 22, 29, 43, 50 and 57	**Details** On laparotomy, patients were randomised by a centralised dynamic method balancing following variables: macroscopic type (type 3 and 4/others), curability of surgery (R0 and R1/R2), age (<75/75/>75 years) and institution. The primary end point was the 2-year survival rate.The prior sample size was 90 to find the	**Results** 86 patients were randomised. Out of 41 patients randomised to IPC group, two refused and the other 39 were included in the analyses. Out of 45 patients randomised to IVC group, one was not resected due to overt peritoneal metastases and excluded from the analyses. 29 in IPC group and 32 in IVC group had	**Limitations** **<u>Cochrane risk of bias tool</u>** Selection bias • random sequence generation: Yes • allocation concealment: Yes Performance bias • blinding: unclear Detection bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
CancerGastric Cancer, 20, 190-199, 2017 **Ref Id** 589168 **Country/ies where the study was carried out** Japan **Study type** RCT **Aim of the study** To evaluate the intraperitoneal versus intravenous administration of paclitaxel that begins on the day of radical surgery for gastric cancer in addition to the feasibility of intraperitoneal administration via an indewelling catheter **Study dates**	cancer with a particularly high risk of peritoneal carcinomatosis • histologically proven adenocarcinoma of stomach • Type 3 or Type 4 cancer or patients suspected of having small quantitites of peritoneal deposits or those with positive peritoneal washing cytology • No lymph node metastasis and distant metastasis • No history of chemo or radiotherapy • ECOG performance 0-1 • > 20years • considered as having resectable disease **Exclusion criteria**		improvement of 10% by intraperitoneal therapy. 86 patients were randomised. Out of 41 patients randomised to IPC group, two refused and the other 39 were included in the analyses. Out of 45 patients randomised to IVC group, one was not resected due to overt peritoneal metastases and excluded from the analyses. 29 in IPC group and 32 in IVC group had completed all 7 cycles.	completed all 7 cycles. one death due to pulmonary thrombosis on 44th postop day after completion of 4 IV PTX in IVC arm. Grade 3-4 neutropenia: 8/39 IPC vs 11/44 IVC	• blinding: unclear Attrition bias • ITA analyses Reporting bias • outcomes stated in the objective were not reported Overall assessment: UNCLEAR risk of bias due to inadequate blinding and outcome reporting biases **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
June 2011 and November 2014 **Source of funding** supported in part by the Epidemiological and Clinical Research Information Network	• Patients with ischaemic heart disease and arrhymia needing treatment or myocardial infarction within 6 months of onset, liver cirrhosis, interstitial pneumonitis, gastrointestinal bleeding in need of repeated blood transfusion, uncontrolled diabetes mellitus, bowel obstruction rendering treatment with oral drugs impractical or patients considered as inappropriate for inclusion for drug treatment				
Full citation	**Sample size**	**Interventions**	**Details**	**Results**	**Limitations**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Leong, T., Smithers, B. M., Haustermans, K., Michael, M., Gebski, V., Miller, D., Zalcberg, J., Boussioutas, A., Findlay, M., O'Connell, R. L., Verghis, J., Willis, D., Kron, T., Crain, M., Murray, W. K., Lordick, F., Swallow, C., Darling, G., Simes, J., Wong, R., TOPGEAR: A Randomized, Phase III Trial of Perioperative ECF Chemotherapy with or Without Preoperative Chemoradiation for Resectable Gastric Cancer: Interim Results from an International, Intergroup Trial of the AGITG, TROG, EORTC and CCTG, Annals of Surgical OncologyAnn Surg Oncol, 23, 23, 2017 **Ref Id** 610853	n=120; ECF only=60 versus CRT = 60 **Characteristics** Male=91/120 (76%) Age ≥ 70=32/120 (27%) Tumour site: GJ junction=32/120 Lower third=31/120 Upper/middle third=57/120 T3/4=99/120 (83%) N0=57/120 (48%) ECX %= 46/120 (38%) **Inclusion criteria** • histologically proven adenocarcinoma of the stomach or gastroesophageal junction (Siewert types II and III) that was stage IB (T1N1 only) to IIIC (i.e. T3–T4 and/or N-positive) and that	ECF: three preoperative and three postoperative cycles of ECF chemotherapy (epirubicin 50 mg/m2 intravenously day 1, cisplatin 60 mg/m2 intravenously day 1, and 5-fluorouracil 200 mg/ m2/day intravenously via 21-day continuous infusion. In some patients, capecitabine 625 mg/m2 twice daily on days 1–21 was substituted for 5-fluorouracil according to centerspecific preferences (ECX) CRT: two cycles of ECF followed by chemoradiation prior to surgery, and then, following surgery, three further cycles of ECF were administered. begin 2–4 weeks after the completion of cycle 2 of induction ECF and	Eligible patients were centrally randomized with registration/consent to trial undertaken blinded to treatment allocation.The 1:1 randomization schedule was generated by the Clinical Trials Centre, using minimization for stratification in the final analysis. The interim analysis of the first 120 patients was planned to examine treatment toxicity, surgical complications, tolerance and delivery of therapy, and pathological response rates by the Independent Data and Safety	90% in CRT group and 93% in ECF group received all planned cycles of preoperative ECF. In CRT group, 55/60 (92%) received CRT, of whom, 91% received 80% of planned protocol dose. 85% in CRT group and 90% in ECF group were proceeded to surgery. Among those who underwent surgery, 53%(27/51) in CRT and 65% (35/54)in ECF group received postop ECF. Complications of surgery Anastomotic leak ECF: 3/54 CRT: 4/51	**Cochrane risk of bias tool** Selection bias • random sequence generation: unclear • allocation concealment: low risk Performance bias • blinding: low risk Detection bias • blinding: low risk Attrition bias • Interim analysis and incomplete treatment protocol due to disease severity were acceptable: low risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out 51 sites from Australia, New Zealand, Europe, and Canada **Study type** Randomized, Phase III Trial **Aim of the study** to investigate whether perioperative epirubicin, cisplatin and 5-fluorouracil (ECF) plus preoperative chemoradiation improves overall survival compared with perioperative ECF alone among people with resectable gastric cancers **Study dates** September 2009 and June 2014	was considered operable following initial staging investigations • Eastern Cooperative Oncology Group (ECOG) performance status 0–1, and adequate bone marrow, liver, and renal function **Exclusion criteria**	consisted of 45 Gy in 25 fractions, 5 days per week for 5 weeks, plus continuous infusional 5-fluorouracil 200 mg/m2/day, 7 days per week throughout the entire period of radiotherapy (or capecitabine 825 mg/m2 twice daily, days 1–5 each week of radiotherapy). Patients underwent surgery 4–6 weeks following completion of preoperative therapy. D2 gastrectomy where possible, with a minimum approach being a D1? gastrectomy aiming for complete resection of the primary cancer and its draining nodes	Monitoring Committee (IDSMC), with recruitment planned to continue provided chemoradiation was deemed to be safe and feasible without clear evidence of lack of improved activity. Following the IDSMC review, selected safety and compliance data unrelated to the primary endpoints of the trial were unblinded to investigators.	Overall surgical complications (Anastomotic leak, intraabdominal sepsis, wound infection, chest infection, respiratory failure, cardiac ischaemia) ECF: 12/54 CRT: 11/51 Chest infection ECF: 5/54 CRT: 5/51 Complications of chemotherapy Overall haematologic (Neutropenia including febrile, leucocytes, anaemia, thrombocytopenia) ECF: 30/60 CRT: 31/60 Neutropenia ECF: 24/60 CRT: 27/60 Overall gastrointestinal (Nausea, vomiting,	Reporting bias • outcomes stated in the objective were reported Overall assessment: UNCLEAR/LOW risk of bias due to inadequate reporting of randomization process. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding grants from the National Health and Medical Research Council (1046425), Canadian Institutes of Health Research (CIHR) Grant No. 119445, the Canadian Cancer Society Research Institute (CCSRI) Grant No. 021039, the Health Research Council of New Zealand (HRC) International Investment Opportunities Fund (contract number 09/624), the EORTC Cancer Research Fund, and the Cancer Australia Priority- Driven Collaborative Research Scheme (Project ID 570996)				dysphagia, oesophagitis, anorexia, diarrhoea) ECF: 19/60 CRT: 18/60 No postoperative death within 30 days of surgery	

F.12 1 Squamous cell carcinoma of the oesophagus

2 **What is the most effective curative treatment of squamous cell carcinoma of the oesophagus?**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Ancona, E., Ruol, A., Santi, S., Merigliano, S., Sileni, V. C., Koussis, H., Zaninotto, G., Bonavina, L., Peracchia, A., Only pathologic complete response to neoadjuvant chemotherapy improves significantly the long term survival of patients with resectable esophageal squamous cell carcinoma: final report of a randomized, controlled trial of preoperative chemotherapy versus surgery alone, CancerCancer, 91, 2165-74, 2001 **Ref Id** 449149 **Country/ies where the study was carried out** Italy **Study type** RCT	**Sample size** N= 94 **Characteristics** Surgery (S) group 38 M/ 9 F Mean age= 58 +/- 9.3 Tumour stage IIA: 31 IIB: 6 III: 11 Chemotherapy (CT) + S group 38 M/ 9 F Mean age= 58 +/- 9.7	**Interventions** **CT+Sx vs Sx alone** **Surgery** Performed immediately after randomisation in the S group and 3-4 weeks after chemo. Esophagectomy was performed through a right thoracotomy, laparotomy, and a left cervical incision when indicated with en bloc lymph node dissection. **CT** Cisplatin 100 mg/m^2 day 1 and 5FU 1000 mg/m^2/day days 1-5 x 3 cycles	**Details** This randomized, controlled trial compared patients with clinically resectable esophageal epidermoid carcinoma who underwent surgery alone (Arm A) with those who received preoperative chemotherapy (Arm B). Overall survival and the prognostic impact of major response to chemotherapy were analyzed. Forty-eight patients were enrolled in each arm. Outcomes	**Results** **1-year Overall Survival** CS group: 35/47 S group: 35/47 **3-year overall survival** CS group: 20/47 S group: 17/47 **5-year overall survival** CS group: 7/47 S group: 3/47	**Limitations** **Cochrane risk of bias tool** Selection bias random sequence generation: random permuted blocks allocation scheme using the Moses-Oakford algorithm allocation concealment: unclear Performance bias blinding: unclear but unlikely due to obvious difference between treatments Detection bias blinding: unclear but unlikely due to

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study The primary objective of this single-center, randomized controlled trial was to analyze the overall prognostic impact of preoperative chemotherapy compared with surgery alone. **Study dates** 1992 until 1997 **Source of funding** Supported in part by a grant from the CNR (project ACRO 012809).	Tumour stage IIA: 32 IIB: 4 III: 12 **Inclusion criteria** clinically resectable squamous cell carcinoma of the esophagus (Stage IIA, IIB, and III; i.e., T2–T3 N0 M0 and T1–T3 N1 M0); ages 18–70 years; adequate cardiac, hepatic, renal, and bone marrow reserve; tolerate both the planned chemotherapy		Survival was measured from the date of randomization to the date of death or last follow-up. Survival rates and standard errors were calculated with the Kaplan–Meier method, including deaths from all causes. All patients had a minimum follow-up of 3 months.		obvious difference between treatments Attrition bias outcome date complete Reporting bias outcomes stated in the objective were reported Overall assessment: UNLCEAR risk of bias due not inadequate reporting of allocation concealment, and blinding. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	regimen and the surgical procedure. **Exclusion criteria** previously undergone treatment for the esophageal carcinoma previous or concomitant primary malignancies. the presence of distant lymph node metastasis (i.e., M1 Lym, Stage IV) excluded patient eligibility				
Full citation	**Sample size**	**Interventions**	**Details**	**Results**	**Limitations**
Apinop, C., Puttisak, P., Preecha, N., A prospective study of combined	n=69	**CRT+Sx vs Sx alone**	Surgery was performed	**Overall survival at 5-years**	**Cochrane risk of bias tool**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
therapy in esophageal cancer, Hepato-GastroenterologyHepatogastroenterology, 41, 391-3, 1994 **Ref Id** 474329 **Country/ies where the study was carried out** Thailand **Study type** RCT **Aim of the study** To report on the results of prospective randomised clinical trial of combined therpy and surgery alone **Study dates** January 1986 to December 1992 **Source of funding** NR	Chemoradiotherapy (CRT) followed by surgery = 35 Surgery alone =34 **Characteristics** Mean age in years: 59.7 Male %: 78.3 **Inclusion criteria** Biopsy-proven previously untreated locoregional squamous-cell carcinoma of the middle or distal esophagus Physically capable of undergoing subsequent surgery Normal FBC, electrolytes and creatinine **Exclusion criteria**	Please find details in Kumagai 2014 SR. CRT followed by surgery versus Surgery alone	approximately 4 weeks after the last day of CT if there was no distant metastatic disease in CRT plus surgery group whereas the treatment plan for surgery group started the second week after admission. Survival percentages were determined using Kaplan-Meier product limit method, in which only tumour-related death was considered as failure.	CRT + S: 24% (n=35) S alone: 10% (n=34)	Selection bias random sequence generation: unclear allocation concealment: unclear Performance bias blinding: unclear Detection bias blinding: unclear Attrition bias No loss of follow up Reporting bias The complete response was mentioned in the method session but not reported. Overall assessment: UNLCEAR risk of bias due to inadequate reporting of randomisation,

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Patients with concomitant second primary lesions				allocation concealment, and blinding. **Other information**
Full citation Araujo, C. M., Souhami, L., Gil, R. A., Carvalho, R., Garcia, J. A., Froimtchuk, M. J., Pinto, L. H., Canary, P. C., A randomized trial comparing radiation therapy versus concomitant radiation therapy and chemotherapy in carcinoma of the thoracic esophagus, CancerCancer, 67, 2258-61, 1991 **Ref Id** 474331 **Country/ies where the study was carried out** Brazil **Study type** RCT **Aim of the study**	**Sample size** N= 59 Radiotherapy (RT)= 31, Chemoradiotherapy (CRT)= 28 **Characteristics** **RT arm** Median age= 55 (range: 42-65) 27 M/ 4 F **CRT arm** Median age= 53 (Range 30-69) 25 M/3 F **Inclusion criteria**	**Interventions** **CRT vs RT** Concomitant CRT CT: 5FU IV infusion day 1-3, mitomycin day 1, bleomycin IM day 1,7,14,21,28 RT: 50 Gy in 25 fr	**Details** Patient Selection Pre-treatment staging evaluation included physical exam, medical history, chest xray, esophagram, esophagoscopy, bronchoscopy, liver scan and blood work. Randomization Patients randomly allocated by drawing cards in sealed envelopes.	**Results** **Treatment-related morbidity: Stenosis** RT group: N=15 CRT group: N= 22	**Limitations** No serious limitations. **Other information** **Cochrane Risk of Bias Tool** Selection Bias random sequence generation: unclear allocation concealment: unclear Performance bias blinding: unclear Detection bias blinding: unclear Attrition bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
To report on the results of a prospective randomized trial comparing RT alone versus RT plus chemotherapy in the treatment of patients with squamous cell carcinoma of the thoracic esophagus. **Study dates** September 1982 to December 1985 **Source of funding** NR	biopsy-proven, squamous cell carcinoma of the thoracic esophagus Stage II age <70 no history of malignancy expected survival time > 3 months adequate hematologic, hepatic and renal functions **Exclusion criteria** endoscopic evidence of tracheal invasion presence of trachea-esophageal fistula demonstration of nodal/visceral metastatic diseases		Outcomes Survival calculated by Kaplan-meier method.		outcome data complete Reporting bias unclear: outcomes were not defined in the objectives Overall assessment: UNCLEAR due to inadequate reporting of allocation concealment, random sequence generation and blinding.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	previous gastrostomy				
Full citation Badwe, R. A., Sharma, V., Bhansali, M. S., Dinshaw, K. A., Patil, P. K., Dalvi, N., Rayabhattanavar, S. G., Desai, P. B., The quality of swallowing for patients with operable esophageal carcinoma: a randomized trial comparing surgery with radiotherapy, CancerCancer, 85, 763-8, 1999 **Ref Id** 474345 **Country/ies where the study was carried out** India **Study type** RCT **Aim of the study**	**Sample size** n=99; [47 Surgery(Sx) and 52 radiotherapy (RT)] randomized and 44 Sx and 43 RT included in analysis **Characteristics** Age (mean) years: 52.2 Male %: 70.8% (32/89) **Inclusion criteria** Histologic confirmation of squamous cell carcinoma of the esophagus affecting the infraaortic thoracic region	**Interventions** **Sx versus RT** **Surgery (Sx):** standard Ivor-Lewis procedure or total oesophagectomy **Radiotherapy (RT):** 50 Gy in 28 fractions followed by an external boost of 15 Gy in 8 fractions or intraluminal radiotherapy of 15 Gy with 200 cGy/hour does rate at 1 cm off axis	**Details** Out of 99 randomized, 47 were in surgery and 52 were in RT. 2 were excluded from Sx arm due to direct spread to the bronchus whereas 10 from RT as 7 of them received RT at other treatment centre and 3 did not take any treatment at all. One patient from RT opted for RT and was included in RT analysis thus, 44 participants and 43 participants were inclued in Sx and RT analyses respectively.	**Results** **Survival at 3-years** Sx: 24/44 RT: 14/43 "There was no difference in the pretreatment swallowing status (p=0.69), disease specific symptoms (p=0.24), functional status(p=0.96), social interaction(p=0.72), and global score(p=0.12) between the two arms." **Treatment-related mortality**	**Limitations** **Cochrane risk of bias tool** Selection bias random sequence generation: unclear allocation concealment: closed envelope method Performance bias blinding: unclear Detection bias blinding: unclear Attrition bias Complete case analysis (unequal loss of participants between the arms)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
To compare surgery and radiotherapy with respect to various disease specific outcome parameters in patients with operable esophageal carcinoma **Study dates** 1993-1994 **Source of funding** NR	Karnofsky performance status >70 Age <65 years Operability was ascertained by ruling out supraclavicular lymphadenopathy and vocal cord paralysis on clinical examination, lung and liver metastasis by radiography of the chest and ultrasonography of the upper abdomen Local disease was assessed by absence of thoracic backache at rest (not related to swallowing), barium swallow and brochoscopy **Exclusion criteria**		Primary outcome was disease specific outcome assessed by disease specific outcome assessement (Quality of swallowing, meal satisfaction, regurgitation/vomiting, loss of appetite, pain, sleep, work, household work, relation with family, socialisation karnofsky performance scale no and global quality of life)	Sx: 3/44 post-operative deaths due to anastomotic dehiscence RT: three patients died during the radiotherapy due to unrelated causes with 2 of 3 having received a total dose of 30 Gy only.	Reporting bias outcomes stated in aim reported Overall assessment: unclear risk of bias due to inadequate reporting of randomization and blinding. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Patients with stenotic primary tumour and total obstruction and those who had received neoadjuvant chemotherapy were excluded from the trial				
Full citation Bedenne, L., Michel, P., Bouche, O., Milan, C., Mariette, C., Conroy, T., Pezet, D., Roullet, B., Seitz, J. F., Herr, J. P., Paillot, B., Arveux, P., Bonnetain, F., Binquet, C., Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCD 9102, Journal of Clinical OncologyJ Clin Oncol, 25, 1160-8, 2007 **Ref Id** 474356	**Sample size** N= 259 **Characteristics** Surgery (Sx) group: 93% Male Histology: 89.1% epidermoid/10.9 % adenocarcinoma Mean age= 55.8 +/- 10.28	**Interventions** **CRT+Sx versus CRT alone** **Sx + induction CRT** (15 Gy/3Gy x2 concurrent cisplatin 5Fu x2 OR 46 gy/2Gy concurrent cisplatin 5FUx2) **CRT alone:** 15 Gy/3Gy x3 concurrent cisplatin 5Fu x3 OR 66 Gy/2Gy concurrent cisplatin 5FUx2	**Details** **CT** - Patients received two cycles of fluorouracil (FU) and cisplatin (days 1 to 5 and 22 to 26) and either conventional (46 Gy in 4.5 weeks) or split-course (15 Gy, days 1 to 5 and 22 to 26) concomitant radiotherapy. Patients with response and no contraindication to either treatment	**Results** **1-year overall survival** CRT +Sx: 79/129 CRT alone: 84/130 **3-year overall survival** CRT +Sx: 23/129 CRT alone: 25/130	**Limitations** **Cochrane risk of bias tool** Selection bias random sequence generation: unclear allocation concealment: randomisation assigned through data centre Performance bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out France **Study type** RCT Also reported in Bonnetain, 2006 **Aim of the study** To compare the longitudinal quality of life (QoL) between chemoradiation with or without surgery in patients with locally advanced squamous resectable esophageal cancer included in a randomized multicentre phase III trial. **Study dates** Patients recruited from February 1993 and December 2000. **Source of funding** Grants from the Ligue nationale Contre le Cancer (LNCC), the Fonds	Chemoradiotherapy (CRT) +Sx group: 93.8% Male Histology: 88.5% epidermoid/11.5 % adenocarcinoma Mean age= 57.74 +/- 10.19 **Inclusion criteria** a locally advanced epidermoid or adenocarcinoma of the thoracic esophagus (T3–4/ N0–1/ M0); a WHO performance status of 0 to 2; eligibility for surgery (i.e. no contraindication); tumor judged resectable. **Exclusion criteria**		were randomly assigned to surgery (arm A) or continuation of chemoradiation (arm B; three cycles of FU/cisplatin and either conventional [20 Gy] or split-course [15 Gy] radiotherapy). **RT** - either split course or conventional(Split course was delivered in daily fractions of 3 Gy, including two sequences (day 1 to 5 and 22 to 26; 30 Gy) before random assignment and one sequence (days 43 to 47; 15 Gy) after random assignment (total, 45 Gy); Conventional - delivered in 5 daily	**Spitzer Quality of Life Index** Baseline CRT+Sx group N=110 Mean (SD): 8.44 (1.58) CRT alone group N= 113 Mean (SD): 8.70 (1.26) At 5th follow-up (5-25 months) CRT+Sx group N= 25 Mean (SD): 8.76 (2.02) CRT alone group N= 37 Mean (SD): 7.81 (2.57)	blinding: unclear but unlikely due to obvious difference between treatments Detection bias blinding: unclear but unlikely due to obvious difference between treatments Attrition bias outcome date complete Reporting bias outcomes stated in the objective were reported Overall assessment: UNLCEAR risk of bias due not inadequate reporting of randomization process and blinding. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
de la Recherché de la Societe Nationale Francaise Gastroenterologie (SNFGE), the Programme Hospitalier pour la Recherché Clinique (PHRC) and the Association pour la Recherché contre le Cancer (ARC).	tracheo-bronchial involvement, lost more than 15% of their body weight, evolutive coronary heart disease, decompensated cirrhosis or respiratory insufficiency.		fractions per eek of 2 Gy during the 4.5 weeks before random assignment (46 Gy) and the 2 weeks after random assignment (20 Gy) for a total of 66 Gy. **Surgery** – No type of surgery was recommended. The Spitzer QoL Index was scored (0–10) at inclusion and at each follow-up, every 3 months during 2 years. QoL at baseline and longitudinal changes were respectively compared with univariate ANOVA and mixed-model analysis of variance for repeated measurements. The time interval		Additional data collected from Bonnetain. F., Bouche, O., Michel, P., Mariette, C., et al. (2006) Comparative longitudinal quality of life study using the Spitzer quality of life index in a randomised multicenter phase III trial (FFCD 9102): chemoradiation followed by surgery compared with chemoradiation alone in locally advanced squamous resectable thoracic oesophageal cancer. Annals of Oncology. 17: 827-834.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			between the follow-up was assessed and the same analyses were performed among survivors with 2 years of follow-up.		
Full citation Boonstra, J. J., Kok, T. C., Wijnhoven, B. P. L., van Heijl, M., van Berge Henegouwen, M. I., ten Kate, F. J. W., Siersema, P. D., Dinjens, W. N. M., van Lanschot, J. J. B., Tilanus, H. W., van der Gaast, A., Chemotherapy followed by surgery versus surgery alone in patients with resectable oesophageal squamous cell carcinoma: Long-term results of a randomized controlled trial, BMC CancerBMC Cancer, 11 (no pagination), 2011	**Sample size** N= 169 (Chemotherapy (CT) +Surgery (Sx) group= 85, Sx alone group= 84) **Characteristics** Median age= 60 (Range 35-79) 126 M/43 F	**Interventions** **CT+Sx versus Sx alone** **CT** Cisplatin, at a dose of 80 mg/m^2 was given intravenously over 4 hours on day one of each cycle preceded and followed by adequate hydration. Etoposide, at a dose	**Details** Randomisation Central randomisation took place at the Erasmus University Medical Center in Rotterdam. Random assignment was stratified by age. Follow-up	**Results** **1-year Disease-Free Survival** CT+Sx group: 38 (N=85) Sx group: 22 (N=84) **3-year disease free survival**	**Limitations** No serious limitations **Cochrane risk of bias tool** Selection bias random sequence generation: unclear allocation concealment:

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref Id 474388 **Country/ies where the study was carried out** Netherlands **Study type** RCT **Aim of the study** we report the design and long-term results of a randomized controlled trial in patients with resectable OSCC, comparing preoperative chemotherapy with cisplatin and etoposide followed by surgery to surgery alone. **Study dates**	The two groups were similar in terms of age, sex, and performance status. Distribution according to weight loss and size of the tumour was also balanced. **Inclusion criteria** histologically confirmed squamous cell carcinoma of the intra-thoracic ooesophagus. clinically limited to the locoregional area (tumour stage 1, 2 or 3; any nodal	of 100 mg/m^2, was administered intravenously over 2 hours on day 1 (before cisplatin) and day 2, followed by etoposide 200 mg/m^2 orally on days 3 and 5. This course was repeated in week 4. In case of clinical response, two subsequent courses of chemotherapy were administered in week 8 and 11. **Surgery** For carcinomas of the upper half of the intra-thoracic ooesophagus a right-sided thoracotomy was performed. For carcinomas of the lower half of the intra-thoracic ooesophagus a transhiatal oesophagectomy was done. The tumour and its adjacent lymph	Intervals of 3-4 months in the first year, every 6 months for the second year and annually for up to 5 years post surgery. Statistical Analysis Hazard ratios (HR) were calculated with the use of a Cox regression model including treatment alone (primary analysis) and after adjustment for baseline stratification factors.	CT+Sx group= 25 (N=85) Sx group= 15 (N=84) **5-year disease-free survival** CT+Sx group= 19 (N=85) Sx group= 9 (N=84) **Post-Op Treatment Related Morbidity-Anastomotic** CT+Sx group: 8 (N=85) Sx group: 9 (N=84)	randomisation took place centrally Performance bias blinding: unclear but unlikely due to obvious difference between treatments Detection bias blinding: unclear but unlikely due to obvious difference between treatments Attrition bias outcome date complete Reporting bias outcomes stated in the objective were reported Overall assessment: UNLCEAR risk of bias due not inadequate reporting

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Between January, 1989, and January, 1996 **Source of funding** NR	stage and no metastases). Patients with carcinoma of the distal oesophagus and suspected celiac lymph nodes involvement (M1a) were also considered eligible for surgery. Patients had to be below 80 years of age, in adequate physical condition (Karnofsky score >70) to undergo surgery adequate hepatic, renal and bone marrow function. **Exclusion criteria** synchronous cancer	nodes were dissected en bloc. The left gastric artery was transected at its origin, with resection of local lymph nodes. The continuity of the digestive tract was restored by means of gastric tube reconstruction or colonic interposition with a cervical anastomosis.			of randomization process and blinding. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	tumour localization in the cervical ooesophagus , severe cardiovascular or pulmonary disease. Patients with previous malignancies (patients were eligible if more than 5 years had elapsed from diagnosis without evidence of tumour recurrence; exceptions were made for adequately treated basal cell cancer of the skin or carcinoma in situ of the cervix				
Full citation Bosset, J. F., Gignoux, M., Triboulet, J. P., Tiret, E., Mantion, G., Elias, D., Lozach, P., Ollier, J. C., Pavy, J. J., Mercier, M., Sahmoud, T.,	**Sample size** n=282 **Characteristics**	**Interventions** **Chemoradiotherapy (CRT)+ Surgery (Sx) versus Sx alone**	**Details** With 80% power, one-sided type I error of 0.05, the study had enough	**Results** **T0 stage tumour after curative resection**	**Limitations** **Cochrane risk of bias tool** Selection bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Chemoradiotherapy followed by surgery compared with surgery alone in squamous-cell cancer of the esophagus, New England Journal of MedicineN Engl J Med, 337, 161-7, 1997 **Ref Id** 474390 **Country/ies where the study was carried out** France **Study type** Multicentred randomised trial **Aim of the study** To initiate a prospective, multicenter, randomised tiral comparing preoperative CRT followed by surgery with surgery alone. The main endpoint was overall survival. Secondary endpoint were disease free survival and survival free of local disease or distant metastatses. **Study dates** January 1989 to June 1995	Age (mean) in years: 56.7 Male %: 93.3 Node +ve tumour %: 23 **Inclusion criteria** Invasive SCC ECOG performance status of 0 to 2 <70years Resectable tumour Participants with T1N0, T1N1, T2N0, T2N1, T3N0 **Exclusion criteria** if participants had lost more than 15 percent of their body weight if they had previously undergone treatment for this	Details of interventions can be found in Kumagai 2014.	power to detect an improvement in five-year survival from 15 percent in Sx alone gorup to 25 % in CRT +Sx group.	CRT+S: 29/112 S alone: 0/94 **Disease free survival (longer in CRT + S group)** RR (95% CI): 0.6 (0.4 to 0.9)	random sequence generation: unclear allocation concealment: unclear Performance bias blinding: unclear Detection bias blinding: unclear Attrition bias No loss of data Reporting bias outcomes stated in aim reported Overall assessment: unclear risk of bias due to inadequate reporting of randomization and blinding **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding Grant from Ligue Departmental de Lutte contre le Cancer du Doubs, France	disease or any other cancer except basal cell-carcinoma of the skin Tumour located within the first 4 cm of the esophagus, metastases in cervical lymph nodes, evidence of invasion of the bronchus on bronchoscopy, and tumour classified as T3N1, T4N0 or T4N1				
Full citation Burmeister, B. H., Smithers, B. M., Gebski, V., Fitzgerald, L., Simes, R. J., Devitt, P., Ackland, S., Gotley, D. C., Joseph, D., Millar, J., North, J., Walpole, E. T., Denham, J. W., Findlay, M., Dhillon, H., Stockler, M., Coates, A., Matthews, J., Beller, E., Gray, E., Dodds, H., Marks, P., Hayden, P., Erratt, A., Monro, C., Pike, R., Thomson, D., Harvey, J.,	**Sample size** n=256 **Characteristics** Age (years): ~ 61.5 Gender: Male %: 82 SCC %: 37	**Interventions** **Chemoradiotherapy (CRT) + Surgery (Sx) versus Sx alone** Please find in Kumagai 2014 SR	**Details** The primary endpoints was progression-free survival from date of randomisation. Of 129 and 128 participants allocated to CRT plus S and S alone	**Results** **Progression-free survival (HR (95% CI))** All participants: CRT + S vs Sx alone: 0.82 (0.61-1.10), p=0.18	**Limitations** **Cochrane risk of bias tool** Selection bias --> Low risk random sequence generation: central telephone

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Martin, I., Burmeister, E., Jamieson, G., Borg, M., Yeoh, E., Olver, I., Caruso, D., Game, P., Spry, N., Minchin, D., Cameron, F., Faulkner, K., Einhorn, S., Dewar, J., Gillies, J., Johnson, C., Kilmurray, J., Neely, M., Carmody, M., Mackintosh, J., O'Brien, P., Schwartz, M., Smith, R., Woods, S., Nathanson, L., O'Loughlin, B., Grimes, D., Cheuk, R., Dickie, G., Keller, J., Archer, S., Bayliss, E., Gray, B., Trotter, J., Ransom, D., Shepherd, J., Stone, C., Thompson, I., Guiney, M., Henderson, M., Thomas, R., Kian, M., Ngan, S., Rischin, D., Walcher, V., Zalcberg, J., Costello, S., Perez, D., Whitely, D., Wyllie, A., Avramovic, J., Donnolly, P., Fon, P., Collins, M., McIntosh, R., Melville, P., Bell, R., Kirrof, G., Harris, I., McLennan, R., Monro, W., Aroney, R., Falconer, K., Cullingford, G., Davidson, A., Randell, C., Berry, M., Delaney, G., Moylan, E., Burns, D., Goldstein, D., Surgery alone versus chemoradiotherapy followed by surgery for resectable cancer of the oesophagus: A randomised controlled phase III trial, Lancet	+ve regional node %: 15.5 **Inclusion criteria** Histologically confirmed invasive cancer of the thoracic esophagus Restricted to esophagus and regional lymph nodes (clinical T 1to3, N 0-1 disease) with resectable nodes to be removed as part of the planned surgical procedure (participants with involvement of gastric cardia confined to the lower third of the esophagus were also eligible if the tumour was mainly in the esophagus) Participants with no previous		respectively, 105 in the former and 110 in the latter received the allocated treatment. After randomisation, 1 participant from CRT plus S (SCC in situ on biopsy) was found to be ineligible and excluded from the analysis. Analyses were done by ITT (n=128 in each group). Sample size calculations were made on the basis of a projected 3-year progression-free survival of 35% for patients assigned chemoradiotherapy and of 20% for those assigned to surgery alone.With an overall two-	SCC only : CRT+ Sx: 30/45 versus Sx alone: 16/50 **Overall survival (HR (95% CI))** All participants: CRT+ Sx vs Sx alone: 0.89(0.67,1.19), p=0.44 SCC only: CRT+Sx: 8/45 Sx alone: 4/50 **Number going on to salvage resection:** CRT+Sx : 105/128 Sx alone: 110/128	randomisation in block of four --> low risk allocation concealment: yes to all central staff --> low risk Performance bias --> Unclear/Low risk blinding: research staff and investigators blinded but not patients Detection bias --> Low risk blinding of research staff Attrition bias --> Low risk ITT analysis Reporting bias --> Low outcomes stated in the method session reported except

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
OncologyLancet Oncol, 6, 659-668, 2005 **Ref Id** 474400 **Country/ies where the study was carried out** Australia, New Zealand, Singapore **Study type** Multicentred RCT **Aim of the study** To assess whether downstaging of the tumour as a result of chemoradiotherapy improved progression-free survival and overall survival after surgery **Study dates** Nov 1994 to Sep 2000 **Source of funding** National Health and Medical Research Council of Australia (NHMRC)	radiotherapy or chemotherapy ECOG (Eastern Cooperative Oncology Group) performance status of the patients had to be 0 or 1 Normal FBC and serum biochemistry Creatinine clearance > 1.0 mL/s (Gault and Cockcroft formula) and > 0.83mL/s by direct measurement Note - Participants with any malignant disease other than non-melanomatous skin cancer or cervical carcinoma in situ were eligible if there had been no recurrence for at least 5 years before randomisation		sided significance level of 5% and a stiatiscal power of 80% to detect a difference of 15% in 3-year progression-free survival, 4 years' accrual, and 4 years' follow-up, the calculated sample size was 230 patients. Planned interimi analysis were performed to exclude major differences in outcomes between groups. Progression-free and overall survival were estimated withh the Kaplan-Meier method and groups were compared by use of the log-rank test. Age, tumour location and tumour grade were		quality of life which the authors mentioned to be reported elsewhere Overall assessment: Low risk of bias **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Exclusion criteria Patients with tumours localised to the cervical esophagus and those with involvement of the coeliac nodes		included in the multivariate anslaysis. The Cox proportional models was used oto define diffences in survival between groups and subgroups.		
Full citation Cao, X. F., He, X. T., Ji, L., Xiao, J., Lv, J., Effects of neoadjuvant radiochemotherapy on pathological staging and prognosis for locally advanced esophageal squamous cell carcinoma, Diseases of the EsophagusDis Esophagus, 22, 477-81, 2009 **Ref Id** 474408 **Country/ies where the study was carried out** China **Study type**	**Sample size** N= 473 **Characteristics** Chemotherapy (CT) + Surgery (Sx) group 65 M / 54 F Stage: II 8/ III 108/ IV 3 Chemoradiotherapy (CRT) + Sx group:	**Interventions** **CT+Sx versus CRT+Sx versus Sx alone** **CT** Cisplatin+5-fluorouracil+mitomycin (PFM) regimen was used, including mitomycin (MMC, 10 mg/m^2/day) administered as short-term infusion on day 1, while cisplatin (DDP, 20 mg/m^2/day) and 5-fluorouracil (5-FU, 500 mg/m^2/day)	**Details** 473 patients with advanced esophageal carcinoma diagnosed by endoscopic biopsy underwent surgical resection in our center. With informed consent, they were randomized into four groups: neoadjuvant chemotherapy, neoadjuvant radiotherapy,	**Results** **3-year overall survival** C + S group: 57.1% CRT + S group: 73.3 % S alone group: 53.4% Uncertainty NR. **Postoperative Anastomotic Leakage**	**Limitations** **Inclusion and exclusion criteria very poorly defined or not reported.** **Cochrane risk of bias tool** Selection bias random sequence generation: unclear allocation concealment: unclear Performance bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
RCT **Aim of the study** The aim of this study was to evaluate the effects of neoadjuvant radiochemotherapy on pathological staging and prognosis in the patients with locally advanced esophageal squamous cell carcinoma. **Study dates** February 1991 and December 2000 **Source of funding** NR	60 M/ 58 F Stage: II 9/ III 103/ IV 6 Sx alone group: 67 M/51 F Stage: II 6/ III 108/ IV 4 **Inclusion criteria** patients with esophageal squamous cell carcinoma **Exclusion criteria** NR	as continuous infusion over 24 h on days 1–5 CRT concomitant CT: as above **RT:** daily fractions of 2 Gy (days 1–5, 8–12, 15–19, and 22–26) to a total dose of 40 Gy by using a double fields technique **Surgery** Esophagectomy	neoadjuvant radiochemotherapy, and surgery alone (control group). The preoperative computed tomography staging criteria were the following: Stage I, the tumor limited to the esophageal lumen or the thickness of the esophageal wall varied between 3–5 mm; Stage II, the thickness exceeds 5 mm but no invasion to the mediastinum or distant metastasis; Stage III, the tumor invades adjacent mediastinal structure; and Stage IV, there is distant metastasis. The tumor resection rate, pathological stage,	C+S group: 0/119 CRT + S group: 3/118 S alone: 1/118 **Postoperative Stricture** C+ S group= 0/119 CRT + S group= 2/118 S alone= 1/118	blinding: unclear but unlikely due to obvious difference between treatments Detection bias blinding: unclear but unlikely due to obvious difference between treatments Attrition bias outcome date complete Reporting bias outcomes stated in the objective were reported Overall assessment: UNLCEAR risk of bias due not inadequate reporting of allocation concealment, randomization process and blinding. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			treatment-related complication, and survival among groups were compared.		
Full citation Chiu, P. W., Chan, A. C., Leung, S. F., Leong, H. T., Kwong, K. H., Li, M. K., Au-Yeung, A. C., Chung, S. C., Ng, E. K., Multicenter prospective randomized trial comparing standard esophagectomy with chemoradiotherapy for treatment of squamous esophageal cancer: early results from the Chinese University Research Group for Esophageal Cancer (CURE), Journal of Gastrointestinal SurgeryJ Gastrointest Surg, 9, 794-802, 2005 **Ref Id** 474434 **Country/ies where the study was carried out**	**Sample size** N= 80 (Surgery (Sx)= 44, Chemoradiotherapy (CRT)= 36) **Characteristics** Mean Age: Sx: 62 (+/- 9.7) CRT: 62 (+/- 8.6) Recruited patients were comparable between groups in terms of tumour site, length and stage. Tumour stage:	**Interventions** **Surgery alone versus CRT** Surgery: Standard esophagectomy with two-field lymphandenectomy. CRT: 3-weekly cycle of cisplatin and 5FU X2 3-dimensional RT with 50-60 Gy given in 20-30 fr over 5-6 weeks	**Details** Follow-up 6-8 weekly follow up in the 1st year, 3 monthly in the 2nd year and yearly after. Local and systemic recurrences documented. Outcomes Primary outcome was 2 year survival. Secondary outcomes included disease-free survival and hospital stay.	**Results** **Overall Survival at 2-years** Sx: 24/44 CRT: 21/36 p-value: 0.34 **Disease-Free Survival at 2-years** Sx: 24/44 CRT: 20/36 **Number going on to salvage resection**	**Limitations** **Cochrane risk of bias tool** Selection bias random sequence generation: unclear allocation concealment: unclear Performance bias blinding: unclear but unlikely due to obvious difference between treatments Detection bias blinding: unclear but unlikely due to

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
China **Study type** RCT **Aim of the study** To compare the efficacy and survival outcome by chemoradiation with by esophagectomy as curative treatment. **Study dates** From July 2000 to December 2004. **Source of funding** Research Grant Council of Hong Kong Special Administrative Region, China.	T2: 10 Sx/ 13 CRT T3: 34 Sx/ 23 CRT N1: 23 Sx/ 14 CRT Compliance to treatment was high in both groups. 80.6% of CRT patients completed the full course. 3 patients did not receive surgery as the tumour was deemed inoperable. **Inclusion criteria** younger than 75 years resectable mid or lower thoracic esophageal squamous cell carcinoma **Exclusion criteria** evidence of distant metastasis or		Analysis SPSS software used to analyse data. Analysis was based on intention-to-treat principle.	Sx: NA CRT: 6/36 **Participants without any recurrence upon follow-up** Sx: 26/44 CRT: 20/36 **Mortality from chemoRT (30 days)** CRT: 0% **Operative mortality (30 days)** Sx: 3/44 (2 from pneumonia and 1 from sepsis) **Mean blood loss, ml** Sx (mean±SD): 726±704	obvious difference between treatments Attrition bias outcome date complete Reporting bias outcomes stated in the objective were reported Overall assessment: UNLCEAR risk of bias due not inadequate reporting of allocation concealment, randomization process and blinding. **Other information** Additional data were collected from Tech, A.Y.B., Chiu, P.W.Y., Yeung, W.K., et al. (2012) Long-term survival

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	adjacent organ invasion premorbid condition precluded a thoracotomy creatinine clearance was less than 50 mL/min			**5-year overall survival (p=0.241)** Sx: 10/44 CRT: 17/36 **5-year disease-free survival (p=0.068)** Sx: 12/44 CRT: 17/36 **Quality of life** "Worsened physical functioning was observed up to 6 months after surgery (p<0.001) whereas in the CRT group, deteriorations were most significant at 3 months after treatment (p=0.009). As for the symptom scales, significantly worst fatigue symptoms were observed up	outcomes after definitive chemoradiation versus surgery in patients with resectable squamous carcinoma of the oesophagus: results from a randomised controlled trial. Annals of Oncology. 24: 165-170. Teoh, A.Y.B., Chiu, P.W.Y., Wong, T.C.L., et al. (2011) Functional performance and Quality of life in patients with squamous oesophageal carcinoma receiving surgery or chemoradiation. Results from a Randomised Trial. Annual of Surgery. 253; 1: 1-5

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				to 6 months after surgery (p=0.021) whereas in CRT group, no obvious changes were present at any time period (p=0.978). Patients with surgery also had significantly more diarrhoeal symptoms at 6 months (p=0.021) and this became insignificant at 2 years (p=0.0249). In the global health status score, no significant longitudinal changes were present in either group. When comparing between groups, no significant changes were present in the functional and	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				symptom scales at any time point."	
Full citation Fok, M., McShane, J., Law, S. Y. K., Wong, J., Prospective randomised study on radiotherapy and surgery in the treatment of oesophageal carcinoma, Asian Journal of Surgery, 17, 223-229, 1994 **Ref Id** 474515 **Country/ies where the study was carried out** Hong Kong **Study type** RCT **Aim of the study** To determine the operative morbidity and mortality, failure pattern and clinical outcome of the primary	**Sample size** n=74 Surgery alone (Sx)= 39 Radiotherapy alone (RT) = 35 **Characteristics** Age (mean) in years: 56 **Inclusion criteria** Patients with potentially curable middle third squamous cell carcinoma of the oesophagus Patients with middle third lesions (D4 to D8) of less than 5	**Interventions** **Sx vs RT** Surgery alone: three-phase oesophagectomy Radiotherapy alone: 45 to 53 Gy over four to five weeks	**Details** The 156 patients entered the trial were randomly assigned to four treatment groups. Because of the limitations of staging, the numbers in each group were not identical.	**Results** **Operative mortality** Sx:3/39 RT: 7/35 (13 patients had persistent unrelieved dysphagia from residual tumour which required surgery for palliation. The operative mortality for these patients were at high at 54%). **Post-operative complications (only surgery group)**	**Limitations** **Cochrane risk of bias tool** Selection bias random sequence generation: unclear allocation concealment: unclear Performance bias blinding: unclear but unlikely Detection bias blinding: unclear but unlikely Attrition bias Six patients were loss to follow-up within five

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
treatment and survival among four methods of treatment: surgery alone, preoperative radiotherapy, postoperative radiotherpy and radiotherpy. Note: Surgery alone versus Radiotherapy alone comparison was considered for this review. **Study dates** 1968 and 1981 **Source of funding** NR	cm in length on barium swallow, with no clinical evidence of extensive local infiltration or metastases and who were clinically fit to undergo surgery **Exclusion criteria**			Chest infection: Sx (15/39) Anastomotic leakage: Sx (7/39) **Overall survival rate at 5 years** Sx: 16% RT: 7%	years of entry to the study Reporting bias outcomes stated in the objective were reported Overall assessment: UNLCEAR risk of bias due not inadequate reporting of randomisation and allocation concealment. **Other information**
Full citation Hatlevoll, R., Hagen, S., Hansen, H. S., Hultborn, R., Jakobsen, A., Mantyla, M., Modig, H., Munck-Wikland, E., Nygaard, K., Rosengren, B., Tausjo, J., Elgen, K., Bleomycin/cis-platin as neoadjuvant chemotherapy before radical radiotherapy in localized, inoperable carcinoma of the esophagus. A prospective randomized multicentre	**Sample size** n=100 Chemoradiotherapy (CRT) = 49 Radiotherapy (RT) = 51 **Characteristics**	**Interventions** **CRT vs RT** Please find details in Wong 2006 MA	**Details** The treatment was carried out as planned in 39 patients from RT group and in 26 patients from the CRT. In 6 patients no information on the treatment was obtained. 8	**Results** Fatal bleeding was cause of death in 4/49 CRT group and 1/51 RT group.	**Limitations** **Cochrane risk of bias tool** Selection bias random sequence generation: unclear allocation concealment: unclear

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
study: The second scandinavian trial in esophageal cancer, Radiotherapy and Oncology, 24, 114-116, 1992 **Ref Id** 474573 **Country/ies where the study was carried out** Denmark **Study type** Multicentered RCT **Aim of the study** To evaluate the effect of chemotherapy as an adjunct to irradiation on survival and swallowing function **Study dates** NR **Source of funding** NR	Age (median) in years: 66 Male %: 81 N0 %: 72 M0%: 92 **Inclusion criteria** Previously untreated patients less than 75 years old with histolgically verified squamous cell carcinoma and with performance status (Karnofsky index) > 50 Patients having medical contraindications to surgery or patients refusing surgery before randomisation were also included. The criteria for inoperability were tumour classified		patients did not complete treatment in RT group, five due to poor general condition or progressive disease while three patients died during the treatment. The cause of death was pneumonia in one and cancer progression in two patients. Of the 18 patients who did not complete the combined treatment, one patient had adverse reaction to CT an, three refused CT, nine had progression of the disease or poor general condition. The median survival time was 5.5 months in both groups.		Performance bias blinding: unclear Detection bias blinding: unclear Attrition bias There were 3 patients with loss to follow up in CRT group. Reporting bias outcomes stated in the objective were reported Overall assessment: UNLCEAR risk of bias due not inadequate reporting of randomization, allocation concealment, and blinding. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	T3, Nx of any localization, or all tumours localised to the upper third of the esophagus (<20 cm from incisors, or proximal to the 5th thoracic vertebra) even if they were less advanced. **Exclusion criteria**				
Full citation Klevebro, F., von Dobeln, G. A., Wang, N., Johnsen, G., Jacobsen, A. B., Friesland, S., Hatlevoll, I., Glenjen, N. I., Lind, P., Tsai, J. A., Lundell, L., Nilsson, M., A randomized clinical trial of neoadjuvant chemotherapy versus neoadjuvant chemoradiotherapy for cancer of the oesophagus or gastro-oesophageal junction, Annals of OncologyAnn Oncol, 27, 660-667, 2016 **Ref Id** 474709	**Sample size** n=181 (Chemoradiotherapy (CRT) +Surgery (Sx)= 90 versus Chemotherapy (CT) + Surgery (Sx) =91 **Characteristics** Age (median): 63 Male %: 83 N0 tumour %: 37 SCC %: 28	**Interventions** **CRT+Sx versus CT+Sx alone** **Chemotherapy (CT):** 3 cycles of cisplatin, 100 mg/m^2 day 1 and fluorouracil 750 mg/m^2/24 hr, days 1-5. Each cycle lasted 21 days **Radiotherapy (RT);** 40Gy (2 Gy/day in 20 fractions, 5 days a week) with	**Details** All participants being randomised were included in analysis. The sample size was based on the intention of showing a difference in the primary end point of 15% between treatment arms with a power of 80% which	**Results** **90-day mortality** CT+Sx: 2/91 CRT+Sx: 5/90 **Treatment-related morbidity (Any complication)** CT+Sx: 35/91 CRT+Sx: 42/90 **Treatment-related morbidity**	**Limitations** **Cochrane risk of bias tool** Selection bias random sequence generation: unclear allocation concealment: unclear Performance bias blinding: unclear Detection bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out Norway and Sweden **Study type** RCT **Aim of the study** Phase II ranodmised trial comparing the rate of histological complete response after nCRT with that after nCT. Overall survival, number of lymph node metastases R0-resection rate, progression-free survival, and site of recurrence were evaluated as secondary end points **Study dates** 2006-2013 **Source of funding** Swedish Society of Medicine, the Swedish Cancer Society, The Cancer Research Foundations of Radiumhemmet, and the Stockholm County Council	**Inclusion criteria** Patients with histologically confirmed SCC or AC of the esophagus or GOJ (including Siewert type I and II) who were eligible for curative treatment with surgical resection were enrolled. Clinical tumour stage; T1-3, any N (with the exception of T1N0) Cervical cancers were required to be resectable without laryngectomy **Exclusion criteria** None	chemotherapy cycles 2 and 3 (concurrent) **Surgery (Sx):** Ivour Lewis procedure or McKeown procedure (if middle and upper thirds of oesophagus) or transhiatal approach	required 172 patients.	**(Anastomotic leakage)** CT+Sx: 7/91 CRT+Sx: 10/90 **Treatment-related morbidity (Cardiovascular complication)** CT+Sx: 4/91 CRT+Sx: 7/90 **R0 resection** Total: CT+Sx: 58/91 CRT+Sx: 68/90 SCC: CT+Sx: 16/25 CRT+Sx: 20/25 **3-year overall survival** Total: CT+Sx: 45/91 CRT+Sx: 42/90 SCC:	blinding: All surgical specimens were reviewed by an expert pathologist who was blinded to randomisation Attrition bias No loss of follow-up data Reporting bias outcomes stated in aim reported Overall assessment: unclear risk of bias due to inadequate reporting of randomization and blinding. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				CT+Sx: 13/25 CRT+Sx: 14/25 **Progression-free survival** Total CT+Sx: 40/91 CRT+Sx: 40/90 SCC CT+Sx:13/25 CRT+Sx: 14/25	
Full citation Kumagai, K., Rouvelas, I., Tsai, J. A., Mariosa, D., Klevebro, F., Lindblad, M., Ye, W., Lundell, L., Nilsson, M., Meta-analysis of postoperative morbidity and perioperative mortality in patients receiving neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal and gastro-oesophageal junctional cancers, British Journal of SurgeryBr J Surg, 101, 321-38, 2014	**Sample size** Studies= 23 8 relevant studies comparing C+S vs S alone (post 1990). 3 relevant studies comparing C+S vs CRT+S (SCC only). **Characteristics**	**Interventions** C+S vs S CRT+S vs S CRT+S vs C+S See Characteristics column for intervention details.	**Details** Database Search Medline, Cochrane Database and Embase were search for studies published up to March 2013. Manual searching of reference lists to further identify potentially relevant studies.	**Results** **C+S vs S** **Anastomotic Leak** Studies= 8 Risk Ratio (95% CI): 0.96 (0.65-1.43) **30-day mortality** Studies= 5	**Limitations** Long-term survival not included as an outcome. **Other information** ROBIS tool for bias risk assessment in systematic reviews: Study Eligibility Criteria

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref Id 474733 **Country/ies where the study was carried out** Sweden **Study type** Systematic review of RCTs **Aim of the study** To systematically review and complete a meta-analysis to compare the survival of neoadjuvant chemotherapy versus chemoradiotherapy for esophageal cancer. **Study dates** RCTs range 1992- 2012 **Source of funding** No funding reported.	All patients T0-3 N0-1 tumour stage. No major differences in other patient characteristics. **C+S vs S** **Law 1997** n= 147 SCC CT: Cisplatin 100 mg/m2 on days 1 and 22, 5Fu 500mg/m2 per day on days 1-5 and 22-26 S: Laparotomy and right thoracotomy with mediastinal lymphadenectomy for those with cardiopulmonary reserves **Baba 2000** n= 42		Data Data was extracted by author with discrepancies dealt with by discussion with other authors. Bias Assessment Jadad's score was used to evaluate the risk of bias in individual studies. Analysis Stata was used to analyse data and a random-effects model was used to estimate RRs and CIs. Higgins statistic was used to assess heterogeneity. Sensitivity analysis was performed.	Risk Ratio (95% CI): 0.97 (0.66-1.42) **Total Postoperative Mortality** Studies= 7 Risk Ratio (95% CI): 0.99 (0.72-1.38) **Treatment-related Mortality** Studies= 6 Risk Ratio (95% CI): 1.20 (0.71-2.03) **C+S vs CRT+ S** **Anastomotic Leak** Studies= 2 Risk Ratio (95% CI): 1.51 (0.14-	Did the review adhere to pre-defined objectives and eligibility criteria? Yes Were the eligibility criteria appropriate for the review question? Yes Were the eligibility criteria unambiguous? Yes Were all the restrictions on eligibility criteria based on study characteristics appropriate? Probably Yes Were any restrictions in eligibility criteria based on sources of information available? Yes Concern regarding specification of study eligibility criteria: Low

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	SCC CT: Cisplatin 70 mg/m^2 on days 1 and 28, 5Fu 700mg/m^2 per day on days 1-5 and 28-32, folinic acid 20 mg/m2 on days 1-5, 28-32 S: right thoracotomy, laparotomy and cervicotomy including coeliac nodes with oeophagogastric anastomosis in the left neck (two-field resection) **Ancona 2001** n= 96 SCC CT: Cisplatin 100 mg/m^2 on days 1 and 22, 5Fu 1000mg/m^2 per day			16.21) (favours C+S) **30-day mortality** Studies= 1 Risk Ratio (95% CI):1.16 (0.44-3.07) **Total Postoperative Mortality** Studies= 1 Risk Ratio (95% CI): 1.16 (0.44-3.07) **Treatment-related Mortality** NR **CRT+S vs S** **Any complication** N=4 (SCC only) RR (95% CI): 1.07 (0.84, 1.36)	Identification and Selection of Studies Did the search include an appropriate range of databases/electronic sources for published and unpublished reports? Probably Yes Were the methods additional to database searching used to identify relevant reports? Yes Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible? Yes Were restrictions based on date, publication format or language appropriate? Probably yes

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	on days 1-5 and 22-26 S: Laparotomy, right thoracotomy and left cervical incision with en bloc lymph node dissection **Medical Research Council 2002** n= 802 SCC and AC CT: Cisplatin 80 mg/m^2 on days 1 and 22, 5Fu 1000mg/m^2 per day on days 1-4 and 22-25 S: Surgical approach depending on tumour site and local practice **Boonstra 2011** n= 169 SCC			**Cardiac complication** **Respiratory complication** N=10 (SCC=7; ACC and SCC=3) SCC --> RR(95% CI): 1.42 (0.76, 2.67) AC and SCC --> RR(95% CI): .99 (0.81, 1.21) **Anastomotic leak** N=10 (SCC=6; AC and SCC=4) SCC --> RR(95% CI): 1.40 (0.68, 2.88) AC and SCC --> RR(95% CI): 0.92 (0.66, 1.29) **30-day mortality**	Were efforts made to minimise error in selection of studies? Yes Concern regarding methods used to identify or select studies: Low Data Collection and Study Appraisal Were efforts made to minimise error in data collection? Probably Yes were sufficient study characteristics available? Yes Were all relevant study results collected for use and synthesis? Yes Was risk of bias formally assessed using appropriate criteria? Yes

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	CT: Cisplatin 80 mg/m^2 on days 1 and 22, etoposide (IV) 100mg/m^2 on days 1,2,22,23; etoposide (oral) 200mg/m^2 days 3,5,24,26 S: Right thoracotomy or transhiatal for lower half oesophagus; the tumour and its adjacent lymph nodes were dissected en bloc. **C+S vs CRT+S** **Nygaard 1992** n= 217 SCC only CT: cisplatin 20 mg/m2 on days 1-5 and 15-19; bleomycin 5 mg/m^2			N=3 (SCC=2; AC and SCC=1) SCC --> RR(95% CI): 1.29 (0.46, 3.63) AC and SCC --> RR(95% CI): 0.89 (0.24, 3.24) **Total Postoperative Mortality** N=10 (SCC=6; AC and SCC=4) SCC --> RR(95% CI): 1.95(1.06, 3.60) AC and SCC --> RR(95% CI): 0.79(0.39, 1.61) **Treatment-related Mortality** N=11 (SCC=7; AC and SCC=4)	Were efforts made to minimise error in risk of bias assessment? No information Concern: Unclear Synthesis and Findings Did the synthesis include all studies it should? Yes Were all pre-defined analyses reported and departures explained? Yes Was the synthesis appropriate given the nature and similarity in the research questions? Yes Was heterogeneity minimal or addressed? Yes Were the findings robust as demonstrated though funnel plot or

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	on days 1-5 and 15-19 RT: 35 Gy, 1.75 Gy per fr over 4 weeks (sequential) S: Laparotomy with right thoracotomy **Cao 2009** n= 473 SCC only CT: cisplatin 20 mg/m^2 on days 1-5; 5FU 500mg/m^2 per day on days 1-5; mitomycin 10 mg/m^2 per day on day 1 RT: 40 Gy, 2 Gy per fr over 4 weeks (concurrent) S: oesophagectomy through left thoracotomy with 2-field lymphadenectomy **Cao 2009 (**n=473)			SCC --> RR(95% CI): 1.97 (1.07, 3.64) AC and SCC --> RR(95% CI): 0.85 (0.43, 1.71)	sensitivity analysis? Yes Were biases in primary studies minimal or addressed in the synthesis? Yes Concern= LOW Risk of bias in the review Did the interpretation of findings address all the concerns identifies in 1-4? Yes Was the relevance of identified studies to the review's research question appropriately considered? Yes Did the reviewers avoid emphasizing results on the basis of their statistical significance? Yes Risk of bias= LOW

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	CT: Cisplatin 20mg/m^2 per day on days 1-5; FU 500 mg/m^2 per day on days 1-5; mitomycin 10 mg/m^2 per day on day 1 AND 40Gy, 2 Gy per fraction over 4 weeks (concurrent) S: oesophagectomy through left thoracotomy with 2-field lymphadenectomy **CRT+S vs S** **Apinop 1994** (n=69) SCC only CRT+S: Cisplatin 100 mg/m^2 on days 1 and 29; FU 1000 mg/m^2 per day on days 1-4 and 29-32 AND 40Gy, 2Gy per fraction over 4 weeks (concurrent)				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	S: right thoracotomy and laparotomy and anastomosis in the chest **Le Prise 1994** (n=86) SCC only CRT+S: Cisplatin 100mg/m^2 on days 1 and 21; FU 600 mg/m^2 per day on days 2-5 and 22-25 AND 20Gy in 10 fractions over 12 days (sequential) S: not reported **Bosset 1997** (n=297) SCC only CRT+S: Cisplatin 80 mg/m^2 0-2 days before each course of radiotherapy AND 37 Gy, 3.7Gy per fraction in two 1-week courses, separated by 2 weeks (sequential)				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	S: 2 or 3 stage surgical approach depending on the site of tumour and two-field lymph node resection **Lee 2004** (n=101) SCC only CRT+S: Cisplatin 60 mg/m^2 on days 1 and 22; FU 1000mg/m^2 per day on days 2-5 AND 45.6 Gy, 1.2 Gy per fraction over 28 days (concurrent) S: 2-stage or 3-stage approach and en-bloc lymph node dissection included ithe perioesophageal, infracranial, posterior mediastinal and paracardinal lymph nodes and those located along the				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	lesser gastric curvature and the origin of the left gastric artery, coeliac trunk, common hepatic artery and splenic artery **Burmeister 2005** (n=256) SCC and AC CRT+S: Cisplatin 80 mg/m^2 on day 1; FU 800 mg/m^2 per day on days 1-4 AND 35 Gy in 15 fractions over 3 weeks (concurrent) S: No particular approach was stipulated and radical lymphadenectomy is not mandatory **Natsugoe 2006** (n=45) SCC only CRT+S: Cisplatin 7 mg days 1-5, 8-12,				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	15-19 and 22-26; FU 350 mg/day on days 1-28 AND 40 Gy, 2 Gy per fraction over 4 weeks (concurrent) S: not reported **Nygaard 1992** CRT+S: Cisplatin 20 mg/m^2 on days 1-5 and 15-19; bleomycin 5 mg/m^2 on days 1-5 and 15-19 AND 35 Gy, 1.75 Gy per fraction over 4 weeks (sequential) S: Lapartomy with right thoractomy **van Hagen 2012** (n=368) SCC and AC CRT+S: 5 weeks concurrent chemotherpy; carboplatin area under curve 2 mg				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	per ml per min and paclitaxel 50 mg/m^2 on day 1 weekly AND 41.4 Gy, 1.8 Gy per fraction over 4.6 weeks (concurrent) S: transthoracic approach with 2-field lymph node dissection for tumour extending to tracheal bifurcation; transhiatal resection for those extending to oesophagogastric extension and gastric tube reconstruction and cervical anastomosis is preferred method **Cao 2009 (**n=473) CT:: Cisplatin 20mg/m^2 per day on days 1-5; FU 500 mg/m^2 per day on days 1-5; mitomycin 10 mg/m^2 per day				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	on day 1 AND 40Gy, 2 Gy per fraction over 4 weeks (concurrent) S: oesophagectomy through left thoracotomy with 2-field lymphadenectomy **Inclusion criteria** RCTs compared postoperative morbidity/mortality after neoadjuvant chemotherapy or neoadjuvant chemoradiotherapy **Exclusion criteria** full texts not available in English				
Full citation	**Sample size** n=129	**Interventions** **CRT versus RT**	**Details**	**Results**	**Limitations**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Kumar, S., Dimri, K., Khurana, R., Rastogi, N., Das, K. J., Lal, P., A randomised trial of radiotherapy compared with cisplatin chemo-radiotherapy in patients with unresectable squamous cell cancer of the esophagus, Radiotherapy & OncologyRadiother Oncol, 83, 139-47, 2007 **Ref Id** 474734 **Country/ies where the study was carried out** India **Study type** RCT **Aim of the study** To evaluate the efficacy of adding chemotherapy to radiotherapy in patients with unresectable squamous cell carcinoma of the esophagus The primary outcome of the study was overall survival with secondary	Chemoradiotherapy (CRT)= 66 and Radiotherapy (RT) = 63 **Characteristics** Age (median) in year: 57 Male %: 74 N0 %: 47 **Inclusion criteria** Inoperable OG cancer Karnofsky performance status of ≥50, normal FBC, liver and renal function tests **Exclusion criteria** Patients with adenocarcinoma, a second primary neoplasm, recurrence or metastatic disease	Please find details in Zhu 2015 SR.	With α=0.05 and β=0.10, 251 patients was planned so that an improvement of 10% could be detected from 10% (for the RT group) to 20% (in CRT group). But, the study was prematurely closed due to insufficient interest on the part of referring physicians in the belief that more dose-intensive CRT schedules were warranted	Strictures needing dilatation CRT: 18/65 RT: 8/60	**Cochrane risk of bias tool** Selection bias random sequence generation: unclear allocation concealment: unclear Performance bias blinding: unclear Detection bias blinding: unclear Attrition bias The study did not meet the prior sample size requirement. Reporting bias outcomes stated in the objective were reported Overall assessment: UNLCEAR risk of

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
outcomes being compliance and morbidity of treatment. **Study dates** April 1999 and December 2005 **Source of funding** NR					bias due not inadequate reporting of randomisation, allocation concealment, blinding and sample size. **Other information**
Full citation Law, S., Fok, M., Chow, S., Chu, K. M., Wong, J., Preoperative chemotherapy versus surgical therapy alone for squamous cell carcinoma of the esophagus: a prospective randomized trial, The Journal of thoracic and cardiovascular surgery, 114, 210-7, 1997 **Ref Id** 474743 **Country/ies where the study was carried out** **Study type**	**Sample size** N= 147 Chemotherapy (CT) + Surgery (Sx) (n=74) versus Sx alone (n=73) **Characteristics** Age (mean): 63.5 years Male %: 85 **Inclusion criteria** histologic evidence of squamous cell carcinoma	**Interventions** **CT +Sx versus Sx alone** **CT** Cisplatin 100 mg/m^2 day 1 and 5 FU 500 mg/m^2/day day 1-5 Cycle repeated on days 22-26 Surgery performed on day 42 **Surgery**	**Details** A prospective randomized trial was undertaken in 147 patients: 74 received preoperative chemotherapy comprising cisplatin and 5-fluorouracil and 73 had surgical therapy alone. End points were cancer and therapy-related deaths.	**Results** **Treatment-related morbidity** Blood loss CS group (n=60): 795 mL +/- 58 S group (n=69): 733 mL +/- 30 Wound infection CS group: 4/60 S group: 7/69	**Limitations** No serious limitations. **Cochrane risk of bias tool** Selection bias random sequence generation: unclear allocation concealment: unclear Performance bias blinding: unclear but unlikely due to obvious difference between treatments

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
RCT **Aim of the study** This study investigated the role of preoperative chemotherapy in squamous cell cancer of the esophagus. **Study dates** December 1989 to January 1995 **Source of funding** NR	thoracic tumour site **Exclusion criteria** nonregional lymph node metastases distant metastases tumour infiltration to trachea or bronchi inadequate renal, bone marrow function history of cancer in last 5 years	Abdominal and right thoracotomy incisions with a mediastinal lymphadenectomy.			Detection bias blinding: unclear but unlikely due to obvious difference between treatments Attrition bias outcome date complete Reporting bias outcomes stated in the objective were reported Overall assessment: UNLCEAR risk of bias due not inadequate reporting of allocation concealment, randomization process and blinding. **Other information**
Full citation	**Sample size**	**Interventions**	**Details**	**Results**	**Limitations**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Le Prise, E., Etienne, P. L., Meunier, B., Maddern, G., Ben Hassel, M., Gedouin, D., Boutin, D., Campion, J. P., Launois, B., A randomized study of chemotherapy, radiation therapy, and surgery versus surgery for localized squamous cell carcinoma of the esophagus, CancerCancer, 73, 1779-1784, 1994 **Ref Id** 474749 **Country/ies where the study was carried out** France **Study type** RCT **Aim of the study** To evaluate the contribution of sequential preoperative chemotherapy and radiation therapy to the treatment of localised SCC of esophagus **Study dates**	n=86; Chemoradiotherapy (CRT) + Surgery (Sx) = 39 Sx alone = 47 **Characteristics** Median age(years) and range: 56 (32 to 69) Male %: 93 **Inclusion criteria** Histologically proven SCC esophagus <70years WHO status <2 Estimated survival time of > 3months No previous treatment of cancer	**CRT + Sx versus Sx alone** Details can be found in Kumagai 2014 SR.	A sample of 150 patients was planned, so that an improvement in 2-year survival rate from 10% to 30% could be detected with type I error of 0.05. The study was ended at 104 patients which were considered for randomisation. Out of 104, 18 was found to be unsuitable. Finally, 86 were randomised and included in anlaysis(statistical power 0.7)	**T0 stage after resection** CRT +S: 5/39 S alone: 1/47 **Disease free survival (median in months)** CRT+S: 7.6 months S alone: 5 months **Survival at 3-years follow-up** CRT+S: 19.2% S alone: 13.8%	**Cochrane risk of bias tool** Selection bias random sequence generation: unclear allocation concealment: unclear Performance bias blinding: unclear Detection bias blinding: unclear Attrition bias High as the study stopped recruitment without fulfilling the initial sample size. Reporting bias outcomes stated in aim reported Overall assessment: unclear risk of bias due to inadequate

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
January 1988 to April 1991 **Source of funding** NR	Informed consent **Exclusion criteria** Loss of body weight >15% normal Tracheosophageal fistula or histologic proof of tracheobronchial invasion Metastatic deposits in other viscera Supraclavicular lymph node involvement Paralysis of the recurrent laryngeal nerve History of cancer except skin cancers or CIS cervix or respiratory or GI without evidence of recurrence for at least 5 years				reporting of randomization and blinding **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Lee, J. L., Park, S. I., Kim, S. B., Jung, H. Y., Lee, G. H., Kim, J. H., Song, H. Y., Cho, K. J., Kim, W. K., Lee, J. S., Kim, S. H., Min, Y. I., A single institutional phase III trial of preoperative chemotherapy with hyperfractionation radiotherapy plus surgery versus surgery alone for resectable esophageal squamous cell carcinoma, Annals of OncologyAnn Oncol, 15, 947-54, 2004 **Ref Id** 474752 **Country/ies where the study was carried out** Korea **Study type** RCT **Aim of the study** A prospective phase III study of concurrent CRT followed by surgery (CRT+S) versu surgery alone for	**Sample size** n=101 Chemoradiotherapy (CRT) +Surgery (Sx)= 51 Sx alone = 50 **Characteristics** Median age, years (range) 63 (39 - 75) Gender: male ; 92% ECOG perfomance 0/1 : 5/96 (out of 101 total participants) node +ve tumour %: 64 **Inclusion criteria** Previously untreated, biopsy proven invasive SCC of the esophagus	**Interventions** **CRT +Sx versus Sx alone** Please find in Kumagai 2014 for details	**Details** Survival time was calculated from the date of randomisation to the date of death due to any cause. Event free survival was definded as the time from the date of randomisation to the date of first observation of disease progression or relapse or death due to any cause. The survival anlalysis was performed by the actuarial Kaplan-Meier method and differences between the curves were analysed using the log-rank test.	**Results** number going to surgery: CRT +S: 35/51 (the rest 16: 10 refused, 2 inoperable, 2 unresectable and 2 died) S alone: 48/50 (the rest 2 refused) **Number going to R0 resection among those going for surgery:** CRT +S: 35/35 S alone: 42/48 **Survival rates at 2-years** CRT+S: 55% S alone: 57%	**Limitations** **Cochrane risk of bias tool** Selection bias --> Unclear risk random sequence generation: unclear allocation concealment: unclear Performance bias --> Unclear risk blinding: unclear Detection bias ---> unclear blinding: unclear Attrition bias --> Low risk No loss of data Reporting bias --> Low risk outcomes stated in aim reported

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
patients with resectable SCC. The primary endpoint was overall survival. Secondary endpoints were event-free survival, pathological response to CRT and pattern of failure. **Study dates** March 1999 to May 2002 **Source of funding** NR	clinically resectable esophageal carcinoma (IIA, IIB and III; T2-3N0M0 and T1-3N1M0) according to American Joint Committee on Cancer Classification ≥18 years Eastern Cooperative Oncology Group (ECOG) performance status ≥2 Adequate bone marrow reserve consisting of WBC count of >3500 cells/ul and a platelet count of >100000/ul Adequate renal function with serum creatinine level of <1.5 mg/dl		Sample size calcualation: needed 190 patients to dtect improvement in median survival from 15 to 22 months , corresponding to an increase in the 2-year survival rate from 30% to 50% (Hazard ratio 0.625) 80% power and α of 0.05.	**Event free interval at 2 years** CRT+S: 49% S alone: 51%	Overall assessment: unclear risk of bias due to inadequate reporting of randomization and blinding. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	bilirubin <1.5 mg/l no history of prior malignancy excluding surgically cured basal cell carcinoma of the skin **Exclusion criteria** if the primary tumour was located in the cervical esophagus (upper border, <18 cm from the incisor teeth) or if there were cervical or coeliac lymph node involvement or evidence of distant metastasis or if they had previously undergone treatment for esophageal carcinoma				
Full citation	**Sample size**	**Interventions**	**Details**	**Results**	**Limitations**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Lv, J., Cao, X. F., Zhu, B., Ji, L., Tao, L., Wang, D. D., Long-term efficacy of perioperative chemoradiotherapy on esophageal squamous cell carcinoma, World Journal of GastroenterologyWorld J Gastroenterol, 16, 1649-54, 2010 **Ref Id** 474813 **Country/ies where the study was carried out** China **Study type** 3-armed study (CRT followed by Sx versus Sx followed by CRT vs Sx alone) **Aim of the study** To investigate the role of perioperative CRT in the treatment of locally advanced thoracic eosphageal SCC **Study dates**	n=160 Chemoradiotherapy (CRT) + Surgery (Sx) = 80 Sx + CRT: 80 Sx alone: 80 **Characteristics** Age (≥60 years) %: 56 Male %: 64 **Inclusion criteria** Stage II to III thoracic esophageal SCC (diagnosed by endoscopic biopsy and histopathology diagnosed by endoscopic biopsy and histopathology) Stage II: thickness exceeded 5mm but no invasion of the mediastinum or distant metastasis	**CRT+Sx versus Sx+CRT versus Sx alone** **Concomitant CRT:** Preop CRT: radiation therapy (RT) was delivered in a total dose of 40 Gy (20 fractions at 2 Gy per fraction) i. Postop CRT: radiation was Delivered in daily fractions of 2 Gy to a total dose of 40Gy over 4 week Then, 10Gy boost was delivered through parallel opposed lateral or oblique portals for limitationof spinal cord radiation dose. Chemotherapy – 2 cycles on days 1-3 and 22-24 of RT.	The primary endpoint of the study was Progression free survival and the secondary was overall survival.	**Radical resection (n)** CRT+Sx: 76/80 Sx+CRT: 61/78 Sx alone: 64/80 **10 year progression free survival** CRT+Sx: 18.1% (15/80) Sx+CRT: 17.8% (14/78) Sx alone: 6.2% (5/80) **10 year overall survival** CRT+Sx: 24.5% (20/80) Sx+CRT: 24.4% (19/78) Sx alone: 12.5% (10/80) **Haemorrhage during surgery (>300 mL)**	**Cochrane risk of bias tool** Selection bias random sequence generation: Computer generated allocation concealment: unclear Performance bias blinding: unclear Detection bias blinding: unclear Attrition bias No loss of data Reporting bias outcomes stated in aim reported Overall assessment: unclear risk of bias due to inadequate reporting of

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
January 1997 and June 2004 **Source of funding** NR	Stage III: invaded the adjacent mediastinal structure **Exclusion criteria**	Paclitaxel + cisplatin was used including (135 mg/m^2 per day) as a short-term infusion on day 1 of each cycle, while DDP (20 mg/m^2 per day) was delivered as a continuous infusion over 24 hour on days 1-3 of each cycle. The dose in second cycle was adjusted according to haematological toxicities. **Surgery:** Oesophagectomy through left or right thoracotomy with 2-field lymphadenectomy		CRT+Sx: 8/80 Sx+CRT: 2/78 Sx alone: 2/80 **Stomal leakage** CRT+Sx: 1/80 Sx+CRT: 0/78 Sx alone: 0/80 **Stomal stricture** CRT+Sx: 2/80 Sx+CRT: 3/78 Sx alone: 1/80 **Treatment-related death** CRT+Sx: 3/80 Sx+CRT: 0/78 Sx alone: 0/80	randomization and blinding. **Other information**
Full citation Maipang, T., Vasinanukorn, P., Petpichetchian, C., Chamroonkul, S., Geater, A., Chansawwaang, S., Kuapanich, R., Panjapiyakul, C.,	**Sample size** N=46 (Chemotherapy(CT) + Surgery (Sx)= 24,	**Interventions** **CT +Sx versus Sx alone** **Induction CT**	**Details** Randomisation After determination of eligibility and	**Results** **Median survival** CT+Sx: 17 months	**Limitations** Uncertainty NR. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Watanaarepornchai, S., Punperk, S., Induction chemotherapy in the treatment of patients with carcinoma of the esophagus, Journal of Surgical OncologyJ Surg Oncol, 56, 191-7, 1994 **Ref Id** 474823 **Country/ies where the study was carried out** Thailand **Study type** RCT **Aim of the study** Evaluate the effect of chemotherapy regimen in squamous cell carcinoma of the esophagus and to determine whether induction chemotherapy improves symptom-free period and survival in these patients compared with surgery alone. **Study dates** Carried out from August 1988 to December 1990.	Sx alone =22) **Characteristics** Mean age: 64.5 years **Inclusion criteria** previously untreated documented squamous cell carcinoma <75 years ECOG performance status of 0,1,2 adequate renal, hepatic, bone marrow function FEV1> 1.2 litres free from infection **Exclusion criteria** evidence of locally advanced disease (invasion, fistula, obstruction)	Cisplatin 100mg/m^2 IV day 1 Vinblstine 3 mg/m^2 IV Days 1,8,15,22 Bleomycin 10 mg/m^2 IV day 3, 10mg/m^2/day over 4 days Cycle repeated on Day 29 Surgery performed 2 weeks after completion of 2nd cycle **Surgery** Standard Ivor-Lewis esophagectomy with 5 cm surgical margin Reconstruction: esophagogastrostomy or colon interposition. Cervical anastomosis was performed for	before the institution of treatment. Follow-up Every 4 weeks in the first year and 2-3 month intervals in the second and third year.	S: 17 months (P=0.186) **6-month overall survival** CT+Sx: 69% Sx: 89% (uncertainty NR) **3-year overall survival** CT+Sx: 31% Sx: 36% (uncertainty NR) **Treatment-related mortality** CT+Sx: N= 4 Sx: N=0	**Cochrane risk of bias tool** Selection bias random sequence generation: unclear allocation concealment: unclear Performance bias blinding: unclear but unlikely due to obvious difference between treatments Detection bias blinding: unclear but unlikely due to obvious difference between treatments Attrition bias outcome date complete Reporting bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding Support from a Thai government grant to the Faculty of Medicine, Prince of Songkla University.	distant mets other primary cancer within 5 years cricoid or cervical esophageal cancer	upper oesophageal cancer.			outcomes stated in the objective were reported Overall assessment: UNLCEAR risk of bias due not inadequate reporting of allocation concealment, randomization process and blinding.
Full citation Mariette, C., Dahan, L., Maillard, E., Mornex, F., Meunier, B., Boige, V., Surgery alone versus chemoradiotherapy followed by surgery for stage I and II oesophageal cancer: Final analysis of a randomised controlled phase iii trial-FFCD 9901, Diseases of the EsophagusDis Esophagus, 25, 53A, 2012 **Ref Id**	**Sample size** n=195 Chemoradiotheray (CRT) plus surgery (Sx) = 98 Surgery alone = 97 **Characteristics** Age (years) median and range : 57.8 years, (36.9 to 76.4)	**Interventions** **CRT + Sx versus Sx alone** **Chemoradiotherapy (CRT) (Concurrent):** 2 cycles of fluorouracil and cisplatin (FU 800 mg/m^2 per 24 hours from days 1 to 4 and 29 to 32; Cisplatin [75 mg/m^2 by infusion on day 1 or 2 and again	**Details** Eligible patients were randomly assigned to receive either NCRT followed by surgery or surgery alone group in 1:1. Patients were stratified according to centre, histology, disease stage (I v IIA v IIB) and tumour location	**Results** **Disease-free survival (DFS)** CRT+S: 14/98 S alone: 7/96 **Overall survival at 8 years** CRT+Sx: 15/98 Sx alone: 11/96	**Limitations** **Cochrane risk of bias tool** Selection bias random sequence generation: "centrally with a minimization technique" allocation concealment: unclear Performance bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
474834 **Country/ies where the study was carried out** French **Study type** Multi-centred RCT **Aim of the study** To assess whether neoadjuvant chemoradiotherapy improves outcomes for patients with stage I or II locally advanced esophageal cancer. The primary endpoint was overall survival. Secondary end points included disease-free survival (DFS), in-hospital postoperative mortality and morbidity and identification of prognostic factors for OS. **Study dates** June 2000 to June 2009 **Source of funding** French National Cancer Institute and Lile University Hospital	Male %: 85.6 SCC %: 70.3 N0 %: 72.3 **Inclusion criteria** Patients age < 75 years, judged suitable for curative resection with untreated stage I or II (T1 or T2, N0 or N1 and T3N0, M0) thoracic esophageal adenocarcinoma or squamous cell carcinoma,as assessed by CT and Endoscopic USG Capable of receiving either treatment with WHO performance status of 0 or 1 **Exclusion criteria** Weight loss > 10% at baseline and respiratory, liver or cardiac insufficiency	on day 29 or 30] or [15 mg/m2 from days 1 to 5 and 29 to 33] and a total dose of 45 Gy in 25 fractions (5 fractions per week) over 5 weeks **Surgery:** performed 4 to 6 weeks after completion of NRCT in group CRT and within 4 weeks of random assignment in group S. Surgery: Transthoracic oesophagectomy with extended two-field lymphadenectomy and high intrathoracic anastomosis for tumours with infracardinal proximal margin or cervical anastomosis when the proximal margin was above the carina.	(above or below carina). Out of 98 being assigned to CRT and surgery, 84 patients completed 2 cycles of chemotherapy. Three patients with non-resectable primary tumour were removed from the analysis and finally, 81 patients were inclued in the analysis. There were no treatment-related deaths before surgery. Out of 97 being assigned to Surgery alone, 91 patients underwent surgery whereas si x patients did not undergo sugery for metastaes on exploration(n=3) or liver cirrhosis discovere	**30-day postoperative mortality** CRT+S: 6/81 Sx alone: 1/89 **In-hospital postoperative mortality** CRT+S: 9/81 S alone: 3/89 **Post-operative complication (Any)** CRT+S: 18/81 Sx alone: 25/89 **Post-operative complication (infection)** CRT+S: 8/81 Sx alone: 5/89 **HR for death of SCC subgroup** CRT+S: 42/67 S alone: 46/70	blinding: unclear Detection bias blinding: unclear There is no difference in baseline characters between the two groups Attrition bias High risk Reporting bias outcomes stated in aim reported Overall assessment: unclear risk of bias due to inadequate reporting **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Patients with a previously treated malignancy, evidence of supraclavicular or celiac nodes, a multifocal tumour, tumour with a proximal limit < 19 cm from the incisor teeth or Evidence of invasion of the tracheobronchial tree		d at surgery (n=1) or unavailabl e data (n=2). Two patients with unresectable tumour were subsequently removed and finally, 89 patients were inclued in analysis.	**R0 resection** CRT+S: 76/81 S alone: 82/89	
Full citation Medical Research Council Oesophageal Cancer Working, Group, Surgical resection with or without preoperative chemotherapy in oesophageal cancer: a randomised controlled trial, LancetLancet, 359, 1727-33, 2002 **Ref Id** 474851	**Sample size** N=802 Chemotherapy (CT) + Surgery (Sx): 400 Sx alone: 402 **Characteristics** Median age= 63 (range 30-84)	**Interventions** **CT + Sx versus Sx alone** **CT** Preoperative chemotherapy comprised 2 cycles of cisplatin 80mg/m^2 by intravenous infusion over 4 hours on day 1	**Details** The study recruited 802 patients, 400 on CS and 402 on S. The nature of the first recurrence event and cause of death are detailed. Statistics	**Results** **1- year Overall Survival** CT+Sx group: 231/400 Sx group: 185/402 **3-year overall survival**	**Limitations** Preoperative RT offered to some patients. 9% of patient in each arm received pre-op RT. **Cochrane risk of bias tool**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out UK **Study type** RCT **Aim of the study** We aimed to assess the effects of preoperative chemotherapy on survival, dysphagia, and performance status in patients with esophageal cancer undergoing resection. **Study dates** Between March, 1992, and June, 1998 **Source of funding**	605 M/ 197 F Histology: SCC %: 31 AC: 533 Undifferentiated:21 Unknown: 1 **Inclusion criteria** previously untreated cancer of the oesophagus that was judged resectable microscopically confirmed as squamous carcinoma, adenocarcinoma, or undifferentiated carcinoma. tumours of the upper, middle, or lower third of the oesophagus and of the cardia	and fluorouracil 1,000 mg/m^2 daily as a continuous infusion over 96 hours repeated every 3 weeks. **Surgery** The surgical procedure was selected by the surgeon according to tumor site and local practice. Preoperative radiotherapy was permitted because at the time of recruitment there was still uncertainty about its role. Clinicians who chose to use it had to use it for all patients irrespective of random assignment group	Overall survival was calculated from the date of random assignment to date of death from any cause and surviving patients were censored at the date they were last known to be alive. Disease-free survival was calculated from a landmark time of 6 months from random assignment to allow for the difference in timing of surgery between the two groups. In this analysis, events including macroscopically incomplete resection, local and distant recurrence, and death arising within the first 6 months after	CT+Sx group: 81/400 Sx group: 70/402 **5-year overall survival** CT+Sx group: 14/400 Sx group: 10/402 **Treatment-related morbidity: Infection** CT+Sx group: 21/400 Sx group: 32/402 **SCC subgroup: overall survival at 5 years** CT + Sx: 9/123 Sx alone: 5/124	Selection bias random sequence generation: unclear allocation concealment: randomization by telephone call to clinical trials unit Performance bias blinding: unclear but unlikely due to obvious differences between treatments Detection bias blinding: unclear but unlikely due to obvious differences between treatments Attrition bias outcome data complete Reporting bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
The trial was funded by the British Medical Research Council	**Exclusion criteria** postcricoid cancers comorbid contraindications to surgery or chemotherapy		random assignment were regarded as events at this landmark time.		outcomes stated in aim reported Overall assessment: unclear risk of bias due to inadequate reporting of randomization and blinding. **Other information** Same trial as reported in Allum, 2009
Full citation Nygaard, K., Hagen, S., Hansen, H. S., Hatlevoll, R., Hultborn, R., Jakobsen, A., Mäntyla, M., Modig, H., Munck-Wikland, E., Rosengren, B., Pre-operative radiotherapy prolongs survival in operable esophageal carcinoma: a randomized, multicenter study of pre-operative radiotherapy and chemotherapy. The second Scandinavian trial in esophageal cancer, World Journal of	**Sample size** n=217 (n=186 included in analysis); **50 in Surgery (Sx) alone; 56 in Chemotherapy (CT) followed by Sx**; 58 in RT followed by Sx; **53 in Chemoradiotherap**	**Interventions** **CRT + Sx versus CT +Sx** Details of the interventions can be found in Kumagai 2014 SR.	**Details** **Surgery (Sx)**: 50 being randomized; 41 being analysed **Chemotherapy (CT) followed by Sx**: 56 being randomized, 50 being analysed **Chemoradiotherapy (CRT) followed**	**Results** **number of participants with curative resection** Sx: 15/41 CT+Sx: 22/50 CRT+Sx: 26/47	**Limitations** **Cochrane risk of bias tool** Selection bias random sequence generation: unclear allocation concealment: unclear Performance bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
SurgeryWorld J Surg, 16, 1104-9; discussion 1110, 1992 **Ref Id** 474919 **Country/ies where the study was carried out** Norway **Study type** RCT **Aim of the study** To compare 4 treatment alternatives, surgery alone or surgery combined with pre-operative chemotherapy, radiotherapy, or a combination of these in esophageal cancer **Study dates** January 1983 to January 1988 **Source of funding** NR	**y (CRT) followed by Sx** **Characteristics** Age (median) years: 62.6 Male %: 71 **Inclusion criteria** <75 years Karnofsky performance state 50 No other diseases contraindicating surgery Tumour stage T1 or T2, Nx, M0, located at least 21 cm form the incisor teeth or below the 5th thoracic vertebra Histologically verified SCC **Exclusion criteria** None		**by Sx:** 53 being randomized, 47 being analysed ITT being performed did not differ from analyses of the 186 correctly treated and reported patients.	**Probability of being alive at 36 months** Sx: 0.09 CT+Sx: 0.03 CRT+Sx: 0.17 There was significant difference between survival in CRT+Sx and CT+ Sx.	blinding: unclear Detection bias blinding: unclear Attrition bias ITT analysis did not differ from complete case analysis - low risk Reporting bias outcomes stated in aim reported - low risk Overall assessment: unclear risk of bias due to inadequate reporting of randomization and blinding. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Pottgen, C., Stuschke, M., Radiotherapy versus surgery within multimodality protocols for esophageal cancer--a meta-analysis of the randomized trials, Cancer Treatment ReviewsCancer Treat Rev, 38, 599-604, 2012 **Ref Id** 474969 **Country/ies where the study was carried out** Germany (RCTs: China, USA, Germany, Scandinavia) **Study type** Systematic Review of RCTs **Aim of the study** Perform a meta-analysis of the published randomized trials investigating radiotherapy versus surgery within multimodality protocols for esophageal cancer.	**Sample size** 6 RCTs (N= 929 total) Chemoradiotherapy (CRT) plus Surgery versus chemoradiotherapy (3 RCTs; N=489) (Gray 2005, Stahl 2005/2008, Bedenne 2007) Surgery alone versus chemoradiotherapy(3 RCTs; N=440) (Chiu 2005, Sun 2006, Carstens 2007) **Characteristics** Studies compared definitive chemoradiotherapy to surgery alone or	**Interventions** **CRT+Sx vs CRT (3 RCTs)** **CRT vs Sx (3 RCTs)** **Chiu 2005** Sx alone two or three stage approach with two-field lymphadenectomy CRT: concurrent 50-60 Gy/ 2 Gy Ciplatin/5-FU **Stahl 2005/2008** Sx+induction CRT :(two-stage approach with two-field lymphadenectomy). The resected oesophagus was usually replaced by the stomach, with a cervical	**Details** Database Search PubMed, Medline and Web of Science have been search to identify RCTS. Studies published as conference abstracts were analysed using the full meeting presentation. Analysis Hazard Ratios were the principle data extracted from studies. SAS and RevMan were used to analyse data. In order to make RT doses comparable, BED was used. Bias Assessment	**Results** **Overall Mortality estimates (death per number of randomized patients)** Studies= 6 N=929 Hazard Ratio (95% CI)= 0.98 (0.83, 1.16) Chiu 2005 : Sx: 20/44 versus CRT: 15/36 Sun 2006: Sx: 63/135 versus CRT: 65/134 Carstens 2007: Sx arm: 42/45 versus CRT arm: 37/46 Gray 2005 Sx+CRT: 13/31 versus CRT:11/27	**Limitations** Results of bias assessment NR. **Other information** ROBIS tool for bias risk assessment in systematic reviews: Study Eligibility Criteria Did the review adhere to pre-defined objectives and eligibility criteria? Yes Were the eligibility criteria appropriate for the review question? Probably Yes Were the eligibility criteria unambiguous? Probably No Were all the restrictions on

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates RCTs included 2005-2008 **Source of funding** No funding reported.	surgery plus induction treatment with potentially resectable carcinoma. **Chiu 2005** N= 80 Histology= SCC Country= China Inc. Criteria= resectable thoracic esophagus **Gray 2005** N= 58 Histology= SCC/AC Country= USA Inc. Criteria= Stage I-III esophagus or junctional carcinoma	oesophagogastric anastomosis. Induction CRT (5FU Leucovorin Etoposide Cisplatin X3 40 Gy/2 Gy concurrent) CRT: 60 Gy/2 Gy concurrent cisplatin etoposide, brachytherapy OR 50 Gy/2 Gy concurrent cisplatin etoposide + 15 Gy/ 1.5 Gy bid **Bedenne 2007** Sx+ Induction CRT: No type of surgery recommended induction CRT (15 Gy/3Gy x2 concurrent Cisplatin 5Fu x2 OR 46 gy/2Gy concurrent cisplatin 5FUx2) CRT: 15 Gy/3Gy x3 concurrent Cisplatin 5Fu x3 OR 66	Quality of studies was assessed using the SIGN critical appraisal checklist. Publication bias was assessed using a funnel plot.	Stahl 2005/2008: Sx+CRT: 69/86 versus CRT: 75/86 Bedenne 2007 Sx+CRT: 90/129 versus CRT: 91/130 **Overall survival at 4 years % (95% CI)** Chiu 2005 : Not given Sun 2006: Sx: 31(23, 39) versus CRT: 36(28, 44) Carstens 2007: Sx arm: 23(10, 36) versus CRT: 29(16, 43) Gray 2005 Sx+CRT: 49(32, 66) versus CRT: 51(32, 70)	eligibility criteria based on study characteristics appropriate? Yes Were any restrictions in eligibility criteria based on sources of information available? Yes Concern regarding specification of study eligibility criteria: UNCLEAR- exclusion criteria not made explicit in the review Identification and Selection of Studies Did the search include an appropriate range of databases/electronic sources for published and unpublished reports? Yes Were the methods additional to database searching used to

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Stahl 2005 N= 174 Histology= SCC Country= Germany Inc. Criteria= uT3-4 N0-1 M0 thoracic esophagus **Sun 2006** N= 269 Histology= SCC/AC Country= China Inc. Criteria= resectable thoracic esophagus **Bedenne 2007** N= 259 Histology= SCC/AC Country= NR	Gy/2Gy concurrent cisplatin 5FUx2		Stahl 2005/2008: Sx+CRT: 30(14, 45) versus CRT: 20(5,36) Bedenne 2007 Sx+CRT: 23(15, 32) versus CRT: 26(17, 34) **Treatment Related Mortality (death per number of randomized patients)** Chiu 2005: Sx: 3/44 versus CRT: 0/36 Sun 2006: Sx: NR Carstens 2007: Sx : 1/45 versus CRT arm: 0/46 Gray 2005: NR Stahl 2005/2008: Sx+CRT: 11/86 versus CRT: 3/86	identify relevant reports? Yes Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible? Probably Yes Were restrictions based on date, publication format or language appropriate? Probably Yes Were efforts made to minimise error in selection of studies? Yes Concern regarding methods used to identify or select studies: LOW Data Collection and Study Appraisal Were efforts made to minimise error in data

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Inc. Criteria= uT3 N0-1 M0 thoracic esophagus **Castens 2007** N= 91 Histology= SCC/AC Country= Scandinavia Inc. Criteria= resectable thoracic esophagus **Inclusion criteria** English studies potentially resectable oesophageal carcinoma studies comparing definitive chemoradiotherapy to surgery alone or			Bedenne 2007 Sx+CRT: 12/129 versus CRT: 1/130 **Postoperative deaths due to surgical complications** Chiu 2005: Sx: 3/41 Sun 2006: Sx: NR Carstens 2007: Sx : 1/35 Gray 2005: 8/31 Stahl 2005/2008: Sx+CRT: 7/55 Bedenne 2007 Sx+CRT: 6/110	collection? No information were sufficient study characteristics available? Probably Yes Were all relevant study results collected for use and synthesis? Yes Was risk of bias formally assessed using appropriate criteria? Probably Yes Were efforts made to minimise error in risk of bias assessment? No information Concern: HIGH- data extraction methods not reported, quality assessment methods and results not reported Synthesis and Findings

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	with induction treatment intention-to-treat analysis only **Exclusion criteria** NR				Did the synthesis include all studies it should? Yes Were all pre-defined analyses reported and departures explained? Yes Was the synthesis appropriate given the nature and similarity in the research questions? Yes Was heterogeneity minimal or addressed? Yes Were the findings robust as demonstrated though funnel plot or sensitivity analysis? Yes Were biases in primary studies minimal or addressed in the synthesis? Probably Yes

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					Concern= LOW Risk of bias in the review Did the interpretation of findings address all the concerns identifies in 1-4? Yes Was the relevance of identified studies to the review's research question appropriately considered? Yes Did the reviewers avoid emphasizing results on the basis of their statistical significance? Probably Yes Risk of bias= HIGH-quality assessment unclear with results not reported
Full citation	**Sample size**	**Interventions**	**Details**	**Results**	**Limitations**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Rajabi Mashhadi, M., Bagheri, R., Abdollahi, A., Ghamari, M. J., Shahidsales, S., Salehi, M., Shahkaram, R., Majidi, M. R., Sheibani, S., The Effect of Neoadjuvant Therapy on Early Complications of Esophageal Cancer Surgery, Iranian journal of otorhinolaryngologyIran, 27, 279-84, 2015 **Ref Id** 474987 **Country/ies where the study was carried out** Iran **Study type** RCT **Aim of the study** To evaluate early post-operative side effects of oesophagectomy among two groups of patients: those undergoing surgery followed by neoadjuvant chemoradiotherapy (NACR) and those undergoing surgery with no NACR	n=100 Chemoradiotherapy (CRT) followed by surgery (Sx) (n=50) versus Surgery alone (n=50) **Characteristics** Age (mean) in years: 55 Male % = 53 SCC % = 72 **Inclusion criteria** Lower oesophageal cancer General condition suitable for cancer as well as lack of previous cardiac, pulmonary, or renal problems No contraindication to neoadjuvant treatment	**CRT + Sx versus Sx alone** **CRT:** Cisplatin followed by 50 Gy radiation. The radiation consisted of 4000 cGy and on the first and final days of radiotherapy, patients received chemotherapy with cisplatin (20 mg/m^2) and 5-fluorouracil (5FU) (700 mg/m^2/infusion over 24 hours). **Surgery**: Transhiatal oesophagectomy and cervical anastomosis	Preoperative staging was performed in all patients including a laboratory examination, endoscopic ultrasound scan and a computed tomography scan of the thorax and upper abdomen, as well as abdominal sonography and barium swallow.	**Anastomotic leakage** CRT followed by surgery: 0/50 Surgery alone: 1/50 **Cardiovascular complications** CRT followed by surgery: Surgery alone: **Hospital mortalities** CRT followed by surgery: 5/50 Surgery alone: 6/50 **Blood loss in the surgery** CRT followed by surgery: 400cc±25 Surgery alone: 390cc±15	**Cochrane risk of bias tool** Selection bias random sequence generation: Computer-generated random numbers allocation concealment: unclear Performance bias blinding: unclear Detection bias blinding: unclear Attrition bias No loss of follow up data Reporting bias Outcomes stated in method session (e.g. resectability of the tumour) was not reported

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates 2009 and 2011 **Source of funding** NR	lack of distant macroscopic metastases **Exclusion criteria** Cervical, upper and middle-part oesophageal cancer No desire for surgery following neoadjuvant chemoradiotherapy (NACR) Intolerance to surgery after receiving NACR acute malnutrition (albumin<2.5g/dl) macrometastases (Stage 4) and serious complication during surgery such as airway damage or intense bleeding				Overall assessment: unclear risk of bias due to inadequate reporting of methodology **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Schlag, P. M., Randomized trial of preoperative chemotherapy for squamous cell cancer of the esophagus. The Chirurgische Arbeitsgemeinschaft Fuer Onkologie der Deutschen Gesellschaft Fuer Chirurgie Study Group, Archives of SurgeryArch Surg, 127, 1446-50, 1992 **Ref Id** 475040 **Country/ies where the study was carried out** Germany **Study type** RCT **Aim of the study** To test the efficacy of of preoperative chemotherapy for squamous cell carcinoma of the esophagus	**Sample size** n= 46 Chemotherapy (CT) followed by surgery (Sx) = 22 versus Surgery alone = 24 **Characteristics** Age (median) years = 56.8 Male %: 89 There was no relevant differences between the groups in age, sex, tumour length or tumour location. **Inclusion criteria** Histologically confirmed squamous cell carcinoma of the oesophagus, potentially curable by surgery alone	**Interventions** **CT + Sx versus Sx alone** **CT**: fluorouracil 1000 mg/m^2 per day, by 24 hour continuous infusion for 5 days; cisplatin (20mg/m^2) was administerted on days 1 to 5 by IV short-term infusion. The schedule was repeated on days 22 and 43. Surgery was performed approximately 2 to 3 weeks after the last chemotherapeutic cycle. **Surgery:** Abdominothoracic oesophagectomy was performed only for tumours localised in the oesophagogastric junction. For all other patients a thoracoabdominocervi	**Details** With ∝=0.05 and 80% power, 57 patients in each group was required to detect an increase in resectability rate from 60% to 80%. The study discontinued after one year for the following reasons: 1) if the treatment-related mortality rate in the surgery and chemotherapy group was significantly higher than in the patients treated with surgery alone group; 2) if the probability of healthy survival in one therapy group was smaller than in the other group.	**Results** **Chemotherapy-related mortality** C+S: 2/21 (due to myelotoxicity) **Number going for salvage resection** C+S: 7/21 S alone: 10/24 Note - in C+S group, 1 patient violated protocol and removed from the analysis; 1 patient had compete remission; 2 patients died; 2 patients refused surgery and thus only 16 patients underwent surgery. But, the analysis considered was based on all	**Limitations** **Cochrane risk of bias tool** Selection bias random sequence generation: unclear allocation concealment: unclear Performance bias blinding: unclear Detection bias blinding: unclear Attrition bias one out of 22 patient in C+S group violated protocol. Reporting bias outcomes stated in the objective were reported

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Note - Non-randomised participants were excluded from this review. (31 out of 77 eligible participants) **Study dates** NR **Source of funding** NR	No evidence of distant metastases by computed tomographic scan of chest and abdomen and liver ultrasound No tumour infiltration or fistula to the trachea Age under 68 years No previous chemotherapy or radiotherapy Karnofsky performance status above 70% Normal FBC, liver and pulmonary function tests Patients agreed for randomisation **Exclusion criteria** None	cal approach was chosen. Dissection of cervical lymph nodes and posterior mediastinectomy with resection of paraoesophageal and paratracheal lymph nodes were mandatory.	There was one protocol violation (a patient unable to undergo chemotherapy after randmisation) and one patient unavailable to follow-up.	patients undergoing chemotherapy.	Overall assessment: UNLCEAR risk of bias due not inadequate reporting of randomisation, allocation concealment, and blinding. **Other information**
Full citation	**Sample size**	**Interventions**	**Details**	**Results**	**Limitations**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Smith, T. J., Ryan, L. M., Douglass, H. O., Jr., Haller, D. G., Dayal, Y., Kirkwood, J., Tormey, D. C., Schutt, A. J., Hinson, J., Sischy, B., Combined chemoradiotherapy vs. radiotherapy alone for early stage squamous cell carcinoma of the esophagus: a study of the Eastern Cooperative Oncology Group, International Journal of Radiation Oncology, Biology, PhysicsInt J Radiat Oncol Biol Phys, 42, 269-76, 1998 **Ref Id** 475081 **Country/ies where the study was carried out** USA **Study type** RCT **Aim of the study** Determine whether the combined use of 5Fu, mitomycin C and RT improved the disease-free survival and overall survival of patients with	N= 119 Chemoradiotherapy (CRT) + Surgery (Sx)= 59, Radiotherapy (RT) + Surgery (Sx)=60) **Characteristics** Stage I: 38 Stage II: 81 Location of Tumour: Upper 2/3: 60 Lower 1/3: 59 Male: 95 Female: 24 **Inclusion criteria** Stage I or II ECOG performance status 0, 1, 2	**CRT + Sx versus RT+Sx** **RT:** Cobalt-60 machines or linear accelerators. Dose to spinal cord could not exceed 4400 cGy and the total dose for patients being treated by radiation or chemoradiation without surgery was 6000 cGy to be given over 6.5 to 7 weeks. **CT:** Initiated with 24 hours of commencing RT. 5FU 1000 mg/m^2/day day 2-4, repeated on day 28 Mitomycin 10mg/m^2 day 2	Participants randomized to RT alone or RT plus chemo. Patients randomized with permuted blocks through the ECOG operations office. Follow-up Patients evaluated at 3 monthly intervals following therapy. Statistical analysis Fisher's exact and chi-squared used to compare patient characteristics. Comparison of survival based on log rank test and survival curves using the Kaplan-Meier method.	**1-year survival** RT+Sx: 33% CRT+Sx: 54% **3-year survival** RT+Sx: 8% CRT+Sx: 13% **5-year survival** RT+Sx: 7% CRT+Sx: 9% **Treatment-related mortality** RT+Sx: N=2 CRT+Sx: N=0	**Cochrane Risk of Bias Tool** Selection Bias random sequence generation: low risk- Patients randomized with permuted computerized-generated blocks allocation concealment: low risk- randomization through the ECOG operations office Performance Bias blinding: unclear but unlikely due to difference between treatments Detection Bias blinding: unclear but unlikely due to difference between treatments Attrition Bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
carcinoma of the esophagus, compared to those who received RT alone. **Study dates** July 1982- July 1988 **Source of funding** Public Health Service grants from the NCI, National Institutes of Health, and the Department of Health and Human Service.	adequate renal, hepatic and bone marrow status no infection no previous chemo or radiotherapy for this disease no other cancer within 5 years except for nonmelanoma skin cancer **Exclusion criteria** cervical carcinoma multiple tumours of the esophagus	**Surgery** After 4000 cGy patients could be evaluated for elective surgical resection at the discretion of the treating physician.			assessment made for main outcomes Reporting bias outcome reported complete Other: None Overall assessment: Moderate risk of bias due to adequate randomization but lack of blinding **Other information** .
Full citation Van Hagen, P., Hulshof, M. C. C. M., Van Lanschot, J. J. B., Steyerberg, E. W., Van Berge Henegouwen, M. I., Wijnhoven, B. P. L., Richel, D. J.,	**Sample size** n=368 Chemoradiotherapy (CRT) + Surgery (Sx) = 178	**Interventions** **CRT + Sx versus Sx alone** Please find in Kumagai 2014 SR.	**Details** 368 underwent randomisation. 180 and 188 were assigned to CRT+S	**Results** **Survival at 60 months** CRT+S: 28/178	**Limitations** **Cochrane risk of bias tool** Selection bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Nieuwenhuijzen, G. A. P., Hospers, G. A. P., Bonenkamp, J. J., Cuesta, M. A., Blaisse, R. J. B., Busch, O. R. C., Ten Kate, F. J. W., Creemers, G. J., Punt, C. J. A., Plukker, J. T. M., Verheul, H. M. W., Spillenaar Bilgen, E. J., Van Dekken, H., Van Der Sangen, M. J. C., Rozema, T., Biermann, K., Beukema, J. C., Piet, A. H. M., Van Rij, C. M., Reinders, J. G., Tilanus, H. W., Van Der Gaast, A., Preoperative chemoradiotherapy for esophageal or junctional cancer, New England Journal of MedicineN Engl J Med, 366, 2074-2084, 2012 **Ref Id** 475175 **Country/ies where the study was carried out** Netherlands **Study type** multi-centred phase III RCT **Aim of the study** To compare neoadjuvant chemoradiotherapy followed by surgery with surgery alone in	Sx alone = 188 **Characteristics** Age: Median: 60 years Gender: Male % : 78 Tumour type: SCC %: 23 Tumor staging: T2 and above %: 98 +ve lymph node %: 65 N1: 116/178 **Inclusion criteria** 18-75 years of age, WHO performance status ≤2 Participants withHistologically confirmed, potentially curable		and S alone respectively. 178 in CRT+S and 188 in S gourp were included in ITT analysis. A resection was not possible in 7 in CRT+S and 25 in S alone group because of the primary tumour or lymph nodes were identified as unresectable during surgery. CRT+S: 7 participants did not receive any CRT (5 because of disease progression before commencing therapy and 2 because of declination). A total of 162 (91%) received the full treatment regimen of five cycles of chemotherpy and 164 (92%) received	S alone: 17/188 *At 84.1 median follow-up, Median overall survival* *CRT +S: 48.6 months(95% CI 32.1 to 65.1)* *S alone: 24 months(95%CI 14.2 to 33.7)* **Survival at 60 months among SCC group** CRT+S: 8/41 S alone: 4/43 *At 84.1 median follow-up, Median overall survival (SCC subgroup)(* *CRT +S: 81.6 months(95% CI 47.2 to 116.0)* *S alone: 21.1 months(95%CI 15.4 to 26.7)*	random sequence generation: unclear allocation concealment: unclear Performance bias blinding: unclear but the baseline characters (age, gender, tumor type, locations and staging) were similar between the two groups Detection bias blinding: unclear Attrition bias ITT analysis Reporting bias High: One of the interested outcomes (quality of life) in the protocol was not reported in the study.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
patients with potentially curable esophageal or esophagogastric junction carcinoma **Study dates** March 2004 to December 2008 **Source of funding** Dutch Cancer Foundation	squamous-cell carcinoma, adenocarcinoma or large-cell undifferentiated carcinoma of the esophagus or esophagogastric junction (i.e., tumour involving both the cardia and the eosphagus on endoscopy) The upper border of tumor had to be at least 3cm below the upper esophageal sphincter. Only patients with tumours of clinical stage T1N1 or T2-3 N0-1 and no clinical evidence of metastatic spread Patients with adequate haematologic, renal, hepatic and pulmonary function		the full dose of radiotherapy. 2 participants (1%) received a higher dose of RT (45 and 54 Gy). The most common reason for not completing treatment was low platelet count.	**Grade 3 haematologic toxic effects among CRT+S group:** 12/171 (7%) Unadjusted and Adjusted Hazard ratio (HR (95%CI)): Any histology: 0.66 (0.50, 0.87) and 0.67 (0.50, 0.88) SCC only: 0.45(0.24, 0.84) and 0.42 (0.23, 0.79) **Number going to salvage resection:** CRT+S: 161/178 S alone: 161/188	Overall assessment: unclear risk of bias due to inadequate reporting of randomization and blinding. **Other information** Data were also taken from the protocol of the trial van Heijl, M., van Lanschot, J., Koppert, L.B., et al. (2008) Neoadjuvant chemoradiation followed by surgery versus surgery alone for patients with adenocarcinoma or squamous cell carcinoma of the esophagus (CROSS) BMC Surgery 8:21 Netherlands Trial Register number, NTR487

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	as well as no history of other cancer or previous radiotherapy or chemotherapy **Exclusion criteria** Participants with proximal gastric tumours with minimal invasion of the esophagus Lenght of tumor >8cm or width of tumor >5 cm				Shapiro, J., Lanschot, J.J.B.v., Hulshof, M.C., et al. (2015) Neoadjuvant chemoradiotherapy plus surgery alone for esophageal or junctional cancer (CROSS): long term results of randomised controlled trial. Lancet. 16
Full citation Wong, R., Malthaner, R., Combined chemotherapy and radiotherapy (without surgery) compared with radiotherapy alone in localized carcinoma of the esophagus, Cochrane database of systematic reviews (Online), CD002092, 2006 **Ref Id**	**Sample size** 19 RCTs included in the review. These studies pertain to 2013 patients. 15 of these studies pertain to this review question (published after	**Interventions** **RT VS CRT** **Araujo 1991** Concomitant CTRT CT: 5FU IV infusion day 1-3, mitomycin	**Details** **Databases Searched** The Cochrane Controlled Trials Register (CENTRAL) and MEDLINE, EMBASE and	**Results** **Mortality- Overall Survival (all studies)** Concomitant RT Studies= 11 n=998	**Limitations** No serious limitations. **Other information** ROBIS tool for bias risk assessment in systematic reviews: Study Eligibility Criteria

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
475219 **Country/ies where the study was carried out** Canada **Study type** Cochrane Systematic Review **Aim of the study** To compare the effectiveness of combined chemotherapy (CT) and radiotherapy (RT) with radiotherapy alone in the treatment of patients affected by localized carcinoma of the esophagus. **Study dates** Searches were run in 2005 **Source of funding** No funding declared.	1990). These are: Araujo 1991; Cooper 1999, Gao 2002; Hatlewoll 1992; Hishikawa 1991; Ji 2002; Kaneta 1997; Li 2000; Lu 1995; Roussel 1994; Slabber 1998; Tian 2000; Wobbes 2001; Zhou 1991; Zhu 2000. **Characteristics** Tumour location was thoracic (Araujo, Cooper, Ji, Zhu), cervical and thoracic (Hartlevoll, Slabber, Wobbes) or not reported. Trials excluded patients with distant metastasis. Most trials excluded patients with poor general health with small variation.	day 1, bleomycin IM day 1,7,14,21,28 RT: 50 Gy in 25 fr (BED= 38) **Cooper 1999** Concomitant CTRT CT: 5FU infusion day 1-4, for weeks 1,5,8,11 RT: 50 Gy in 25 fr (BED = 38) (RT only arm) 64 Gy in 32 fr (BED= 44.8) (CRT arm) **Gao 2002** Concomitant CTRT CT: Cisplatin 20 mg/d day 1-5, for weeks 1,4 RT: 30 Gy in 15 fr, OD, week 1-3, then	CancerLIT were searched. Trials Central, Centrer Watch, clinical trials.gov, current controlled tirals, national research register, Medical Research council Trials Central and Physicians Data Query were also searched for open, closed, unpublished and published trials. The standard cohcrane search strategy filter was applied. **Data Collection and Analysis** Data extraction sheets were designed a priori and data extraction was performed in duplicate. Only published data were used.	Peto OR (95% CI)= 0.73 (0.64, 0.84) Sequential RT Studies= 8 n=857 Peto OR (95% CI)= 0.87 (0.74, 1.02) **Overall Survival (concomitant RT studies)** **Araujo 1991 (n/N)** CRT: 25/28 RT: 30/31 Peto OR (95% CI): 0.64 (0.36, 1.14) **Cooper 1999** CRT: 48/61 RT: 62/62	Did the review adhere to pre-defined objectives and eligibility criteria? Yes Were the eligibility criteria appropriate for the review question? Yes Were the eligibility criteria unambiguous? Yes Were all the restrictions on eligibility criteria based on study characteristics appropriate? Yes Were any restrictions in eligibility criteria based on sources of information available? Y Concern regarding specification of study eligibility criteria: Low

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Araujo 1991 Operability not stated SCC only Stage II Survival > 3m Others: thoracic, <70 yrs, no fistula **Cooper 1999** Operability not stated SCC and AC Karnofsky performance status >50 Others: include mediastinal and supraclavicular lymph nodes	30 Gy in 20 fr, BID, week 4-5 (BED= 51) **Hatlevoll 1992** Sequential CT-RT CT: cisplatin day 1-5, day 15-19, bleomycin day 1-5, day 15-19 RT: 35 Gy in 20 fr, 3 week gap, 28 Gy in 16 fr (BED= 25) **Hishiwaka 1991** sequential CTRT Gap between CT-RT: 1 mth CT: futrafur 600 mg/po/od for at least 1 mth RT: 2 groups ext beam alone: 60-70 Gy in 33-35 fr (BED 45-51)	Biological effective dose (BED) was used in this review to compare between different regimens of radiotherapy. Homogeneity of the results was assessed through a visual plot and formal statistical testing. The data was combined using meta-analysis techniques to provide a summary statistic if the results appeared homogenous (chi squared test for homogeneity less than 0.1). RevMan was used to pool results and for meta-analysis. Reasons for heterogeneity were explored as follows:	Peto OR (95% CI): 0.59 (0.45, 0.77) **Gao 2002** CRT: 24/40 RT: 27/41 Peto OR (95% CI): 0.79 (0.46, 1.37) **Kaneta 1997** CRT: 10/12 RT: 11/12 Peto OR (95% CI): 0.75 (0.23, 2.40) **Li 2000** CRT: 38/48 RT: 46/48 Peto OR (95% CI): 0.65 (0.43, 1.00)	Identification and Selection of Studies Did the search include an appropriate range of databases/electronic sources for published and unpublished reports? Yes Were the methods additional to database searching used to identify relevant reports? Yes Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible? Probably Yes Were restrictions based on date, publication format or language appropriate? Probably Yes

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Gao 2002 Operability not stated SCC only Age </= 70 Others: primary tumour length 3-10 cm, no supraclavicular lymph nodes, no distant metastases **Hatlevoll 1992** Inoperable SCC only Karnofsky performance >50 Others: <75 yrs, **Hishikawa 1991**	ext beam/brachytherapy: 50-60 Gy in 28-30 fr/ 10-15 Gy (BED= 59-72) plus brachytherapy **Ji 2002** Sequential CTRT CT: 5FU continuous infusion day 1-5 500 mg/m^2; cisplatin IV day 1 60 mg/m^2; bleomycin IV 8 mg day 1,3,5 Interval between CT-RT: 3-7 days RT: 40-44 Gy in 20-22 fr, boost 24-28 Gy in 12-14 fr (BED= 53.9) **Kaneta 1997** concomitant CTRT	study quality type of chemotherapy used concomitant versus sequential radiotherapy radiotherapy dose fractionation Risk of Bias Quality of studies were assessed using two quality assessment tools: the Jadad scale and Detsky tool. The Jaded scale examines the adequacy of randomization process, whether the study was double blinded and whether all patients were accounted for. The Detsky tool	**Roussel 1994** CRT: 98/110 RT: 96/111 Peto OR (95% CI): 0.82 (0.62, 1.09) **Slabber 1998** CRT: 33/34 RT: 35/36 Peto OR (95% CI): 0.83 (0.50, 1.40) **Zhu 2000** CRT: 23/33 RT: 29/33 Peto OR (95% CI): 0.62 (0.36, 1.06)	Were efforts made to minimise error in selection of studies? Yes Concern regarding methods used to identify or select studies: LOW Data Collection and Study Appraisal Were efforts made to minimise error in data collection? Yes were sufficient study characteristics available? Yes Were all relevant study results collected for use and synthesis? Yes Was risk of bias formally assessed using appropriate criteria? Yes Were efforts made to minimise error in risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Resectability not stated SCC only <80 years old PS 0-3 **Ji 2002** Operability not stated SCC only Karnofsky performance status >/= 60 Others: tumour length </= 7 cm, exclude supraclavicular lymph nodes **Kaneta 1997** Resectability not stated	CT: cisplatin 5mg/m^2/day RT: 60 Gy in 30 fr, boost 10-12 Gy in 2-6 fr (BED= 45-52) **Li 2002** Concomitant CTRT CT: cisplatin IV 20 mg day 1-5, 5FU IV 500 mg day 1-5 RT: 60-70 Gy in 25-40 fr (BED=40-47) (RT only arm) 50-60 Gy in 30-35 fr (BED 35-40) (CRT arm) **Lu 1995** Sequential CT-RT (3 week gap) CT: intraarterial Adriamycin 60 mg,	examines five domains: randomization process outcome assessment inclusion exclusion criteria details of intervention appropriateness of statistics All studies were randomized with no blinding of patients of investigators. Based on these characteristics, most received a Jaded score of 2 with the exception of Zhu 2000 with a score of 1.	**Overall Survival (sequential RT studies)** **Hatlevoll (n/N)** CRT: 0/46 RT: 5/51 Peto OR (95% CI): 1.21 (0.77, 1.90) **Hishiwaka (n/N)** CRT: 20/24 RT: 21/25 Peto OR (95% CI): 1.04 (0.38, 2.81) **Ji 2002 (n/N)** CRT: 69/82 RT: 73/80 Peto OR (95% CI): 0.70 (0.50, 0.97)	of bias assessment? Yes Concern: LOW Synthesis and Findings Did the synthesis include all studies it should? Yes Were all pre-defined analyses reported and departures explained? Probably yes Was the synthesis appropriate given the nature and similarity in the research questions? Yes Was heterogeneity minimal or addressed? Yes Were the findings robust as demonstrated though funnel plot or

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	measurable disease SCC Performance status 0-2 Others: thoracic, <79 yrs, **Li 2000** Operability not stated Pathologically confirmed SCC and AC Karnofsky performance status >70 Others: <70 yrs, tumour length >/= 7 cm **Lu 1995**	5FU 1g, cisplatin 40 mg for 2 cycles each 3-4 weeks apart RT: 50 Gy in 25 fr (BED= 40) (CRT arm) 60-70 Gy in 30-35 fr (BED= 45-51) (RT only arm) **Roussel 1994** Concomitant CTRT CT: cisplatin 100 mg/m^2 day 1,23 RT: 20 Gy in 5 fr, 15 day gap, 20 Gy in 5fr (BED=34) **Slabber 1998** Concomitant CTRT CT: cisplatin 15 mg/m^2/day bolus, 5FU 600 mg/m2/day infusion day 1-5,29,33		**Lu 1995 NR** **Tian 2000** CRT: 45/56 RT: 49/56 OR- NR **Wobbes 2001** CRT: 104/110 RT: 110/111 Peto OR (95% CI): 0.83 (0.63-1.09) **Zhou 1991** CRT: 18/32 RT: 25/32 OR- NR **Mortality-Disease Free**	sensitivity analysis? Yes Were biases in primary studies minimal or addressed in the synthesis? Yes Concern= LOW Risk of bias in the review Did the interpretation of findings address all the concerns identifies in 1-4? Yes Was the relevance of identified studies to the review's research question appropriately considered? Yes Did the reviewers avoid emphasizing results on the basis of their statistical significance? Yes Risk of bias= LOW

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Advanced esophageal cancer Pathology not specified **Roussel 1994** Inoberable SCC **Slabber 1998** SCC T3NxM0 ECOG PS 0-2 **Tian 2000** Operability not stated Histology NR Karnofsky performance >70	RT: 20 Gy in 5 fr day 1-5, then 20 Gy in 5 fr day 29-33 (BED= 34) **Tian 2000** Sequential CT-RT CT: cisplatin IV 20 mg/day, day 1-5; 5Fu infusion 500 mg/day, day 1-5; vincristine IV: 2 mg day 1 RT: 50-60 Gy in 6-7 weeks after chemo (BED= 33-37) **Wobbes 2001** Sequential RT-CT RT: 20 Gy in 5 fr; 2 week gap; 20 Gy in 5 fr (BED= 45) CT: cisplatin 100 mg/m^2 3-4 days before RT x2		**Survival (all studies)** Concomitant RT Studies= 2 n=199 Peto OR (95% CI)= 0.56 (0.40, 0.78) **Cooper 1999** CRT: 35/57 RT: 54/61 Peto OR (95% CI): 0.46 (0.30-0.70) **Gao 2002** CRT: 16/40 RT: 13/41 Peto OR (95% CI): 0.79 (0.46-1.37) **Treatment Related**	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Others: exclude distant mets, supraclavicular lymph nodes **Wobbes 2001** SCC only Age <70 PS (WHO) 0-2 T1-3 Not operable because of physical condition or refused surgery Exclude: cervical/supraclavicular fossa lymph nodes; distant metastases; weight loss >20%; tumour to pharyngeal or gastric junction; tracheo or bronchial involvement	then q3-4 weekly x6 cycles in total **Zhou 1991** Sequential CTRT Gap 2-27 days CT: cisplatin day 1-2; 5FU day 3,6,10,13 RT: 65-75 Gy in 6-7 weeks (BED=49-56) **Zhu 2000** Concomitant RTCT CT: carboplatin 100mg/d x 5 days Day 1-5, 27-31 RT: external beam: A/D: 60 Gy in 30 fr, B/C: 38 Gy in 19 fr, then 12 Gy in 6 fr, then intracavitary		**Mortality- Toxic Deaths (all studies)** Concomitant RT Studies= 11 n=1011 OR, M-H (95% CI)= 1.79 (0.55, 5.90) **Araujo 1991** CRT: 0/28 RT: 1/31 OR M-H (95% CI): 0.36 (0.01-9.12) **Cooper 1999** CRT: 1/61 RT: 0/60 OR M-H (95% CI): 3.00 (0.12-75.11) **Slabber 1998** CRT: 2/34	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Zhou 1991 Early esophageal carcinoma <7.5cm length primary **Zhu 2000** Age <70 PS >/= 60 Thoracic Esophagus </=10 cm Exclude: supraclavicular fossa lymph nodes; vocal cord paralysis; fistula **Inclusion criteria**	intracavitary: B/C: 15-16 Gy in 3 fr (BED= 45)		RT: 2/36 OR M-H (95% CI): 1.06 (0.14, 8.00) (*All other studies 0 reported in both arms)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Only randomized studies included in this review. Both published and unpublished studies, full articles and abstracts, satisfying the criteria listed below were included. Patients with localized carcinoma of the esophagus who were candidates for potentially curative local regional radiotherapy (with or without chemotherapy) were the focus of this review. The control arm was radiotherapy alone. The intervention arm was				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	combination chemo-radiotherapy (no surgery). Treatment had to be given as curative intent. Either timing of chemo-radiotherapy were included. Primary outcome of interest was mortality. Secondary outcomes included disease specific survival, local recurrence rate, acute and chronic toxicities. **Exclusion criteria** Non-RCTs excluded. Studies that included surgery as part of the treatment were excluded. Other interventions excluded:				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	chemotherapy only, radiosensitizers, immunotherapy, hyperthermia, RCTs comparing RT courses without chemotherapy.				
Full citation Zhao, K. L., Shi, X. H., Jiang, G. L., Yao, W. Q., Guo, X. M., Wu, G. D., Zhu, L. X., Late course accelerated hyperfractionated radiotherapy plus concurrent chemotherapy for squamous cell carcinoma of the esophagus: a phase III randomized study, International Journal of Radiation Oncology, Biology, PhysicsInt J Radiat Oncol Biol Phys, 62, 1014-20, 2005 **Ref Id** 475273 **Country/ies where the study was carried out** China	**Sample size** N= 111 (Radiotherapy (RT)= 57, Chemoradiotherapy (CRT)= 54) **Characteristics** **RT group** 36 M/21 F Median age= 61.0 (41-74) Lesion location: 3 cervical/ 18 upper thorax/ 34 middle thorax/ 2 lower thorax	**Interventions** **CRT vs RT** **RT:** Late Course Accelerated Fractionated (LCAF) Radiotherapy 1st phase: 1.8 Gy/fr, 5 fr a week to 41.4 Gy/23fr in 4.6 weeks 2nd phase: 1.5 Gy/fr, 10 fr a week to 27 Gy/18fr in 1.8 weeks (A total of 68.4 Gy was irradiated in 41 fractions for 6.4 weeks)	**Details** Randomisation Randomized into two groups by random number table. Intervention Same RT schedule to both arms. Follow-up Every 4 months for 1 year, every 6 months for 2 years and then annually.	**Results** Overall, 94 patients died by the last follow-up visit in December 2010 and 17 patients survived with 9 patients in RT and 8 patients in CRT. **Treatment Related Mortality** CRT = 5/54 RT = 2/57 (poor nutrition and/or pulmonary toxicity)	**Limitations** Cochrane risk of bias assessment: Selection bias random sequence generation: LOW risk-random number table used allocation concealment: UNCLEAR Performance bias blinding: UNCLEAR Detection bias blinding: UNCLEAR

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type RCT **Aim of the study** To investigate the efficacy and the long-term outcomes of esophageal squamous cell carcinoma (SCC) treated by irradiation with or without concurrent chemotherapy **Study dates** March 1998- July 2000. **Source of funding** NR	Stage: T1-2N0M0= 11, T3-4N0M0= 37, T1-4N1M0= 9 **CRT group** 42 M/12 F Median age= 54.5 (39-74) Lesion location: 4 cervical/ 12 upper thorax/ 36 middle thorax/ 2 lower thorax Stage: T1-2N0M0= 11, T3-4N0M0= 37, T1-4N1M0= 6 **Inclusion criteria** confirmation of esophageal SCC by histology or cytology	**CT:** cisplatin 25 mg/m^2/day and 5FU 600 mg/m^2 IV day 1-3, every 4 weeks, with the 1st and 2nd cycle given during RT		**Treatment related morbidity:** Grade 3 esophageal stenosis --> 2/54 CRT vs 6/57 RT Grade 3 pulmonary complication --> 5/54 CRT vs 7/57 RT Grade 4 eosphageal and/or pulmonary complications --> 1/54 CRT vs 1/57 RT **Treatment related morbidity: Cumulative late toxicity incidences**	Attrition bias outcome data complete Reporting bias all outcomes of interest reported Overall assessment: Unclear risk of bias due to inadequate reporting of allocation concealment and blinding. **Other information** Additional data were taken from Liu, M., Shi, X., Guo, X. et al. (2012) Long term outcome of irradiation with or without cheomotherpy for esophageal squamous cell carcinoma: a final report on a prospective trial.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Clinical stage T1-4 N0-1 M0 adequate white blood cell count and renal function karnofsky performance >= 70 no prior therapy no previous malignancies no serious medical conditions that would preclude treatment **Exclusion criteria** evidence of esophageal perforation deep ulceration complete obstruction of esophageal lumen			5 years: 21% CRT vs 30% RT 8 years:26% CRT vs 33% RT 10 years: 26% CRT vs 33% RT **Treatment related morbidity: Intercurrent diseases** CRT: 3/54 RT: 2/57 **Median survival times** CRT: 32 months (CI: 8.6,55.4) RT: 25 months (CI: 21.3, 28.7)	Radiation Oncology, 7:142

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	esophageal bleeding involvement of supraclavicular lymph nodes distant metastases			**Overall survival rate at** **5 years:** 40% CRT vs 28% RT **8 years:** 29% CRT vs 21% RT **10 years:** 23% CRT vs 19% RT	
Full citation Zhu, L. L., Yuan, L., Wang, H., Ye, L., Yao, G. Y., Liu, C., Sun, N. N., Li, X. J., Zhai, S. C., Niu, L. J., Zhang, J. B., Ji, H. L., Li, X. M., A meta-analysis of concurrent chemoradiotherapy for advanced esophageal cancer, PLoS ONE [Electronic Resource]PLoS ONE, 10 (6) (no pagination), 2015 **Ref Id**	**Sample size** No. studies= 9 N= 1,135 Median age for the CRT group was 61 (Range 24-70) and 60 (range 34-76) for the RT group. Tumour stage NR.	**Interventions** **CRT versus RT** **Han 2012** CRT: nedaplatin + 5FU CF 64-66 Gy RT: CF 64-66 Gy **Herskovic 1992**	**Details** **Database Searches** Medline, Embase and Cochrane library were primary sources. Additional articles were identified with manual searching of reference	**Results** **Survival** **1-year survival rate (all studies)** Studies= 9, n= 1135 Risk Ratio, M-H (95% CI)= 1.14 (1.04, 1.24)	**Limitations** No serious limitations. **Other information** ROBIS tool for bias risk assessment in systematic reviews: Study Eligibility Criteria

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
475284 **Country/ies where the study was carried out** China **Study type** Systematic review of RCTs **Aim of the study** To compare the therapeutic effects of concurrent chemoradiotherapy and radiotherapy alone in local advanced esophageal cancer using meta-analysis. **Study dates** Databases searches were performed to identify all eligible published literature between May 1991 and December 2014. **Source of funding** American Heart Association, National High Technology Research and Development Program of China and Science and Technology Development Plan.	**Characteristics** All studies are relevant to this review question. 6 are described below. 3 studies (Araujo 1991, Cooper 1999 and Gao 2002) have already been described in the Wong, 2006 systematic review. **Han 2012** n= 130 country= China Tumour location= 67 upper, 59 middle, 5 lower **Herskovic 1992** n= 121 country= England	CRT: cisplatin 5FU + CF 50 Gy RT: CF 50 Gy **Kumar 2007** CRT: cisplatin CF + LCAF 50-64 Gy RT: CF + LCAF 50-64 Gy **Mirinezhad 2013** CRT: cisplatin 5FU DRT 40-44 Gy RT: DRT 40-44 Gy **Sheng 2011** CRT: Capecitabine CF + LCAF 64-69 Gy RT: CF + LCAF 64-69 Gy **Zhao 2005** CRT: Cisplatin + 5FU CF + LCAF 68.4 Gy	sections of topical papers. **Selection of studies** 426 articles were screened. 26 full-text articles were read in full with 9 selected to be analysed. Two independent researchers selected articles. **Data Extraction and Management** Data extraction was completed by 3 researchers. Data analysis was performed in Review Manager. Q statistics were applied to test the heterogeneity of qualifying studies with P<0.05 indicating heterogeneity.	**Han 2012 (events/total)** CRT: 46/65 RT: 48/65 RR M-H (95 CI%): 0.96 (0.77-1.19) **Herskovic 1992 (events/total)** CRT: 28/61 RT: 17/60 RR M-H (95 CI%): 1.62 (1.00-2.63) **Kumar 2007 (events/total)** CRT: 33/65 RT: 18/60 RR M-H (95 CI%): 1.69 (1.07-2.63) **Mirinezhad 2013 (events/total)**	Did the review adhere to pre-defined objectives and eligibility criteria? Yes Were the eligibility criteria appropriate for the review question? Yes Were the eligibility criteria unambiguous? Yes Were all the restrictions on eligibility criteria based on study characteristics appropriate? Probably Yes Were any restrictions in eligibility criteria based on sources of information available? Yes Concern regarding specification of study eligibility criteria: Low

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Tumour location= 23 upper, 59 middle, 39 lower SCC and AC **Kumar 2007** n= 125 country= India Tumour location= 23 upper, 20 middle, 22 lower **Mirinezhad 2013** n= 267 country= Iran Tumour location= 35 upper, 94 middle, 138 lower SCC and AC **Sheng 2011** n= 128	RT: CF + LCAF 68.4 Gy	**Assessment of Risk of Bias** Studies were assessed for bias based on the Cochrane Handbook for Systematic Reviews. All RCTs were assessed on three fronts: blinding, randomization and allocation concealment. Bias was assessed by three researchers. Most studies had a moderate risk of bias as they were randomized and controlled however did not clearly describe blinding and allocation concealment.	CRT: 120/175 RT: 58/92 RR M-H (95 CI%): 1.09 (0.90-1.31) **Sheng 2011 (events/total)** CRT: 54/63 RT: 43/55 RR M-H (95 CI%): 1.10 (0.92-1.30) **Zhao (events/total)** CRT: 36/54 RT: 44/57 RR M-H (95 CI%): 0.86 (0.68-1.09) **3-year survival rate (all studies)**	Identification and Selection of Studies Did the search include an appropriate range of databases/electronic sources for published and unpublished reports? Probably No Were the methods additional to database searching used to identify relevant reports? Yes Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible? Probably Yes Were restrictions based on date, publication format or language appropriate? Probably No

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	country= China Tumour location= 66 upper, 39 middle, 13 lower **Zhao 2005** n= 111 country= China Tumour location= 37 upper, 70 middle, 4 lower **Inclusion criteria** Criteria of eligible studies: Compared concomitant CRT and RT alone on advanced esophageal cancer and were published in English RCTs had a total of more than 50 samples, follow-up rates above 90%			Studies= 9, n= 1135 Risk Ratio, M-H (95% CI)= 1.66 (1.34, 2.06) **Han 2012 (events/total)** CRT: 26/65 RT: 12/65 RR M-H (95 CI%): 2.17 (0.77-3.91) **Herskovic 1992 (events/total)** CRT: 7/61 RT: 0/60 RR M-H (95 CI%): 14.65 (0.86-252.80) **Kumar 2007 (events/total)** CRT: 12/65	Were efforts made to minimise error in selection of studies? Yes Concern regarding methods used to identify or select studies: UNCLEAR. Rationale: not clear why dates were limited to 1991, sample size also restricted without clear rationale, unpublished reports not sought. Data Collection and Study Appraisal Were efforts made to minimise error in data collection? No information were sufficient study characteristics available? Probably No

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	and follow-up periods not less than 3 years Esophageal SCC and AC were confirmed by histological cytology. There was no statistically significant difference in patient disease features studies obtained informed consent outcomes included overall response rate, survival rate, toxic effects, rate of persistence and recurrence and rates of metastasis. **Exclusion criteria** The following studies were excluded:			RT: 7/60 RR M-H (95 CI%): 1.58 (0.67-3.75) **Mirinezhad 2013 (events/total)** CRT: 20/175 RT: 10/92 RR M-H (95 CI%): 1.05 (0.51-2.15) **Sheng 2011 (events/total)** CRT: 35/63 RT: 20/55 RR M-H (95 CI%): 1.53 (1.01-2.31) **Zhao (events/total)** CRT: 24/54 RT: 22/57	Were all relevant study results collected for use and synthesis? Yes Was risk of bias formally assessed using appropriate criteria? Yes Were efforts made to minimise error in risk of bias assessment? Yes Concern: LOW Synthesis and Findings Did the synthesis include all studies it should? Yes Were all pre-defined analyses reported and departures explained? Probably Yes Was the synthesis appropriate given the nature and similarity

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	patients in early stages of cancer patients who had undergone esophagectomy or had chemotherapy contraindications studies did not involve RCTs any study that did not include survival rate, rates of recurrence or distant metastasis			RR M-H (95 CI%): 1.15 (0.74-1.79) **5-year survival rate (all studies)** Studies= 5, n= 536 Risk Ratio, M-H (95% CI)= 2.43 (1.63, 3.63) **Sheng 2011 (events/total)** CRT: 23/63 RT: 9/55 RR M-H (95 CI%): 2.23 (1.13-4.41) **Zhao (events/total)** CRT: 19/54 RT: 13/57	in the research questions? Yes Was heterogeneity minimal or addressed? Yes Were the findings robust as demonstrated though funnel plot or sensitivity analysis? Yes Were biases in primary studies minimal or addressed in the synthesis? Yes Concern= LOW Risk of bias in the review Did the interpretation of findings address all the concerns identifies in 1-4? Yes Was the relevance of identified studies to the review's research question

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				RR M-H (95 CI%): 2.43 (1.63-3.63)	appropriately considered? Probably Yes Did the reviewers avoid emphasizing results on the basis of their statistical significance? Yes Risk of bias= LOW

F.13 Non-metastatic oesophageal cancer not suitable for surgery

What is the optimal treatment for adults with non-metastatic disease in the oesophagus who are not suitable for surgery?

Study details	Participants	Intervention and Methods	Outcomes and Results Bias Assessment
Full citation Gao, F., Jia, L., Du, H., Kuang, X., Wang, Y., Han, J., A clinical study of combination of radiotherapy and IP regimen	**Sample size** N = 68 **Characteristics** **Characteristic** | **Radiotherapy plus chemotherapy group n = 35** | **Radiothe group n = 33**	**Interventions** **Chemotherapy group** Intravenous irinotecan was administered (65mg/m²) on the first day. Intravenous cisplatin (30mg/m²) was administered on the first and eighth day. Cycles were repeated every 21	**Results** Survival **Overall survival: 1 year** Radiotherapy + chemotherapy group: 72.6% Radiotherapy group: 69.7% **Overall survival: 2 year** Radiotherapy + chemotherapy group: 54.5% Radiotherapy group: 31.0%

Study details	Participants			Intervention and Methods	Outcomes and Results Bias Assessment
in the treatment of patients with local advanced esophageal cancer, Chinese-German Journal of Clinical Oncology, 8, 506-509, 2009 **Ref Id** 488811 **Country/ies where the study was carried out** China **Study type** Randomised controlled trial. **Aim of the study** To compare the efficacy of radiotherapy to	*Sex*			days for a total of four cycles. **Radiotherapy (both groups)** Tumour size and location was established by CT and barium swallow. Upper and lower bounds for the radiation field were approximately 3 to 4cm above and below the lesion. Side-bounds were approximately 2-3cm from the exterior margin. The radiation field was extended to include supraclavicular lymph nodes for participants with metastasis to these nodes.The total dose administered was 60Gy (fractions not described). **Methods Details** The methods of randomisation for the study groups are not reported.	**Progression-free survival: 1 year** Radiotherapy + chemotherapy group: 69.8% Radiotherapy group: 43.0% **Progression-free survival: 2 years** Radiotherapy + chemotherapy group: 44.2% Radiotherapy group: 19.5% Treatment-related toxicity **Grade III/IV nausea and vomiting** Radiotherapy + chemotherapy group: 2/35 (5.7%) Radiotherapy group: 1/33 (3%) **Grade III/IV 'decline in leucocytes'** Radiotherapy + chemotherapy group: 4/35 (11.4%) Radiotherapy group: 1/33 (3%) **Grade III/IV esophagitis** Radiotherapy + chemotherapy group: 24/35 Radiotherapy group: 22/33 **Limitations** Overall: Serious risk of bias. **Cochrane risk of bias tool** Selection bias
	Male	23	22		
	Female	12	11		
	Age (years)				
	Median	56.8	60		
	Range	33-76	40-78		
	Stage				
	II	23	24		
	III	12	9		
	Pathological type				
	Squamous cell carcinoma	34	32		
	Adenocarcinoma	1	0		
	Small cell carcinoma	0	1		
	Location				
	Cervical	2	2		

Study details	Participants	Intervention and Methods	Outcomes and Results Bias Assessment
radiotherapy plus chemotherapy (irinotecan plus cisplatin) for the treatment of locally advanced oesophageal cancer. **Study dates** June 2005 to November 2007. **Source of funding** Not reported.	<table><tr><td>Upper thoracic</td><td>7</td><td>5</td></tr><tr><td>Middle thoracic</td><td>18</td><td>16</td></tr><tr><td>Lower thoracic</td><td>8</td><td>10</td></tr></table> **Inclusion criteria** Histological confirmation of oesophageal cancer. Karnofsky Performance Status score 70-90 (median 80). Lesion length less than 10cm. Normal liver and kidney function. **Exclusion criteria** Active bleeding from oesophageal lesion, or perforating lesion. Tracheoesophageal fistula. Distant metastasis.	It is unclear whether chemotherapy was administered concurrently with radiotherapy, or sequentially, for the combined group. Participants were followed up for two years. The follow up schedule was for review every three months during the first year, then every six months during the second year.	- random sequence generation: unclear - allocation concealment: unclear Performance bias - blinding: unclear Detection bias - blinding: unclear Attrition bias - all groups followed for equal amount of time lost to follow up and those not completing treatment not reported Reporting bias - outcomes stated in the objective were reported objective outcome- mortality, progression free survival and grading scales for toxicity not defined Overall assessment: Serious risk of bias due to unclear and inadequate reporting of allocation concealment, randomization process, blinding and outcome evaluation criteria. **Other information**
Full citation Ajani, J. A., Winter, K., Komaki, R.,	**Sample size** N = 84 **Characteristics**	**Interventions** **Arm A: Fluorouracil-based therapy** Fluorouracil 700mg/m²/24 hours via an outpatient	**Results** *Overall survival* **Median survival** Fluorouracil-based arm: 29 months (95% CI 18 months to not calculable)

Study details	Participants		Intervention and Methods	Outcomes and Results Bias Assessment
Kelsen, D. P., Minsky, B. D., Liao, Z., Bradley, J., Fromm, M., Hornback, D., Willett, C. G., Phase II randomized trial of two nonoperative regimens of induction chemotherapy followed by chemoradiation in patients with localized carcinoma of the esophagus: RTOG 0113, Journal of Clinical OncologyJ Clin Oncol, 26, 4551-6, 2008 **Ref Id** 474300		**Fluorouracil-based arm (n = 37)**	portable pump on days 1 through 5, cisplatin 15mg/m² on days 1 through 5, andpaclitaxel 200mg/m² as a 24 hour infusion on day 1. Granulocyte colony stimulating factor or pegfilgrastim was started or administered on day 6. This regimen was repeated on day 29 provided patients had recovered to grade ≤1 of related toxicity, and had no evidence of local progression. During radiation, patients received fluorouracil 300mg/m² as continuous infusion for 96 hours (Monday to Friday) during each of the 5 radiation therapy weeks, and paclitaxel 50mg/m² over three hours once per week during each of the radiation weeks. **Arm B: Non-Fluorouracil-based therapy**	Non-Fluorouracil-based arm: 15 months (95% CI 12 to 26 months) **1-year survival** Fluorouracil-based arm: (28/37) 76% Non-Fluorouracil-based arm: (24/35) 69% **2-year survival** Fluorouracil-based arm: (18/37) 56% Non-Fluorouracil-based arm: (12/35) 37% *Treatment-related morbidity* **Grade 3 chemotherapy and acute radiotherapy toxicity** Fluorouracil-based arm: 54% Non-Fluorouracil-based arm: 40% **Grade 4 chemotherapy and acute radiotherapy toxicity** Fluorouracil-based arm: 27% Non-Fluorouracil-based arm: 40% **Late chemotherapy and acute radiotherapy toxicity** Fluorouracil-based arm: 8% Non-Fluorouracil-based arm: 12% *Treatment-related mortality* Fluorouracil-based arm: n = 1 (GI haemorrhage during the concurrent phase)
	Characteristic	**No. of patients**	**%**	**No. of patients**	**%**
	Age, years				
	Median	61	66		
	Range	41-80	28-77		
	Weight loss in last 6 months				
	<10%	25	68	22	63
	≥10%	12	32	12	34
	Unknown	0	0	1	3
	Sex				
	Male	28	76	28	80
	Female	9	24	7	20
	Tumour size, cm				
	≤5	23	62	22	63
	>5	14	38	13	37

Study details	Participants		Intervention and Methods	Outcomes and Results Bias Assessment
Country/ies where the study was carried out USA **Study type** Randomised controlled trial. **Aim of the study** To compare two chemoradiotherapy regimens (including induction chemotherapy, followed by chemoradiotherapy) in patients with localised oesophageal cancer, with respect to one year survival.	*Zubrod performance status*		Paclitaxel 175mg/m² was administered over 3 hours, followed by cisplatin 75mg/m² on day 1. This regimen was repeated on day 21 provided patients had recovered to grade ≤1 of related toxicity, and had no evidence of local progression. During radiation, patients received cisplatin 30mg/m² on days 1,8,15,22,29 and 36, and paclitaxel 60mg/m² as a continuous infusion over 96 hours on the same days. **Both arms: Radiation therapy** Radiation therapy was administered using the three-dimensional planning technique. Daily fractions size was 1.8Gy, and the total dose was 50.4Gy delivered in 28 fractions. Megavoltage photon energy > 6 MV was used. Computerised imaging	Non-Fluorouracil-based arm: n = 2 (neutropenic sepsis after completion of induction chemotherapy, and upper GI bleed 6 moths after treatment completion) **Limitations** Indirectness: 1 patient with T1 oesophageal cancer. Overall: low risk of bias. **Cochrane risk of bias tool** Selection bias - random sequence generation: low risk - allocation concealment: unclear Performance bias - blinding: unclear but low risk due to objective outcome measures Detection bias - blinding: unclear but low risk due to objective outcome measures Attrition bias - outcome date complete, 2 participants in each group did not complete treatment, outcome data available for all patients Reporting bias
	0	19	51	19	54
	1	18	49	16	46
	Histology				
	Squamous cell	13	35	12	34
	Adenocarcinoma	24	65	23	68
	Extent of dysphagia				
	Asymptomatic	5	14	4	11
	Symptomatic: unrestricted diet	14	38	11	31
	Symptomatic: soft foods only	13	35	14	40
	Symptomatic: liquids only	3	8	5	14
	Cannot swallow	2	5	1	3
	Primary T classification				
	T1: invasion of lamina propria or submucosa	1	3	0	0
	T2: invasion of muscular propria	7	19	11	31

Study details	Participants	Intervention and Methods	Outcomes and Results Bias Assessment
Study dates April 2001 to April 2005. **Source of funding** Supported by Grant Nos. CA21661, CA37422, and 32115 from the National Cancer Institute.	T3: invasion of adventitia 27 73 21 60 T4: invasion of adjacent structures 2 5 1 3 TX 0 0 2 6 **Inclusion criteria** Biopsy proven squamous cell or adenocarcinoma from the thoracic or cervical oesophagus or gastro-oesophageal junction, with cancer that extends ≤2cm beyond the stomach. Adequate bone marrow, liver and renal function. Caloric intake of ≥1700kcal per day. Zubrod performance score of 0 or 1. Clinical T1N1M0 disease or T2-4 N+/- M0 Deemed to have technically unresectable disease, or declined surgery, or medically unfit for surgery. **Exclusion criteria** Tracheoesophageal fistula. Evidence of metastatic cancer. Lack of comprehension of the study protocol. Inability to comply with the study protocol.	was used to define the gross tumour volume, and locoregional lymph nodes were included in the clinical target volume (CTV). CTV was defined as having a 3-cm cephalad and caudad margin beyond the gross tumour volume. The planning target volume included up to a 2cm margin around the CTV. For cervical primaries, bilateral cervical lymph nodal regions were included. For both arms, if local progression was identified during the initial chemotherapy phase, participants moved directly to chemoradiotherapy. If distant metastasis was identified during the initial chemotherapy phase, participants were taken off treatment and observed for survival.	- outcomes stated in the objective were reported, objective defined outcomes reported Overall assessment: Low risk of bias due to adequate reporting of randomization process and objective outcome measures. **Other information** In addition, outcomes were compared to a historic cohort (who received 50.4Gy radiotherapy with fluorouracil plus cisplatin) and no statistically significant difference was identified.

Study details	Participants	Intervention and Methods	Outcomes and Results Bias Assessment
		Methods Details All patients had a complete history and physical examination performed pre-treatment. CT of the chest and abdomen was obtained. Patients had an upper OGD with endoscopic ultrasonography. Bronchoscopy was performed when cancer was located less than 26cm from the incisor. All patients provided approved informed consent, and institutional review boards of participating institutions approved the protocol prior to patient recruitment. Patients were randomly assigned to receive one of the two therapies. The permuted block randomisation method was used. Patients were stratified according to	

Study details	Participants	Intervention and Methods	Outcomes and Results Bias Assessment
		weight loss, length of the lesion and histology. The primary end-point was one-year overall survival. Secondary endpoints included treatment completion and safety. On the basis of 1-year survival rate of 60%, it was decided that either of the two arms would be of interest for a phase III trial if the 1-year survival rate was ≥77.5%. 38 assessable patients for each treatment were needed to test this hypothesis, giving a hazard reduction of 50%, with a one-sided type 1 error of 0.05% and 80% power. Patients underwent complete history and physical examinations approximately 6 weeks after the completion of therapy. Complete blood count, biochemistry, chest radiograph, CT and	

<table>
<tr><th>Study details</th><th>Participants</th><th>Intervention and Methods</th><th>Outcomes and Results

Bias Assessment</th></tr>
<tr><td></td><td></td><td>endoscopic evaluation were performed. Patients were then observed every 4 months during the first year, every 6 months for 2 additional years, and then on a yearly basis.</td><td></td></tr>
<tr><td>Full citation

Javed, A., Pal, S., Dash, N. R., Ahuja, V., Mohanti, B. K., Vishnubhatla, S., Sahni, P., Chattopadhyay, T. K., Palliative stenting with or without radiotherapy for inoperable esophageal carcinoma: A randomized trial, Journal of Gastrointestinal Cancer, 43, 63-69, 2012</td><td>Sample size
N= 79
Stenting alone= 37
Stenting followed by Rt= 42

Characteristics
<table>
<tr><th>Characteristic</th><th>Stenting Group</th><th>Stenting + RT group</th></tr>
<tr><td>Mean age</td><td>58.1 +/1 12.44</td><td>58.6 +/- 12.13</td></tr>
<tr><td>Sex</td><td>10 F/ 27 M</td><td>13 F/ 29 M</td></tr>
<tr><td>BMI</td><td>16.6 +/- 2.10</td><td>16.5 +/- 2.65</td></tr>
<tr><td>Mean tumour length</td><td>7.05 +/- 1.86 cm</td><td>7.15 +/- 1.97 cm</td></tr>
<tr><td>Histology</td><td></td><td></td></tr>
</table></td><td>Interventions
In Group I, patients underwent esophageal stenting alone. In Group II, palliative EBRT was administered approximately 4–6 weeks after stent placement.

<u>Stenting</u>

The length of the malignant stricture determined the length of the SEMS (10, 12, or 15 cm) deployed (covered Ultraflex esophageal stent system; Microvasive, Boston Scientific). The body and flare diameters</td><td>Results
<u>Median Survival</u>
Stent group: 120 days
Stent + Rt group: 180 days (p=.009)
<u>Median Survival- Squamous Cell Carcinoma</u>
Stent group: 134 days
Stent + Rt group: 240 days (p=.006)
<u>Median Survival- Adenocarcinoma</u>
Stent group: 60 days
Stent + Rt group: 120 days (p=.84)

<u>Overall Survival at Study end</u>
Stent group: 2/37
Stent + RT group: 12/42

Stent +Rt versus stent alone
Hazard Ratio** (95% CI)= 1.92 (1.18 to 3.15)

<u>Disease related morbidity- Recurrent Dysphagia*</u>
Stent group: 9/37</td></tr>
</table>

Study details	Participants	Intervention and Methods	Outcomes and Results Bias Assessment
Ref Id 477946 **Country/ies where the study was carried out** India **Study type** RCT **Aim of the study** To compare the duration of relief of dysphagia in patients with inoperable esophageal cancer treated with esophageal stenting alone or a combination of	<table><tr><td>Adenocarcinoma</td><td>6</td><td>7</td></tr><tr><td>Squamous cell carcinoma</td><td>31</td><td>35</td></tr></table> **Inclusion criteria** - Esophageal cancer patients with locally advanced unresectable cancer (such as invasion of tracheobronchial tree, aorta, pulmonary vascular structures), metastatic disease, poor performance status (Eastern Cooperative Oncology Group performance status 3, 4), and comorbid conditions precluding major surgical procedure (such as severe cardiopulmonary, hepatic, and renal diseases) - with grades 3 and 4 dysphagia **Exclusion criteria** • Patients with carcinoma of the cervical esophagus	of the stent were 18 and 23 mm, respectively. <u>Radiotherapy</u> Palliative radiotherapy consisted of EBRT by Cobalt-60 linear accelerator. All patients underwent simulator-based radiotherapy planning so that the position of the stent could be assessed and the radiotherapy portals defined. Whenever there was a doubt, a CT scan was done to plan the radiotherapy portals. Two-dimensional dose calculation was done, and a total dose of 30 gray (Gy) in ten fractions was administered over 2 weeks to all patients. **Methods Details** Patients with inoperable esophageal cancer and	Stent + RT group: 6/42 Due to stent obstruction *plus one additional due to stent migration (intervention group NR) <u>Dysphagia-free survival</u> Stent-group: mean= 96.8 +/- 43 days Stent + RT group= 118.6 +/- 55.8 (p=0.054) <table><tr><th>QOL parameter</th><th>Group I (n=37)</th><th></th><th>Group II (n=42)</th><th></th><th></th></tr><tr><td></td><td>Baseline</td><td>Post-stent</td><td>Baseline</td><td>Post-stent</td><td>Post-RT#</td></tr><tr><td>Physical functioning</td><td>50.6 ±21.1</td><td>68.9± 17.3</td><td>35.4± 23.7</td><td>72.9±16.5</td><td>70.3 ±18.8</td></tr><tr><td>Role functioning</td><td>27.9± 19.7</td><td>54.9± 16.2a</td><td>26.7 ±18.7</td><td>67.5± 16.4a</td><td>56.7± 18.8a</td></tr></table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Intervention and Methods</th><th>Outcomes and Results

Bias Assessment</th></tr>
<tr>
<td>esophageal stenting and external beam radiotherapy (EBRT), and to assess overall survival, treatment-related complications, and quality of life (QOL) in the two groups.

Study dates

April 2007 and March 2009

Source of funding

This study was supported by All India Institute of</td>
<td>• those who had received prior radiotherapy, chemotherapy, or any other modality of treatment, were excluded</td>
<td>with high grade dysphagia were randomized to receive esophageal stenting with self-expandable metal stent (Ultraflex) alone (Group I), versus a combination of stenting followed by EBRT (30 gray in ten divided fractions over 2 weeks) (Group II). Dysphagia relief, overall survival, QOL (using European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire- C30, version 3), and treatment-related complications were assessed in the two groups.

<u>Follow-up</u>

Patients were followed up regularly every 2 weeks. Those who could not come for follow-up were contacted on telephone. Dysphagia scores were assessed at baseline</td>
<td>
<table>
<tr><td>Cognitive functioning</td><td>54.9±23.3</td><td>76.4±17.9a</td><td>46.5±21.2</td><td>80.9±15.2a</td><td>74.2±15.4a</td></tr>
<tr><td>Emotional functioning</td><td>35.1±22.1</td><td>63.8±17.9a</td><td>30.3±20.6</td><td>73.3±14.9a</td><td>66.2±14.3a</td></tr>
<tr><td>Social functioning</td><td>28.9±19.9</td><td>54.6±19.9a</td><td>25.4±16.3</td><td>69.2±15.2a</td><td>57.5±15.6a</td></tr>
<tr><td>Global health</td><td>35.4±13.2</td><td>57.4±12.2a</td><td>35.3±13.9</td><td>71.8±13.1a</td><td>58.3±11.5a</td></tr>
</table>
** Calculated by NGA technical team through method described by Tierney et al. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 2007 8:16

Limitations
<u>Cochrane risk of bias tool</u>
Selection bias
- random sequence generation: computer-generated random number table</td>
</tr>
</table>

Study details	Participants	Intervention and Methods	Outcomes and Results Bias Assessment
Medical Sciences, New Delhi, India. No financial grants or other funding was received for this study.		(before the start of therapy), 1 week after esophageal stenting, 1 week after completion of radiotherapy (in Group II), and every 2 months thereafter until death or until completion of the study. Endoscopic evaluation was performed for recurrent dysphagia, gastrointestinal bleeding, or suspicion of tracheoesophageal fistula. Statistics Statistical significance of continuous data was determined by Student's t-test, and that of categorical data by chi-square and Fisher exact tests (wherever applicable). The Kaplan–Meier method was used to analyze the overall survival in both groups.	- allocation concealment: sealed envelope technique used for randomisation unclear how allocation concealment was maintained Performance bias - blinding of patients: unclear but unlikely due to obvious difference between treatments Detection bias - blinding of investigators: unclear but low risk of bias due to objective outcome measures (survival) and patient reported outcomes (QLQ-C30 for Quality of Life) Attrition bias - outcome date complete Reporting bias - not detected Overall assessment: Low risk of bias due to adequate reporting of allocation concealment, randomization process and objective outcome measures. **Other information** Of the 84 patients, complete data were available for 79 patients: 37 in Group I and 42 in Group II. In Group I, 3 patients were lost to follow-up, and 2 patients could not be stented

<table>
<tr><th>Study details</th><th>Participants</th><th>Intervention and Methods</th><th>Outcomes and Results

Bias Assessment</th></tr>
<tr><td></td><td></td><td></td><td>due to the long length of the stricture (13 and 15 cm, respectively).

Population indirectness: 18% of patients with metastatic disease.</td></tr>
<tr><td>Full citation

Kumar, S., Dimri, K., Khurana, R., Rastogi, N., Das, K. J., Lal, P., A randomised trial of radiotherapy compared with cisplatin chemo-radiotherapy in patients with unresectable squamous cell cancer of the esophagus, Radiotherapy & OncologyRadiot</td><td>Sample size
N = 125

Characteristics<table><tr><th>Characteristics</th><th>Radiotherapy group n = 60</th><th>Chemoradiotherapy group n = 65</th></tr><tr><td>Age (years)</td><td></td><td></td></tr><tr><td>Median (range)</td><td>56 (34 - 76)</td><td>58 (24 - 76)</td></tr><tr><td>Sex</td><td></td><td></td></tr><tr><td>Male (%)</td><td>49 (82)</td><td>43 (66)</td></tr></table></td><td>Interventions
Chemotherapy group
Patients in the combined chemoradiotherapy arm received (in addition to radiotherapy described below) once weekly cisplatin 35mg/m² for a total of 6-7 cycles. After adequate hyrdration and anti-emetic cover, this was given as a 30 minute infusion, followed by mannitol diuresis and post chemotherapy hydration. On the day of chemotherapy, radiation was delivered within 30-60 minutes following the infusion. Chemotherapy</td><td>Results
Median follow up 23 months.

Median projected survival
Radiotherapy group: 7.1 months
Chemoradiotherapy group: 13.4 months

1 year survival
Radiotherapy group: 18/60
Chemoradiotherapy group: 33/65

2 year survival
Radiotherapy group: 9/60
Chemoradiotherapy group: 17/65

3 year survival
Radiotherapy group: 7/60
Chemoradiotherapy group: 12/65

5 year survival</td></tr>
</table>

Study details	Participants			Intervention and Methods	Outcomes and Results Bias Assessment
her Oncol, 83, 139-47, 2007 **Ref Id** 474734 **Country/ies where the study was carried out** India **Study type** Randomised controlled trial. **Aim of the study** To compare radiotherapy with combned chemoradiotherapy in patients with cancer of the oesophagus.	*Karnofsky Performance Scale*			was postponed by a week if the total leucocyte count fell below 3.5x10³/mm³, but no dose modifications were made. **Radiotherapy (both groups)** External beam radiotherapy was administered to a dose of 50Gy in 25 fractions over 5 weeks, followed 1-2 weeks later with 2 applications of 6Gy high-dose-rate intralumenal radiotherapy - spaced one week apart, if the oesophageal lumen could be negotiated without resorting to endoscopic dilatation. If the passage had not opened up sufficiently, an additional 10-16Gy external beam radiotherapy was planned with a second attempt at brachytherapy following 60Gy. Following participants until December 2001 showed	Radiotherapy group: 3/60 Chemoradiotherapy group: 8/65 **Chemoradiotherapy compared with radiotherapy** Hazard ratio: 0.65 (0.44 to 0.98) P=0.038 15 patients in the radiotherapy group were lost to follow up. Of these, 12 were know to have disease relapse, and 3 known to have disease controlled at the time of loss to follow up. 8 patients in the chemotherapy group were lost to follow up. Of these, 5 were known to have disease relapse and 3 were known to have disease controlled at the time of loss to follow up. For the purposes of survival analysis, all participants lost to follow up were treated as events. <u>Treatment related toxicity</u> **Grade II/III oesophagitis** Radiotherapy group: 15/60 (25%) Chemoradiotherapy group: 25/65 (38.5%) OR: 0.53 (95% CI 0.23 to 1.23) **Ulcers** Radiotherapy group: 3/60 (5%) Chemoradiotherapy group: 10/65 (15%)
	50-70	17	13		
	80-90	42	52		
	no data	1	0		
	Pre-treatment weight loss (%)				
	Median (range*)	10.5 (0 - 28)	8 (0 - 27)		
	no data	7	10		
	Haemoglobin (gm/dl)				
	Median (range*)	12 (8 - 14.4)	12.1 (10 - 14)		
	Dysphagia duration (months)				
	Median (range*)	3 (1.5 - 11.7)	4 (1.5 - 12)		

<table>
<tr><th>Study details</th><th>Participants</th><th>Intervention and Methods</th><th>Outcomes and Results

Bias Assessment</th></tr>
<tr>
<td>Study dates
April 1999 to December 2005.

Source of funding
Not reported.</td>
<td>
<table>
<tr><td>Dysphagia grade</td><td></td><td></td></tr>
<tr><td>Swallow solids/soft solids with difficulty</td><td>39</td><td>49</td></tr>
<tr><td>Swallow liquids with difficulty/total obstruction</td><td>21</td><td>16</td></tr>
<tr><td>Site</td><td></td><td></td></tr>
<tr><td>Upper:Middle:Lower</td><td>11:36:13</td><td>12:44:9</td></tr>
<tr><td>Length (cm)</td><td></td><td></td></tr>
<tr><td>Median, range*</td><td>7.2 (4 - 13)</td><td>8 (4.8 - 11.5)</td></tr>
<tr><td>Previous interventions</td><td></td><td></td></tr>
<tr><td>Dilatation, number (%)</td><td>5 (8)</td><td>7 (11)</td></tr>
<tr><td>Intubation, number (%)</td><td>2 (3)</td><td>0</td></tr>
<tr><td>Feeding tube, number (%)</td><td>1 (1)</td><td>0</td></tr>
</table>
</td>
<td>an unusual number of patients requiring dilatations for symptomatic strictures in the combined chemoradiotherapy group. This prompted a temporary halt in recruitment for one year.
Recruitment was then resumed with an amendment to the radiotherapy regimen, which was altered to 66Gy in 33 fractions over 6.5 weeks and the exclusion of brachytherapy.
External beam radiotherapy was administered with megavoltage radiation equipment, with a minimum source to axis distance of 80cm. The gross tumour extent was defined by information from the CT scan, endoscopy report and barium contrast. The first 36Gy was delivered with a 5cm cradio-caudal and 2cm radial margin. The</td>
<td>Strictures
Radiotherapy group: 8/60 (13%)
Chemoradiotherapy group: 18/65 (28%)

<u>Disease-related mobidity</u>
Dysphagia score improved by one or more grades
RT group: 73% (p=0.00)
CRT group: 71% (p=0.00)

Limitations
Population indirectness: 2 patients with T1 oesophageal cancer.

Overall: low risk of bias

<u>Cochrane risk of bias tool</u>
Selection bias
- random sequence generation: low risk
- allocation concealment: unclear
Performance bias
- blinding: unclear but low risk because outcome ascertainment was objective (mortality)
Detection bias
- blinding: unclear
Attrition bias
- all groups followed for equal amounts of time</td>
</tr>
</table>

Study details	Participants	Intervention and Methods	Outcomes and Results Bias Assessment
	<table><tr><td>*T stage*</td><td></td><td></td></tr><tr><td>T1:T2:T3</td><td>2:34:24</td><td>0:39:26</td></tr><tr><td>*N stage*</td><td></td><td></td></tr><tr><td>N0:N1</td><td>30:30</td><td>29:36</td></tr></table> * range given as 10th to 90th percentile **Inclusion criteria** Deemed inoperable, or declined surgery. Karnofsky Performance status ≥ 50. Haemoglobin ≥ 10gm/dl Total leucocyte count ≥ 4 x 10^3/mm^3 platelet count ≥ 100,000/mm^3 serum creatinine ≤1.6mg% serum aspartate aminotransferase ≤40/L serum alanine aminotransferase ≤40U/L **Exclusion criteria** Adenocarcinoma. Second primary malignancy. Recurrent or metastatic disease.	supraclavicular fossa was included bilaterally for tumours arising above the carina. The subsequent 14Gy (or 30Gy for those who did not receive brachytherapy) was delivered with reduced cranio-caudal and radial margins of 2cm. Brachytherapy (where used, n = 53) was delivered with a 6mm (n=46) or 10mm (n=7) diameter applicator. A dose of 6Gy in each application was prescribed at 5mm from the surface of the applicator and the entire pre-treatment length of tumour (with a 2cm cranio-caudal margin) was treated. **Methods Details** Prior to commencing treatment, the extent of disease and general health was evaluated according	- no outcome data available for 15/60 in RT group and 6/65 in CRT group - 13/60 in the RT group and 7/65 in CRT group did not complete treatment Reporting bias - outcomes stated in the objective were reported Overall assessment: low risk of bias due to adequate reporting of randomization process and objective outcome measures. **Other information**

Study details	Participants	Intervention and Methods	Outcomes and Results Bias Assessment
		to an inventory that included endoscopy, barium contrast, spiral CT, chest X-ray and blood tests. If clinically indicated a radionuclide bone scan was also performed. A random number table was used for randomisation. Participants were seen once a week during their treatment to assess their general condition, swallowing status, nutritional intake and toxicities of therapy. The first post-treatment evaluation was performed a month following completion, with subsequent follow-up at 2 monthly intervals for the first year, and 3-4 monthly thereafter. Clinical assessment and a barium oesophagram was performed routinely, with endoscopy and biopsy only in cases of recurrent	

Study details	Participants	Intervention and Methods	Outcomes and Results Bias Assessment
		or persistent dysphagia not otherwise explained. Patients were considered to be locally disease free only if a barium swallow was smooth, with no signs or symptoms of disease spread to the mediastinum (such as vocal cord palsy), and a negative biopsy, whenever performed. Ulcers within the oesophagus (observed at endoscopy) were biopsied and scored as treatment related if reported negative for malignant cells. A total of 129 patients were randomised, without meeting the target accrual, and the trial was prematurely closed. Overall, 53 patients received external beam and brachytherapy, while 52 patients received external beam radiotherapy only. 13 and	

<table>
<tr><th>Study details</th><th>Participants</th><th>Intervention and Methods</th><th>Outcomes and Results

Bias Assessment</th></tr>
<tr><td></td><td></td><td>7 patients in the radiotherapy and combined groups did not receive the full complement of radiotherapy. This was due to progressive disease or participant refusal in the majority of cases.</td><td></td></tr>
<tr><td>Full citation

Liu, M., Shi, X., Guo, X., Yao, W., Liu, Y., Zhao, K., Jiang, G. L., Long-term outcome of irradiation with or without chemotherapy for esophageal squamous cell carcinoma: a final report on a prospective trial, Radiation OncologyRadiat, 7, 142, 2012</td><td>Sample size
N = 111

Characteristics
<table>
<tr><th>Characteristics</th><th>Radiotherapy group (n = 57)</th><th>Radiotherapy plus chemotherapy group (n = 54)</th></tr>
<tr><td>Sex, n (%)</td><td></td><td></td></tr>
<tr><td>Male</td><td>36 (63)</td><td>42 (78)</td></tr>
<tr><td>Female</td><td>21 (39)</td><td>12 (22)</td></tr>
</table></td><td>Interventions
Chemotherapy group
In addition to radiotherapy (see below), participants in this arm received concurrent chemotherapy of once daily cis-platinum 25mg/m² and 5-Fluorouracil of 600mg/m² for three consecutive days. This was administered once per month for four months, during and after irradiation.

Radiotherapy (both groups)
This consisted of 2 phases. In the first phase,</td><td>Results
Median follow up time was 24 months.

<u>Overall survival</u>
Median survival time
Radiotherapy group: 25 months (95% CI 21.3 to 28.7)
Chemoradiotherapy group: 32 months (95% CI 8.6 to 55.4)

1 year survival(ZHAO, 2005)
RT group: 44/57
CRT group: 36/54

3 year survival (ZHAO 2005)
RT group: 22/57
CRT group: 24/54

5 year survival</td></tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Intervention and Methods</th><th>Outcomes and Results

Bias Assessment</th></tr>
<tr>
<td>Ref Id

474789

Country/ies where the study was carried out

China

Study type
Randomised controlled trial

Aim of the study
To compare outcomes for patients with squamous cell oesophageal cancer undergoing radiotherapy or combined chemoradiotherapy.</td>
<td>
<table>
<tr><td>Age (years)</td><td></td><td></td></tr>
<tr><td>Median (range)</td><td>61.0 (41-74)</td><td>54.5 (39-74)</td></tr>
<tr><td>KPS, n (%)</td><td></td><td></td></tr>
<tr><td>70</td><td>3 (5)</td><td>2 (4)</td></tr>
<tr><td>80-100</td><td>54 (95)</td><td>52 (96)</td></tr>
<tr><td>Lesion location, n (%)</td><td></td><td></td></tr>
<tr><td>Cervical</td><td>3 (5)</td><td>4 (7)</td></tr>
<tr><td>Upper thorax</td><td>18 (32)</td><td>12 (22)</td></tr>
<tr><td>Middle thorax</td><td>34 (60)</td><td>36 (67)</td></tr>
<tr><td>Lower thorax</td><td>2 (3)</td><td>2 (4)</td></tr>
<tr><td>Tumour length, cm</td><td></td><td></td></tr>
<tr><td>Median (range)</td><td>6.0 (1-10)</td><td>6.0 (2-9)</td></tr>
</table>
</td>
<td>41.4Gy in 23 fractions was delivered by conventional fractionation (1.8Gy per fraction, one fraction per day, five fractions per week). In the second phase, 27 Gy was given in 18 fractions by two 1.5Gy fractions per day, with an interval of > 6 hours. This gave a total of 68.4Gy in 41 fractions for 6.4 weeks. A 6MV photon was used. The primary tumour and metastatic nodes were identified by CT and barium images. Margins of 2-3cm were added. At the long axis a 3cm proximal and 5cm distal margin was set. In the second phase, fields were reduced to 2cm margins beyond the superior and inferior ends of the lesions. No prophylactic irradiation was given to the supraclavicular regions.</td>
<td>Radiotherapy group: 28%
Chemoradiotherapy group: 40%

8 year survival
Radiotherapy group: 21%
Chemoradiotherapy group: 29%

10 year survival
Radiotherapy group: 19%
Chemoradiotherapy group: 23%

CRT versus RT
Hazard Ratio** (95% CI): 0.91 (0.60 to 1.38) P= 0.653

<u>Treatment related mortality</u>
Acute treatment related death†
Radiotherapy group: 0/57 (0%)
Chemoradiotherapy group: 3/54 (6%)
(deaths were due to poor nutrition or inadequate supportive treatment with pulmonary infection or oesophagitis: one death on completion of the second cycle of chemotherapy, and two deaths after completion of the third cycle)

Late treatment related death†
Radiotherapy group: 2/57 (3.5%)
Chemoradiotherapy group: 2/54 (3.7%)
(deaths were due to pulmonary complications).
N.B. Liu et al. reports on one further late treatment-related death (at the later follow-up</td>
</tr>
</table>

Study details	Participants	Intervention and Methods	Outcomes and Results Bias Assessment
Study dates March 1998 to July 2000. **Source of funding** Not reported.	*Stage, N (%)* T1-2N0M0: 11 (19); 11 (20) T3-4N0M0: 37 (65); 37 (69) T1-4N1M0: 9 (16); 6 (11) **Inclusion criteria** Oesophageal squamous cell carcinnoma, confirmed by histology or cytology. Clinical stages T1-4, N0-1 M0. Baseline laboratory tests met criteria for chemoradiation (full blood count, renal and liver function) Karnofsky performance status ≥70 No prior therapy No previous malignancies No serious comorbidity that would preclude safe administration of treatment. **Exclusion criteria** Evidence of oesophageal perforation or deep ulceration Complete obstruction of the oesophageal lumen.	**Methods Details** No details are provided with regard to the randomisation process. Follow up was performed every four months for the first year, every six months for years 2 and 3, annually for years 4 and 5, and biannually thereafter. Each follow up included compelte history, physiacl examination, quality of life evaluation, blood tests, chest X-ray, oesophageal barium radiography and a chest CT. Late treatment related toxicity was scored by RTOG criteria. Locoregional recurrence was defined as oesophageal and/or regional lymph node failures. One oesophageal recurrence was suspected, a biopsy was required. CT/MRI or PET-CT was performed in cases of suspected nodal	point), also due to pulmonary fibrosis, but it is unclear which treatment group this occurred in. Treatment-related morbidity **Grade III or IV acute toxicity†** Radiotherapy group: 14/57 (25) Chemoradiotherapy group: 24/54 (44%) **Grade III or higher late toxicity‡ at 5 years** Radiotherapy group: 30% Chemoradiotherapy group: 21% **Grade III or higher late toxicity‡ at 8 and 10 years (data identical at both time points)** Radiotherapy group: 33% Chemoradiotherapy group: 26% † Data obtained from Zhao 2005, earlier report of the same trial ‡ includes pulmonary fibrosis, oesophageal stenosis and pericarditis ** Calculated by NGA technical team through method described by Tierney et al. Practical methods for incorporating summary time-to-event data into meta-analysis. *Trials* 2007 8:16 **Limitations** Overall: unclear but likely low risk of bias

Study details	Participants	Intervention and Methods	Outcomes and Results Bias Assessment
	Oesophageal bleeding Involvement of supraclavicular lymph nodes Distant metastases.	metastasis. Lymph node recurrence was defined as one of: node reappearance after complete disappearance, node enlargement after remaining stable, or new nodes of >1cm in mediastinal or abdominal regions where no nodes were identified prior to irradiation.	**Cochrane risk of bias tool** Selection bias - random sequence generation: unclear - allocation concealment: unclear Performance bias - blinding: unclear but low risk due to objective outcomes Detection bias - blinding: unclear but unlikely due to obvious difference between treatments Attrition bias - outcome date complete for all participants - All patients received full course of RT, only 43% received 4 courses of CT. Reporting bias - outcomes stated in the objective were reported Overall assessment: UNCLEAR risk of bias due not inadequate reporting of allocation concealment, randomization process and blinding. **Other information** Data from an earlier publication from the same study (Zhao et al 2005) are also included here.

<table>
<tr><th>Study details</th><th>Participants</th><th>Intervention and Methods</th><th>Outcomes and Results

Bias Assessment</th></tr>
<tr>
<td>Full citation

Wobbes, T., Baron, B., Paillot, B., Jacob, J. H., Haegele, P., Gignoux, M., Michel, P., Couvreur, M. L., Prospective randomised study of split-course radiotherapy versus cisplatin plus split-course radiotherapy in inoperable squamous cell carcinoma of the oesophagus, European journal of cancer (Oxford, England : 1990), 37, 470-7, 2001</td>
<td>Sample size
N=221
(RT= 111, CRT= 110)

Characteristics
<table>
<tr><td>Characteristic</td><td>RT</td><td>CRT</td></tr>
<tr><td>Median age (range)</td><td>61 (44-75)</td><td>62 (40-75)</td></tr>
<tr><td>Sex</td><td>96 M/5 F</td><td>100 M/2 F</td></tr>
<tr><td>T category</td><td>T1 21
T2 66
T3 13
Unknown 1</td><td>T1 12
T2 70
T3 20
Unknown 0</td></tr>
<tr><td>N category</td><td>N0 69
N1 4
N2 1
N3 1
NX 26</td><td>N0 68
N1 3
N2 1
N3 0
NX 30</td></tr>
</table>
</td>
<td>Interventions
<u>Radiotherapy</u>
Radiotherapy two courses of 20 Gy in 5 fr of 4 Gy in 5 days
Rest interval 2 weeks
Total doses= 55-60 Gy in classical fractionated protocol.

<u>Chemoradiotherapy</u>
RT protocol as above
CT given 3-4 days before RT and then every 3-4 weeks.
Cisplatin 100 mg/m^2 given 2-4 days before each RT course and then every 3-4 weeks to a total of 6 cycles

Methods Details
Patients were randomized by the EORTC data centre in Brussels.

<u>Evaluation</u>
Main criteria were overall survival, progression-free</td>
<td>Results
<u>Overall Survival</u>
<u>1-year overall survival</u>
RT group: 32/111
CRT group: 50/110
<u>3-year overall survival</u>
RT group: 13/111
CRT group: 10/111
<u>Median Overall Survival</u>
RT group: 7.9 months (95% CI: 7.3-9.4)
CRT group: 9.6 months (95% CI 8-13.5)

CRT versus RT unstratified HR (95% CI)= 0.83 (0.63-1.09) P=0.173

<u>Progression Free Survival</u>
<u>1-year progression free survival</u>
RT group: 18/111
CRT group: 34/110
<u>3-year progression free survival</u>
RT group: 8/111
CRT group: 9/110
<u>Median progression Free Survival</u>
RT group: 5.0 months (95% CI: 4.6-5.7)
CRT group: 6.9 months (95% CI: 5.3-8.7)

CRT versus RT
Unstratified HR (95% CI)= 0.78 (0.69-1.02) P= 0.067</td>
</tr>
</table>

Study details	Participants	Intervention and Methods	Outcomes and Results Bias Assessment
Ref Id 475213 **Country/ies where the study was carried out** France, Belgium, Netherland **Study type** RCT **Aim of the study** To compare split-course radiation with split-course radiation plus cisplatin in patients with inoperable squamous cell carcinoma.	<table><tr><td>M Category</td><td>M0 97 M1 4</td><td>M0 100 M1 2</td></tr></table> **Inclusion criteria** • squamous cell carcinoma • age <70 years • no prior chemotherapy • WHO performance status 0-2 • any T1-3 lesion • without superficial lymph node metastases or distant metastases • patients who are inoperable because of local physical condition or refused surgery **Exclusion criteria** • weight loss > 20% • extension of tumour to the pharyngeal or gastric junction • tracheal or bronchial involvement • evidence of distant metastasis or supraclavicular lymph nodes • no previous malignancy except basal cell carcinoma of the skin	survival and time to local progression and time to local or distant progression. Follow-up Visits of the patients were planned on 2nd and 4th months after the start of the treatment, then every 3rd month until 18 months and finally every 6th month until death. Statistics An estimated 400 patients in each would provide statistical power. Treatment comparisons were performed for all randomised patients according to an intent-to-treat policy. Time=to-event end-points were estimated using the Kaplan-Meier technique. Differences were compared using a Lon-rank test.	**Treatment-related Morbidity** Haematological Toxicity- Grade II/IV RT group: 1/111 CRT group: 6/110 Nausea/Vomiting- Grade III/IV RT group: 0/111 CRT group: 12/110 **Limitations** Some indirectness of population- 2% M1 stage, 14.9% T1 oesophageal cancer. **Cochrane risk of bias tool** Selection bias - random sequence generation: unclear - allocation concealment: randomization through EORTC data centre Performance bias - blinding: unclear but likely low risk due to objective outcome measures Detection bias - blinding: unclear but likely low risk as above Attrition bias - outcome date complete Reporting bias - evaluation criteria stated in the methods were reported in results

Study details	Participants	Intervention and Methods	Outcomes and Results Bias Assessment
Study dates December 1983 to February 1989 **Source of funding** Grant number 2U10 CA11488-13 though 5U CA1488-29 from the National Cancer Institute (USA).	• contraindication to chemotherapy		Overall assessment: UNLCEAR risk of bias due to inadequate reporting of randomization process and blinding. **Other information**

1

F.14 First-line palliative chemotherapy

What is the optimal palliative first-line systemic chemotherapy for locally advanced and/or metastatic oesophago-gastric cancer?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Al-Batran, S. E., Pauligk, C., Homann, N., Hartmann, J. T., Moehler, M., Probst, S., Rethwisch, V., Stoehlmacher-Williams, J., Prasnikar, N., Hollerbach, S., Bokemeyer, C., Mahlberg, R., Hofheinz, R. D., Luley, K., Kullmann, F., Jager, E., The feasibility of triple-drug chemotherapy combination in older adult patients with oesophagogastric cancer: a randomised trial of the Arbeitsgemeinschaft Internistische Onkologie (FLOT65+), European Journal of CancerEur J Cancer, 49, 835-42, 2013 **Ref Id** 451965 **Country/ies where the study was carried out** Germany **Study type** RCT	**Sample size** n=143 patients **Characteristics** FLOT n=72 (21F/51M) Median age 69y Tumour site: OG junction 37.5 %/ Gastric 45% 69.4 % metastatic FLO n=71 (26F/45M) Median age 70y Tumour site: Of junction 33.8%/ Gatric 66.2% **Inclusion criteria** • ≥65 years • locally advanced or metastatic adenocarcinoma of the stomach or oesophagogastric junction • Locally advance patients: lymph node involvement (>2 cm)	**Interventions** **DOCETAXEL versus NON-DOCETAXEL** **FLOT** oxaliplatin 85 mg/m^2 + leucovorin 200 mg/m^2 + docetaxel 50 mg/m^2, each as an intravenous infusion followed by 5-FU 2600 mg/m^2 as a 24-h continuous infusion x8 cycles **FLO** oxaliplatin 85 mg/m^2 + leucovorin 200 mg/m^2 each as an intravenous infusion followed by 5-FU 2600 mg/m^2 as a 24-h continuous infusion x8 cycles	**Details** Patients were stratified by centre, tumour status, ECOG status, presence of liver metastases and pharmacogenetic risk and randomly assigned to receive FLO or FLOT. Each patient received 8 cycles, investigator could extend to 12 cycles. Primary objective of the study was tolerability and feasibility. Response rates were 30% and 50% with FLO and FLOT, respectively. The resulting sample size was 140 patients, using an 80% power at one-sided significance level of 0.05. PFS and OS were also measured. Quality of life assessment Quality of life (QoL) was evaluated using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ C30). QoL was assessed within seven days prior the first cycle and at eight, 16 and 24	**Results** **Treatment-related toxicity** Significantly more patients had treatment-related NCI-CTC grade 3/4 adverse events in the FLOT arm (FLOT, 81.9%; FLO, 38.6%; P < .001) Neutropenia, leukopenia, nausea: FLOT sig more grade 3/4 instances (p<.001, p<.001, p=.006). Alopecia and diarrhoea: FLOT sig more cases (p<.001; p=.006). **Treatment-related morbidity** 1 death in FLO group: intestinal mucositis **Progression free survival** FLOT: 9.0m FLO: 7.1m No sig difference (p=.079) **Overall survival** FLOT: 17.3m FLO: 14.5m No sig difference (p=.39) **QoL** No sig difference between arms in QoL status scores FLOT: Baseline mean (SD): 56.5 (24.4)	**Limitations** **Cochrane risk of bias tool** Selection bias • random sequence generation: unclear • allocation concealment: unclear Performance bias • blinding: unclear Detection bias • blinding: unclear Attrition bias • outcome date complete Reporting bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study The aim of this present study was to determine if the docetaxel-based triplet regimen FLOT is feasible in elderly patients with oesophagogastric cancer. **Study dates** August 2007 and October 2008 **Source of funding** The Institute of Clinical Research at Krankenhaus Nordwest University Cancer Center Frankfurt, with partial funding from Sanofi Aventis.	• ECOG performance status 0–2 • sufficient bone marrow and kidney function • **Exclusion criteria** • concurrent uncontrolled medical illness • prior chemotherapy		weeks thereafter. According to EORTC guidelines, patients filled out the QoL questionnaires before the tumour assessment was performed.	24 weeks mean (SD): 53.7 (22.8) FLO: Baseline mean (SD): 49.4 (24.7) 24 weeks mean (SD): 55.5 (16.9)	• outcomes stated in the objective were reported Overall assessment: UNLCEAR risk of bias due not inadequate reporting of allocation concealment, randomization process and blinding. Limited detail provided on methodology. **Other information** Elderly patients only. Included in Wagner MA.
Full citation Curran, D., Pozzo, C., Zaluski, J., Dank, M., Barone, C., Valvere, V., Yalcin, S., Peschel, C., Wenczl, M., Goker, E., Bugat, R., Quality of life of palliative chemotherapy naive patients with advanced adenocarcinoma	**Sample size** n=337 **Characteristics** **IF** n=170 Sex: 125 M/45 F Median age: 58 (range 29-76) **CF**	**Interventions** **IRINOTECAN VERSUS CISPLATIN BASED COMBINATION** Patients randomized to the IF arm received irinotecan 80 mg/m^2 as a 30-min i.v. infusion, followed by FA 500 mg/m^2 as a 2-h i.v. infusion, immediately followed by 5-FU 2000	**Details** The primary objective of this phase III study was to detect a statistically significant increase in TTP for the IF test arm relative to the CF control arm in the full-analysis population (i.e. all treated subjects analyzed in the arm to which they were	**Results** **Treatment-Related Mortality** IF group: 1/170 CF group: 5/ 163 **Quality of Life** at secondary QL endpoint **Global health status** IF group: n= 116	**Limitations** **Cochrane risk of bias tool** Selection bias • random sequence generation: coin toss method

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
of the stomach or esophagogastric junction treated with irinotecan combined with 5-fluorouracil and folinic acid: results of a randomised phase III trial, Quality of Life ResearchQual Life Res, 18, 853-61, 2009 **Ref Id** 475528 **Country/ies where the study was carried out** Ireland; Multi-centre **Study type** RCT **Aim of the study** To assess QL of advanced gastric cancer patients receiving IF or CF. **Study dates** January 2000 - March 2002 **Source of funding** Pfizer, Inc.	n=163 Sex: 108 M/ 55 F Median age: 59 (28-77) **Inclusion criteria** • Locally recurrent/metastatic adenocarcinoma of stomach or oesophagastric junction • 18-75y • Karnofsky performance status >70% • life expectancy > 3 months • adequate haematological parameters • **Exclusion criteria** • resectable locally advanced disease • pregnancy or lactation • prior palliative chemo or treatment with camptothecin	mg/m^2 as a 22-h i.v. infusion, day 1 every week for 6 weeks followed by a 1-week rest. In the CF, patients received cisplatin 100 mg/m^2 as a 1- to 3-h i.v. infusion, day 1, followed by 5-FU 1000 mg/m^2/day as a 24-h i.v. infusion, days 1–5, every 4 weeks. Treatment was administered until disease progression, unacceptable toxicity or consent withdrawal. All patients received antiemetic prophylaxis with i.v. ondansetron and dexamethasone. CF patients also received hyperhydration and metoclopramide and dexamethasone p.o. for 2–3 days after infusion. Granulocyte colony-stimulating factors (day 4 until recovery to ANC 1.0 · 109/l) were recommended for febrile neutropenia, neutropenic infection or neutropenia grades 3–4 >7 days. Atropine was administered for grades 2–4 acute cholinergic syndrome and loperamide for delayed diarrhea [21]. Treatment cycles could be delayed by up to 2 weeks for recovery from neutropenia ‡grade 2 or	randomized). The secondary end points were response rates, duration of response, time to treatment failure (TTF) and OS. The safety analysis included all patients according to the actual treatment received. For the primary efficacy analysis, it was assumed that TTP in the IF and CF arms would be 6 and 4 months, respectively [hazard ratio (HR) of 1.5], and that a total of 263 events, corresponding to 318 patients (159 per arm) with a 5% lost to follow-up rate, would be necessary to provide a 90% power to detect the difference in TTP at a two-sided 5% significance level using an unadjusted log-rank test. Randomization was carried out using a biased coin method, applying stratification according to measurable versus evaluable disease, liver involvement (yes versus no), baseline weight loss £5% (yes versus no), prior surgery (yes versus no) and treatment center. TTP was measured from randomization until the date of progression or death, if death occurred within 12	mean (SD)= 62.41 (20.050 CF group: n= 101 mean (SD)= 56.95 (21.10) **Physical Functioning** IF group: n= 117 mean (SD)= 79.60 (17.68) CF group: n= 101 mean (SD)= 71.05 (22.55) **Social Functioning** IF group: n= 116 mean (SD)= 76.28 (22.25) CF group: n= 102 mean (SD)= 70.62 (26.72) **Pain** IF group: n= 117 mean (SD)= 21. 54 (23.24) CF group: n= 102 mean (SD)= 24.65 (26.51) **Nausea/Vomiting** IF group: n= 116 mean (SD)= 13.62 (16.80) CF group: n= 102 mean (SD)= 20.82 (23.06) **EQ5D Thermometer** IF group: n= 87 mean (SD)= 73.66 (16.56) CF group: n= 69 mean (SD)= 64.80 (17.49) **EQ5D HUI**	• allocation concealment: unclear Performance bias • blinding: unclear Detection bias • blinding: unclear Attrition bias • outcome date complete Reporting bias • outcomes stated in the objective were reported Overall assessment: UNLCEAR risk of bias due not inadequate reporting of allocation concealment and blinding. **Other information** Some data included from other publication on same study: Dank 2008 (Participant

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	• further outlined in Dank et al. 2008	any thrombocytopenia or diarrhea. Dose reductions for one or both study medications were planned in the event of severe toxic effects. Patients discontinued if they failed to recover after 2 weeks delay, needed more than two dose reductions, had grade 4 stomatitis or grades 3–4 peripheral neurotoxicity/ototoxicity.	weeks of the last evaluable tumor assessment. Patients without progression at last contact or receiving new antitumor therapy were censored at the date of their last assessment before last contact or new therapy, respectively. TTF was from randomization to progression, death or treatment discontinuation. The cut-off for the TTP analysis was set at the date that the 263rd event was obtained. Te primary QoL parameter was time to definitive deterioration by 5% of the global health status scale of the EORTC QLQ-C30 instrument, with time to 5% deterioration of the EQ-5D instrument also analyzed.	IF group: n= 86 mean (SD)= 0.76 (0.23) CF group: n= 66 mean (SD)= 0.66 (0.27)	characteristics, non-QoL outcomes, methodological details)
Full citation Kim, N. K., Park, Y. S., Heo, D. S., Suh, C., Kim, S. Y., Park, K. C., Kang, Y. K., Shin, D. B., Kim, H. T., Kim, H. J., A phase III randomized study of 5-fluorouracil and cisplatin versus 5-fluorouracil, doxorubicin, and mitomycin C versus 5-fluorouracil alone in the treatment of	**Sample size** n= 214 FP= 112, FU= 102, (FAM arm not relevant) **Characteristics** Median age= 54 (19-77) 205 M/ 90 F	**Interventions** **FU ALONE VERSUS COMBINATION** In all three regimens, 5-FU was diluted in 1000 ml of 5% dextrose and infused intravenously over 12 hours. Drug administration was postponed by 1 week if there was no hematologic recovery (leukocyte count > 3000/mm^3 or platelet count > 75,000/mm^3).	**Details** A total of 324 patients were entered into the trial and 295 patients (103 for FP, 98 for FAM, 94 for FU) were evaluable. The patients were randomized to re-ceive FP, FAM, or FU after stratifying by the following factors: performance status, presence of measurable dis- ease, and resection of the primary tumor.	**Results** Median time to progression FP: 21.8 weeks FU arm: 9.1 weeks P<0.005 Treatment-related toxicity: Grade 3/4 hematologic toxicity FP: 8/ 589 cycles FU: 3/ 416 cycles	**Limitations** **Cochrane risk of bias tool** Selection bias • random sequence generation: unclear • allocation concealment: unclear

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
advanced gastric cancer, CancerCancer, 71, 3813-8, 1993 **Ref Id** 475855 **Country/ies where the study was carried out** Korea **Study type** RCT **Aim of the study** To perform a randomized, controlled study comparing this FP regimen with the FAM and FU regimens in unresectable, recurrent, or metastatic gastric adenocarcinoma. **Study dates** From August, 1986 to June, 1990 **Source of funding** NR	**Inclusion criteria** • histological confirmation of adenocarcinoma in gastric mucosa • unresectable, recurrent, metastatic disease • measurable or evaluable disease • inadequate bone marrow, hepatic and renal function **Exclusion criteria** • ECOG performance status 4 • active infections • invasive neoplasms in other sites • active heart disease • previous cytotoxic chemotherapy or radiotherapy	5-FU: 1000 mg/m^2 IV Days 1-5 every 3 wks 5-FU + cisplatin: as above + cisplatin 60 mg/m^2 IV Day 1 every 3 wks	Statistical Analysis Response rates and the severity of toxicity were com- pared using the chi-square method. Time to progression and survival were recorded and calculated, for all pa- tients regardless of measurable disease, from the start- ing date of the first treatment, using the life table method. Overall comparisons between the treatment groups were made by the log-rank test.	Treatment-related toxicity: nausea/vomiting (> grade 2) FP: 60/ 103 patients FU: 24/94 patients Treatment-related toxicity: infection/fever (> grade 2) FP: 4/103 patients FU: 2/ 94 patients	Performance bias • blinding: unclear Detection bias • blinding: unclear Attrition bias • outcome date complete Reporting bias • outcomes stated in the objective were reported Overall assessment: UNLCEAR risk of bias due not inadequate reporting of allocation concealment, randomization process and blinding. Very limited methodological details reported. **Other information**
Full citation	**Sample size**	**Interventions**	**Details**	**Results**	**Limitations**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Kim, Y. S., Sym, S. J., Park, S. H., Park, I., Hong, J., Ahn, H. K., Park, J., Cho, E. K., Lee, W. K., Chung, M., Lee, J. H., Shin, D. B., A randomized phase II study of weekly docetaxel/cisplatin versus weekly docetaxel/oxaliplatin as first-line therapy for patients with advanced gastric cancer, Cancer Chemotherapy and Pharmacology, 73, 163-169, 2014 **Ref Id** 475859 **Country/ies where the study was carried out** Korea **Study type** RCT **Aim of the study** this randomized, non-comparative phase II trial evaluated two weekly docetaxel-based regimens to determine which is the most promising in terms of efficacy and safety as a front-line therapy in advanced gastric cancer.	N= 77 **Characteristics** D + cisplatin: Median= 56 (range 35-74) 74% male Previous adjuvant chemo: 42% D+ oxaliplatin: Median= 58 (range 39-75) 67% male previous adjuvant chemo: 26% **Inclusion criteria** • histologically confirmed gastric adenocarcinoma • inoperable locally advanced, recurrent or metastatic disease • adequate bone marrow, hepatic and renal function • age <= 75 years **Exclusion criteria** • prior palliative chemotherapy	**CISPLATIN VERSUS OXALIPLATIN** Chemotherapy consisted of docetaxel (35 mg/m^2 on days 1 and 8) plus cisplatin (60 mg/m^2 on day 1 every 3 weeks) or oxaliplatin (120 mg/ m^2 on day 1 every 3 weeks). Docetaxel was infused intravenously in 200 ml of 5 % glucose over 60 min, cisplatin was administered in 150 ml of normal saline over 60 min with intravenous pre- and post-hydration, and oxaliplatin was diluted in 500 ml of 5 % glucose solution and administered over 90 min. all patients were premedicated with 12 mg dexamethasone i.v. before each docetaxel infusion to prevent fluid retention and hypersensitivity reactions.	Chemotherapy-naïve patients with measurable unresectable and/or metastatic gastric adenocarcinoma were randomly assigned to receive docetaxel (35 mg/m2) weekly on days 1 and 8 of a 21-day cycle plus either cisplatin (60 mg/m2 on day 1) (wDP) or oxaliplatin (120 mg/m2 on day 1) (wDO). Statistical Analysis The primary end point of this trial was objective response rate (Orr), and the secondary end points were toxicity, progression-free survival (PFS), and overall survival (OS). to estimate the activities and safeties of the wDO and wDP regimens simultaneously and to minimize patient selection bias, the study was conducted using a randomized, noncomparative phase II design. PFS was calculated from the date of treatment commencement to the date of first documentation of disease progression or date of death from any cause. OS was defined as the time between treatment commencement and date of death or last followup. PFS	Overall Survival DP group: 9.7 months (95% CI 6.2-13.3 months) DO group: 12.3 months (95% CI 9.7- 14.9 months) P=0.581 Progression-Free Survival DP group: 4.9 months (95% CI 3.7-6.1 months) DO group: 4.4 months (95% CI 4.0- 4.9 months) P=0.324 Treatment-Related Mortality DP group: 1/38 DO group: 1/39 Treatment-Related Morbidity: Vomiting DP group: 63% DO group: 39% P= 0.039 Treatment-Related Morbidity: Peripheral Neuropathy DP group: 39% DO group: 68% P= 0.011	**Cochrane risk of bias tool** Selection bias • random sequence generation: unclear • allocation concealment: unclear Performance bias • blinding: unclear Detection bias • blinding: unclear Attrition bias • outcome date complete Reporting bias • outcomes stated in the objective were reported Overall assessment: UNLCEAR risk of bias due not inadequate reporting of allocation concealment, randomization process and

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates March 2007 and July 2009 **Source of funding** This study was supported by a grant from gachon University gil Hospital. Study drug (oxaliplatin, eloxatin®) was kindly provided by Sanofi-aventis.	• prior treatment with taxanes • another malignancy • brain metastases • uncontrolled co-morbid illness		and OS were estimated using the Kaplan–Meier method. Pearson's chi-squared or Fisher's exact tests were used to compare categorical variables in the two arms, and the log-rank test was used to evaluate survival differences in the two arms. Cox proportional hazard method was used to identify independent prognostic factors of survival. Statistical significance was accepted for P values <0.05. all analyses were performed using SPSS for Windows ver. 19.0 (SPSS Inc., Chicago, Il, USa).	Treatment-Related Morbidity: Serious adverse events (Grade 3/4) DP group: 66% DO group: 68% P= 0.807	blinding. Limited methodological details provided. **Other information**
Full citation Lee, S. J., Kim, S., Kim, M., Lee, J., Park, Y. H., Im, Y. H., Park, S. H., Capecitabine in combination with either cisplatin or weekly paclitaxel as a first-line treatment for metastatic esophageal squamous cell carcinoma: a randomized phase II study, BMC CancerBMC Cancer, 15, 693, 2015 **Ref Id**	**Sample size** N= 94 (CC arm= 46, CP arm= 48) **Characteristics** Median age= 63 years (range 34-82) 98% male 59 primary advanced disease/ 35 recurrent disease (after surgery or dCRT) Previous chemotherapy: 19	**Interventions** **TAXANE COMBINATION VERSUS CISPLATIN COMBINATION** CC = capecitabine 1000 mg/m2 orally twice a day on days 1–14 plus 75 mg/m^2 of cisplatin intravenously on day 1 CP= capecitabine as for CC plus 80 mg/m^2 of paclitaxel intravenously on days 1 and 8 An identical dose regimen of capecitabine was used for both treatment arms. Study treatment was	**Details** Patients with recurrent or metastatic esophageal squamous cell carcinoma were enrolled in this open-label, phase II, randomized trial. Patients were assigned to either the CC arm (days [D]1–14 capecitabine 1000 mg/m2 twice daily+D1 cisplatin 75 mg/m2, every 3 weeks) or the CP arm (D1–14 capecitabine 1000 mg/m2 twice daily+D1, 8 paclitaxel 80 mg/m2, every 3 weeks). The primary endpoint of the	**Results** Overall Survival CC group: Median O survival (95% CI)= 10.5 months (9.2-11.9 months) CP group: Median O survival (95% CI)= 13.2 months (9.4-17.0) P=0.217 (log rank) Progression Free Survival CC group:	**Limitations** **Cochrane risk of bias tool** Selection bias • random sequence generation: unclear • allocation concealment: unclear Performance bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
474754 **Country/ies where the study was carried out** Korea **Study type** RCT **Aim of the study** The aim of this study was to assess the efficacy and safety of a combination regimen of capecitabine plus cisplatin (CC) or capecitabine plus paclitaxel (CP) as a first-line treatment in patients with metastatic esophageal squamous cell carcinoma. **Study dates** October 2008 and October 2012 **Source of funding** Study drugs (capecitabine and paclitaxel) were kindly provided by Roche and CJ (Seoul, Korea), respectively. Neither company was involved in collection or analysis of the	**Inclusion criteria** • recurrent or metastatic disease • squamous cell carcinoma of the esophagus • no previous palliative chemo • at least one measurable metastatic lesion • ECOG performance status 0-2 • life expectancy at least 3 months • adequate hematologic, renal and liver function • **Exclusion criteria** • radiotherapy within last 4 months • adjuvant chemotherapy within last 6 months • active infection	repeated every 3 weeks until documented disease progression, unacceptable toxicity, or patient refusal. Supportive care, including adequate pre- and post-hydration for patients in the CC arm and corticosteroids for patients in the CP arm, was provided according to guidelines.	study was response rate and secondary endpoints were progression-free survival (PFS), overall survival (OS), toxicity and quality of life. Patient Assessment Baseline evaluation included a complete medical history and physical examination, blood counts, serum chemistry, chest x-ray, and chest computed tomography (CT) scan. Follow-up history, physical examination and toxicity assessment were performed before each 3-week cycle of treatment. Toxicity grading was based on the National Cancer Institute criteria (NCICTCAE version 3). The first evaluation with imaging was performed 6 weeks after the start of study treatment. Response was evaluated according to the RECIST criteria and was assessed by chest CT or by the same tests that were initially used to stage the tumor. In case of complete radiologic response, endoscopic evaluation of the primary tumor, if present, was mandatory. Progression in non-measurable lesions that led to deterioration of patient	Median PF survival (95% CI)= 5.1 months (4.0-6.2 months) CP group: Median PF survival (95% CI)= 6.7 months (4.9-8.5) P=0.260 (log rank) Discontinuation due to Toxicity CC= 9% CP= 13% Treatment-related severe toxicity (Grade 3/4) CC= 27/46 CP= 33/48 Treatment-related mortality CC= 1/46 (tumour bleeding) CP= 2/48 (neutropenic sepsis, respiratory failure) Quality of Life No difference at baseline QoL questionnaires no difference post-treatment. Symptom scales: CC: reflux improved CP: dry mouth aggravated (Numerical data NR)	• blinding: unclear Detection bias • blinding: unclear Attrition bias • outcome date complete Reporting bias • outcomes stated in the objective were reported Overall assessment: UNLCEAR risk of bias due not inadequate reporting of allocation concealment, randomization process and blinding. Limited methodological detail available. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
data, or in the preparation of the manuscript	• severe comorbid conditions • CNS metastasis • pregnant or lactating women		status was classified as progressive disease regardless of the status of the measurable lesions. We also assessed quality of life (QOL) using the EORTC-QLQOES18, which contains four scales that address dysphagia, eating difficulties, reflux, and esophageal pain, and six single items for problems with coughing, dry mouth, taste, choking when swallowing, speech, and swallowing saliva. These self-administered questionnaires were completed by patients at baseline, every two cycles, and at the end of treatment. QOL scores were descriptively recorded as baseline values and changes from baseline. As a general criterion for clinically significant improvement or deterioration, we defined a difference of ten or greater from baseline mean score as a clinically significant change. <u>Outcome Assessment</u> The primary objective of this study was to assess the response rate in both treatment arms. Secondary objectives included		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			assessment of PFS, OS, toxicity and QOL. Statistical Analysis PFS and OS were estimated according to the Kaplan-Meier method, and the changes in QOL scores were calculated with a paired t-test. Since the study was designed to assess chemotherapy outcomes for two regimens simultaneously, exploratory analyses of efficacy were carried out using the Cox regression model. All data were analyzed using R for Windows software.		
Full citation Mohammad, N. H., ter Veer, E., Ngai, L., Mali, R., van Oijen, M. G. H., van Laarhoven, H. W. M., Optimal first-line chemotherapeutic treatment in patients with locally advanced or metastatic esophagogastric carcinoma: triplet versus doublet chemotherapy: a systematic literature review and meta-analysis, Cancer and Metastasis Reviews, 34, 429-441, 2015	**Sample size** Twenty-two studies with in total 3475 participants investigating a triplet versus a doublet were included. **Characteristics** 6 relevant articles are detailed below. Other articles in the review were already included in the Wagner et al. meta-analysis, not relevant	**Interventions** **Guimbaud 2014** 1. epirubicin + cisplatin + capetibacine 2. FU + irinotecan **Li 2011** 1. placitaxel + cisplatin + FU 2. cisplatin + FU	**Details** Search Strategy A search was conducted at the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, and EMBASE up to March 2015. The search strategy contained medical subject headings (MESH) and text words for esophageal and gastric cancer and all established chemotherapy compounds in esophageal and gastric cancer. We	**Results** **Overall Survival** **Guimbaud 2014** epirubicin + cisplatin + capetibacine 209/ FU + irinotecan 207 log HR (SE)= 0.0083 (0.1055) HR (95% CI)= 1.01 (0.82, 1.24) **Li 2011** placitaxel + cisplatin + FU 50/ cisplatin + FU 44 log HR (SE)= 0.0032 (0.2538)	**Limitations** ROBIS tool for bias risk assessment in systematic reviews: Study Eligibility Criteria 1.Did the review adhere to pre-defined objectives and eligibility criteria? Y 2.Were the eligibility criteria appropriate for the review question? Y 3.Were the eligibility criteria unambiguous? Y 4.Were all the restrictions on eligibility criteria based on study characteristics appropriate? Y

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref Id 476079 **Country/ies where the study was carried out** The Netherlands **Study type** Systematic review of RCTs **Aim of the study** review the available literature To assess the efficacy and safety of triplet versus doublet chemotherapy as a first-line treatment in patients with advanced esophagogastric cancer **Study dates** Search limits between 1980 and March 2015	(outside date limits, wrong intervention) or conference abstract without relevant data. **Guimbaud 2014** n= 416 Median age= 61 (range 28-84) 84% metastatic 74.5% male **Li 2011** n= 94 Median age= 58.5 (Range 20-75) 58.5% metastatic 69% male **Park 2008** n= 91 Median age= 53.5 (range 26-73) 100% metastatic 67% male **Van Cutsem 2015** n= 254 Median age= 59 100% metastatic 69% male **Wang 2015** n= 234 Median age= 57.5 (Range 19-80) 76% metastatic 72.5% male **Yun 2010** n= 91 Median age= 56.5 (Range 33-75) NR% metastatic 68% male	**Park 2008** 1. cisplatin + irinotecan + FU 2. cisplatin +FU **Van Cutsem 2015** • docetaxel + oxaliplatin + FU • docetaxel + oxaliplatin + capecitabine • docetaxel + oxaliplatin **Wang 2015** 1. docetaxel + cisplatin + FU 2. cisplatin + FU **Yun 2010** 1. epirubicin + cisplatin + capecitabine 2. cisplatin + capecitabine	searched all abstracts from the American Society of Clinical Oncology (ASCO) and the ESMO conferences held between 1990 and 2014. The research question was registered in PROSPERO in September 2014 (registration: CRD42014014480). <u>Data Extraction</u> 3 researcher scrutinized the studies. 3 researchers extracted the study characteristics and outcome data. The primary outcome was overall survival (OS). Overall survival was defined as the time between date of randomization and date of death or last date of follow-up. <u>Bias Assessment</u> All selected studies were critically appraised using an assessment form designed for the topic of this review according to the Cochrane Handbook for Systematic Reviews of Interventions. Risk of bias caused by the absence of blinded review	HR (95% CI)= 1.00 (0.61, 1.65) **Park 2008** cisplatin + irinotecan + FU 45/ cisplatin +FU 46 log HR (SE)= -0.1805 (0.3628) HR (95% CI)= 0.83 (0.41, 1.70) **Van Cutsem 2015** docetaxel + oxaliplatin + FU/capecitabine 175 / docetaxel + oxaliplatin 79 log HR (SE)= -0.4902 (0.1614) HR (95% CI)= 0.61 (0.45, 0.84) **Wang 2015** docetaxel + cisplatin + FU 121/ cisplatin + FU 122 log HR (SE)= -0.3422 (0.1591) HR (95% CI)= 0.71 (0.52, 0.97) **<u>Progression Free Survival</u>** **Guimbaud 2014** epirubicin + cisplatin + capetibacine 209/ FU + irinotecan 207 log HR (SE)= -0.0101 (0.1024) HR (95% CI)= 0.99 (0.81, 1.21)	5.Were any restrictions in eligibility criteria based on sources of information available? Y 6.Concern regarding specification of study eligibility criteria: Low Identification and Selection of Studies 1.Did the search include an appropriate range of databases/electronic sources for published and unpublished reports? Y 2.Were the methods additional to database searching used to identify relevant reports? Y 3.Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible? NI 4.Were restrictions based on date, publication format or language appropriate? PY 5.Were efforts made to minimise error in selection of studies? Y 6.Concern regarding methods used to identify or select studies: LOW Data Collection and Study Appraisal 1.Were efforts made to minimise error in data collection? Y 2.were sufficient study characteristics available? Y

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding NR	**Inclusion criteria** • Randomized phased II or III studies were included • Abstract only if information on study design, characteristics of participants, interventions, and outcomes was available in English. • Patients had advanced, recurrent, or metastatic adenocarcinoma of the distal esophagus, gastroesophageal junction, or stomach. • treatment was defined as oral or IV chemotherapy **Exclusion criteria**		of CT scans was not scored as high risk, since our primary outcome OS would not be influenced by this parameter. If data were missing, we contacted the first author to obtain further information.	**Park 2008** cisplatin + irinotecan + FU 54/ cisplatin +FU 56 log HR (SE)= -0.2437 (0.2319) HR (95% CI)= 0.78 (0.50, 1.23) **Van Cutsem 2015** docetaxel + oxaliplatin + FU/capecitabine 175 / docetaxel + oxaliplatin 79 log HR (SE)= -1.0668 (0.1706) HR (95% CI)= 0.34 (0.25, 0.48) **Wang 2015** docetaxel + cisplatin + FU 121/ cisplatin + FU 122 log HR (SE)= -0.5453 (0.1644) HR (95% CI)= 0.58 (0.42, 0.80) **Yun 2010** epirubicin + cisplatin + capecitabine 44/ cisplatin + capecitabine 47 log HR (SE)= -0.0468 (0.254) HR (95% CI)= 0.95 (0.58, 1.57)	3.Were all relevant study results collected for use and synthesis? Y 4.Was risk of bias formally assessed using appropriate criteria? Y 5.Were efforts made to minimise error in risk of bias assessment? Y 6.Concern: LOW Synthesis and Findings 1.Did the synthesis include all studies it should? Y 2.Were all pre-defined analyses reported and departures explained? PY 3.Was the synthesis appropriate given the nature and similarity in the research questions? Y 4.Was heterogeneity minimal or addressed? Y 5.Were the findings robust as demonstrated though funnel plot or sensitivity analysis? Y 6.Were biases in primary studies minimal or addressed in the synthesis? Y 7.Concern= LOW Risk of bias in the review 1.Did the interpretation of findings address all the concerns identifies in 1-4? Y 2.Was the relevance of identified studies to the review's research question

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	• crossover studies and quasi randomized studies • not previously treated with chemotherapy (or ≥6 months ago in adjuvant setting) • targeted therapy/biological therapy. •				appropriately considered? Y 3.Did the reviewers avoid emphasizing results on the basis of their statistical significance? Y 4. Risk of bias= LOW **Other information**
Full citation Roth, A. D., Fazio, N., Stupp, R., Falk, S., Bernhard, J., Saletti, P., Koberle, D., Borner, M. M., Rufibach, K., Maibach, R., Wernli, M., Leslie, M., Glynne-Jones, R., Widmer, L., Seymour, M., De Braud, F., Docetaxel, cisplatin, and fluorouracil; docetaxel and cisplatin; and epirubicin, cisplatin, and fluorouracil as systemic treatment for advanced gastric carcinoma: A randomized	**Sample size** N=119 **Characteristics** ECF group: median age (range)= 59 (32-71) 75% male 83% metastatic disease previous gastrectomy: 18% TC group: median age (range)= 58 (40-70)	**Interventions** **ANTHRACYCLINE CONTAINING REGIMEN VERUS NON-ANTHRACYCLINE CONTAINING** Patients received 3-weekly cycles of ECF (epirubicin 50 mg/m^2 intravenous [IV] bolus on day 1, cisplatin 60 mg/m^2 4-hour IV infusion on day1, and FU 200mg/m^2/d continuous IV infusion on days 1 to 21), TC (docetaxel 85 mg/m^2 1-hour IV infusion on day 1 and cisplatin 75 mg/m^2 4-hour	**Details** Patient Assessment Responses were assessed (using WHO criteria) every 6 weeks by computed tomography scans, chest x-ray, or magnetic resonance imaging and were confirmed 4weeks later. All responses were confirmed by an independent panel of radiologists and an oncologist. After completion or withdrawal of treatment, disease status was assessed every 3 months. Toxicities were assessed	**Results** Quality of Life Similar scores at baseline Median change in QoL score at cycle 6 **Domain: role functioning** ECF group: 0 TC group: 0 TCF group: -16.7 **Domain: emotional fucntioning** ECF group: +8.3 TC group: +8.3 TCF group: +8.3 **Domain: constipation** ECF group: 0 TC group: 0	**Limitations** **Cochrane risk of bias tool** Selection bias • random sequence generation: unclear • allocation concealment: randomly assigned at research coordinating centre

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
phase II trial of the Swiss group for clinical cancer research, Journal of Clinical OncologyJ Clin Oncol, 25, 3217-3223, 2007 **Ref Id** 476277 **Country/ies where the study was carried out** Switzerland; Multiple **Study type** RCT **Aim of the study** This randomized phase II trial evaluated two docetaxel-based regimens to see which would be most promising according to overall response rate (ORR) for comparison in a phase III trial with epirubicin-cisplatin-fluorouracil (ECF) as first-line advanced gastric cancer therapy. **Study dates** September 1999 and July 2003	76% male 82% metastatic disease previous gastrectomy: 24% <u>TCF group:</u> median age (range)= 61 (35-78) 73% male 95% metastatic disease previous gastrectomy: 32% **Inclusion criteria** • chemotherapy naïve • gastric adenocarcinoma • measurable • unresectable, locally advanced, non-metastatic • adequate hematologic, renal and hepatic function **Exclusion criteria**	IV infusion on day 1), or TCF (TC plus FU 300 mg/m^2/d continuous IV infusion on days 1 to 14) for up to eight cycles or until disease progression ,unacceptable toxicity, or consent withdrawal.	using National Cancer Institute of Canada Clinical Trials Group expanded common toxicity criteria. Febrile neutropenia was defined by fever 38.1°C and grade 4 neutropenia. All randomly assigned patients were asked to complete the European Organisation for Research and Treatment of Cancer Quality of Life QuestionnaireC30(EORTC QLQ-C30;version3.0). <u>Statistical Analysis</u> TTP was measured from random assignment to progression or death without progression, and OS was measured from random assignment to death. Indicators of QOL were descriptive and evaluated as changes from baseline. The two items for numbness/paresthesia were averaged (average internal consistency under treatment: .82). Effects of treatment, time, and treatment-time interactions were longitudinally analysed by a non parametric mixed-effects model using all available data within the prefailure observation period. For all measures, a	TCF group: +16.7 **Domain: numbness/paresthesia** ECF group: 0 TC group: -25.0 TCF group: -16.7 **Domain: global health status/QoL** ECF group: +8.3 TC group: 0 TCF group: 0 **Domain: treatment burden** ECF group: 0 TC group: -8.3 TCF group: -16.7 ** NB: uncertainty not reported	Performance bias • blinding: unclear Detection bias • blinding: unclear Attrition bias • outcome date complete Reporting bias • outcomes stated in the objective were reported Overall assessment: UNLCEAR risk of bias due not inadequate reporting of randomization process and blinding. **Other information** Other outcomes included in Wagner meta-analysis.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding Supported in part by Sanofi-aventis.	• history of anaphylaxis • peripheral neuropathy		10-point change from baseline was defined as a clinically substantial change. The observed changes between baseline and cycle2 were compared with the rating of subjective change within patients. All tests were two sided. No adjustment was made for multiple testing. Reported Pvalues have descriptive value only		
Full citation Sadighi, S., Mohagheghi, M. A., Montazeri, A., Sadighi, Z., Quality of life in patients with advanced gastric cancer: a randomized trial comparing docetaxel, cisplatin, 5-FU (TCF) with epirubicin, cisplatin, 5-FU (ECF), BMC CancerBMC Cancer, 6, 274, 2006 **Ref Id** 454876 **Country/ies where the study was carried out** Iran	**Sample size** N= 86 **Characteristics** ECF group N= 41 Mean age (SD)= 57.32 (9.83) 81 % male 71% primary disease/ 29% recurrent TCF group N= 44 Mean age (SD)= 55.4 (14.04) 70% male 75% primary disease/ 25% recurrent	**Interventions** **DOCETAXEL VERSUS NON_DOCETAXEL REGIMEN** three to six cycles every 3 weeks ECF: epirubicin 60 mg/m^2, cisplatin 60 mg/m^2 and 5-FU 750 mg/m^2/day as 5 days continuous infusion TCF: docetaxel 60 mg/m^2, cisplatin 60 mg/m^2 and 5-FU 750 mg/m^2 in the same dose and schedule of ECF	**Details** Quality of Life Assessment QOL was assessed using the Iranian version of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, EORTC QLQ-C30. Statistical Analysis For comparing patients' characteristics in two groups t-test or chi-square were used. The QLQ-C30 responses were scored and analyzed according to the scoring manual provided by the EORTC Study Group on Quality of Life [8]. First, the mean baseline scores for each treatment groups were calculated. Then, after	**Results** Quality of Life Baseline similar between groups. For HRQOL evaluation, only 71 patients were included in the comparative analysis because 15 patients did not complete the QOL measurements at the beginning of the study. Mean Score Changes (SD) **Physical Functioning** ECF group: 4.1 (13.6)	**Limitations** **Cochrane risk of bias tool** Selection bias • random sequence generation: unclear • allocation concealment: unclear Performance bias • blinding: unclear Detection bias • blinding: unclear

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type RCT **Aim of the study** This study aimed to compare HRQOL in patients with advanced gastric cancer (GC) receiving either a standard or an experimental treatment. **Study dates** January 2002 and January 2005, **Source of funding** NR	**Inclusion criteria** • histologically confirmed gastric adenocarcinoma • primary or recurrent disease (stage III or IV) **Exclusion criteria** • not reported		treatment, the mean change score from baseline was calculated for all patients and compared between the two treatment groups. Two-related sample t-test (paired samples t-test) was used for statistical comparison. Survival analysis was performed using the Kaplan-Meier test.	TCF group: 2.3 (14.8) **Role functioning** ECF group: 0.57 (14.3) TCF group: 2.7 (18.9) **Emotional Functioning** ECF group: -0.06 (8.3) TCF group: 8.0 (15.4) **Cognitive Functioning** ECF group: -2.5 (13.4) TCF group: -6.1 (17.0) **Social Functioning** ECF group: -2.3 (14.6) TCF group: 5.2 (14.1) **Global quality of life** ECF group: 2.4 (14.5) TCF group: 9.7 (16.8) **Symptom: nausea and vomiting** ECF group: -3.5 (19.6) TCF group: -1.4 (29.9) **Symptom: constipation**	Attrition bias • outcome date complete Reporting bias • outcomes stated in the objective were reported Overall assessment: Serious risk of bias due not inadequate reporting of allocation concealment, randomization process and blinding. Very limited methodological details, limited information on inclusion/exclusion criteria. **Other information** Other outcomes reported in Wagner meta-analysis.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				ECF group: -1.1 (29.4) TCF group: 0.92 (36.9) 1 For functioning scores positive values show improvements and negative values indicate deteriorations. 2 For symptom scores negative values show improvements and positive values indicate deteriorations.	
Full citation Wagner, A. D., Unverzagt, S., Grothe, W., Kleber, G., Grothey, A., Haerting, J., Fleig, W. E., Chemotherapy for advanced gastric cancer, Cochrane Database of Systematic Reviews, CD004064, 2010 **Ref Id** 454937 **Country/ies where the study was carried out** Switzerland & Germany	**Sample size** No. studies=35 trials included in meta-analysis n=5726 Median age unknown **Characteristics** All relevant studies described below Studies excluded due to out of date range (Cullinan 1985, De Lisi 1986, GITSG 1988, Levi 1986), chemotherapy regime outside protocol (Barone 1998, Moehler 2005, Cocconi 2003, Cocconi 1994, Koizumi 2008,	**Interventions** **Comparison 1: 5-FU/cis/anthra vs 5-FU/cis** **KRGGC 1992** 1. Cisplatin+5-FU 2. Cisplatin+5-FU+Epirubicin **Kim 2001** 1. Cisplatin+5-FU 2. Cisplatin+5-FU+Epirubicin **Comparison 2: Combo vs single agent** **Bouche 2004**	**Details** **Search strategy** We originally identified trials by searching the Cochrane Central, MEDLINE and EMBASE up to February 2004 and reference lists of articles. We also contacted pharmaceutical companies as well as national and international experts. We updated searches in all databases in March 2009. We handsearched reference lists from trials selected by electronic searching to identify further relevant trials.We also handsearched published abstracts from conference	**Results** **Comparison 1: 5FU/cis/anthra vs 5FU/cis** **OVERALL SURVIVAL** **KRGGC 1992** n= 47 HR (95% CI)= 0.57 (0.27, 1.20) **Kim 2001** n= 120 HR (95% CI)= 0.83 (0.42, 1.61) **Comparison 2: Combo vs single agent** **OVERALL SURVIVAL** **Bouche 2004** n= 134 HR (95% CI)= 0.65 (0.45, 0.94) **Colucci 1995**	**Limitations** ROBIS tool for bias risk assessment in systematic reviews: Study Eligibility Criteria 1. Did the review adhere to pre-defined objectives and eligibility criteria? Y 2. Were the eligibility criteria appropriate for the review question? Y 3. Were the eligibility criteria unambiguous? Y

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type Systematic review of RCTS **Aim of the study** To assess the efficacy of chemotherapy versus best supportive care, combination versus single agent chemotherapy and different combination chemotherapy regimens in advanced gastric cancer **Study dates** Databases searched up until March 2009; selected conference abstracts up until 2008 **Source of funding** Internal sources: Departments of Internal Medicine I & IV and Institute of Medical Epidemiology, Biometry and Informatics, Martin-Luther-University Halle-Wittenberg, Germany Co-ordinating Centre for Clinical Trials, Halle, Germany	Yamamura 1998, Ross 2002, Shinoda 1995, Webb 1997) or use best supportive care (Murad 1993). **Comparison 1: 5-FU/cis/anthra vs 5-FU/cis** **KRGGC 1992** n=60 Median age= NR **Kim 2001** n=121 Median age= NR **Comparison 2: combo vs single-agent** **Bouche 2004** n=134 Median age=65 **Colucci 1995** n=71 Median age=60 **Koizumi 2008** n=305 Median age=62 **Loehrer 1994 (2 arms only relevant to this review question)** n=165 Median age=60 **Lutz 2007** n=90 Median age=62 **Ohtsu 2003 (2 arms only relevant to this review question)** n=280 Median age=62 **Popov 2002** n=60	1. Lv+FU bolus+5-FU infusion 2. Cisplatin+Lv+5-FU bolus + 5-FU infusion 3. Irinotecan+Lv+5-FU bolus + 5-FU infusion **Colucci 1995** 1. 5-FU+Lv 2. Epirubicin+5-FU+Lv **Cullinan 1994 (see individual study for arm specific results)** 1. 5-FU+adriamycin + triazinate + methyl-CCNU (this arm not included in protocol) 2. 5-FU+triazinate+adriamycin+methyl-CCNU (this arm not included in protocol) 3. 5-FU +adriamycin+cisplatin 4. 5FU	proceedings from the European Society for Medical Oncology 1978 to 2008 (published in the Annals of Oncology), the European Council of Clinical Oncology 1981 to 2007 (published in the European Journal of Cancer), as well as the American Society for Clinical Oncology 1981 to 2008. **Selection of studies** Two independent authors initially scanned the title, abstract section and keywords of every record retrieved. We retrieved full article for further assessment if the information given suggested that the study included participants with histologically confirmed, inoperable adenocarcinoma of the stomach or gastroesophageal junction, used random allocation to the comparison groups.	n= 71 HR (95% CI)= 0.70 (0.42, 1.16) **Lutz 2007** n= 145 HR (95% CI)= 0.76 (0.54, 1.07) **Popov 2002** n= 60 HR (95% CI)= 0.86 (0.32, 2.29) **TREATMENT-RELATED MORTALITY** **Bouche 2004** combination: 1/89 single agent: 1/45 **Colucci 1995** combination: 0/35 single agent: 1/36 **Lutz 2007** combination: 1/108 single agent: 0/37 **Popov 2002** combination: 1/30 single agent: 0/30 **Comparison 4. 5FU/Cis/Anthra Vs 5FU/anthra** **OVERALL SURVIVAL** **Kikuchi 1990** n= 65 HR (95% CI)= 0.58 (0.36, 0.95) **Roth 1999** n= 112	4. Were all the restrictions on eligibility criteria based on study characteristics appropriate? Y 5. Were any restrictions in eligibility criteria based on sources of information available? Y 6. Concern regarding specification of study eligibility criteria: Low Identification and Selection of Studies 1. Did the search include an appropriate range of databases/electronic sources for published and unpublished reports? Y 2. Were the methods additional to database searching used to identify relevant reports? Y 3. Were the terms and structure of the search strategy likely to

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Median age=56 **Comparison 4. 5FU/Cis/Anthra Vs 5FU/anthra** **Kikuchi 1990** n=77 Median age=blank **Cullinan 1994 (2 arms only relevant to this review question)** n=252 Median age=62 **Roth 1999** n= 122 Median age= 55 **Comparison 5: Irinotecan versus non-irinotecan containing regimens** **Bouche 2004** n= 134 Median age= 65 **Dank 2008** n= 337 Median age= 59 **Moehler 2009** n= 118 Median age= 62.5 **Comparison 6: Doxetaxel-containing regimens versus non-docetaxel containing regimes** **Thuss-Patience 2005** n= 90 Median age: 62.5 **Van Cutsem 2006** n= 445 Median age: 55	**Loehrer 1994 (see individual study for arm specific results)** 1. 5-FU 2. Epirubicin (this arm not in protocol) 3. 5-FU+Epirubicin **Lutz 2007** 1. 5-FU 2. 5-FU+FA 3. 5-FU +Cisplatin+FA **Ohtsu 2003 (see individual study for arm specific results)** 1. 5-FU 2. 5-FU+Cisplatin 3. Uracil+Mitomycin (this arm not included in protocol) **Popov 2002** 1. 5-FU 2. Cisplatin+ etoposide+ Adriamycin	**Data Extraction** Two authors independently extracted details of study population, interventions and outcomes by using a standardised data extraction form. This was tested in a pilot study. We resolved differences in data extraction by consensus with a third author, referring back to the original article. If data were missing in a published report, we contacted the primary author. **Bias Assessment** Two independent and unblinded authors assessed the quality of the eligible studies,with disagreements resolved by a third author until consensus was obtained. Bias assessed using Cochrane risk of bias tool.	HR (95% CI)= 0.74 (0.55, 0.99) **Comparison 5: Irinotecan versus non-irinotecan containing regimens** **OVERALL SURVIVAL** **Bouche 2004** n= 89 HR (95% CI)= 0.84 (0.54, 1.32) **Dank 2008** n= 333 HR (95% CI)= 0.92 (0.73, 1.17) **Moehler 2009** n= 103 HR (95% CI)= 0.77 (0.51. 1.17) **PROGRESSION FREE SURVIVAL** **Dank 2008** n= 333 HR (95% CI)= 0.81 (0.64, 1.03) **Moehler 2009** n= 103 HR (95% CI)= 1.14 (0.59, 2.21) **TREATMENT_RELATED MORTALITY** **Bouche 2004** Irinotecan group= 0/45 Non-irinotecan group= 1/45 **Dank 2008** Irinotecan group= 1/170 Non-irinotecan group= 5/163 **Moehler 2009** Irinotecan group= 0/53	retrieve as many eligible studies as possible? PY 4. Were restrictions based on date, publication format or language appropriate? PY 5. Were efforts made to minimise error in selection of studies? Y 6. Concern regarding methods used to identify or select studies: LOW Data Collection and Study Appraisal 1. Were efforts made to minimise error in data collection? Y 2. were sufficient study characteristics available? Y 3. Were all relevant study results collected for use and synthesis? Y 4. Was risk of bias formally assessed using appropriate criteria? Y 5. Were efforts made to minimise error

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Ridwelski 2008 n= 273 Median age= 62 **Sadighi 2006** n= 86 Median age= 56 **Roth 2007** n= 121 median age= 59 **Comparison 7: Oral 5FU versus IV 5FU** **Kang 2009** n= 316 Median age= 56 **Comparison 8: Cisplatin versus Oxaplatin** **Al-Batran 2008** n=220 Median age= 64 **Popov 2008** n= 72 Median age= 56 **Other comparison: cisplatin regime versus 5FU regime** **De Lisi 1996** n= 102 Median age NR **Inclusion criteria** • Randomised controlled trials,	**Comparison 4. 5-FU/Cis/Anthra Vs 5-FU/anthra** **Kikuchi 1990** 1. 5-FU+Adriamycin 2. 5-FU +Adriamycin+Cisplatin **Cullinan 1994** 1. 5-FU+adriamycin+ Adriamycin + triazinate + methyl-CCNU (this arm not in protocol) 2. 5-FU +triazinate+adriamycin+methyl-CCNU (this arm not included in protocol) 3. 5-FU+ adriamycin+cisplatin 4. 5-FU **Roth 1999** 5-FU + epirubicin 5-FU + epirubicin + cisplatin **Comparison 5: Irinotecan versus non-irinotecan containing regimens** **Bouche 2004**		Non-irinotecan group= 2/50 **TREATMENT DISC DUE TO TOXICITY** **Bouche 2004** Irinotecan group= 5/45 Non-irinotecan group= 2/45 **Dank 2008** Irinotecan group= 17/170 Non-irinotecan group= 35/163 **Moehler 2009** Irinotecan group= 10/53 Non-irinotecan group= 16/50 **Comparison 6: Docetaxel versus non-docetaxel containing regimens** **OVERALL SURVIVAL** **Thuss-Patience 2005** n= 90 HR (95% CI)= 1.02 (0.68, 1.54) **Van Cutsem 2006** n= 445 HR (95% CI)= 0.78 (0.62, 1.00) **Ridwlski 2008** n= 270 HR (95% CI)= 1.06 (0.82, 1.37) **TIME TO PROGRESSION** **Thuss-Patience 2005** n= 90 HR (95% CI)= 0.96 (0.63, 1.48) **Ridwlski 2008** n= 270 HR (95% CI)= 1.10 (0.85, 1.42)	in risk of bias assessment? Y 6. Concern: LOW Synthesis and Findings 1. Did the synthesis include all studies it should? Y 2. Were all pre-defined analyses reported and departures explained? PY 3. Was the synthesis appropriate given the nature and similarity in the research questions? Y 4. Was heterogeneity minimal or addressed? Y 5. Were the findings robust as demonstrated though funnel plot or sensitivity analysis? Y 6. Were biases in primary studies minimal or addressed in the synthesis? Y 7. Concern= LOW Risk of bias in the review

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	with or without blinding • Abstracts or unpublished data included if sufficient info provided • Histologically confirmed, advanced, recurrent or metastatic adenocarcinoma of stomach or gastroesophageal junction • No prior chemo/radiotherapy • Patients with adenocarcinoma of distal oesophagus **Exclusion criteria** • Cross-over studies • Quasi-randomised studies	1. leucovorin + 5-FU 2. leucovorin + 5-FU + cisplatin 3. leucovorin + 5-FU + irinotecan **Dank 2008** 1. irinotecan + 5-FU + 2. cisplatin + 5-FU + FA **Moehler 2009** 1. capecitabine + irinotecan 2. capecitabine + cisplatin **<u>Comparison 6: Docetaxel versus non-docetaxel containing regimens</u>** **Thuss-Patience 2005** 1. docetaxel + 5-FU 2. epirubicin + cisplatin + 5-FU **Van Cutsem 2006** 1. docetaxel + cisplain + 5-FU 2. cisplatin + 5-FU **Ridwlski 2008** 1. docetaxel + cisplatin 2. 5-FU + leucovorin + cisplatin **Sadighi 2006** 1. epirubicin + 5-FU + cisplatin 2. docetaxel + 5-FU + cisplatin **Roth 2007**		**TREATMENT-RELATED MORTALITY** **Thuss-Patience 2005** docetaxel group: 0/45 non-docetaxel group: 1/45 **Van Cutsem 2006** docetaxel group= 6/221 non-docetaxel group= 10/224 **Roth 2007** docetaxel group= 1/79 non-docetaxel group= 0/40 **Ridwlski 2008** docetaxel group= 2/133 non-docetaxel group= 0/137 **TREATMENT DISC DUE TO TOXICITY** **Thuss-Patience 2005** docetaxel group: 4/45 non-docetaxel group: 5/45 **Van Cutsem 2006** docetaxel group= 59/221 non-docetaxel group= 56/224 **Roth 2007** docetaxel group= 8/79 non-docetaxel group= 7/40 **Ridwlski 2008** docetaxel group= 13/133 non-docetaxel group= 27/137 **<u>Comparison 7: Oral 5FU versus IV 5FU</u>** **OVERALL SURVIVAL** **Kang 2009** n= 316 HR (95% CI)= 0.85 (0.65, 1.11)	1. Did the interpretation of findings address all the concerns identifies in 1-4? Y 2. Was the relevance of identified studies to the review's research question appropriately considered? Y 3. Did the reviewers avoid emphasizing results on the basis of their statistical significance? Y 4. Risk of bias= LOW **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
		1. epirubicin + cisplatin +5 FU 2. docetaxel + cisplatin 3. docetaxel + cisplatin +5-FU **<u>Comparison 7: Oral 5-FU versus IV 5-FU</u>** **Kang 2009** 1. oral capecitabine + cisplatin 2. 5-FU + cisplatin **<u>Comparison 8: Cisplatin versus Oxaplatin</u>** **Al-Batran 2008** 1. Oxaplatin + leucovorin + 5-FU 2. Cisplatin + leucovorin + 5-FU **Popov 2008** 1. oxaliplatin + 5-FU + folinic acid + leucovorin 2. cisplatin + 5-FU+ folinic acid +leucovorin		**PROGRESSION FREE SURVIVAL** **Kang 2009** n= 316 HR (95% CI)= 0.80 (0.62, 1.03) **TREATMENT-RELATED MORTALITY** **Kang 2009** capecitabine group= 1/156 5-FU group= 2/155 **DISCONTINUATION DUE TO TOXICITY** **Kang 2009** capecitabine group= 28/156 5-FU group= 28/155 **<u>Comparison 8: Cisplatin versus Oxaplatin</u>** **OVERALL SURVIVAL** **Al-Batran 2008** n=220 HR (96% CI)= 0.82 (0.47, 1.45) **PROGRESSION FREE SURVIVAL** **Al-Batran 2008** n=220 HR (96% CI)= 0.67 (0.43, 1.04) **TREATMENT RELATED DEATH** **Al Batran 2008** oxaliplatin: 1/112 cisplatin: 0/102 **Popov 2008** oxaliplatin: 0/36 cisplatin: 2/36 **TREATMENT DISC DUE TO TOXICITY**	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
		Other Comparison: Cisplatin regime versus 5Fu regime **De Lisi 1996** 1. Cisplatin + Adriamycin + mitomycin 2. 5-FU + Adriamycin + mitomycin		oxaplatin: 12/112 cisplatin: 11/102 **Other comparison: cisplatin regime versus 5FU regime** **De Lisi 1996** results not reported in meta-analysis see De Lisi in data extraction table	
Full citation Van Cutsem, E., Moiseyenko, V. M., Tjulandin, S., Majlis, A., Constenla, M., Boni, C., Rodrigues, A., Fodor, M., Chao, Y., Voznyi, E., Risse, M. L., Ajani, J. A., V. Study Group, Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group, Journal of Clinical OncologyJ Clin Oncol, 24, 4991-7, 2006 **Ref Id** 487805	**Sample size** N= 445 (DCF= 221, CF= 224) **Characteristics** 71% male Median age= 55 (Range: 25-79) Tumour site: 22% GE Junction/ 78% Gastric 97% metastatic disease Previous chemotherapy: 3% Previous radiotherapy: 2% Previous surgery: 31% **Inclusion criteria** • 18 years and older	**Interventions** **DOCETAXEL VERSUS NON DOCETAXEL COMBINATION** Docetaxel 75 mg/m^2 (1-hour intravenous infusion) plus cisplatin 75 mg/m^2 (1- to 3-hour intravenous infusion) on day 1, followed by fluorouracil 750 mg/m^2/d (continuousintravenousinfusion) for 5 days (DCF) every 3 weeks cisplatin 100 mg/m^2 on day 1 followed by5-FUl 1,000mg/m^2/d for 5 days (CF) every 4 weeks. Dose modification criteria were predefined. All patients received appropriate hydration and premedications as previously reported.20 Treatment continued until	**Details** QoL Assessment Quality of life was assessed at the same intervals as tumor assessments and data were collected every 3 months after disease progression, using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (QLQ) -C30, version 3.22 Time to 5% definitive deterioration in global health status assessed by QLQ-C30 was the primary quality of life parameter; time to definitive worsening of Karnofsky performance status by one or more categories was the primary clinical benefit endpoint.	**Results** Quality of Life The time to 5% deterioration of global health status (QLQ-C30) was significantly longer for DCF than CF (HR 1.44; 95% CI, 1.08 to 1.93; log-rank P.01). Furthermore, the time to definitive worsening of Karnofsky performance status was significantly longer for DCF than CF (log-rank P.009; HR 1.38; 95%CI, 1.08 to 1.76). No other QoL data reported.	**Limitations** **Cochrane risk of bias tool** Selection bias • random sequence generation: unclear • allocation concealment: centralized randomization Performance bias • blinding: unclear Detection bias • blinding: unclear

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out Multiple; Europe **Study type** RCT **Aim of the study** To investigate whether adding docetaxel to a reference regimen of cisplatin and fluorouracil (CF) could improve patient outcomes (time-to-progression [TTP], overall survival [OS], quality of life, and response rate for palliation), a multinational, multi-institutional, open-label, randomizedphase II/IIIstudy, V325, was designed. **Study dates** November 1999 and January 2003 **Source of funding** Funded by sanofi-aventis	• histologically proven gastric or esophagogastric junction adenocarcinoma • measurable/assessable metastatic disease or locally recurrent disease • Karnofsky performance >70 • adequate hepatic, renal and bone marrow function **Exclusion criteria** • prior palliative chemotherapy • surgery within 3 weeks • radiotherapy within 6 weeks • concurrent cancer • CNS involvement • uncontrolled, significant comorbid conditions • patients that could not comprehend the purpose of the study or comply	disease progression, unacceptable toxicity, death, or consent withdrawal.	Statistical Assessment The primary objective was to demonstrate superiority in TTP for DCF over CF, using an unstratified log-rank test with a two-sided 5% significance level, from 4 months (CF) to 6months (DCF), corresponding to a hazard ratio (HR) of 1.5 with a 95% power, requiring at least 325 events with 230 patients per arm. The major secondary objective was to demonstrate superiority in OS for DCF over CF, using the unstratified log-rank test with a two-sided 5% significance level, from 8 months to 12 months, corresponding to a HR of 1.5, and requiring at least 325 events. The Kaplan-Meier method was used to calculate TTP and OS.		Attrition bias • outcome data complete Reporting bias • outcomes stated in the objective were reported Overall assessment: UNLCEAR risk of bias due not inadequate reporting of allocation concealment, randomization process and blinding. **Other information** Other outcomes reported in Wager meta-analysis.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	with the requirements				
Full citation Bouche, O., Raoul, J. L., Bonnetain, F., Giovannini, M., Etienne, P. L., Lledo, G., Arsene, D., Paitel, J. F., Guerin-Meyer, V., Mitry, E., Buecher, B., Kaminsky, M. C., Seitz, J. F., Rougier, P., Bedenne, L., Milan, C., Federation Francophone de Cancerologie Digestive, Group, Randomized multicenter phase II trial of a biweekly regimen of fluorouracil and leucovorin (LV5FU2), LV5FU2 plus cisplatin, or LV5FU2 plus irinotecan in patients with previously untreated metastatic gastric cancer: a Federation Francophone de Cancerologie Digestive Group Study--FFCD 9803, Journal of Clinical OncologyJ Clin Oncol, 22, 4319-28, 2004 **Ref Id** 487183 **Country/ies where the study was carried out**	**Sample size** N= 134 **Characteristics** Median age= 65 (range 37-76) 100% metastatic disease 50% received prior surgery 31 % cardiac, 69% gastric cancer **Inclusion criteria** • metastatic gastric or cardial adenocarcinoma • histologically proven • no brain metastasis • at least one measurable metastatic lesion • between 18-75 years • WHO performance status <= 2 • life expectancy > 2 months	**Interventions** Patients assigned to the LV5FU2 arm (arm A) received LV 200 mg/m^2 IV over 2 hours followed by FU 400 mg/m^2 IV bolus then FU 600 mg/m^2 continuous infusion over 22 hours on days 1 and 2, repeated every 14 days (one cycle 15 days). No systematic prophylactic premedication was administered. Patients assigned to the LV5-FU2-cisplatin arm (arm B) received cisplatin 50 mg/m^2 IV over 1 hour on day 1 or 2 with LV5FU2 (one cycle 15 days). Prophylactic medication consisted of IV antiemetics (setrons) and methylprednisolone 120 mg 10 minutes before cisplatin administration, hydration (1 L over 3 hours before and after cisplatin), oral antiemetics, and corticosteroids from days 2 to 5. Patients assigned to the LV5-FU2 irinotecan arm (armC) received irinotecan	**Details** Quality of Life Assessment Patients were requested to complete the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (QLQ-C30) before randomization and every 2 months thereafter.38 Completed questionnaires were scored according to guidelines provided by the European Organization for Research and Treatment of Cancer.39 The questionnaire comprises a global QOL scale, five functional scales (physical, role, cognitive, emotional, and social), and nine symptom scales (fatigue, pain, nausea and vomiting, constipation, diarrhea, sleep, dyspnea, appetite, and financial). The functional and global scores range from 0 (worst) to 100 (best), and the symptom scores range from 0 (best) to 100 (worst). Statistics	**Results** Quality of Life No difference in pretreatment arms. Patients in arms B and C had less constipation than patients in arm A (P .01), and patients in arm C slept better than patients in arm A (P .05). Longitudinal analysis showed that 14 mean scores were respectively higher in arm C than in arms A and B,regardless of the first three follow-ups. The patients in all three arms had a significant improvement in QOL scores compared with pretreatment values (global QOL, P .0001; role, P .01; emotional, P .0001; social, P	**Limitations** **Cochrane risk of bias tool** Selection bias • random sequence generation: unclear • allocation concealment: randomized by central research office Performance bias • blinding: unclear Detection bias • blinding: unclear Attrition bias • outcome date complete Reporting bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
France **Study type** RCT **Aim of the study** To determine the efficacy and safety of a biweekly regimen of leucovorin (LV) plus fluorouracil(FU) alone or in combination with cisplatin or irinotecan in patients with previously untreated metastatic gastric adenocarcinoma and to select the best arm for a phase III study. **Study dates** January 1999 and October 2001 **Source of funding** Supported by grants from Aventis, Baxter, and the Association pour la Recherche Contre le Cancer.	• normal hematologic, renal, hepatic and cadiac functions **Exclusion criteria** • adjuvant chemotherapy within the last 6 months • radiotherapy within last 4 weeks • chronic diarrhea • prior enterropathy • extensive intestinal resection	180mg/m^2 IV over 90 minutes on day 1 with LV5-FU2 and no systematic prophylactic premedication (one cycle 15 days).	The QLQ-C30 scores were described as a mean, standard deviation, median, and range at the start of the study and at each 2-monthfollow-upvisit; the mean of available global health scores was graphically reported at each follow-up. The missing data were described as a percentage of the calculated score among patients with follow-up. Prestudy scores were compared between treatment arms using analysis of variance and a Bonferroni test to adjust for multiple comparisons. During the first three follow-ups, the longitudinal change of QLQ-C30 scores was analyzed using a mixed model analysis of variance for repeated measurements to study a global time effect whatever the treatment and to calculate differences in mean QOL scores between treatment arms whatever the follow-up (contrast analysis).	.01; pain, P .0001; sleep ,P .0001; and appetite loss, P .01;) Six functional scores were higher in arm C compared with arm A (mean difference in scores: global,2.2; physical, 2.4; role, 4.6; emotional, 4.1; cognitive, 8.3; and social, 4.7). In addition, with the exception of a worse financial score (2.1), all the symptom scores were improved (range, 1.1 for pain to 11.9 for constipation). Comparison of arms B and C showed that the irinotecanbased therapy was associated with higher global QOL (mean difference in score, 0.8) and functional scores(mean difference in scores ranging from 2.5 for social to 6.7 for emotional) and lower symptom scores (mean difference in scores ranging from 0.3 for constipation to 8.2 for sleep). Uncertainty for mean difference NR.	• outcomes stated in the objective were reported Overall assessment: UNLCEAR risk of bias due not inadequate reporting of randomization process and blinding. **Other information** Other outcomes reported in Wagner meta-analysis. Cardial adenocarcinoma included.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Global QOL data were available for 82%, 75%, and 84% of patients at the time of inclusion compared with 41% (n 22 patients with follow-up), 38% (n 21), and 48% (n29) of patients at the third evaluation in arms A, B,and C, respectively.	
Full citation Loehrer, P. J., Sr., Harry, D., Chlebowski, R. T., 5-fluorouracil vs. epirubicin vs. 5-fluorouracil plus epirubicin in advanced gastric carcinoma, Invest New Drugs, 12, 57-63, 1994 **Ref Id** 545998 **Country/ies where the study was carried out** USA **Study type** RCT **Aim of the study** To compare the ob- jective response rates, survival,	**Sample size** N= 153 5FU arm= 69 5FU = epirubicin arm= 70 epirubicin alone= 26 (not relevant to this review) **Characteristics** 5FU arm: median age (range)= 59 (19-79) previous radiotherapy: 3% 5FU + epirubicin arm: median age (range)= 62 (21-83) previous radiotherapy: 3% **Inclusion criteria** • unresectable or metastatic disease	**Interventions** 5-Fluorouracil (5-FU) alone (500 mg/m^2 days 1-5) OR Combination of Epirubicin (90 mg/m^2 day 1) and 5-FU (400 mg/m^2 days 1-5). Courses were repeated every four weeks.	**Details** Pretreatment evaluation consisted of history and physical examination, performance status, com- plete blood count and serum chemistry panel, and chest radiograph. Computerized tomography of the chest or abdomen and radionuclide bone scan (if indicated) and liver/spleen scan were to be per- formed to document metastatic disease. Echo- cardiographic and radionuclide angiography was performed for those patients receiving epirubicin. These tests and tumor measurements were to be performed every four weeks during the treatment. Statistics Median survival time was determined from the date of randomization until death.	**Results** Overall Survival 5-FU group: Median= 151 days 5-FU + epirubicin: Median= 194 days P-val NR Time to Progression 5-FU group: Median= 241 days 5-FU + epirubicin= 221 days P-val NR Toxicity: Grade 3/4 Vomiting 5-FU group: 6/ 69 5-FU + epirubicin group; 8/70 Toxicity: Infection 5-FU group: 4/69 5-FU + epirubicin group: 3/70 Toxicity: Diarrhoea	**Limitations** **Cochrane risk of bias tool** Selection bias • random sequence generation: unclear • allocation concealment: randomization through central research office. Performance bias • blinding: unclear Detection bias • blinding: unclear Attrition bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
and toxicity of epirubicin alone, 5-FU alone, and combination of epirubicin plus 5-FU. **Study dates** January, 1985, through January, 1987 **Source of funding** This research was supported in part by NCI Grant #2 R 35 CA 39844-08, The Walther Cancer Institute, The Cancer Center Planning Grant #P 20 CA 57114-02, The General Clinical Research Center #MO 1 RR 00750-06, and R 10 CA 28171- 04 from the Public Health Service and in part by Adria Laboratories, Columbus, OH.	• histologically confirmed adenocarcinoma of the stomach • 18 years and older • no previous chemotherapy • adequate hepatic, renal and bone marrow function Patients with previous radiotherapy were eligible if the radiotherapy was prophylactic and patients had recovered from the effects of prior therapy. **Exclusion criteria** • active infection • active secondary cancer • brain metastases • history of congestive heart failure		Time to progres- sion was calculated for responding patients from the date of randomization until progression. Both time to progression and overall survivals were plotted by using the Kaplan-Meier estimate.	5-FU group: 5/69 5-FU + epirubicin group: 2/70	• outcome date complete Reporting bias • outcomes stated in the objective were reported Overall assessment: UNLCEAR risk of bias due not inadequate reporting of randomization process and blinding. **Other information** Only 2 arms of study relevant to this review question.
Full citation Ohtsu, A., Shimada, Y., Shirao, K., Boku, N., Hyodo, I., Saito, H., Yamamichi, N., Miyata, Y.,	**Sample size** N= 280 5-FU alone= 105 FP= 105	**Interventions** The 5-FU-alone regimen consisted of 120-hour continuous-infusion 5-FU 800 mg/m^2/d, which was	**Details** Patient Assessment We adopted the Japanese response criteria proposed by the Japanese Research	**Results** Treatment-Related Mortality 5-FU group: 1/105 FP group: 4/105	**Limitations** **Cochrane risk of bias tool** Selection bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ikeda, N., Yamamoto, S., Fukuda, H., Yoshida, S., Japan Clinical Oncology Group, Study, Randomized phase III trial of fluorouracil alone versus fluorouracil plus cisplatin versus uracil and tegafur plus mitomycin in patients with unresectable, advanced gastric cancer: The Japan Clinical Oncology Group Study (JCOG9205), Journal of Clinical Oncology, 21, 54-9, 2003 **Ref Id** 454841 **Country/ies where the study was carried out** Japan **Study type** RCT **Aim of the study** To compare fluorouracil (FU) alone with FU plus cisplatin (FP) and with uracil and tegafur plus mitomycin (UFTM) for patients with advanced gastric cancer in a prospective, randomized, controlled trial.	UFTM arm= 70 (not relevant to this review question) **Characteristics** <u>Fu group:</u> Median age (range)= 63 (27-75) 75 male/ 29 female 90 metastatic/ 15 locally advanced Prior gastrectomy: 27 <u>FP group:</u> Median age (range)= 63 (19-75) 77 male/ 28 female 90 metastatic/ 15 locally advanced Prior gastrectomy: 29 **Inclusion criteria** • 75 years or younger • ECOG performance status >= 2 • ability to take oral agents • no history other than surgery • adequate hepatic, renal and bone marrow status	repeated every 4 weeks. The dose of 5-FU was reduced to 600 mg/m^2/d if one of the following toxic effects occurred during the previous course: grade 2 or lower stomatitis, diarrhea, thrombocytopenia, or grade 3 or lower leukopenia, bilirubinemia, or creatinine 2.0 mg/dL. The treatment was terminated if the patient did not recover from these toxic effects within 8 weeks after initiating the previous course. The FP regimen comprised continuous-infusion FU 800 mg/m^2/d along with a 30-minute infusion of CDDP 20 mg/m^2/d with adequate hydration for 5 consecutive days.8 Cycles were repeated every 4 weeks for up to six courses; the subsequent courses were administered without CDDP in the same schedule as the 5-FU-alone regimen. The dose of 5-FU was reduced to 600 mg/m^2/d if one of the following toxic effects occurred during the previous course: grade 2 or lower stomatitis, diarrhea, or thrombocytopenia or grade 3 or lower leukopenia or bilirubinemia. If the serum creatinine level elevated to 2.0 mg/dL, the	Society for Gastric Cancer. According to these criteria, the response for unmeasurable primary tumors was assessed by the same criteria on the basis of roentgenographic and endoscopic findings, as published previously.8 For measurable lesions, these Japanese criteria were the same as the standard definitions of World Health Organization response criteria. Objective responses were confirmed by central review at regular group meetings. Toxicity was evaluated using JCOG Toxicity Criteria. These criteria were based on the National Cancer Institute Common Toxicity Criteria. <u>Statistics</u> Comparison of patient characteristics, toxicity, and response rates between groups were calculated by 2 test. All patients registered were included in the survival analysis on an intention-to-treat basis. Overall survival was calculated from the date of registration to the date of death from cause or to the last contact date, using the Kaplan-Meier method. Progression-free survival was calculated from the	<u>Treatment-related toxicity: nausea/vomiting (grade 3/4)</u> 5-FU group: 5.0% FP group: 7.9% <u>Treatment-related toxicity: diarrhoea (grade 3/4)</u> 5-FU group: 0 FP group: 3.0% <u>Progression Free Survival</u> 5-FU group: Median (95% CI) = 1.9 months (1.3-2.7) FP group: Median (95% CI) = 3.9 months (3.1-4.8) P<0.001 <u>Overall Survival</u> 5-FU group: Median (95% CI) = 7.1 months (5.8-8.2) FP group: Median (95% CI) = 7.3 months (6.0-9.7) P= 0.34 <u>One-year survival</u> 5-FU group: 28% FP group: 29% <u>Two-year survival</u> 5-FU group: 7% FP group: 7%	• random sequence generation: unclear • allocation concealment: randomized by central data centre Performance bias • blinding: unclear Detection bias • blinding: unclear Attrition bias • outcome date complete Reporting bias • outcomes stated in the objective were reported Overall assessment: UNLCEAR risk of bias due not inadequate reporting of randomization process and blinding.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates September 1992 and March 1997 **Source of funding** This work was supported by Grant-in-Aid (5S-1, 8S-1, 11S-3, 11S-4) from the Ministry of Health, Labour, and Welfare, Japan	**Exclusion criteria** • serious complications • active carcinoma at other sites • large amounts of ascites	subsequent courses consisted of 5-FU 600 mg/m^2/d and CDDP 15 mg/m^2/d. The treatment was terminated if the patient did not recover from these toxic effects within 8 weeks after initiating the previous course.	date of registration to the date of documented disease progression or the date of death from any cause if there was no disease progression beforehand. If there was no documented disease progression and if the patient had not died, data on progression-free survival were censored on the date that the absence of progression was confirmed. If a patient died without information on progression, data on progression-free survival were censored on the last date on which progression could be ruled out by the review of follow-up forms. Survival and progression-free survival curves were calculated by the Kaplan-Meier method and compared by the log-rank test.		**Other information** Trial number: JCOG9205 Only 2 arms relevant to this review questions.
Full citation Pozzo, C., Barone, C., Szanto, J., Padi, E., Peschel, C., Bukki, J., Gorbunova, V., Valvere, V., Zaluski, J., Biakhov, M., Zuber, E., Jacques, C., Bugat, R., Irinotecan in combination with 5-	**Sample size** N= 146 (I/Fu= 74, I/C= 72) **Characteristics** <u>I + 5-FU group:</u> Median age (range)= 57 (39-75)	**Interventions** Treatment in the irinotecan/ 5-FU/FA arm consisted of a 30-min infusion of irinotecan [80mg/m^2 intravenously (i.v.)] and a 2-h infusion of FA (500mg/m^2 i.v.), followed immediately by a 22-h infusion of 5-FU (2000mg/m^2 i.v.), once	**Details** <u>Patient Assessment</u> Tumor response was assessed every 8 weeks (56 days) during therapy, irrespective of the treatment cycle duration, until disease progression. This 8-week treatment period was a means of assessing the 6-	**Results** <u>Treatment-Related Mortality</u> I+ 5-FU group= 1/ I + cisplatin group= 0/ <u>Discontinuation due to Toxicity</u> I +5- FU group= 8.1% I + cisplatin= 5.6%	**Limitations** **<u>Cochrane risk of bias tool</u>** Selection bias • random sequence generation: unclear

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
fluorouracil and folinic acid or with cisplatin in patients with advanced gastric or esophageal-gastric junction adenocarcinoma: results of a randomized phase II study, Annals of OncologyAnn Oncol, 15, 1773-81, 2004 **Ref Id** 487651 **Country/ies where the study was carried out** Multiple; 13 European and Israel, Lebanon, Turkey, South Africa **Study type** RCT **Aim of the study** To identify the most effective of two combinations, irinotecan/5-fluorouracil (5-FU)/ folinic acid (FA) and irinotecan/cisplatin, in the treatment of advanced gastric cancer, for investigation in a phase III trial. **Study dates**	77% male 82.4% gastric/ 16.4% gastroesophageal junction + fundus 91.9% metastatic <u>I + cisplatin group</u> Median age (range)= 59 (33-74) 63.9% male 68.1% gastric/ 31.9% gastroesophageal junction + fundus 95.8% metastatic **Inclusion criteria** • 18 to 75 years old • histologically confirmed metastatic gastric or esophageal-gastric junction adenocarcinoma • measure/evaluable metastatic disease or lymph nodes • Karnofsky performance status >70 • adequate hematologic, renal, hepatic function	weekly for 6 weeks (on days 1, 8, 15, 22, 29 and 36) followed by a 1-week rest. Cycles were repeated every 7 weeks. Treatment in the irinotecan/cisplatin arm consisted of irinotecan (200mg/m^2 i.v.) administered first as a 30-min infusion on day 1, followed on the same day by hyperhydration (1l normal saline during the first hour), then a 4-h infusion of cisplatin (60mg/m^2 i.v.) followed by 1.5 l normal saline over 3h. Cycles were repeated every 3 weeks. Treatment was continued until disease progression, unacceptable toxicity or withdrawal of consent	weekly cycle (every 7 weeks) (irinotecan/5-FU/FA) and the 3-week cycle (irinotecan/cisplatin) over the same period of time, thereby helping to avoid bias. Response was recorded according to World Health Organization (WHO) criteria. Patients who had disease progression were followed every 3 months until death. Patients who finished treatment but who had not progressed were followed every 8 weeks after the end of treatment until documented progression and every 3 months thereafter. An external response review committee reviewed radiological and clinical documentation for all patients in the study. All adverse events were evaluated and graded according to NCIC CTG criteria. <u>Statistics</u> TTP and OS were estimated by the Kaplan–Meier method and the two arms were compared using a two-sided logrank test with an a error of 5%.	<u>Time to progression</u> I + 5-FU group: Median (95% CI)= 6.5 months (5.59-8.51) I + C group: Median (95% CI)= 4.2 (3.42- 5.45) P<0.0001 Cox HR (95% CI)= 0.410 (0.262, 0.641) (B vs A - favours 5-FU group) <u>Overall Survival</u> I +5- FU group: Median (95% CI)= 10.7 months (8.02-14.62) I + C group: Median (95% CI)= 6.9 (5.55- 8.67) P= 0.0018 Cox HR (95% CI)= 0.561 (0.388, 0.810) (B vs A - favours 5-FU group)	• allocation concealment: unclear Performance bias • blinding: unclear Detection bias • blinding: unclear Attrition bias • outcome date complete Reporting bias • outcomes stated in the objective were reported Overall assessment: UNLCEAR risk of bias due not inadequate reporting of allocation concealment, randomization process and blinding. **Other information** Primary outcome was tumour response.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
January 1999 and April 2000 **Source of funding** This study was sponsored by an educational grant from Aventis Pharma International S.A.	• no previous palliative chemo **Exclusion criteria** • previous adjuvant/neoadjuvant chemo within last 12 months • radiotherapy within 6 weeks • surgery within 3 weeks • previous treatment with camptothecins • previous cumulative dose of cisplatin >300 mg/m2 • bowel obstruction • history of inflammatory enteropathy • peripheral neuropathy • brain metastasis • active disseminated intravascular coagulation • previous or concurrent other malignancy				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	• any severe medical conditions • pregnant or lactating • concurrent treatment with any other anticancer therapy				
Full citation Roy, A., Cunningham, D., Hawkins, R., Sorbye, H., Adenis, A., Barcelo, J. R., Lopez-Vivanco, G., Adler, G., Canon, J. L., Lofts, F., Castanon, C., Fonseca, E., Rixe, O., Aparicio, J., Cassinello, J., Nicolson, M., Mousseau, M., Schalhorn, A., D'Hondt, L., Kerger, J., Hossfeld, D. K., Garcia Giron, C., Rodriguez, R., Schoffski, P., Misset, J. L., Docetaxel combined with irinotecan or 5-fluorouracil in patients with advanced oesophago-gastric cancer: a randomised phase II study, British Journal of CancerBr J Cancer, 107, 435-41, 2012 **Ref Id** 475017	**Sample size** N= 85 (DI n=42, DF n= 43) **Characteristics** 70% male Median age= 61 (Range: 38-76) 94.1% metastatic disease Previous adjuvant/neoadjuvant chemo: 3.5% Previous surgery: 36.5% **Inclusion criteria** • age 18-75 years • measurable/evaluable metastatic disease • histologically proven gastric adenocarcinoma	**Interventions** DI group: docetaxel 60mg/m^2 (1-h IV infusion, Day 1) followed by irinotecan 250mg/m^2 (30- to 90-min IV infusion, Day 1) every 3 weeks (DI), DF group: docetaxel 85mg/m^2 (1-h IV infusion, day 1) followed by 5-FU 750mg/m^2 per day (continuous infusion, days 1 to 5) every 3 weeks (DF). Chemotherapy given until disease progression, unacceptable toxicity or withdrawal of consent.	**Details** Patient Assessment The primary endpoint was a radiological response rate as assessed by the external response review committee. Overall response rates (ORR) was assessed by a CT scan and was defined as the percentage of patients who achieved a complete response (CR) or a partial response (PR). A CR or PR had to be confirmed by two evaluations of the disease taken X4 weeks apart, and all responses were reviewed according to World Health Organization criteria. The CT response assessments were performed every two cycles. Secondary endpoints included TTP, time to treatment failure (TTF), duration of response, OS, treatment	**Results** Overall Survival Median (95% CI)= 8.6 months (6.1-12.2) Median (95% CI)= 4.4 months (7.7-11.0) One-Year Survival DI group: 15/42 DF group: 11/43 Two-Year Survival DI group: 6/42 DF group: 2/43 Time to Progression Median (95% CI)= 3.8 months (2.2-6.0) Median (95% CI)= 4.4 months (2.7-6.8)	**Limitations** **Cochrane risk of bias tool** Selection bias • random sequence generation: unclear • allocation concealment: unclear Performance bias • blinding: unclear Detection bias • blinding: unclear Attrition bias • outcome data complete

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out 6 European countries **Study type** RCT **Aim of the study** This randomised phase II study was designed to assess the efficacy of docetaxel in combination with either irinotecan or 5-FU in advanced oesophago-gastric cancer. **Study dates** August 1999 and August 2000 **Source of funding** NHS funding from the NIHR Biomedical Research Centre and the Peter Stebbings Memorial Charity. This work was partially supported by Sanofi-Aventis Pharmaceuticals.	(including gastro-esophageal junction) • Karnofsky performance status >= 70 • life expectancy > 12 weeks • adequate hematologic, renal, hepatic function Previous neoadjuvant or adjuvant chemo allowed provided a period of 12 months had passed. **Exclusion criteria** • prior palliative chemo • radiotherapy within 6 weeks • surgery within 3 weeks		toxicities and clinical benefit. Clinical benefit was assessed in the intention-to-treat (ITT) population in terms of time to definitive worsening of KPS (a decrease by X1 category compared with baseline without any further improvement); time to definitive weight loss (definitive decrease in weight by X5% compared with baseline); time to definitive worsening of appetite (deterioration of appetite by X1grade on a scale of 1 to 5, where 1¼ very poor and 5¼ excellent) and pain-free survival (time from randomisation to first appearance of Xgrade 1 cancer pain in patients with NCIC-CTGexpanded CTC, version 2, grade 0 cancer pain at baseline). Adverse events (AEs) and laboratory values were graded according to the NCIC-CTG-expanded CTC, version 2. Statistics The primary objective of the study was to rank the two test arms on the basis of their efficacy. No formal statistical comparison was planned to compare the treatment groups.	Treatment-Related Toxicity: Diarrhoea (Grade 3/4) DI group: 18/42 DF group: 7/43 Treatment-Related Toxicity: Nausea (Grade 3/4) DI group: 7/42 DF group: 1/43 Discontinuation due to Toxicity DI group: 6/42 DF group: 10/43	Reporting bias • outcomes stated in the objective were reported Overall assessment: UNLCEAR risk of bias due not inadequate reporting of allocation concealment, randomization process and blinding. **Other information** Primary outcome of interest was efficacy.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Cunningham , David, Starling , Naureen, Rao , Sheela, Iveson , Timothy, Nicolson , Marianne, Coxon , Fareeda, Middleton , Gary, Daniel , Francis, Oates , Jacqueline, Norman , Andrew Richard, Capecitabine and Oxaliplatin for Advanced Esophagogastric Cancer, New England Journal of Medicine, 358, 36-46, 2008 **Ref Id** 546005 **Country/ies where the study was carried out** UK and Australia **Study type** RCT **Aim of the study** The primary goal of the study was to investigate whether capecitabine and oxaliplatin are at least as effective as fluorouracil and	**Sample size** N=1002 ECF= 263 ECX= 250 EOF= 245 EOX= 244 **Characteristics** <u>ECF group</u> Median age (range)= 65 (22-83) 81.1% male Site: 34.9% esophagus/ 29.9% GEJ/ 36.1% stomach 79.5% metastatic Histology: 90% adenocarcinoma/ 7.6% Squamous cell carcinoma/ 2.4% undifferentiated <u>ECX group</u> Median age (range)= 64 (22-82) 80.5% male Site: 29.5% esophagus/ 28.2% GEJ/ 42.3% stomach 76.8% metastatic	**Interventions** ECF: epirubicin + cisplatin +5-FU ECX= epirubicin + cisplatin + capecitabine EOF= epirubicin + oxaliplatin +5-FU EOX= epirubicin + oxaliplatin + capecitabine On day 1 of every 3-week cycle, patients in all study groups received an intravenous bolus of epirubicin (50mg/m^2); cisplatin (60 mg/m^2) was given intravenously with hydration in the ECF and ECX groups, and oxaliplatin (130 mg/m^2) was administered intravenously during a 2-hour period in the EOF and EOX groups. Fluorouracil (200 mg/m^2) and capecitabine (625 mg/m^2) were given throughout treatment in the appropriate groups. Fluorouracil was administered through a CVAD with an empirical dose of 1 mg of warfarin daily for thromboprophylaxis. Antiemetic prophylaxis was routinely administered as	**Details** <u>Patient Assessment</u> Pretreatment evaluation included a full medical history, physical examination, a complete blood count, clotting analysis, serum biochemical analysis, 24-hour urinary clearance or EDTA testing, and electrocardiography (with or without echocardiography or multiple-gated acquisition scanning); audiography was performed when indicated. Baseline chest radiography and computed tomography of the chest, abdomen, and pelvis (with or without upper gastrointestinal endoscopy) were performed within 28 days before the start of therapy. Tumour measurements were performed at baseline and at 12 and 24 weeks, and the response to treatment was recorded according to RECIST guidelines.22 The quality of life was assessed with the use of the 30-item European Organization for Research and Treatment of Cancer Quality of Life	**Results** <u>Overall Survival</u> (intention to treat population) **5-FU versus Capecitabine** 5-FU N= 508, Capecitabine N= 494 Hazard ratio for death, 0.88; 95% CI, 0.77 to 1.00; P = 0.06 **Cisplatin versus Oxaliplatin** C N= 513, O N= 489 Hazard ratio, 0.91; 95% CI, 0.79 to 1.04; P = 0.16 **ECF versus EOX** Hazard ratio, 0.80; 95% CI, 0.66 to 0.97; P = 0.02 The 1-year survival rate in the ECF group was 37.7%, and the median survival was 9.9 months. Survival was longer in the EOX group than in the ECF group, with a 1-year survival rate of 46.8% and a median survival of 11.2 months. <u>Progression-Free Survival</u> (intention to treat population) **5-FU versus Capecitabine** 5-FU N= 508, Capecitabine N= 494 The hazard ratio for progression with the	**Limitations** **<u>Cochrane risk of bias tool</u>** Selection bias • random sequence generation: random permuted blocks • allocation concealment: through central trials office Performance bias • blinding: unclear Detection bias • blinding: unclear Attrition bias • outcome date complete Reporting bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
cisplatin, respectively, in terms of overall survival. **Study dates** June 2000 and May 2005 **Source of funding** Supported in part by Hoffmann–La Roche and Sanofi-Aventis together with the Gastrointestinal Unit Clinical Research Fund of the Royal Marsden Hospital	Histology: 89.6% adenocarcinoma/ 9.5% Squamous cell carcinoma/ 0.8% undifferentiated EOF group Median age (range)= 61 (33-78) 81.3% male Site: 39.6% esophagus/ 23.4% GEJ/ 37% stomach 77% metastatic Histology: 86% adenocarcinoma/ 12.8% Squamous cell carcinoma/ 1.3% undifferentiated EOX group Median age (range)= 62 (25-80) 82.8% male Site: 34.3% esophagus/ 22.2% GEJ/ 43.5% stomach 75.7% metastatic Histology: 87.4% adenocarcinoma/ 12.2% Squamous cell carcinoma/ 0.4% undifferentiated	described previously.21 Treatment cycles were repeated every 3 weeks for a maximum of eight cycles unless there was evidence of disease progression or unacceptable toxicity, or the patient withdrew consent or died.	Questionnaire, version 3,23 before randomization and at 3, 6, 9, and 12 months. Statistics Overall survival was calculated from the date of randomization to the date of death from any cause. Progression-free survival was calculated from the date of randomization to the first date of documented progressive disease or the date of death from any cause. Data from patients who were alive and from those who were free of progression were censored at the date of the last follow-up visit for overall and progression-free survival, respectively. Survival was calculated with the use of the Kaplan–Meier method, and hazard ratios were calculated with the use of the Cox proportional-hazards model. For the secondary analyses, we compared rates of survival in the intention-to-treat population with the use of the unadjusted log-rank test; for the planned comparisons among study groups, the comparator was the ECF group. The planned Cox-regression multivariate analysis of survival included	capecitabine regimens was 0.92 (95% CI, 0.81 to 1.05; P = 0.22) **Cisplatin versus Oxaliplatin** C N= 513, O N= 489 The hazard ratio for progression with the oxaliplatin regimens was 0.92 (95% CI, 0.80 to 1.04; P = 0.19) ECF= 263 ECX= 250 EOF= 245 EOX= 244 Treatment-Related Toxicity: Nausea and Vomiting (Grade 3/4) ECF: 10.2 % ECX= 7.7% EOF= 13.8% EOX= 11.4% Treatment-Related Toxicity: Diarrhoea (Grade 3/4) ECF: 2.6% ECX= 5.1% EOF= 10.7% EOX= 11.9% Treatment-Related Toxicity: Stomatitis (Grade 3/4) ECF: 1.3% ECX= 1.7% EOF= 4.4%	• outcomes stated in the objective were reported Overall assessment: LOW risk of bias due to adequate reporting of allocation concealment and randomization process. Blinding likely not to affect outcome assessment as outcomes were objective. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Inclusion criteria • 18 and over • histologically proven adenocarcinoma, squamous cell carcinoma, undifferentiated carcinoma • locally advanced or metastatic disease • measurable disease • ECOG status 0-2 • adequate hepatic, renal, hematologic function **Exclusion criteria** • previous chemotherapy or radiotherapy (unless the latter was adjuvant treatment with relapse outside the radiotherapy field) • uncontrolled cardiac disease		age, sex, performance status, extent of disease, tumour location, and histologic analysis. Overall response and rates of toxic effects were compared with the use of a chi-square test. All the reported P values are twosided and have not been adjusted for multiple testing; P values of less than 0.05 were considered to indicate statistical significance.	EOX= 2.2% Quality of Life Mean scores at baseline and 12 weeks showed no significant difference (data NR)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	• other clinically significant, uncontrolled coexisting illness • previous or concurrent cancer				
Full citation Guimbaud, R., Louvet, C., Ries, P., Ychou, M., Maillard, E., Andre, T., Gornet, J. M., Aparicio, T., Nguyen, S., Azzedine, A., Etienne, P. L., Boucher, E., Rebischung, C., Hammel, P., Rougier, P., Bedenne, L., Bouche, O., Prospective, randomized, multicenter, phase III study of fluorouracil, leucovorin, and irinotecan versus epirubicin, cisplatin, and capecitabine in advanced gastric adenocarcinoma: a French intergroup (Federation Francophone de Cancerologie Digestive, Federation Nationale des Centres de Lutte Contre le Cancer, and Groupe Cooperateur Multidisciplinaire en Oncologie) study, J Clin Oncol, 32, 3520-6, 2014 **Ref Id**	**Sample size** n= 416 (ECX= 209, FOLFIRI= 207) **Characteristics** Median age (range)= 61.4 (27.9- 83.8) 74.3 % male Tumour location: 32.7 % GEJ/ 65.1 gastric/ 2.2% missing Previous resection: 24.5% Previous CRT: 58.1% Previous chemo alone: 20.9% **Inclusion criteria** • histologically confirmed, unresectable, locally advanced or metastatic gastric or EGJ adenocarcinoma • 18 and over	**Interventions** The ECX regimen consisted of epirubicin 50 mg/m^2 (15-minute IV infusion) plus cisplatin 60 mg/m^2 (1-hour IV infusion) on day 1 followed by oral capecitabine 1 g/m^2 twice per day from day 2 to day 15 every 3 weeks; the maximum cumulative dose of epirubicin authorized was 900 mg/m^2. The FOLFIRI regimen consisted of irinotecan 180mg/m^2 (90-minuteIV infusion) and leucovorin 400 mg/m^2 (2-hour IV infusion) followed by a fluorouracil 400 mg/m^2 IV bolus and then fluorouracil 2,400 mg/m^2 as a 46-hour continuous infusion every 2 weeks. Dose modifications, appropriate hydration, and premedication were predefined in the study protocol.	**Details** Quality of Life Assessment QoL was collected by using the EORTC QLQ-C30 (15 dimensions) and the EORTC QLQ-STO22 (22 questions; the gastric cancer module) questionnaires. Statistics All efficacy analyses were performed on an intent-to-treat principle. The safety population was defined as all patients receiving at least one dose of study treatment. Qualitative variables are described as numbers and percentages, and quantitative variables are described as means, standard deviations, and medians and ranges (minimum-maximum). On-treatment variables (response, duration of treatment) were compared by using the 2 test, Fisher's exact test, or a	**Results** Treatment-Related toxicity: any Grade 3/4 ECX: 84% FOLFIRI: 69% P<0.001 Treatment-Related toxicity: Hematologic Grade 3/4 ECX: 64.5% FOLFIRI: 38% P<0.01 Treatment-Related Mortality* ECX: 7/ 209 FOLFIRI: 5/ 207 * First-line chemo treatment deaths only Quality of Life There was no significant difference in any of these scores between the two arms and no real trend toward a rapid deterioration in QoL. This conclusion	**Limitations** **Cochrane risk of bias tool** Selection bias • random sequence generation: unclear • allocation concealment: unclear Performance bias • blinding: unclear Detection bias • blinding: unclear Attrition bias • outcome date complete • outcomes reported are objective or

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
546006 **Country/ies where the study was carried out** France **Study type** RCT **Aim of the study** To compare epirubicin, cisplatin, and capecitabine (ECX) with fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatments in patients with advanced gastric or esophagogastric junction (EGJ) adenocarcinoma. **Study dates** June 2005 and May 2008 **Source of funding** Supported by Laboratoire Roche and Laboratoire Pfizer, Fédération Francophone de Cancérologie Digestive, Dijon, France; Fédération Nationale des Centres de Lutte Contrele Cancer, Paris, France; and Groupe	• measurable/assessable lesions • WHO performance status <= 2 • ability to take oral medication • no previous palliative chemotherapy • adequate hepatic, renal and hematologic function **Exclusion criteria** • less than 6 months from adjuvant chemotherapy • less than 3 weeks from radiotherapy • history of FU or anthracycline cardiac toxicity • CNS metastasis • other life-threatening cancer • pregnant or breastfeeding • inability to plan regular follow-up for any reason		nonparametric Wilcoxon test, depending on the type and distribution of the variables. Median follow-up was calculated according to reverse Kaplan-Meier estimates. Survival curves were plotted by using Kaplan-Meier estimates and were compared by using the log-rank test. Univariate Cox models were used to calculate the hazard ratio (HRs) with 95% CIs. To assess the assumption of proportional hazards of Cox models, Schöenfeld residuals were plotted. QoL scores were calculated according procedures defined in the EORTCQLQ-C30 scoring manual. An analysis of time until definitive deterioration of QoL (decrease in QLQ-C30 score of five or more points without any improvement) was performed. All analyses were performed by using SASsoftwareversion9.1. The level of statistical significance was P .05.	was confirmed by the time to definitive deterioration. The median time was 7.6 months (95% CI, 6.1 to 8.9months) in the ECX arm versus 7.4 months (95%CI, 6.2 to 8.6 months) in the FOLFIRI arm (P .64). More than 85% of patients in each arm completed at least one QLQ-C30 questionnaire.	use a validated tool Reporting bias • outcomes stated in the objective were reported Overall assessment: UNLCEAR risk of bias due not inadequate reporting of allocation concealment, randomization process and blinding. **Other information** Other outcomes reported in Mohammad meta-analysis. The second-line treatment was predetermined to reduce discrepancies in practices between the arms: second-line FOLFIRI for patients in the ECX arm and second-line ECX for patients in the FOLFIRI arm. The first-line treatment was dispensed until disease progression, unacceptable toxicity, patient's request to stop treatment, or death. The second-line treatment was given after a minimum treatment-free interval of 3

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Coopérateur Multidisciplinaire en Oncologie, Paris, France.	• inability to complete QoL questionnaire				weeks and biologic and clinical recovery. In ECX arm: 101 went on to receive second line FOLFIRF In FOLFIRI arm: 81 went on to receive second line ECX
Full citation Wang, J., Xu, R., Li, J., Bai, Y., Liu, T., Jiao, S., Dai, G., Xu, J., Liu, Y., Fan, N., Shu, Y., Ba, Y., Ma, D., Qin, S., Zheng, L., Chen, W., Shen, L., Randomized multicenter phase III study of a modified docetaxel and cisplatin plus fluorouracil regimen compared with cisplatin and fluorouracil as first-line therapy for advanced or locally recurrent gastric cancer, Gastric CancerGastric Cancer, 19, 234-244, 2016 **Ref Id** 486899 **Country/ies where the study was carried out** China **Study type** RCT	**Sample size** N= 243 (mDCF arm= 121, CF arm= 122) **Characteristics** 72.2% male Median age (range)= 56.1 (19-80) Tumour site: GEJ 20.9%/ Stomach 69.7% / Other or unknown 9.4% 76.1% metastatic disease Previous radiotherapy: 0.4% Previous surgery: 36.3% Previous adjuvant or neoadjuvant chemotherapy: 19.2% **Inclusion criteria** • 18 years and over • histologically proven gastric or	**Interventions** mDCF: docetaxel 60 mg/m^2 (1-h intravenous infusion) plus cisplatin at 60 mg/m^2 (1- to 3-h intravenous infusion) on day 1, followed by 5-FU at 600 mg/m^2/day (continuous intravenous infusion) for 5 days. CF: cisplatin at 75 mg/m^2 on day 1 followed by 5-FU at 600 mg/m^2/day for 5 days. Treatment was given in 3-week cycles. During the study, the dose modification criteria were predefined and were based on toxicities. All patients received appropriate hydration and patients in the mDCF regimen arm also received corticosteroids as premedication. Treatment continued until there was disease progression, unacceptable toxicity,	**Details** Patient Assessment Toxicities were evaluated weekly and were graded according to the National Cancer Institute of Canada Common Toxicity Criteria (NCIC-CTC) version 3.0. Statistics The major secondary end points included OS, overall RR (ORR), TTF, and safety. The Kaplan–Meier curve was used to describe survival data. PFS and OS were compared between arms using the stratified log-rank test as well as the Cox proportional hazards model. ORRs were compared using Fisher's exact test. Safety analyses were based on the safety sets defined as all patients who received at least one dose of the study medication and had at least one follow-up safety assessment. Safety	**Results** Discontinuation due to treatment-related toxicity Similar in both arms (data NR) Treatment-related toxicity: Vomiting (Grade 3/4) DCF: 7.6% CR: 11.3% Treatment-related toxicity: Diarrhoea (Grade 3/4) DCF: 12.6% CR: 0 Treatment-related toxicity: Neutropenia (Grade 3/4) DCF: 60.5% CR: 9.6%	**Limitations** **Cochrane risk of bias tool** Selection bias • random sequence generation: unclear • allocation concealment: randomization was centralized Performance bias • blinding: unclear Detection bias • blinding: unclear Attrition bias • outcome data complete Reporting bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study To investigate the efficacy and safety of a modified DCF (mDCF) regimen for Chinese patients with advanced gastric cancer. **Study dates** NR **Source of funding** The study was funded by Sanofi	GEJ adenocarcinoma • measurable or assessable disease • KPS > 70 • no prior palliative chemotherapy • adequate hepatic, renal and hematologic function **Exclusion criteria** • surgery within 3 weeks • radiotherapy within 6 weeks • concomitant cancer • neuropathy • CNS involvement • uncontrolled, significant comorbid conditions	death, or consent withdrawal	analyses included all adverse events, as well as the events possibly or probably related to study medication, and were performed using Fisher's exact test.		• outcomes stated in the objective were reported Overall assessment: UNLCEAR risk of bias due not inadequate reporting of randomization process and blinding. Majority of outcomes assessment were objective. **Other information** Study dates not reported. Other outcomes included in Mohammad meta-analysis.

1

F.15 Second-line palliative chemotherapy

What is the optimal palliative second-line chemotherapy for locally-advanced or metastatic oesophago-gastric cancer?

Full citation	Inclusion criteria:	Methods:	Cochrane Risk of Study Bias Assessment:
Bang 2015 Bang, Y. J., Im, S. A., Lee, K. W., Cho, J. Y., Song, E. K., Lee, K. H., Kim, Y. H., Park, J. O., Chun, H. G., Zang, D. Y., Fielding, A., Rowbottom, J., Hodgson, D., O'Connor, M. J., Yin, X., Kim, W. H., Randomized, Double-Blind Phase II Trial With Prospective Classification by ATM Protein Level to Evaluate the Efficacy and Tolerability of Olaparib Plus Paclitaxel in Patients With Recurrent or Metastatic Gastric Cancer, Journal of Clinical OncologyJ Clin Oncol, 33, 3858-65, 2015 Study type: randomised double-blind phase II trial Aim of the study: compare the efficacy of olaparib plus paclitaxel with paclitaxel alone in patients with recurrent or metastatic gastric cancer and assess whether low ATM expression is predictive of improved clinical outcome for olaparib plus paclitaxel Study dates: February 2010-May 2012 Source of funding: Astra-zeneca Country: Korea	age≥18 years recurrent or metastatic gastric adenocarcinoma progression after first-line chemotherapy; confirmed ataxia telangiectasia mutated (ATM) status from an archival tumour sample collected and analysed during screening; Eastern Cooperative Oncology Group performance status ≥ 2; and normal hepatic, renal, and bone marrow function. This trial population was enriched for ATMlow patients; 50% of the overall population was ATMlow. ATM expression was determined by IHC analysis of a freshly cut single section from a formalin-fixed, paraffin-embedded archival biopsy or resection tumor sample, collected from the primary tumor or metastases after the original diagnosis and stored at room temperature. IHC methods followed those described in an inter-laboratory concordance study. **Intervention:** 4-week treatment cycles: Olaparib (100 mg orally twice daily) or placebo, in combination with paclitaxel (80mg/m^2 per day intravenously on days 1, 8 and 15). Patients were expected to receive six to 10 paclitaxel treatment cycles. After completing paclitaxel treatment, patients entered the maintenance therapy phase, where they received olaparib (200mg twice per day) or placebo monotherapy until objective progression or toxicity. Toxicities were managed by olaparib and/or paclitaxel dose modifications (reductions and/or interruptions [delays]).	Method of randomization: computer generated Exclusion after randomization: 1 patient in arm1 Lost to follow-up: 1 patient in arm1 Method of allocation concealment: block random assignment stratified by ATM status ensuring that the proportion of ATMlow patients in each arm was 50% Intention-to-treat analysis: yes Description of sample size calculation: yes Blinding: double-blind	Random sequence generation: low risk Allocation concealment: low risk Blinding (performance bias): low risk Blinding of outcome assessment (detection bias): low risk Incomplete outcome data (attrition bias): low risk Selective reporting: low risk Other bias: low risk

Full citation **Bang 2016** Bang, Y. J., Boku, N., Chin, K., Lee, K. W., Park, S. H., Qin, S., Rha, S. Y., Shen, L., Xu, N., Im, S. A., Locker, G., Rowe, P., Shi, X., Hodgson, D., Liu, Y. Z., Xu, R., Olaparib in combination with paclitaxel in patients with advanced gastric cancer who have progressed following first-line therapy: Phase III GOLD study, Annals of Oncology. Conference: 41st European Society for Medical Oncology Congress, ESMO, 27, 2016 Study type: Muli-centre randomised double-blind phase III trial Aim of the study: compare the efficacy of olaparib plus paclitaxel with paclitaxel alone in patients with recurrent or metastatic gastric cancer. Study dates: September 2013-December 2016 Source of funding: AstraZeneca Country: Korea, Japan, China	**Inclusion criteria:** Advanced gastric cancer (including GEJ) that has progressed following first-line therapy. Agee ≥18 years of age. Age ≥20 if Japanese Provision of tumour sample (from either a resection or biopsy). At least one lesion (measurable and/or non-measurable) that can be accurately assessed by imaging (CT/MRI) at baseline and following up visits. **Exclusion criteria** More than one prior chemotherapy regimen (except for adjuvant/neoadjuvant chemotherapy with more than 6 month wash out period) for the treatment of gastric cancer in the advanced setting. Any previous treatment with a Polyadenosine 5'-diphosphoribose [poly-(ADP-ribose)] polymerisation (PARP) inhibitor, including olaparib. Patients with second primary cancer, except: adequately treated non-melanoma skin cancer, curatively treated in-situ cancer of the cervix, or other solid tumours curatively treated with no evidence of disease for ≥5 years. Human Epidermalgrowth Factor Receptor-2 (HER2) positive patients. **Intervention:** 4-week treatment cycles: Olaparib (100 mg orally twice daily) or placebo, in combination with paclitaxel (80mg/m^2 per day intravenously on days 1, 8 and 15). Patients were expected to receive six to 10 paclitaxel treatment cycles. After completing paclitaxel treatment, patients entered the maintenance therapy phase, where	**Methods:** Method of randomization: computer generated Blinding: double-blind	**Cocrane Risk of Study Bias Assessment:** Random sequence generation: low risk Allocation concealment: low risk Blinding (performance bias): low risk Blinding of outcome assessment (detection bias): low risk Incomplete outcome data (attrition bias): low risk Selective reporting: low risk Other bias: low risk

	they received olaparib (200mg twice per day) or placebo monotherapy until objective progression or toxicity. Toxicities were managed by olaparib and/or paclitaxel dose modifications (reductions and/or interruptions [delays]).		

Full citation	Participant Characteristics	Methods:	Cochrane Risk of Study Bias Assessment:
Ford 2014 Ford, H. E. R., Marshall, A., Bridgewater, J. A., Janowitz, T., Coxon, F. Y., Wadsley, J., Mansoor, W., Fyfe, D., Madhusudan, S., Middleton, G. W., Swinson, D., Falk, S., Chau, I., Cunningham, D., Kareclas, P., Cook, N., Blazeby, J. M., Dunn, J. A., Cougar-Investigators, Docetaxel versus active symptom control for refractory oesophagogastric adenocarcinoma (COUGAR-02): an open-label, phase 3 randomised controlled trial, Lancet OncologyLancet Oncol, 15, 78-86, 2014 454700 Study type: open-label phase III randomised controlled trial Aim of the study: To assess whether the addition of docetaxel to active symptom control alone can improve survival and HRQoL for patients. Study dates: April 21, 2008, and April 26, 2012 Source of funding: Cancer research UK Country: UK	**Inclusion criteria:** Patients at least 18 years old with advanced histologically confirmed adenocarcinoma of the oesophagus, oesophago-gastric junction or stomach that had progressed on or within 6 months of treatment with platinum or fluorpyrimidine combination. Eastern Cooperative Oncology Group performance status: 0-2: (0=normal, 2=symptomatic but in a bed or chair less than 50% waking hours). Satisfactory haematological, renal and hepatic function. Baseline haemoglobin> 100g/L **Exclusion criteria:** Disease-free interval longer than 6 months. Chemotherapy with taxane, grade 2-4 peripheral neuropathy, previous malignancy, and cerebral or leptomeningeal metastases. **Intervention**: Docetaxel 75mg/m^2 by IV infusion every 3 weeks for up to six cycles.	Method of randomization: central computerised minimisation procedure (1:1 randomisation). Stratified by disease status, disease duration, duration of response to previous chemotherapy and performance status. Exclusion after randomization: 13 (Docetaxel + BSC 7, BSC: 6) Lost to follow-up: Method of allocation concealment: trial investigator contacted the trials unit for the participant's random allocation sequence. Intention-to-treat analysis: Yes Description of sample size calculation: yes Blinding: open-label: trial investigator and participants aware of treatment allocation.	Random sequence generation: low risk Allocation concealment: low risk Blinding (performance bias): high risk Blinding of outcome assessment (detection bias): high risk Incomplete outcome data (attrition bias): low risk Selective reporting: low risk Other bias: low risk

Full citation	Inclusion criteria:	Methods:	Cochrane Risk of Study Bias Assessment:
Higuchi 2014 Higuchi, K., Tanabe, S., Shimada, K., Hosaka, H., Sasaki, E., Nakayama, N., Takeda, Y., Moriwaki, T., Amagai, K., Sekikawa, T., Sakuyama, T., Kanda, T., Sasaki, T., Azuma, M., Takahashi, F., Takeuchi, M., Koizumi, W., Biweekly irinotecan plus cisplatin versus irinotecan alone as second-line treatment for advanced gastric cancer: A randomised phase III trial (TCOG GI-0801/BIRIP trial), European Journal of Cancer, 50, 1437-1445, 2014 Study type: randomised phase III trial Aim of the study: to compare biweekly irinotecan plus cisplatin with irinotectan alone as second-line chemotherapy for advanced gastric cancer. Study dates: April 2008-July 2011 Source of funding: The Tokyo Cooperative Oncology Group, Tokyo, Japan. Country: Japan	Histological diagnosis of adenocarcinoma of the stomach refractory to S-1 based first-line chemotherapy (excluding irinotecan+S-1) for unresectable advanced or recurrent disease or recurrance within 6 months of completing S-1 adjuvant therapy. Measurable lesion that could be serially evaluated for treatment response, no prior immunotherapy, radiotherapy or S-1 based therapy within 2 weeks before enrolment, previous surgery within 4 weeks of enrolment, ECOG performance score of 2 or less <20 years of age Life expectancy of at least 12 weeks Adequate organ function No serious comorbidities **Intervention**: BIRIP: Irinotecan 60mg/m^2 as 60min IV infusion plus cisplatin 30mg/m^2 as 90min IV infusion with adequate hydration on day 1 every 2 weeks. Irinotecan: 150mg/m^2 as 90min IV infusion on day 1 every 2 weeks. Treatment continued until disease progression, intolerable toxicity, withdrawal of consent. Assessment of disease progression: CT scans 2 weeks before study entry and every 6 weeks after treatment initiation. Treatment response assessed according to the Response evaluation criteria in solid tumours (RECIST)guidelines and adverse events graded according	Method of randomization: minimisation method Exclusion after randomization: none Lost to follow-up: none Method of allocation concealment: minimisation method Intention-to-treat analysis: yes Description of sample size calculation: no Blinding: not reported	Random sequence generation: low risk Allocation concealment: low risk Blinding (performance bias): unreported Blinding of outcome assessment (detection bias): unreported Incomplete outcome data (attrition bias): low risk Selective reporting: low risk Other bias: low risk

	to common terminology criteria for adverse events (CTCAE) v3.0.		

Full citation	Inclusion criteria:	Methods:	Cochrane Risk of Study Bias Assessment:
Hironaka 2013 Hironaka, S., Ueda, S., Yasui, H., Nishina, T., Tsuda, M., Tsumura, T., Sugimoto, N., Shimodaira, H., Tokunaga, S., Moriwaki, T., Esaki, T., Nagase, M., Fujitani, K., Yamaguchi, K., Ura, T., Hamamoto, Y., Morita, S., Okamoto, I., Boku, N., Hyodo, I., Randomized, open-label, phase III study comparing irinotecan with paclitaxel in patients with advanced gastric cancer without severe peritoneal metastasis after failure of prior combination chemotherapy using fluoropyrimidine plus platinum: WJOG 4007 trial, Journal of Clinical Oncology, 31, 4438-44, 2013 Aim of study: to compared weekly paclitaxel and biweekly irinotecan for patients with advanced gastric cancer refractory to treatment with fluoropyrimidine plus platinum. Study dates: August 2007 to August 2010 Study design: randomised open label phase III study Funding: Yakult Pharmaceutical industry Country: Japan	age 20 to 75 years histologically confirmed metastatic or recurrent gastric adenocarcinoma. ECOG performance status of 0 to 2; disease progression confirmed by computed tomography (CT), endoscopy, or other imaging technique during within 1 month after last dose of first-line chemotherapy with fluoropyrimidine plus platinum; no prior chemotherapy with taxanes or irinotecan no severe peritoneal metastasis (defined as ileus or subileus suggested on barium enema examination and moderate to severe ascites exceeding the pelvic cavity on spine CT scan caused by peritoneal metastasis). In case of treatment with adjuvant or neoadjuvant chemotherapy consisting of fluoropyrimidine plus platinum, patients with disease progression within 6 months after treatment completion Adequate bone marrow, hepatic, and renal function **Intervention:** Paclitaxel (80 mg/m^2) was administered intravenously on days 1, 8, and 15, every 4 weeks. Patients were premedicated with histamine receptor-1 and -2 blockers and dexamethasone for prophylaxis of allergic reactions 30 minutes before paclitaxel administration. Irinotecan (150 mg/m^2) was administered intravenously on days 1 and 15, every 4 weeks. Dose reduction and/or cycle delays were permitted according to predefined toxicity criteria. Treatment continued until disease	Method of randomization: 1:1 ratio, at a central data centre using minimisation method with adjustment factors: institution, ECOG PS, absence or presence of measurable lesion. Exclusion after randomization: 3 and 2 in paclitaxel and irinotecan groups respectively Lost to follow-up: 2 patients in paclitaxel arm. Method of allocation concealment: not reported, no blinding to allocated treatment Intention-to-treat analysis: no (patients found to be ineligible after randomisation were excluded) Description of sample size calculation: yes	Random sequence generation: low risk Allocation concealment: moderate risk Blinding (performance bias): high risk Blinding of outcome assessment (detection bias): high risk Incomplete outcome data (attrition bias): low risk Selective reporting: low risk Other bias: low risk

	progression, occurrence of unacceptable serious toxicity, or patient refusal of further treatment. Subsequent chemotherapy was not specified		

Full citation	Inclusion criteria	Methods:	Cochrane Risk of Study Bias Assessment:
Kang 2012 Kang, J. H., Lee, S. I., Lim do, H., Park, K. W., Oh, S. Y., Kwon, H. C., Hwang, I. G., Lee, S. C., Nam, E., Shin, D. B., Lee, J., Park, J. O., Park, Y. S., Lim, H. Y., Kang, W. K., Park, S. H., Salvage chemotherapy for pretreated gastric cancer: a randomized phase III trial comparing chemotherapy plus best supportive care with best supportive care alone, Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 30, 1513-8, 2012 Aims: To establish whether salvage chemotherapy (SLC) in advanced gastric cancer (AGC) resulted in substantial prolongation of survival when compared with best supportive care (BSC). Study design: Randomised trial phase III multi-centre Country: Korea Study dates: 2008 to 2010 Funding: supported by Grant No. CRS-109-08-1 from the Clinical Research Development Program of the Samsung Medical Center, Seoul, Korea.	Histologically confirmed AGC had not seen benefit after one or two chemotherapy regimens for metastatic disease involving fluoropyrimidines and platinum, consisting of either fluoropyrimidine- or platinum-based chemotherapy or a fluoropyrimidine and platinum combination. Adequate organ function and an Eastern Cooperative Oncology Group performance status (PS) of 0 or 1 were confirmed by respective laboratory tests as well as physical examinations. **Exclusion criteria** more than two prior chemotherapy regimens, PS >-2, prior exposure to both taxanes and irinotecan, additional malignancy significant comorbidities. **Intervention** Patients were randomly assigned in a ratio of 2:1 to either second line chemotherapy (SLC) or best supportive care (BSC). In the SLC regimen, the treating physician determined chemotherapy (ie, single-agent docetaxel or irinotecan) for each patient. Prespecified regimens included docetaxel 60 mg/m^2 on day 1 every 3 weeks or irinotecan 150 mg/m^2 every 2 weeks. SLC was continued until disease progression, unacceptable toxicities, or consent withdrawal.	Method of randomization: computerised Exclusion after randomization: 5 in SLC arm, 4 in BSC arm Lost to follow-up: none Method of allocation concealment: not reported Intention-to-treat analysis: yes Description of sample size calculation: yes Median follow-up: 20 months	Random sequence generation: low risk Allocation concealment: unclear risk Blinding (performance bias): unclear risk Blinding of outcome assessment (detection bias): unclear risk Incomplete outcome data (attrition bias): low risk Selective reporting: low risk Other bias: unclear risk Study not blinded but blinding should not influence overall survival – could possibly influence more subjective outcomes

Full citation **Kim B 2015** Kim, B., Lee, K. W., Kim, M. J., Han, H. S., Park, Y. L., Park, S. R., A multicenter randomized phase II study of docetaxel vs. docetaxel plus cisplatin vs. docetaxel plus S-1 as second-line chemotherapy in metastatic gastric cancer patients who had progressed after cisplatin plus either S-1 or capecitabine, European Journal of Cancer, 51, S432, 2015 Aims: to evaluate the concept of reintroduction of previous failed chemotherapeutic agent as combination with a newly introduced agent which has synergistic anti-tumour efficacy. Study dates: November 2008 to September 2012 Study design: a multicentre randomised phase II trial Source of funding: not reported Country: Korea	**Inclusion:** Patients with metastatic gastric cancer who have progressed on or after first-line cisplatin plus S-1 or capecitabine **Exclusion:** Not reported Intervention: 3-week cycles of docetaxel 75mg/m^2 IV day 1 or Docetaxel 60mg/m^2 IV plus cisplatin 60mg/m^2 day 1 or Docetaxel 60mg/m^2 plus oral S-1 30mg/m^2 BD day 1-14	**Methods:** Method of randomization: not reported Exclusion after randomization: 7 in each arm Lost to follow-up: not reported Method of allocation concealment: not reported Intention-to-treat analysis: not reported Description of sample size calculation: no	**Cochrane Risk of Study Bias Assessment:** Random sequence generation: unclear risk Allocation concealment: unclear risk Blinding (performance bias): unclear risk Blinding of outcome assessment (detection bias): unclear risk Incomplete outcome data (attrition bias): unclear risk Selective reporting: unclear risk Other bias: unclear risk

Full citation **Kim JY 2015** Kim, J. Y., Ryoo, H. M., Bae, S. H., Kang, B. W., Chae, Y. S., Yoon, S., Baek, J. H., Kim, M. K., Lee, K. H., Lee, S. A., Song, H. S., Kim, J. G., Multi-center Randomized Phase II Study of Weekly Docetaxel Versus Weekly Docetaxel-plus-Oxaliplatin as a Second-line Chemotherapy for Patients with Advanced Gastric Cancer, Anticancer Research, 35, 3531-6, 2015 Aims: to evaluate the efficacy and safety of weekly docetaxel alone and weekly docetaxel-plus oxaliplatin as a second-line chemotherapy in patients with cisplatin-refractory advanced gastric cancer. Study dates: January 2009-January 2012 Study design: Phase II randomised study Source of funding: Country: Korea	Patients with histologically confirmed metastatic or recurrent gastric adenocarcinoma Radiological disease-progression either during first-line chemotherapy or within six-months after the last dose of a cisplatin-based adjuvant chemotherapy regimen. Exclusion: Previous exposure to docetaxel or oxaliplatin Intervention: Weekly monotherapy of 36mg/m2 docetaxel (given IV on days 1 and 8) or docetaxel combined with 80mg/m2 oxaliplatin (on day 1 every 3 weeks up a maximum of 9 cycles). Docetaxel preceeded by 10mg dexamethasone and antistimatine IV to prevent hypersensitivity. Antiemetics given prior to chemotherapy as prophylaxis. GCSF not allowed during first cycle of treatment. Treatment doses were reduced as per study protocol until neutrophil count was above $1.5x10^9$/L, platelet count above $100x10^9$/L and other treatment-related toxicities of 1 or lower. Patients were excluded if treatment-related toxicity did not improve to 0 or 1 within two weeks.	**Methods:** Method of randomization: stratified to ECOG performance score (0, 1 or 2) then randomised Exclusion after randomization: none Lost to follow-up: none Method of allocation concealment: not reported Intention-to-treat analysis: yes Description of sample size calculation: yes	**Cochrane Risk of Study Bias Assessment:** Random sequence generation: unclear risk Allocation concealment: unclear risk Blinding (performance bias): high risk Blinding of outcome assessment (detection bias): unclear risk Incomplete outcome data (attrition bias): low risk Selective reporting: low risk Other bias: unclear risk

Full citation **Maruta 2007** Maruta, F., Ishizone, S., Hiraguri, M., Fujimori, Y., Shimizu, F., Kumeda, S., Miyagawa, S., A clinical study of docetaxel with or without 5'DFUR as a second-line chemotherapy for advanced gastric cancer, Medical Oncology, 24, 71-5, 2007 Aims: To evaluate the efficacy and safety of the combination of docetaxel and 5′DFUR as a second-line chemotherapy for gastric cancer Study dates: January 2004-December 2005 Study design: randomised clinical pilot study Source of funding: not reported Country: Japan	**Inclusion criteria:** Histologically proven metastatic or recurrent, or unresectable locally advanced, gastric cancer with measurable or evaluable lesions. received first-line chemotherapy and showed no response or demonstrated disease progression after initial response (at least 4 wk interval) age 20–75 yr, performance status of World Health Organization (WHO) 0–2, and an estimated life expectancy of more than 3 mo. **Intervention:** Regimen A: docetaxel (60 mg/m^2 1h IV infusion every 3 wks) alone. Regimen B: docetaxel (60 mg/m^2 1-h IV infusion every 3 wk) and 5′DFUR (600 mg/body orally every day). Both regimens were repeated for at least two cycles. Chemotherapy was delayed until recovery if the hematological toxicity of grade 3–4 or the non-hematological toxicity of grade 2 or more occurred.	Methods: Method of randomization: unclear Exclusion after randomization: unclear Lost to follow-up: unclear Method of allocation concealment: unclear Intention-to-treat analysis: unclear Description of sample size calculation: no	Cochrane Risk of Study Bias Assessment: Random sequence generation: unclear risk Allocation concealment: unclear risk Blinding (performance bias): unclear risk Blinding of outcome assessment (detection bias): unclear risk Incomplete outcome data (attrition bias): unclear risk Selective reporting: unclear risk Other bias: unclear risk

Full citation **Moehler 2013** Moehler, M. H., Thuss-Patience, P. C., Schmoll, H. J., Hegewisch-Becker, S., Wilke, H., Al-Batran, S. E., Weissinger, F., Kullmann, F., Von Weikersthal, L. F., Siveke, J. T., Kanzler, S., Schimanski, C. C., Otte, M., Schollenberger, L., Koenig, J., Galle, P. R., FOLFIRI plus sunitinib versus FOLFIRI alone in advanced chemorefractory esophagogastric cancer patients: A randomized placebo-controlled multicentric AIO phase II trial, Journal of Clinical Oncology. Conference, 31, 2013 Aim: to evaluate the safety and efficacy of SUN as add-on in second-line or third-line FOLFIRI Study design: double-blind randomised placebo-controlled trial Study dates: November 2009-July 2013 Funding: Country: Germany	Inclusion: Aged 18 and older Histological proven gastric adenocarcinoma or adenocarcinoma of the esophagogastric junction or lower esophagus Failure of any prior chemotherapy (docetaxel and/or platinum-based chemotherapy); but patient has not previously received FOLFIRI treatment At least 3 weeks from previous docetaxel- and/or platinum-based chemotherapy Exclusion: History of another primary malignancy >3 years, with the exception of non-melanoma skin cancer and in situ carcinoma of the uterine cervix Prior palliative radiotherapy of the target lesions Concurrent treatment with any other medicinal anti-cancer therapy Prior treatment with a VEGF, VEGFR or RTK inhibitor, or prior enrolment on this study Treatment with potent CYP3A4 inhibitor within 7 days of Sunitinib/placebo dosing or with potent CYP3A4 inducer within 12 days of Sunitinib/placebo dosing Known deficit in dihydropyrimidine dehydrogenase Intervention: 6-week cycles including FOLFIRI two weekly followed by sunitinib 25mg (2 capsules) or placebo (2 capsules) per oral once daily for 4 weeks followed by 2 weeks rest period to complete a 6 week cycle. See trial note: https://clinicaltrials.gov/ct2/show/NCT01020630	Methods: Method of randomization: unclear Exclusion after randomization: unclear Lost to follow-up: unclear Method of allocation concealment: unclear Intention-to-treat analysis: unclear Description of sample size calculation: no	Cochrane Risk of Study Bias Assessment: Random sequence generation: unclear risk Allocation concealment: unclear risk Blinding (performance bias): unclear risk Blinding of outcome assessment (detection bias): unclear risk Incomplete outcome data (attrition bias): unclear risk Selective reporting: unclear risk Other bias: unclear risk

Full citation **Nishikawa 2015** Nishikawa, K., Fujitani, K., Inagaki, H., Akamaru, Y., Tokunaga, S., Takagi, M., Tamura, S., Sugimoto, N., Shigematsu, T., Yoshikawa, T., Ishiguro, T., Nakamura, M., Morita, S., Miyashita, Y., Tsuburaya, A., Sakamoto, J., Tsujinaka, T., Randomised phase III trial of second-line irinotecan plus cisplatin versus irinotecan alone in patients with advanced gastric cancer refractory to S-1 monotherapy: TRICS trial, European Journal of Cancer, 51, 808-16, 2015 Aim: to examine the survival benefit of Irinotecan/cisplatin combination over Irinotecan monotherapy. Study design: multicentre, open-label, randomised phase III trial Funding: not stated Study dates: July 2007-December 2011 Country: Japan	Inclusion criteria: Aged ≥ 20 years Histologically confirmed advanced gastric cancer refractory Tumour progression after at least one cycle of S-1 monotherapy for an advanced cancer, or recurrence within 6 months after the completion of adjuvant therapy with S-1 A treatment-free interval of at least 2 weeks after S-1 monotherapy and 4 weeks after surgery was required to be eligible for the trial. Intervention: Irinotecan /cisplatin: IV Irinotecan (60 mg/m^2) and cisplatin (30 mg/m^2) on day 1 and every 2 weeks thereafter. Irinotecan monotherapy: intravenous Irinotecan (150 mg/m^2) on day 1 and every 2 weeks thereafter.	Methods: Method of randomization: using a centralised dynamic randomisation method with stratification by baseline characteristics. Exclusion after randomization: 2 and 3 patients in Irinotecan /cisplatin and Irinotecan monotherapy arms respectively Lost to follow-up: none reported Method of allocation concealment: as above Intention-to-treat analysis: yes Description of sample size calculation: yes	Cochrane Risk of Study Bias Assessment: Random sequence generation: low risk Allocation concealment: low risk Blinding (performance bias): high risk Blinding of outcome assessment (detection bias): high risk Incomplete outcome data (attrition bias): low risk Selective reporting: low risk Other bias: low risk

Full citation **Nishina 2016** Nishina, T., Takiuchi, H., Boku, N., Mizusawa, J., Shimada, Y., Hamamoto, Y., Yasui, H., Yamaguchi, K., Amagai, K., Ohkawa, S., Kawai, H., Takashima, A., Ohtsu, A., Randomized phase II study of second-line chemotherapy with best-available 5-fluorouracil (5-FU) versus weekly paclitaxel in far advanced gastric cancer (AGC) with peritoneal metastasis (PM) refractory to 5-Fu-containing regimens (JCOG0407), Annals of Oncology, 22, ix60-ix61, 2011 Aim: To compared weekly administration of paclitaxel (wPTX) with the best available 5-fluorouracil (5-FU) regimen as second-line treatment for advanced gastric cancer patients with severe peritoneal metastasis refractory to fluoropyrimidine Study design: multi-centre randomized open arm, phase II study Funding: Ministry of Health, Labour and Welfare, Japan Study dates: July 2005 and December 2008 Country: Japan	Inclusion criteria: Histologically proven gastric adenocarcinoma; unresectable or recurrent disease with peritoneal metastasis diagnosed radiologically, within 28 days before registration (histological confirmation of metastasis was not mandatory); age 20–75 years; One prior chemotherapy consisting of fluoropyrimidine Exclusion criteria: prior chemotherapy with taxanes, or 5-FU-containing regimens comprising both bolus and continuous infusion 5-FU, leucovorin with oxaliplatin (FOLFOX) or irinotecan (FOLFIRI). Prior radiotherapy Intervention Arm A:The 5-FUci regimen was given as 800 mg/m^2/day, on days 1–5, every 4 weeks, and the MTX and 5-FU regimen consisted of weekly MTX bolus infusion (100 mg/m^2/day, day 1), followed by 5-FU bolus infusion (600 mg/m^2/day, day 1) with a 3-h interval, and leucovorin given orally or by intravenous injection (10 mg/m^2, repeated every 6 h, days 2–3). Arm B: Paclitaxel was given as a 1-h infusion (80 mg/m^2/day, days 1, 8, and 15), every 4 weeks.	Methods: Method of randomization: at a central data centre using minimization method of balancing the arms according to baseline characteristics Exclusion after randomization: 1 patient in 5-FU arm Lost to follow-up: none Method of allocation concealment: no Intention-to-treat analysis: yes Description of sample size calculation: yes	Cochrane Risk of Study Bias Assessment: Random sequence generation: low risk Allocation concealment: high risk Blinding (performance bias): high risk Blinding of outcome assessment (detection bias): high risk Incomplete outcome data (attrition bias): low risk Selective reporting: low risk Other bias: low risk

Full citation **Roy 2013** Roy, A. C., Park, S. R., Cunningham, D., Kang, Y. K., Chao, Y., Chen, L. T., Rees, C., Lim, H. Y., Tabernero, J., Ramos, F. J., Kujundzic, M., Cardic, M. B., Yeh, C. G., de Gramont, A., A randomized phase II study of PEP02 (MM-398), irinotecan or docetaxel as a second-line therapy in patients with locally advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma, Annals of Oncology, 24, 1567-1573, 2013 Aim: to evaluate the efficacy and safety of single agent PEP02 (highly stable liposomal nanocarrier formulation of irinotecan) compared with irinotecan or docetaxel in the second-line treatment of advanced oesophago-gastric (OG) cancer. Study design: randomised phase II study Funding: PharmaEngine Study dates: January 2008 and June 2010 Countries: UK, Spain, Taiwan, Croatia, Korea and Bosnia.	Inclusion criteria: ≥18 years of age histologically or cytologically confirmed locally advanced or metastatic gastric or GEJ adenocarcinoma. failed one prior systemic chemotherapy (including patients with disease recurrence within 6 months of (neo)adjuvant chemotherapy). no prior irinotecan/taxane treatment Intervention Patients were randomly assigned 1:1:1 to receive: PEP02 (a highly stable liposomal nanocarrier formulation of irinotecan): 120 mg/m^2 (90-min infusion on day 1 of each cycle), irinotecan: 300 mg/m2 (90-min infusion on day 1 of each cycle) or docetaxel (Taxotere): 75 mg/m^2 (60-min infusion on day 1 of each cycle) intravenously as monotherapy administered every 3 weeks. Only the comparison between arm 2 and 3 was included in the NMA In the PEP02 arm, a protocol-specified dose level increase to 150 mg/m^2 was allowed for patients who did not have a ≥grade 1 adverse event.	Methods: Method of randomization: not reported Exclusion after randomization: 3, 1 and 4 in each respective arm (PEP02, irinotecan or docetaxel) Lost to follow-up: not reported Method of allocation concealment: not reported Intention-to-treat analysis: yes Description of sample size calculation: yes	Cochrane Risk of Study Bias Assessment: Random sequence generation: unclear risk Allocation concealment: unclear risk Blinding (performance bias): unclear risk Blinding of outcome assessment (detection bias): unclear risk Incomplete outcome data (attrition bias): low risk Selective reporting: low risk Other bias: unclear risk

Full citation **Sym 2013** Sym, S. J., Hong, J., Park, J., Cho, E. K., Lee, J. H., Park, Y. H., Lee, W. K., Chung, M., Kim, H. S., Park, S. H., Shin, D. B., A randomized phase II study of biweekly irinotecan monotherapy or a combination of irinotecan plus 5-fluorouracil/leucovorin (mFOLFIRI) in patients with metastatic gastric adenocarcinoma refractory to or progressive after first-line chemotherapy, Cancer Chemotherapy & PharmacologyCancer Chemother Pharmacol, 71, 481-8, 2013 Aim: to evaluate theefficacy of irinotecan (CPT-11) monotherapy and CPT-11 plus 5-fluorouracil (5-FU)/leucovorin (LV) combination (mFOLFIRI) as second-line treatment in patients with advanced gastric cancer (AGC). Study design: open-label, randomized, single-center phase II study. Funding: Study dates: March 2007 to December 2009 Country: Korea	Inclusion criteria Histologically confirmed adenocarcinoma of the gastric or gastro-esophageal junction and with metastatic disease age range 18–75 years disease progression either during first-line chemotherapy or within 6 months after the last dose of a platinum-, fluoropyrimidine- or taxane-based first-line chemotherapy regimen. no previous exposure to irinotecan Intervention Irinotecan: 150 mg/m^2 over 90 min mFOLFIRI: irinotecan 150 mg/m^2 over 90 min (followed by a 30-min break) followed by leucovorin (folic acid) 20 mg/m^2 over 5 min and then 5-FU 1,000 mg/m^2 per day by continuous intravenous infusion over 2 days. Cycles were repeated every 2 weeks for up to a maximum of twelve cycles. Irinotecan administration was preceded with atropine 0.25 mg subcutaneously to prevent cholinergic syndrome. Dexamethasone and a 5-hydroxytryptamine type 3 receptor antagonist were given as antiemetic prophylaxis Loperamide and ciprofloxacin prophylaxis provided if required	Methods: Method of randomization: stratified by ECOG performance score Exclusion after randomization: Lost to follow-up: 4 in irinotecan and 3 in mFOLFIRI arm Method of allocation concealment: unclear Intention-to-treat analysis: for efficacy Description of sample size calculation: yes	Cochrane Risk of Study Bias Assessment: Random sequence generation: unclear risk Allocation concealment: unclear risk Blinding (performance bias): high risk Blinding of outcome assessment (detection bias): high risk Incomplete outcome data (attrition bias): low risk Selective reporting: low risk Other bias: low risk

Full citation **Tanabe 2015** Tanabe, K., Fujii, M., Nishikawa, K., Kunisaki, C., Tsuji, A., Matsuhashi, N., Takagane, A., Ohno, T., Kawase, T., Kochi, M., Yoshida, K., Kakeji, Y., Ichikawa, W., Chin, K., Terashima, M., Takeuchi, M., Nakajima, T., Phase II/III study of second-line chemotherapy comparing irinotecan-alone with S-1 plus irinotecan in advanced gastric cancer refractory to first-line treatment with S-1 (JACCRO GC-05), Annals of Oncology, 26, 1916-1922, 2015 Aim: to determine whether the consecutive use of S-1 plus irinotecan improves survival when compared with irinotecan-alone as second-line treatment for AGC. Study design: multicenter, prospective, randomized open-label trial Funding: Taiho Pharmaceutical Co., Ltd, Japan Study dates: February 2008 to May 2011 Country: Japan	Inclusion criteria Histologically confirmed diagnosis of gastric or esophagogastric junction adenocarcinoma and confirmed disease progression on imaging studies after first-line treatment with S-1-alone, S-1 plus cisplatin or S-1 plus (excluding S-1 plus irinotecan). ≥20 years Exclusion criteria: S-1-based regimens as adjuvant chemotherapy Intervention S-1 plus irinotecan: oral S-1 twice daily on days 1–14 and IV irinotecan (150 mg/m^2) on day 1 of a 21-day cycle. Irinotecan monotherapy: IV dose as above on day 1 of a 14-day cycle. In the event of predefined toxic events, protocol-specified treatment modifications were permitted	Methods: Method of randomization: stratification on baseline characteristics. Method not reported Exclusion after randomization: 8 in S-1+irinotecan and 3 in irinotecan monotherapy arms Lost to follow-up: none reported Method of allocation concealment: not reported Intention-to-treat analysis: modified intention to treat analysis (excluding those excluded after randomisation) Description of sample size calculation:	Cochrane Risk of Study Bias Assessment: Random sequence generation: unclear risk Allocation concealment: unclear risk Blinding (performance bias): high risk Blinding of outcome assessment (detection bias): high risk Incomplete outcome data (attrition bias): low risk Selective reporting: low risk Other bias: low risk

Full citation **Thuss-Patience 2011** Thuss-Patience, P. C., Kretzschmar, A., Bichev, D., Deist, T., Hinke, A., Breithaupt, K., Dogan, Y., Gebauer, B., Schumacher, G., Reichardt, P., Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer--a randomised phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO), European journal of cancer (Oxford, England : 1990), 47, 2306-14, 2011 Aim: to compare second-line chemotherapy to best supportive care (BSC) in second-line therapy for metastatic gastric cancer Study design: multicenter, open label, randomised phase III study Funding: Aventis and Pfizer Study dates: October 2002 until December 2006 Country: Germany	Inclusion criteria: Histologically proven adenocarcinoma of the stomach or gastrooesophageal junction, metastatic or locally advanced with surgical incurability, no pretreatment with more than one prior palliative regimen of chemotherapy (neoadjuvant or adjuvant chemotherapy or radiation was permitted), documented objective imaging proven progression during or within 6months after the end of a first-line chemotherapy. age ≤ 75 years Intervention: BSC + irinotecan: irinotecan 250 mg/m^2 in the first cycle, increased to 350 mg/m^2 in subsequent cycles, administered every 3 weeks with antiemetic cover and subcutaneous atropine (0.25 mg) as cholinergic syndrome prophylaxis. Chemotherapy was administered until objective or clinical tumour progression, side effects, patient's wish or a maximum of 10 cycles.	Methods: Method of randomization: centrally performed using randomisation blocks. Stratification on baseline characteristics. Exclusion after randomization: 2 in each arm Lost to follow-up: none reported Method of allocation concealment: as above Intention-to-treat analysis: modified intention to treat based on those excluded after randomisation Description of sample size calculation: yes	Cochrane Risk of Study Bias Assessment: Random sequence generation: low risk Allocation concealment: low risk Blinding (performance bias): high risk Blinding of outcome assessment (detection bias): high risk Incomplete outcome data (attrition bias): low risk Selective reporting: low risk Other bias: low risk

1

2

F.16 Luminal obstruction

What is the optimal management of luminal obstruction for adults with oesophago-gastric cancer not amenable to treatment with curative intent?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Anand, B. S., Saeed, Z. A., Michaletz, P. A., Winchester, C. B., Doherty, M. A., Liem, J. H., Graham, D. Y., A randomized comparison of dilatation alone versus dilatation plus laser in patients receiving chemotherapy and external beam radiation for esophageal carcinoma, Digestive Diseases & SciencesDig Dis Sci, 43, 2255-60, 1998 **Ref Id** 474316 **Country/ies where the study was carried out** USA **Study type**	**Sample size** n=15; dilatation alone=7 versus dilatation plus laser = 8 **Characteristics** Age (mean) = 61 years Dysphagia score = 1.8 Patients in dilatation groups had higher Karnofsky score (92.8) than those in combined group (80) (p=0.04) (higher, the better performance to function normally) **Inclusion criteria** • Patients with squamous cell carcinoma of the oesophagus	**Interventions** All patients received radiotherapy and chemotherapy as the primary treatment. RT was given as external beam RT, 200 cGy/day on days 1-5, 8-12, 29-33, 36-40 and 57-60. Chemotherapy consisted of cisplatin (100mg/m2 infused at 1mg/min on days 1 and 29) and 5-fluorouracil (1000 mg/m2 by slow IV infusion over 24 hours on days 1-4 and 29-32). Then, the patients were reevaluated for the study eligibility and those who still had tumour were offered surgery.	**Details** Randomisation method was not described in details,	**Results** number of re-intervention Dilatation : 3.4±1.1 Combined : 2.9±0.7 Dysphagia score at 2 months Dilatation: 2.4±0.2 Combined: 2.3±0.2 Number of death at 6 months Dilation: 0/7 Combined: 1/8 At 12 months D: 3/7 C: 5/8 AT 30 months D: 6/7 C: 6/8	**Limitations** **Cochrane risk of bias tool** Selection bias • random sequence generation: unclear • allocation concealment: unclear Performance bias • blinding: unclear Detection bias • blinding: unclear Attrition bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Randomized controlled trial **Aim of the study** To compare dilatation alone versus dilatation plus laser for palliative treatment of people with oesophageal cancers **Study dates** Not reported **Source of funding** Not reported	**Exclusion criteria** • Cervical oesophageal cancer (upper 1/3), abnormal renal function , low white counts and platelet counts	Dilatation - done by "Through The Scope"(TTS) balloons, Savary dilators or both Laser therapy - done by Nd-YAG laser using the "retrograde technique". WIth 60-100 W power, tumour ablation was done. Both groups had follow-up endoscope at 6 months. Recurrence of dysphagia were treated with dilatation alone in both group. Percutaneous endoscopic gastrostomy (PEG) was done as necessary.			• outcome data complete: low risk Reporting bias • Outcomes mentioned in method session were reported. Overall assessment: Unclear risk of bias due to inadequate reporting of randomisation, allocation concealment and blinding **Other information**
Full citation	**Sample size** n=101; 47 Polyflex versus 54 Ultraflex	**Interventions** Ultraflex: covered single-strand, knitted	**Details** Computer-generated	**Results** **Technical success, n(%)**	**Limitations** **Cochrane risk of bias tool**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Conio, M., Repici, A., Battaglia, G., De Pretis, G., Ghezzo, L., Bittinger, M., Messmann, H., Demarquay, J. F., Blanchi, S., Togni, M., Conigliaro, R., Filiberti, R., A randomized prospective comparison of self-expandable plastic stents and partially covered self-expandable metal stents in the palliation of malignant esophageal dysphagia, American Journal of GastroenterologyAm J Gastroenterol, 102, 2667-77, 2007 **Ref Id** 487227 **Country/ies where the study was carried out** 7 hospitals in Italy, 1 hospital in France and 1 hospital in Germany **Study type**	**Characteristics** 82 SCC: 19 AC Age (median) in years= 74.9 Polyflex vs 69.1 Ultraflex , P=0.04 Male%=83 Circumferential tumour extent: 2/3 =30 %and 3/3 = 71% Lower third tumour = 15% stricture length: median (range) in cm= 5.5 (3-17) cm BMI ~ 59.2 number of patients underwent CT and/or RT = 38 before and 7 after and 3 before and after dilatation was performed in 34 (72.3%) Polyflex and 26 (48.1%) patients of the Ultraflex group (p=0.02). **Inclusion criteria** • patients with inoperable histoologicall proven squamous cell	memory metal (nitinol) mesh, flared proximally with uncovered ends; 18/23 mm in diameter Polyflex: polyester mesh stent completely covered by a silicone layer with a smooth inner surface and a structured outer surface Endoscopic stent insertion was performed under propofol. In patients with lower third oesophageal tumour, placing the distal end of the stent was avoided to prevent dislocation. 24 hours later, fluoroscopy was performed and soft diet was resumed, then free diet was encouraged. Follow-up after 1 week, by telephone	random number chart drawn up by a statistician. To detect a difference of 25% between the group (p<0.05 and power 80%) 50 patients in each group were requireed (not reported on the primary outcome). Minor complications included incomplete stent deployment, chest pain and gastrooeophageal reflux Major compliations	46/47(98%) in Polyflex 54/54 in Ultraflex **Dysphagia score (mean±SD)** Day 7: 1.2±0.9 Polyflex vs 1.1 ±0.9 Ultraflex Day 30= 1.2±1.0 in Poly vs 1.1±0.9 Ultra Last follow-up = 2.1±1.2 poly vs 1.9±1.1 Ultra Dysphagia improvement by one grade one week: 100% in Polyflex and 94% in Ultraflex one month: 91% in Polyflex and 88% in Ultraflex **Body weight at 4 weeks, mean±SD** 57.6±12.2 in Poly vs 58.6±9.4 in Ultra **Median survival (days), 95%CI** 134 (100-168) in Polyflex vs 122(84- 160) in Ultraflex **Major complications (early: within 7 days)** < 7 days : 4 (2 haemorrhage and 1 perforation) in Polyflex vs 2 (1 perforation) in Ultraflex (patients did not undergo RT and/or CT) >7 days: 20 (5 hyperplastic	Selection bias • random sequence generation: appropriate • allocation concealment: unclear Performance bias • blinding: unclear but unlikely Detection bias • blinding: unclear but unlikely Attrition bias • outcome data complete: low Reporting bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Randomised multicenter trial **Aim of the study** To compare two different types of covered self-expanding stent (plastic and metal) in the palliation of malignant dysphagia due to unresectable oesophageal cancer **Study dates** December 2004 and January 2006 **Source of funding** None	carcinoma (SCC) or adenocarcinoma (AC) • recurrent dysphagia after failure of chemo/radiotherapy (CT/RT) for oesophageal cancer • deemed unresectable tumour after staging with CT, PET/CT and endoscopic ultrasound • criteria for unresectability included presence of distant metastases, local infiltration in neighboring organs or poor clinical condition due to concomitant disease **Exclusion criteria** • Cancer involving the oesophagogastric junction, oesophagorespiratory fistula, tumour located within 3 cm from the	contact, monthly till death	included perforation, fistula, haemorrhage, migration, ingrowth and overgrowth.	tissue reaction/HTR) in Polyflex vs 17 (4 HTR) in ultraflex GE reflux= 2 in ultraflx within a week **Retrosternal pain** Before = 12 in Poly and 10 in Ultra After = 4/12 in poly and 8/10 in Ultra **Time for recurrence, median days (range)** 107 days (35-270) in Polyflex vs 97 days (59-316) in Ultraflex **Re-intervention** 2 in Poly and 2 in ultra **Followup until March 2006 and all patients dead at the end of the study.**	• Unclear of which outcomes were of interest Overall assessment: UNCLEAR risk of bias due to inadequate reporting of allocation concealment and outcome reporting **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	upper oesophageal sphincert, previous oesophageal surgery, and ECOG performance of > 3				
Full citation Dai, Y., Li, C., Xie, Y., Liu, X., Zhang, J., Zhou, J., Pan, X., Yang, S., Interventions for dysphagia in oesophageal cancer, Cochrane Database of Systematic ReviewsCochrane Database Syst Rev, 10, CD005048, 2014 **Ref Id** 474467 **Country/ies where the study was carried out** multiple **Study type** Systematic review and meta-analyses	**Sample size** K=53; n=3684 **Characteristics** Adam 1997 - 60 patients with squamous and adenocarcinoma done in UK; covered SEM vs uncovered SEM vs laser Alderson 1990 - 40 patients with adeno and squamous carcinoma of middle and lower oesophagus in UK; laser vs plastic tube Amdal 2013 - 41 patients in Norway; SEMS and brachy therapy versus brachytherapy Angelini 1991 - 34 patients with squamous and adenocarcinoma in italy; Laser versus polidocanel injection	**Interventions** • Self-expending metal (SEM) stent insertion • Thermal ablative therapy, laser therapy, argon plasma coagulation, bipolar probe electrocoagulation (BICAP) • Plastic stent insertion • Intraluminal brachytherapy • Photodynamic therapy	**Details** The search databases included MEDLINE, EMBASE, CancerLIT, CENTRAL and Cochrane upper gastrointestinal and pancreatic diseases review group. Data extraction was done using data extraction sheets. Risk of bias assessed by	**Results** 1. SEM versus plastic tube 2. SEM versus laser 3. Laser versus plastic tube 4. Laser versus laser plus brachytherapy 5. Laser versus photodynamic therapy 6. Covered ultraflex SEMS versus covered wallstent 7. SEMS versus plastic tube 8. Antiflex versus standard open stent 9. Brachytherapy versus brachytherapy plus radiotheray	**Limitations** ROBIS tool for bias risk assessment in systematic reviews: Study Eligibility Criteria 1. Did the review adhere to pre-defined objectives and eligibility criteria? Y 2. Were the eligibility criteria appropriate for the review question? Y 3. Were the eligibility criteria

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study To establish the optimal palliative treatment for dysphagia improvement and better quality of life among patients with unresectable or inoperable oesophageal cancer **Study dates** 1966 to January 2014 **Source of funding** Sichuan University, China	Barr 1990 - 40 patients with adeno and squamous carcinoma in UK; laser vs laser plus plastic tube Bergquist 2005 - 65 patients with advanced oesophageal or gastro-oesophageal junctional cancer in Sweden (multicenter); SEMS s brachytherapy (iridium 3 fractions of 7 Gy) Carrazone 1999 - 47 patients fungating adeno and squamous carcinoma in Italy; Laser vs ethanol injection Carter 1992 - 40 patients adeno and squamous carcinoma in UK; plastic tube versus laser Dai 2013 - 67 patients in China; a conventional stent vs an iodine-eluting oesophageal stent Dallal 2001 - 65 patients squamous and adenocarcinoma in UK; SEMS versus laser or APC or both De Palma 1996 - 39 patients with oesophageal carcinoma in Italy; SEMS(covered UF) vs WC plastic tubes	• External beam radiotherapy • Chemoradiotherapy • Chemotherapy • Chemical ablative therapy, alcohol injection, chemotherapeutic agent injection • Oesophageal bypass surgery Comparisons - one or more of the interventions mentioned above or oesophageal dilatation	the Cochrane Handbook for Systematic reviews of Interventions (Higgins 2011). Reasons for missing data were explored and the most common reason for missing data would be patients withdrawal due to disease progression or general deterioration. Last observation carried forward procedure was used as	Downloadable RevMan Data files were available from the Cochrane Library.	unambiguous? Y 4. Were all the restrictions on eligibility criteria based on study characteristics appropriate? Y 5. Were any restrictions in eligibility criteria based on sources of information available? Y 6. Concern regarding specification of study eligibility criteria: Low Identification and Selection of Studies 1. Did the search

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Fu 2004 - 53 patients with squamous and adenocarcinoma in China; SEMS versus SEMS with chemoradiotherapy Fuchs 1991 - 47 patients with adeno and squamous cell carcinoma in Germany; laser versus plastic tube Guo 2008 - 53 patients in China; MTN-S stent versus I125 stent Heier 1995 - 42 patients with squamous or adenocarcinoma, previous failed therapy and refusal of surgery in USA; PDT versus laser Homs 2004a - 209 patients SCC and AC with dysphagia 2-4 in Netherlands; SEMS (covered UF) vs brachytherapy **Inclusion criteria** • Randomised controlled trials • Patients with inoperable or		appropriate. Chi-squared of <0.1 was considered as evidence of herterogeneity. Authors of unpublished studies were contacted for more information. ITT analyses was applied. The primary outcome was improvement in dysphagia grades.		include an appropriate range of databases/electronic sources for published and unpublished reports? Y 2. Were the methods additional to database searching used to identify relevant reports? Y 3. Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible? Y 4. Were restrictions based on

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	unresectable primary oesophageal cancer undergoing palliative treatment • Patients with primary squamous or adenocarcinoma of the oesophagus or the gastro-oesophageal junction **Exclusion criteria** • Patients with extrinsic compression of the oesophagus from other tumours or • Patients with recurrence of dysphagia or recurrence of tumour after previous surgery				date, publication format or language appropriate? Y 5. Were efforts made to minimise error in selection of studies? Y 6. Concern regarding methods used to identify or select studies: Low Data Collection and Study Appraisal 1. Were efforts made to minimise error in data collection? Y 2. were sufficient study characteristic

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					s available? Y 3. Were all relevant study results collected for use and synthesis? PY 4. Was risk of bias formally assessed using appropriate criteria? Y 5. Were efforts made to minimise error in risk of bias assessment? Y 6. Concern: Low Synthesis and Findings 1. Did the synthesis include all

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					studies it should? Y 2. Were all pre-defined analyses reported and departures explained? Y 3. Was the synthesis appropriate given the nature and similarity in the research questions? Y 4. Was heterogeneity minimal or addressed? Y 5. Were the findings robust as demonstrated though funnel plot or sensitivity analysis? Y 6. Were biases in primary studies

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					minimal or addressed in the synthesis? Y 7. Concern= LOW Risk of bias in the review 1. Did the interpretation of findings address all the concerns identifies in 1-4? Y 2. Was the relevance of identified studies to the review's research question appropriately considered? Y 3. Did the reviewers avoid emphasizing results on

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					the basis of their statistical significance? Y 4. Risk of bias= LOW **Other information**
Full citation Dinshaw, K. A., Sharma, V., Pendse, A. M., Telang, C. S., Vege, S. S., Malliat, M. K., Deshpande, R., Desai, P. B., The role of intraluminal radiotherapy and concurrent 5-fluorouracil infusion in the management of carcinoma esophagus: a pilot study, Journal of Surgical OncologyJ Surg Oncol, 47, 155-60, 1991 **Ref Id** 475572	**Sample size** n=50; ILRT alone=25 vs ILRT+5-FU=25 **Characteristics** Median age = 65 years Male = 35/50 Site of lesion: upper/middle/lower = 6/40/4 Dysphagia grade= swallow semisolids only = 43/50 and swallow liquids only = 7/50 No liver metastasis No celiac node involvement **Inclusion criteria**	**Interventions** Patients received external beam radiotherapy 6 MV/ 10 MV 5000 cGy/28 fractions/38 days (180 cGy/fr) Then, 2 weeks later, oesophagoscopy was done to assess the response and randomised to ILRT alone vs ILRT plus 5-FU (concurrent). ILRT = 2500 cGy in 13 hours at 1cm from mid source point in 13 hours	**Details** Randomisation was done by sealed envelope method.	**Results** Overall survival at 2-years ILRT: 15% ILRT+5-FU: 22%; p<0.25 Total number of death n= 32 at 10 months Response Complete regression (on barium swallow and negative biopsy) ILRT: 22/25 (the rest 3 had regression of >50% on barium swallow and -ve biopsy on oesophagoscopy) ILRT+5-FU: 25/25	**Limitations** **Cochrane risk of bias tool** Selection bias • random sequence generation: unclear • allocation concealment: appropriate Performance bias • blinding: unclear

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out India **Study type** Randomised controlled trial **Aim of the study** To evaluate the efficacy of intraluminal radiotherapy (ILRT) with or without concurrent 5-Fluorouacil (5-FU) infusion among people with oesophageal cancer **Study dates** March 1988 to December 1989 **Source of funding** Not reported	Patients with squamous cell carcinoma of the oesophagus **Exclusion criteria**	5-FU = 500 mg/m2 for 24 hours Total dose of 6710 cGy (2.7 times higher than 2500 cGy) received in oesophagus 1 cm from the mid-source point. Follow-up - every 6 weeks ranging from 6 months to 27 months.			Detection bias • blinding: unclear Attrition bias • outcome data complete: low risk Reporting bias • Unclear of which outcomes were of interest Overall assessment: UNCLEAR risk of bias due to inadequate reporting of randomisation, blinding and outcome reporting **Other information**

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
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<tr>
<td>Full citation

Kharadi, M. Y., Qadir, A., Khan, F. A., Khuroo, M. S., Comparative evaluation of therapeutic approaches in stage III and IV squamous cell carcinoma of the thoracic esophagus with conventional radiotherapy and endoscopic treatment in combination and endoscopic treatment alone: a randomized prospective trial, International Journal of Radiation Oncology, Biology, PhysicsInt J Radiat Oncol Biol Phys, 39, 309-20, 1997

Ref Id

474693

Country/ies where the study was carried out

India</td>
<td>Sample size
n=104; 90 without oesophagorespiratory fistula (Group 1) and 14 with oesophagorespiratory fistula (group 2)

Characteristics
<u>Group 1</u>
Male=62%
Age (mean) = 49 years
Dysphagia grade: 3(n=7): 4(n=10)
<u>Group 2</u>
Male%=78%
Age(>60 years) = 5/14(36%)

Inclusion criteria

• Histologically confirmed squamous cell carcinoma of oesophagus
• any length of tumor as measured by endoscopy and</td>
<td>Interventions
The patients who met eligibility criteria were separated into two major groups: Group I : - nonesophagorespiratory fistulae group, i.e., patients who did not have any evidence of esophagorespiratory fistula; and Group 2:- esophagorespiratory fistulae group, i.e.. patients having documented evidence of esophagorespiratory fistula.
RT - The plan consisted ofi 1) patients received a dose of 55 to 65 Gy in 5 to 6 weeks; 2) conventional number of fractions. i.e., once a day, treatment was given</td>
<td>Details
Randomization was stratified to the following parameters: (a) age, (b) sex, (c) length of tumor, (d) ECOG performance status scale, and (e) site of the tumor (upper and midthoracic and Lower thoracic esophagus) The symptomatic response was graded as follows: 1 - complete response: when patient</td>
<td>Results
ECOG performance score in relation to treatment type at 1 month
<table>
<tr><td>ECOG</td><td>1a</td><td>1b</td></tr>
<tr><td>0</td><td>0</td><td>0</td></tr>
<tr><td>1</td><td>32/47</td><td>14/41</td></tr>
<tr><td>2</td><td>12/47</td><td>20/41</td></tr>
<tr><td>3</td><td>3/47</td><td>5/41</td></tr>
<tr><td>4</td><td>0/47</td><td>2/41</td></tr>
</table>
At > 12 months (denomintor = total number of patients alive)
<table>
<tr><td>ECOG</td><td>1a</td><td>1b</td></tr>
<tr><td>0</td><td>0</td><td>0</td></tr>
<tr><td>1</td><td>3/8</td><td>0</td></tr>
<tr><td>2</td><td>5/8</td><td>0</td></tr>
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<td>Limitations
<u>Cochrane risk of bias tool</u>
Selection bias

• random sequence generation: unclear
• allocation concealment: unclear

Performance bias

• blinding: unclear

Detection bias

• blinding: unclear

Attrition bias

• outcome data</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>Study type
A randomised controlled trial

Aim of the study
To define the role of endoscopic dilatation/intubation and radiotherapy in squamous cell carcinoma of oesophagus patients to improve their quality of life

Study dates
Dec 1990 to May 1992

Source of funding
Not reported</td>
<td>barium swallow or both;
• patients with any grade of dysphagia from Grade 0 to Grade 4;
• patients with any ECOG performance score

Exclusion criteria

• patients with Stage I and II disease; and
• patients who had already received radiation or chemotherapy or any other modality of treatment.</td>
<td>for 5 days a week; 3) dose per fraction delivered was 2 Gy; 4) rest period was given (7- 10 days) ; and 5) treatment was given either by a three-field technique (one anterior, one right posterior oblique, and one left posterior oblique) or by parallel opposing portals (one anterior and one posterior) up to the tolerance of the spinal cord, i.e., 415 Gy and then supplemented by the three-field technique. Endoscopic dilatation - Intubation was carried out using a tube introducer (Nottingham’s introducer) after endoscopic examination. The lumen was dilated to</td>
<td>was free of all symptoms including dysphagia; 2-partial response: downgrading of dysphagia by one or more than one grade; and 3-no response : either no change or worsening of symptoms. Each patient was reexamined at 1 month after successful completion of the treatment and subsequently at 3-month interv</td>
<td>
<table>
<tr><td>3</td><td>0</td><td>1/1</td></tr>
<tr><td>4</td><td>0</td><td>0</td></tr>
</table>
Body weight at 1 month, 6 months and > 12 months (mean±SD)
<table>
<tr><td>month</td><td>1a</td><td>1b</td></tr>
<tr><td>1</td><td>42.74±9.62 (n=47)</td><td>42.29±6.76 (n=41)</td></tr>
<tr><td>6</td><td>40.70±9.24 (n=30)</td><td>32.43±4.58 (n=9)</td></tr>
<tr><td>>12</td><td>47.11±8.36 (n=8)</td><td>30.01±0.00 (n=1)</td></tr>
</table>
radiation oesophagitis
Grade 1 = 36/51
Grade 2 = 9/51
Grade 3 = 6/51
Survival (median months, mean±SD)
1a = 7
1b =3
2a=4.25 (3.94±1.51)
2b=3.6(3.6±2.77)
Only 3 patients from Group 1a survived more than 18</td>
<td>complete: low risk

Reporting bias

• Outcomes mentioned in the method session were all reported

Overall assessment: UNCLEAR risk of bias due to inadequate reporting of randomisation, allocation concealment, blinding.

Other information</td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
		a size of 50 French gauge olive (16.6 mm diameter), using the Savary Gilliard dilators. A suitable prosthetic tube was selected (e.g., Atkinson's tube) and attached to the introducer. Group 1 patients were randomly allocated to one of the two treatment groups: Group Ia:- receiving both endoscopic treatment as well as radiotherapy. or Group Ib:- receiving endoscopic treatment alone. Similarly, Group 2 patients were randomly allocated to one of the two treatment groups: Group 2a:-receiving both endoscopic treatment as well as	als by history, physical examination, radiography of the chest, hemogram, serum biochemistry , ultrasonography of abdomen, and isotope scans of liver and bone, when ever necessary	months, while no patient from Groups Ib, 2a, or 2b survived for more than 1 year.	

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr><td></td><td></td><td>radiotherapy, or
Group 2b:-
receiving endoscopic treatment alone.<table><tr><td>Group</td><td>number of patients</td></tr><tr><td>1a</td><td>47</td></tr><tr><td>1b</td><td>43</td></tr><tr><td>2a</td><td>4</td></tr><tr><td>2b</td><td>10</td></tr></table></td><td></td><td></td><td></td></tr>
<tr><td>Full citation

Kim, C. G., Choi, I. J., Lee, J. Y., Cho, S. J., Park, S. R., Lee, J. H., Ryu, K. W., Kim, Y. W., Park, Y. I., Covered versus uncovered self-expandable metallic stents for palliation of malignant pyloric obstruction in gastric cancer patients: a randomized, prospective study, Gastrointestinal EndoscopyGastrointest Endosc, 72, 25-32, 2010</td><td>Sample size
n=80; covered stent= 40 vs uncovered stent=40

Characteristics

Inclusion criteria

• histologically confirmed gastric adenocarcinoma,</td><td>Interventions
Different through-the-scope SEMS were used. Niti-S pyloric stents were used until February 2006 and the Niti-S Comvi pyloric stents were used. Niti-S pyloric stents were covered stents where as Niti-S Combi were double-layered stents with nitinol layers.</td><td>Details
Groups were assigned by randomisation using computer-generated random number, stratified by chemotherapy. Patients were blinded throughout.</td><td>Results

Technical success (adequate placement of the SEMS across the stenosis confirmed by a combination of endoscopy and fluoroscopy)
Covered: 40/40
Uncovered: 40/40
Clinical success (relief of GOO-compatible symptoms or improvement of GOOSS score at 3 days after SEMS insertion)</td><td>Limitations
<u>Cochrane risk of bias tool</u>
Selection bias

• random sequence generation: low risk
• allocation concealment: unclear

Performance bias</td></tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref Id 490106 **Country/ies where the study was carried out** Korea **Study type** Prospective randomised study **Aim of the study** To compare covered self-expanding metallic stent (SEMS) with uncovered SEMS among people with malignant pyloric gastric obstruction **Study dates** December 2003 to September 2007 **Source of funding** National cancer centre, Korea	• a pyloric obstruction confirmed by endoscopy, • symptoms compatible with GOO, an inoperable condition because of metastatic disease, • an Eastern Cooperative Oncology Group performance status of 0 to 3 **Exclusion criteria** • previously received a SEMS, • undergone gastric surgery, • had intractable ascites	In uncovered group, enteral wallstents were used initially and from october 2005, WallFlex duodenal stents were used. Wallstent was made of Elgiloy and Wallflex was made of nitinol.	The primary endpoint was SEMS patency at 8 weeks. The secondary were technical and clinical success rates and SEMS patency at follow-up. A sample size of 80 patients were anticipated to detect the 30% difference in 8-week patency between covered SEMS (90%) and uncovered (60%) with 80% power	Covered: 38/40 Uncovered: 36/40 GOOSS score median and rage at 3-days post-insertion Covered: 3 (0 to 3) Uncovered: 2.5 (0 to 3) Patency at 8 weeks postinsertion ; total follow-up Covered: 19/31; 14/31 Uncovered: 22/36; 13/36 Major complication necessitating surgical interventilons Covered: 2/40 Uncovered: 0/40	• blinding: only blinded to patients Detection bias • blinding: unclear Attrition bias • outcome data complete: low risk Reporting bias • Outcomes mentioned in method session were reported. Overall assessment: Unclear risk of bias due to inadequate reporting of allocation

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			and 0.05 significance.		concealment and blinding **Other information**
Full citation Lee, H., Min, B. H., Lee, J. H., Shin, C. M., Kim, Y., Chung, H., Lee, S. H., Covered metallic stents with an anti-migration design vs. uncovered stents for the palliation of malignant gastric outlet obstruction: a multicenter, randomized trial, American Journal of GastroenterologyAm J Gastroenterol, 110, 1440-9, 2015 **Ref Id** 487485 **Country/ies where the study was carried out** Korea	**Sample size** n=102; uncovered SEMS (UCS) group = 51 or WAVE-covered SEMS (WCS) group = 51 **Characteristics** Mean age = 58 years Male= 70/101(69%) Cancer stage IV= 100% post-stenting chemotherapy = 61/101 **Inclusion criteria** • The presence of pathologically confirmed gastric adenocarcihoma inoperable due to	**Interventions** Wave-covered SEMS - a partially covered stent with several features preventing migration. SEMS was placed under endoscope. For WCS group, the stent was repositioned after deployment using lasso under fluoroscopic guidance, aligning the central portion of the stricture with the central portion of the stent, fitting the central portion of the stent reducing radial force and indentation.	**Details** Randomised using a centralized, web-based computer generated randomisation system. The primary endpoint was 8-week stent patency after SEMS insertion. A sample of 100 patients were required to detect the 29% difference in patency rate	**Results** Technical success UCS: 49/51 WCS: 50/51 Re-intervention rate at 8-weeks follow-up UCS: 10.8% (/37) WCS:(9.5%)(42) Re-intervention rate at 16-week follow-up, UCS: 37.8%(/37) WCS: 14.3%(/42) Overall survival number of detath on 30 Nov 2014 UCS: 25 (49%) WCS: 19(37.3%) HR 0.62 (0.34 to 1.14); p=0.122 favouring WCS group survival at 56 weeks UCS: 23% WCS; 37%	**Limitations** **Cochrane risk of bias tool** Selection bias • random sequence generation: low risk • allocation concealment: unclear Performance bias • blinding: unclear Detection bias • blinding: unclear

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type a prospective, multicenter, double-arm patient-blinded randomised trial **Aim of the study** To examine the role of newly developed WAVE (stent with anti-migration properties) stent compared with uncovered self-expanding metallic stent (SEMS) for the relieving symptoms of malignant GOO in patients with inoperable gastric cancer **Study dates** July 2012 and July 2014 **Source of funding** Stents were provided by Standard Sci Tech but the company did not involve in conducting the study.	distant metastasis or severe morbidity • Upper endoscopy or abdominal computed tomography findings that were consistent with GOO at the distal antrum, pylorus or duodenal bulb • the presence of GOO symptoms (early satiety, nausea or vomiting) and a Gastric Outlet Obstruction Scoring system (GOOSS) score ≤ 2 **Exclusion criteria** • inability to provide informed consent • multiple-level bowel obstruction confirmed on radiographic studies such as small bowel series or abdominal computed tomography	Technical success = adequate placement of SEMS across the stenotic area confirmed by endoscopy and fluoroscopy.	(89% in WCS vs 60% in US), 80% powere nad 0.05 error rate. There were 14 in UCS and 9 in WCS who were loss to follow-up. Modified intention to treat population was performed with 37 people in UCS and 42 people in WCS groups.		Attrition bias • outcome data complete: low risk Reporting bias • all the outcomes in the method session were reported Overall assessment: UNCLEAR risk of bias due to inadequate reporting of allocation concealment and blinding **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	• previous history of stent insertion or endoscopic dilatation for GOO treatment • prior gastric surgery • inability to undergo an upper endoscopy • Boorrman type IV advanced cancer				
Full citation Maetani, I., Mizumoto, Y., Shigoka, H., Omuta, S., Saito, M., Tokuhisa, J., Morizane, T., Placement of a triple-layered covered versus uncovered metallic stent for palliation of malignant gastric outlet obstruction: a multicenter randomized trial, Digestive EndoscopyDig, 26, 192-9, 2014 **Ref Id** 487545 **Country/ies where the study was carried out**	**Sample size** n=62; covered SEMS =31 vs uncovered SEMS=31 **Characteristics** mean age = 69 years Male= 30/62 Site of obstruction- (pylorus=20; Duodenum Pars I=12, Duodenum Pars II+III+IV=23; Gastroduodenostomy =4; gastrojejunostomy=3 Median GOOSS (Gastric outlet obstruction scoring system)= 0 Chemotherapy before stenting = 42/62	**Interventions** Stents used were Niti-S stent (woven of nitinol wires) and the covered ComVi stent (triple-labyered SEMS woven of nitisol wires with a polyetrafluoroethylene membrane). The endoscope used was a GIF 2T-200 or TJF-240 (Olympus, Tokyo, Japan), with a large working channel.All procedures were carried out under endoscopic and fluoroscopic control.	**Details** (80% power, 0.5 error) to detect 35% difference in 120-day patency (5% covered and 40% uncovered) group, 28 patients were required in each group. Randomisation - using opaque sealed envelopes	**Results** \clinical success rate UnCovered: 29/31 covered: 27/31 Median GOOSS UnCovered: 3 (2, 3) covered: 3 (2, 3) Degree of GOOSS (0/1/2/3) UnCovered: 2/5/7/17 covered: 3/1/12/15 Persistent obstructive symptoms UnCovered: 2/31 covered: 5/31 Recurrent obstructive symptoms UnCovered: 9/31 covered: 1/31 Adverse events (occulsion, migration, stent fracture)	**Limitations** **<u>Cochrane risk of bias tool</u>** Selection bias • random sequence generation: unclear • allocation concealment: low risk Performance bias • blinding: high risk Detection bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Japan **Study type** Multicenter randomised controlled trial **Aim of the study** `to evaluate a triple-layered covered self-expanding metallic stent (SEMS) compared with uncovered SEMS for the palliation of malignant gastric outlet obstruction **Study dates** June 2007 to February 2010 **Source of funding** Not reported	No significant difference between the groups. **Inclusion criteria** • Patients with symptomatic GOO as a result of unresectable malignant tumours • Pyloroduodenal obstruction presenting with obstructive symptoms **Exclusion criteria** • evidence of multiple stritures in the distal intestinal tract • evidence of perforation • duodenal stricture near the papilla for which stent would crossbridge the papilla	Technical success was defined as satisfactory deployment and precise positioning at the location of the stenosis, and clinical success as at least one grade of improvement in GOOSS at any visit compared to baseline. Failure of SEMS patency was defined as a condition involving stent dysfunction arising from any cause, including tumor ingrowth/overgrowth, stent migration, stent fracture, or unsatisfactory expansion. Adverse events were defined as any event that prevented completio n of the planned procedure and/or	prepared by investigators with no clinical involvement. The primary end point was failed SEMS patency during complete follow up and the secondary endpoint was success rate and adverse events.	UnCovered: 10/31 covered: 6/31 Perforation UnCovered: 0/31 covered: 1/31 Bleeding UnCovered: 1/31 covered: 0/31 Median days in patient survival; p=0.3448 UnCovered: 93 covered: 73 All patients were death at the end of study (May, 2012) with no loss of follow-up	• blinding: high risk Attrition bias • outcome data complete: low risk Reporting bias • Outcomes mentioned in method session were reported. Overall assessment: Unclear/High risk of bias due to inadequate reporting of randomisation and no blinding **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
		resulted in admission to hospital, prolongation of an existing hospital stay, another procedure, or subsequent medical consultation. Insufficient expansion was defined as deployment of <50% at 3 days after placement. Persistent obstructive symptoms were defined as continuing symptoms up to or occurring within 4 weeks after initial treatment,1 and recurrent obstructive symptoms as those occurring more than 4 weeks after treatment.1 These two types of symptoms were			

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
		determined by patient complaints.			
Full citation Nunes, C. C., Waechter, F. L., Sampaio, J. A., Pinto, R. D., Alvares-Da-Silva, M. R., Pereira-Lima, L., Comparative post-operative study of prostheses, with and without an anti-reflux valve system, in the palliative treatment of esophageal carcinoma, Hepato-GastroenterologyHepatogastroenterology, 46, 2859-64, 1999 **Ref Id** 492538 **Country/ies where the study was carried out** Brazil **Study type**	**Sample size** n=22; oesophageal prosthesis without anti-flux valve mechanism (n=11) vs surgical prosthesis coupled to anti-reflux valve system (n=11) **Characteristics** Age (mean)= 62 years Male= 13/22 **Inclusion criteria** • irresectable epidermoid carcinoma of the distal oesophagus submitted to palliative surgical treatment **Exclusion criteria**	**Interventions** One group was given a number 19 Malafaia oesophageal prosthesis without the valve mechanism while another group were given the same prosthesis but adapted with valve made of latax rubber (cylindrical). The prosthesis was positioned through gastrostomy and the latex valve left extended over the posterior wall of the gastric body. In both groups, two Dobb-Hoff catheters were placed under surgery.	**Details** Methods of randomisation were not described in details.	**Results** Complication Pyrosis With: 1/11 Without: 8/11 pneumonia With: 0/11 Without: 2/11 pH measurement at seated with 1M acetic acid instillation With: 7.33±0.33 Without: 2.17±0.38 pH measurement at dorsal decubitus with 1M acetic acid instillation With:5.3±1.69 Without: 3.55±0.56 Reflux examined by oesophagus/stomach fluoroscopy Without: No reflux With: 11/11	**Limitations** **Cochrane risk of bias tool** Selection bias • random sequence generation: unclear • allocation concealment: unclear Performance bias • blinding: unclear Detection bias • blinding: unclear Attrition bias • outcome data

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
A randomised controlled study **Aim of the study** TO assess the use of anti-flex valve mechanism of the prosthesis among patients with irresistable neoplasm of the distal oesophagus **Study dates** January 1994 to December 1997 **Source of funding** Not reported					complete: low risk Reporting bias • Outcomes mentioned in method session were reported. Overall assessment: Unclear risk of bias due to inadequate reporting of randomisation, allocation concealment and blinding **Other information**
Full citation Sur, R. K., Levin, C. V., Donde, B., Sharma, V., Miszczyk, L., Nag, S., Prospective randomized	**Sample size** n=232; HDR-ILBT of 16 Gy in 2 fractions within 3 days - 8Gy per fractions given on alternate days (Group A) =120 vs HDR-ILBT of 18 Gy	**Interventions** Treatment was given using a Microselectron HDR (Nucletron, The Netherlands). Patien	**Details** Randomizati on was done using random	**Results** 222 patients completed treatment (118 in Group A and 104 in Group B)	**Limitations** **Cochrane risk of bias tool** Selection bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
trial of HDR brachytherapy as a sole modality in palliation of advanced esophageal carcinoma--an International Atomic Energy Agency study, International Journal of Radiation Oncology, Biology, PhysicsInt J Radiat Oncol Biol Phys, 53, 127-33, 2002 **Ref Id** 475120 **Country/ies where the study was carried out** South Africa, Poland and India **Study type** A multicenter prospective randomised study **Aim of the study** **Study dates** September 1996 to September 1999	in 3 fractions within 5 days - 6 Gy per fraction given on alternate days (Group B)=112 **Characteristics** Mean age = 57 years Male = 154/232 Ethnic : White/Black/Asians/Others = 7/202/21/2 Dysphatia score: 1/2/3/4= 205/16/6/5 Previous treatment = 33/232 (mainly dilatation) **Inclusion criteria** • histologically proven squamous cell carcinoma; • tumor 5 cm in length on endoscopy and/or barium swallow; • Karnofsky performanc e score 50; • age 17–70 years; • primary disease in the thoracic esophagus;	ts with painful metastatic bone disease were given a single fraction of 8 Gy to the metastatic site, and patients with brain secondaries were given whole brain radiation of 20 Gy in 5 fractions during 1 week.	number tables.	Median survivals (p>0.05) A (8 Gy): 207 days B (6 Gy): 273 days Tracheooesophageal fistula A: 11/118 B: 12/104 Fibrous strictures A: 12/118 B: 13/104 Mean time to onset of strictures p>0.05 A: 170 days B: 172 days Patients necessitation additional treatment after brachytherapy A: 37 B: 45; p>0.05 Dysphagia free survival A: 182 days B: 238 days; p>0.05 Mean time to onset of fistula p>0.05 A: 140 days B: 136 days	• random sequence generation: h igh risk (random number table) • allocation concealment: unclear Performance bias • blinding: unclear Detection bias • blinding: unclear Attrition bias • outcome data complete: low risk Reporting bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding	• no prior malignancy in the past 5 years, • any N or M status, • unsuited for curative surgery **Exclusion criteria** • cervical esophagus tumor, • tumor extending to 1 cm from the gastroesophageal junction, • Karnofsky performance score 50, • tracheoesophageal fistula, • altered mental status, • extension to great vessels on CT.				• all the outcomes stated in method session were reported Overall assessment: UNCLEAR/HIGH risk of bias due to inadequate reporting of allocation concealment, blinding and outcome reporting **Other information**
Full citation Teli, M. A., Mushood, G. N., Zargar, S. A., Andrabi, W. H., Comparative	**Sample size** n=69; 34 in re-irradiation vs 35 in dilatation group	**Interventions** Re-irradiation : telecobalt unit (theratron-780); dose depending on	**Details** not mention in details about	**Results** Dysphagia grade at 4 weeks grade / re-irradiation / dilatation	**Limitations** **Cochrane risk of bias tool** Selection bias

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>evaluation between re-irradiation and demand endoscopic dilatation vs endoscopic dilatation alone in patients with recurrent/reactivated residual in-field esophageal malignancies, Journal of Cancer Research & TherapeuticsJ Cancer Res Ther, 4, 121-5, 2008

Ref Id

495350

Country/ies where the study was carried out

India

Study type
Randomised controlled trial

Aim of the study
To compare external beam re-irradiation with demand dilatation vs per-oral endoscopic dilatation alone among oesophageal</td>
<td>Characteristics
Age (mean) years = 58 years
Male = 37/69
Dysphagia: 3(n=36) and 4 (n=4)

Inclusion criteria

• patients with in-field residual/recurrent tumour
• patients with tumour in middle and lower third of the oesophagus
• presence of tumour confirmed radiologically, endoscopically and histopathologically
• history of having treated with radical doses of external beam radiotherapy for the primary tumour with a time interval of at least 6 months between the initial radical radiotherapy</td>
<td>the interval after the previous radiotherpy (45 to 60 Gy for 5 to 6 weeks, five, five fractions/week; the further, the greater the dose); Patients were also scheduled for dilatation if indicated. Followed up at 4-6 week intervals
Dilatation : flexible fibreoptic endoscope was used to assess the stricture. Savary-Gillard dilatators (5,7,9,11,12.8,14,15 mm) were used for dilatation. Dilatation was continued, using dilatators of increasingly greater insize until some blood stain was noticed on dilataor.</td>
<td>methodology</td>
<td>
<table>
<tr><td>0</td><td>0</td><td>0</td></tr>
<tr><td>1</td><td>20</td><td>3</td></tr>
<tr><td>2</td><td>14</td><td>19</td></tr>
<tr><td>3</td><td>0</td><td>13</td></tr>
<tr><td>4</td><td>0</td><td>0</td></tr>
</table>
Treatment-related toxicities within 4 weeks
<table>
<tr><td></td><td>re-irradiation (n=34)</td><td>dilatation (n=35)</td></tr>
<tr><td>oesophagitis</td><td>20/34</td><td>9/35</td></tr>
<tr><td>haematemesis</td><td>1/34</td><td>0/35</td></tr>
<tr><td>epigastric pain</td><td>26/34</td><td>35/35</td></tr>
<tr><td>acute chest pain (within 24</td><td>0</td><td>35/35</td></tr>
</table>
</td>
<td>• random sequence generation: unclear
• allocation concealment: unclear

Performance bias

• blinding: unclear

Detection bias

• blinding: unclear

Attrition bias

• outcome data complete: unclear

Reporting bias

• Unclear of which outcomes</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>cancer patients with residual/recurrent disease after radiation therapy

Study dates
May 2000 to May 2002

Source of funding
Not reported</td>
<td>and the irradiation treatment protocol
• Karnofsky performance > 50% or WHO >/= 4 and dysphagia grade I to IV

Exclusion criteria

• Patients with tracheoesophageal/bronchoesophageal fistula
• Radiation-induced stricture/fibrosis
• distant metastases to vital organs like brain and lung with life expectancy of less than 2-3 months
• patients with comorbid conditions
• Karnofsky performance scores of < 50% or WHO </=4</td>
<td></td>
<td></td>
<td>
<table>
<tr><td>hrs of dilatation)</td><td></td><td></td></tr>
<tr><td>edema feet</td><td>10/34</td><td>17/35</td></tr>
<tr><td>chest infection</td><td>4/34</td><td>7/35</td></tr>
</table>
after 6-10 weeks
<table>
<tr><td></td><td>re-irradiation (n=34)</td><td>dilatation (n=35)</td></tr>
<tr><td>epigastric pain</td><td>22/34</td><td>28/35</td></tr>
<tr><td>recurrent chest infection</td><td>8/34</td><td>3/35</td></tr>
<tr><td>interstitial fibrosis</td><td>3/34</td><td>0/35</td></tr>
<tr><td>tumor bleed</td><td>4/34</td><td>5/35</td></tr>
<tr><td>tracheooesophageal fistula</td><td>0/34</td><td>6/35</td></tr>
</table>
survival (p>/= 0.05)
number of death
re-irradiation= 18/34 (at</td>
<td>were of interest

Overall assessment: UNCLEAR risk of bias due to inadequate reporting of all risks of bias

Other information</td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				closure of study) dilatation alone=19/35 (at closure of study) No patients in re-irradiation group needed peroral dilatation mean duration between 1st and 2nd dilatation= 35.6±2.81 days mean duration between 2nd and 3rd dilatation = 36±4.42 days	
Full citation White, R. E., Chepkwony, R., Mwachiro, M., Burgert, S. L., Enders, F. T., Topazian, M., Randomized Trial of Small-diameter Versus Large-diameter Esophageal Stents for Palliation of Malignant Esophageal Obstruction, Journal of Clinical GastroenterologyJ Clin Gastroenterol, 49, 660-5, 2015	**Sample size** n=100; 50 in small diameter stent vs 50 in large diameter stent **Characteristics** Age: p=0.09 small= 61.8±12.7 Large= 57.1 ±14.6 Male= 60/100 weight = 44 kg (n= 81) largest dilator used before stent placemnent	**Interventions** 18mm shaft/23mm proximal flange or 23mm shaft/ 28mm proximal flange partially covered Ultraflex esophageal stent	**Details** Block randomization with 1:1 allocation was performed using a computer-generated random sequence and the sealed envelope	**Results** Dysphagia score <2 small=95% large= 95% Immediate adverse events (chest/back pain requiring hospitalisation, persistent dysphagia, dyspnoea, GI haemorrhage, Arrhythmia) small=2/50 large=0/50 Recurrent dysphagia small=25/50 large=21/50	**Limitations** **<u>Cochrane risk of bias tool</u>** Selection bias • random sequence generation: low risk • allocation concealment: low risk Performance bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref Id 487846 **Country/ies where the study was carried out** South Africa **Study type** A prospective randomized trial **Aim of the study** To assess the effect of esophageal stent diameter on outcomes of patients with malignant esophageal obstruction **Study dates** September 2003 to May, 2009 **Source of funding**	small: 41.8±3.3 large: 38.6±12.4 **Inclusion criteria** dysphagia due to unresectable ESCC (ESCC was deemed unresectable if patient age was above 70 years or there was vocal cord or diaphragmatic paralysis, malignant pleural effusion, extreme cachexia, poor physiological reserve or exercise tolerance, or metastases detected on examination, endoscopy, or chest x-ray.), residence within 50km of Tenwek Hospital, tumor size r9 cm in length and >2cm distal to the upper esophageal sphincter **Exclusion criteria** Participants with ERF or suspected perforation		technique, with 10 participants in each block; Allocation was concealed from participants, caregivers, and study personnel until randomization occurred during an endoscopic procedure. After randomization, stent diameters were known to the endoscopy staff and listed in the medical record. All randomized participants correctly	GI haemorrhage small=3 large=6 ER fistula small=2 large=5 Stent occlusion small=11 large=7 New GERD small=13 large= 12 Any delayed adverse events small=30 large= 29 Total re-stenting procedure at follow-up small=9 large=8 Median survival months (p=0.10) small=5.9 mths large= 3mths Overall survival rate at 6 mths small=50% large=30% No statistically difference on recurrent dysphagia, survival free of adverse events or survival	• blinding: High risk Detection bias • blinding: High risk Attrition bias • outcome data complete: high risk Reporting bias • Low risk Overall assessment: Unclear/High risk of bias due to no blinding of clinical staff and insufficent sample recruitment and loss of data and unclear analysis of missing data

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			received a stent of the allocated diameter, and remained blinded to the stent diameter they received. (80% power, 0.05 error rate, 50% recurrent dysphagia rate) - 100 in each group were required to detect the difference of 20% recurrent dysphagia (score 2 to 4) between the group.		**Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Zhu, H. D., Guo, J. H., Mao, A. W., Lv, W. F., Ji, J. S., Wang, W. H., Lv, B., Yang, R. M., Wu, W., Ni, C. F., Min, J., Zhu, G. Y., Chen, L., Zhu, M. L., Dai, Z. Y., Liu, P. F., Gu, J. P., Ren, W. X., Shi, R. H., Xu, G. F., He, S. C., Deng, G., Teng, G. J., Conventional stents versus stents loaded with (125)iodine seeds for the treatment of unresectable oesophageal cancer: a multicentre, randomised phase 3 trial, Lancet OncologyLancet Oncol, 15, 612-9, 2014 **Ref Id** 490528 **Country/ies where the study was carried out** China **Study type** multicentre, single-blind, randomised, phase 3 trial	**Sample size** n=160; irradiation stent (n=80) or a conventional stent (n=80). **Characteristics** Age in median (range) = 71(60 -79) years Male= 84% in irradiation vs 71% in control group Dysphagia score: 3 (n=98) and 4 (n=50) Previous CRT n= 59 **Inclusion criteria** adult (≥20 years) patients with endoscopically and histologically confi rmed oesophageal cancer, progressive dysphagia with a dysphagia score of 3 or 4,13 unresectable tumours due to extensive lesions, metastases, or poor medical condition, and patients with clear consciousness, cooperation,	**Interventions** The ^{125} I radioactive seeds (CIAE-6711; Chinese Atomic Energy Science Institution, Beijing) were preloaded in the sheaths (4·8 mm long and 0·8 mm wide), which were attached to the outer surface of the stent immediately before stent insertion. We defi ned the average activity as the average among all patients' total activity of ^{125} I seeds (activity per seed by number of loaded seeds) in the irradiation The procedure was done under either fl uoroscopy or endoscopy. The technique for placement with an irradiation stent was the same	**Details** Participants were randomly assigned (1:1) to receive either an oesophageal stent loaded with ^{125} I seeds (irradiation group) or a conventional self-expandable covered nitinol stent (control group). The randomisation sequence was generated by computer using a procedure of "PROC PLAN". We	**Results** 73 in irradiation group and 75 in control group were included in analyses (7 in irradiation and 5 in control withdrew without treatment, excluded) Number of death= 66 in irradiation group and 64 in the control group, median overall survival p value= 0.0046; overall survial at 180 days = 35.6% in control group and 49.7% in irradiation group), HR= 0.595[95%CI 0.412 - 0.859], p=0.0060) after adjusting tumour location, sex, previous CRT Technical success 100% Dysphagia score in median Before: 3 (3 -4) in irradiation vs 3 (3-4) in control After: 1 (0-4) in irradiatio vs 1 (0-3) in control Severe chest pain= 17/73 in irradiation vs 15/75 in control Fistula formation = 6/73 in irradiation vs 5/75 in control recurrent dysphagia= 21/73 in irradiation vs 20/75 in control	**Limitations** **Cochrane risk of bias tool** Selection bias • random sequence generation: appropriate • allocation concealment: appropriate Performance bias • blinding: yes except performing physicians Detection bias • blinding: yes Attrition bias • outcome data complete: yes

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study to compare the irradiation stent with a conventional self-expandable nitinol alloy covered stent for palliative treatment of malignant oesophageal stricture **Study dates** Nov 1, 2009, and Oct 31, 2012 **Source of funding** National High-tech Research Foundation of China (863 project #2009AA02Z402, 2012AA022701), the National Basic Research Program of China (973 Program # 2013CB733800, 2013733803), the Jiangsu Provincial Special Program of	and an Eastern Cooperative Oncology Group (ECOG) performance status score of 0–3 **Exclusion criteria** ECOG performance status of 4, dysphagia not caused by oesophageal cancer, slight dysphagia with a dysphagia score of 1 or 2,13 non-cooperative, the superior border of the lesion extending beyond the level of the seventh cervical vertebrae, ulcerative oesophageal cancer, oesophageal fi stula, white blood cell concentration of less than 3000 cells per μL, and severe hepatic inadequacy or renal inadequacy hepatic inadequacy as a Child-Pugh class C and severe renal inadequacy as a glomerular fi ltration rate of less than 30 mL/min per 1·73 m²	as for a conventional covered stent, apart from the pre-loading of ^{125} I seeds into the sheaths. All patients were hosted in radioprotective rooms after stent insertion until discharge (3 days or longer). Patients were followed up every month after stent placement. All physicians who did the procedures had received standardised training.	chose block length of 20Survival analyses were done in a modifi ed intention-to-treat group.We kept the coded treatment assignments in sealed, consecutivel y numbered, opaque envelopes, which were unsealed by the staff members at the dedicated trial offi ce, then we randomised the participants. We allowed	haemorrhage = 5/73 irradiation vs 5/75 control	Reporting bias • outcomes stated in the objective were reported Overall assessment: LOW risk of bias **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Medical Science (BL2013029), the National Scientifi c and Technical Achievement Translation Foundation ([2012]258), and the National Natural Science Foundation of China (81230034, 81071238).	(chronic kidney disease stage 4–5).		patients to be treated with chemothera py or alternative medicine before, concurrently with, or after stent placement.E xcept for the physicians who did the procedure, all other personnel, including the patients, the statistician doing the analyses, and the nurses who provided follow-up care for the patients, were masked to the type		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			of stent used. the primary endpoint of the trial was overall survival, which was defi ned as the time from stent insertion until death from any cause. Secondary endpoints included dysphagia score and frequency of complications and side-eff ects related to the stent insertion and technical success.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			We projected an enrolment period of 3 months, an entire trial period of 18 months, a twosided α-level test of 0·05 and 90% power, resulting in a minimum sample size of 152. We estimated that by 18 months, all data collection including overall survival coul d be completed. Including dropouts, we originally estimated a		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			sample size of 180 would be necessa		
Full citation Shi, D., Ji, F., Bao, Y. S., Liu, Y. P., A multicenter randomized controlled trial of malignant gastric outlet obstruction: Tailored partially covered stents (placed fluoroscopically) versus standard uncovered stents (placed endoscopically), Gastroenterology Research and Practice, 2014, no pagination, 2014 **Ref Id** 486639 **Country/ies where the study was carried out** China **Study type** A multicenter, randomized controlled trial	**Sample size** n=65; GOO-tailored group =33 vs control group = 32 **Characteristics** Age (mean) = 76 years Male = 35/65 Chemotherapy= 3/65 GOOSS (gastric outlet obstruction score) (mean) = 4.3 **Inclusion criteria** • decreased oral intake due to gastric outlet obstruction • obstruction due to primary distal stomach cancer • site of stenosis between the gastric body and duodenum bulb	**Interventions** GOO-tailored stent: shape of the GOO (cup-shaped, funnel-shaped) was determined by stomach opacification using contrast media in all patients. Stents were then designed accordingly. Both the middle and bottom of the proximal cup segment and a part of proximal funnel segment were covered by a polyetheylene membrane Standard uncovered stent were used in the control group. GOO-tailored stent were inserted by a peroral method	**Details** Randomisation using random number tables. Primary outcomes were the stent complications ingrowth/overgrowth and stent migration and secondary outcomes were the adverse events due to interventions.	**Results** Technical success:(accurate stent placement in the targeted lesion site) GOO: 96.9% Std: 96.9% Clinical success: (resolution of obstructive symptoms and the ability to restart a low residue diet after stent placement) GOO: 93.8% Std: 93.5% GOOSS change GOO: 3.2±0.5 Std: 3.1±0.4 Re-intervention rate using a standard uncovered stent GOO: 9.4% Std: 22.6% Bleeding GOO: 11/33 Std: 2/32 Survival days GOO: 231±23 days	**Limitations** **Cochrane risk of bias tool** Selection bias • random sequence generation: high risk • allocation concealment: unclear Performance bias • blinding: unclear Detection bias • blinding: unclear Attrition bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study To evaluate the 'outlet-shape' tailored stents in comparison with standard stents for relief of gastric outlet obstruction (GOO) **Study dates** May 2009 to March 2013 **Source of funding** Not reported	• patients with inoperable cancers **Exclusion criteria** • patients who can swallow a liquid diet • clinical evidence of perforation or peritonitis • evidence of multiple small bowel obstuctions because of peritoneal seeding • disease that can affect the intestinal motality • use of promotility agents	under fluoroscopic guidance where as the standard uncovered stents were placed by a thorough-the-scope method.		Std: 212±22 days	• outcome data complete: low risk Reporting bias • Outcomes mentioned in method session were reported. Overall assessment: High risk of bias due to inadequate reporting of allocation concealment and blinding **Other information**

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2

F.17 1 Curative treatment

2 **What is the effectiveness of nutritional support interventions for adults undergoing curative treatment for oesophago-gastric cancer?**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Bowrey, D. J., Baker, M., Halliday, V., Thomas, A. L., Pulikottil-Jacob, R., Smith, K., Morris, T., Ring, A., A randomised controlled trial of six weeks of home enteral nutrition versus standard care after oesophagectomy or total gastrectomy for cancer: report on a pilot and feasibility study, Trials [Electronic Resource]Trials, 16, 531, 2015 **Country/ies where the study was carried out** UK **Study type** RCT **Aim of the study**	**Sample size** 41 **Ref Id** 487185 **Characteristics** Oesophageal (66%) or gastric (34%) cancer	**Interventions** Continued nutritional support after discharge from hospital. Enteral feeds (50 % of energy and protein requirements) via jejunostomy at home N=20 Starting at discharge from hospital, for at least six weeks	**Details** Discontinuation of jejunostomy feeds (restarted only if deemed necessary) N=21	**Results** See Forest plots	**Limitations** Random sequence generation (selection bias)+ Allocation concealment (selection bias)+ Blinding of participants and personnel (performance bias) - Blinding of outcome assessment (detection bias) - Incomplete outcome data (attrition bias) ? Selective reporting (reporting bias) +

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
trial of continued nutritional support after discharge from hospital					KEY: + is low risk, - high risk, ? unclear risk
Full citation Marano, L., Porfidia, R., Pezzella, M., Grassia, M., Petrillo, M., Esposito, G., Braccio, B., Gallo, P., Boccardi, V., Cosenza, A., Izzo, G., Martino, N., Clinical and immunological impact of early postoperative enteral immunonutrition after total gastrectomy in gastric cancer patients: a prospective randomized study, Annals of Surgical OncologyAnn Surg Oncol, 20, 3912-8, 2013 **Country/ies where the study was carried out** Italy **Study type** RCT	**Sample size** 109 **Ref Id** 503886 **Characteristics** Gastric cancer	**Interventions** Arginine, Omega-3 fatty acids and RNA, N=54 versus Isocaloric, isonitrogenous N=55	**Details** Timing: POD 1-7 Approach: jejunostomy	**Results** See Forest plots	**Limitations** Random sequence generation (selection bias) ? Allocation concealment (selection bias) ? Blinding of participants and personnel (performance bias) ? Blinding of outcome assessment (detection bias) ? Incomplete outcome data (attrition bias) +

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study Trial comparing immunonutrition with standard nutrition in the perioperative period					Selective reporting (reporting bias) + KEY: + is low risk, - high risk, ? unclear risk
Full citation Ryan, A. M., Reynolds, J. V., Healy, L., Byrne, M., Moore, J., Brannelly, N., McHugh, A., McCormack, D., Flood, P., Enteral nutrition enriched with eicosapentaenoic acid (EPA) preserves lean body mass following esophageal cancer surgery: results of a double-blinded randomized controlled trial, Annals of SurgeryAnn Surg, 249, 355-63, 2009 **Country/ies where the study was carried out** Ireland **Study type**	**Sample size** 53 **Ref Id** 471700 **Characteristics** Oesophageal cancer	**Interventions** Omega-3 fatty acid, N=28 versus Isocaloric, isonitrogenous N=25	**Details** Timing: Preop 5 days, POD 1-21 Approach: Oral(preop), jejunostomy	**Results** See Forest plots	**Limitations** Random sequence generation (selection bias)+ Allocation concealment (selection bias) ? Blinding of participants and personnel (performance bias) + Blinding of outcome assessment (detection bias) +

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
RCT **Aim of the study** Trial comparing immunonutrition with standard nutrition in the perioperative period					Incomplete outcome data (attrition bias) + Selective reporting (reporting bias) + KEY: + is low risk, - high risk, ? unclear risk
Full citation Senkal, M., Kemen, M., Homann, H. H., Eickhoff, U., Baier, J., Zumtobel, V., Modulation of postoperative immune response by enteral nutrition with a diet enriched with arginine, RNA, and omega-3 fatty acids in patients with upper gastrointestinal cancer, The European journal of surgery = Acta chirurgica, 161, 115-22, 1995 **Country/ies where the study was carried out** Germany	**Sample size** 154 **Ref Id** 503890 **Characteristics** Oesophageal (19%), gastric (51%) and pancreatic (30%) cancer **Inclusion criteria**	**Interventions** Arginine, Omega-3 fatty acids and RNA, N=78 Isocaloric nutrition, N=76	**Details** Timing: POD 1-5 Approach: Jejunostomy	**Results** See Forest plots	**Limitations** Random sequence generation (selection bias)+ Allocation concealment (selection bias)? Blinding of participants and personnel (performance bias) +

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type RCT **Aim of the study** Trial comparing immunonutrition with standard nutrition in the perioperative period					Blinding of outcome assessment (detection bias) + Incomplete outcome data (attrition bias) ? Selective reporting (reporting bias) + KEY: + is low risk, - high risk, ? unclear risk
Full citation Cong, M. H., Li, S. L., Cheng, G. W., Liu, J. Y., Song, C. X., Deng, Y. B., Shang, W. H., Yang, D., Liu, X. H., Liu, W. W., Lu, S. Y., Yu, L., An interdisciplinary nutrition support team improves clinical and hospitalized outcomes of esophageal cancer patients with concurrent chemoradiotherapy, Chinese	**Sample size** 50 **Ref Id** 471598 **Characteristics** Oesophageal cancer	**Interventions** Nutrition support team: nutrition risk screening, nutrition assessment, nutrition intervention, nutrition monitoring, and evaluation via standardised clinical nutrition process. Versus	**Details** Nutritional support included diet counselling ONS, EN, and PN Timing: During chemo-radiotherapy, for 28 days	**Results** See Forest plots	**Limitations** Random sequence generation (selection bias) ? Allocation concealment (selection bias) ? Blinding of participants and

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Medical JournalChin Med J, 128, 3003-3007, 2015 **Country/ies where the study was carried out** China **Study type** RCT **Aim of the study** trial of additional nutritional support during chemotherapy or chemoradiotherapy		Nutrition supervised by radiotherapy team			personnel (performance bias) - Blinding of outcome assessment (detection bias) - Incomplete outcome data (attrition bias) ? Selective reporting (reporting bias) ? KEY: + is low risk, - high risk, ? unclear risk
Full citation Faber, J., Uitdehaag, M. J., Spaander, M., van Steenbergen-Langeveld, S., Vos, P., Berkhout, M., Lamers, C., Rumke, H., Tilanus, H., Siersema, P., van Helvoort, A., van der Gaast, A., Improved body weight and performance status and reduced serum PGE<inf>2</inf> levels after nutritional intervention with a	**Sample size** 49 **Ref Id** 504147 **Characteristics** Oesophageal or gastro-oesophageal junctional cancer	**Interventions** Energy dense nutritionally complete supplement (FortiCare), N=24 versus Placebo or isocaloric product if weight loss >5%, N=23	**Details** Timing: Starting soon after diagnosis and lasting 4 weeks	**Results** See Forest plots	**Limitations** Random sequence generation (selection bias)+ Allocation concealment (selection bias)?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
specific medical food in newly diagnosed patients with esophageal cancer or adenocarcinoma of the gastro-esophageal junction, Journal of Cachexia, Sarcopenia and Muscle, 32-44, 2015 **Country/ies where the study was carried out** Netherlands **Study type** RCT **Aim of the study** trial of oral nutrition supplements					Blinding of participants and personnel (performance bias) + Blinding of outcome assessment (detection bias) + Incomplete outcome data (attrition bias) ? Selective reporting (reporting bias) + KEY: + is low risk, - high risk, ? unclear risk
Full citation Gavazzi, C., Colatruglio, S., Valoriani, F., Mazzaferro, V., Sabbatini, A., Biffi, R., Mariani, L., Miceli, R., Impact of home enteral nutrition in malnourished patients	**Sample size** 79 **Ref Id** 477598	**Interventions** Home enteral nutrition versus counselling	**Details** In all patients, a fine needle catheter jejunostomy was implanted at the end of scheduled surgery.	**Results** See Forest plots	**Limitations** Random sequence generation (selection bias)+

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
with upper gastrointestinal cancer: A multicentre randomised clinical trial, European Journal of Cancer, 64, 107-112, 2016 **Country/ies where the study was carried out** Italy **Study type** RCT **Aim of the study** To compare home enteral nutrition with counselling in post-surgical patients with GI cancer. **Study dates** 2008-2011	**Characteristics** Upper GI cancer: oesphagus (17%), pancreas (12%), gastric (63%) and biliary tract (7%) **Inclusion criteria** Patients with upper GI cancer and candidates for major surgery with nutritional risk screening (NRS 2002) score of 3.		Enteral nutrition was started on post-operative day 1 and it was progressively increased, oral intake was allowed from post-operative day 2, and when it was regularly reassumed, enteral nutrition was reduced or stopped. In the home enteral nutritiion (HEN) group, enteral nutrition was planned to cover the basal energy and was administrated preferentially overnight as an integration of oral diet. HEN included any standard polymeric formula providing 1 - 1.5 kcal/ml with 50- 60% carbohydrates, 25 - 35% lipids and 12 - 20% proteins. HEN could be withdrawn after 2 months from discharge whenever a weight gain 5% was reported and oral diet		Allocation concealment (selection bias)? Blinding of participants and personnel (performance bias) - Blinding of outcome assessment (detection bias) - Incomplete outcome data (attrition bias) + Selective reporting (reporting bias) + KEY: + is low risk, - high risk, ? unclear risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			was regular and adequate. Before discharge, patients and/or caregivers were trained for the correct use of HEN, and all required materials were provided by the regional healthcare system. In the control group, specific nutritional indications including total energy and protein requirements were provided to patients by an experienced dietitian working with cancer patients; oral nutritional supplements could be prescribed as necessary. The same HEN protocol described above could be started in patients assigned to the control group, not before 2 months from discharge if a further weight loss 5% was reported.		

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Imamura, H., Nishikawa, K., Kishi, K., Inoue, K., Matsuyama, J., Akamaru, Y., Kimura, Y., Tamura, S., Kawabata, R., Kawada, J., Fujiwara, Y., Kawase, T., Fukui, J., Takagi, M., Takeno, A., Shimokawa, T., Effects of an Oral Elemental Nutritional Supplement on Post-gastrectomy Body Weight Loss in Gastric Cancer Patients: A Randomized Controlled Clinical Trial, Annals of Surgical OncologyAnn Surg Oncol, 23, 2928-2935, 2016 **Country/ies where the study was carried out** Japan **Study type** RCT **Aim of the study** trial of oral nutrition supplements	**Sample size** 110 **Ref Id** 485779 **Characteristics** Gastric cancer	**Interventions** Elemental diet supplement (Elental), N=53 versus Regular diet alone, N=47	**Details** Timing: Post gastrectomy, as soon as soft food was tolerated and lasting 6-8 weeks	**Results** See Forest plot	**Limitations** Random sequence generation (selection bias)+ Allocation concealment (selection bias)? Blinding of participants and personnel (performance bias) - Blinding of outcome assessment (detection bias) - Incomplete outcome data (attrition bias) + Selective reporting (reporting bias) + KEY: + is low risk, - high risk, ? unclear risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Lobo, D. N., Williams, R. N., Welch, N. T., Aloysius, M. M., Nunes, Q. M., Padmanabhan, J., Crowe, J. R., Iftikhar, S. Y., Parsons, S. L., Neal, K. R., Allison, S. P., Rowlands, B. J., Early postoperative jejunostomy feeding with an immune modulating diet in patients undergoing resectional surgery for upper gastrointestinal cancer: A prospective, randomized, controlled, double-blind study, Clinical NutritionClin Nutr, 25, 716-726, 2006 **Country/ies where the study was carried out** UK **Study type** RCT **Aim of the study**	**Sample size** 108 **Ref Id** 471658 **Characteristics** Oesophageal (59%), gastric (27%) and pancreatic (14%) cancer	**Interventions** Glutamine, Arginine (Stresson), N=54 versus Isocaloric, isonitrogenous (Nutrison high protein) N=54	**Details** timing: POD 10 to 14 Approach: jejunostomy	**Results** See Forest Plots	**Limitations** Random sequence generation (selection bias)? Allocation concealment (selection bias)+ Blinding of participants and personnel (performance bias) + Blinding of outcome assessment (detection bias) + Incomplete outcome data (attrition bias) + Selective reporting (reporting bias) +

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
trial comparing immunonutrition with standard nutrition in the perioperative period					KEY: + is low risk, - high risk, ? unclear risk
Full citation Swails, W. S., Babineau, T. J., Ellis, F. H., Kenler, A. S., Forse, R. A., The role of enteral jejunostomy feeding after esophagogastrectomy: A prospective, randomized study, Diseases of the Esophagus, 8, 193-199, 1995 **Country/ies where the study was carried out** USA **Study type** RCT **Aim of the study** trial comparing early enteral nutrition with no feeding after surgery	**Sample size** 25 **Ref Id** 479403 **Characteristics** Oesophageal cancer	**Interventions** Jejunostomy, N=13 versus No feeding, N=12	**Details** Duration of nutrition support - NR	**Results** See Forest plots	**Limitations** Random sequence generation (selection bias)? Allocation concealment (selection bias)? Blinding of participants and personnel (performance bias) ? Blinding of outcome assessment (detection bias) ? Incomplete outcome data (attrition bias) ?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					Selective reporting (reporting bias) ? KEY: + is low risk, - high risk, ? unclear risk
Full citation Takesue, T., Takeuchi, H., Ogura, M., Fukuda, K., Nakamura, R., Takahashi, T., Wada, N., Kawakubo, H., Kitagawa, Y., A Prospective Randomized Trial of Enteral Nutrition After Thoracoscopic Esophagectomy for Esophageal Cancer, Annals of Surgical OncologyAnn Surg Oncol, 22 Suppl 3, S802-9, 2015 **Country/ies where the study was carried out** Japan **Study type** RCT **Aim of the study**	**Sample size** 27 **Ref Id** 471719 **Characteristics** Oesophageal cancer **Inclusion criteria**	**Interventions** Jejunostomy, N=24 versus Central vein PN, N=23	**Details** Duration of nutrition support: POD 1-7	**Results** See Forest plots	**Limitations** Random sequence generation (selection bias)? Allocation concealment (selection bias)? Blinding of participants and personnel (performance bias) - Blinding of outcome assessment (detection bias) -

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Trial comparing early enteral nutrition with parenteral nutrition after surgery					Incomplete outcome data (attrition bias) ? Selective reporting (reporting bias) ? KEY: + is low risk, - high risk, ? unclear risk
Full citation Wei, Z., Wang, W., Chen, J., Yang, D., Yan, R., Cai, Q., A prospective, randomized, controlled study of omega-3 fish oil fat emulsion-based parenteral nutrition for patients following surgical resection of gastric tumors, Nutrition JournalNutr J, 13, 25, 2014 **Country/ies where the study was carried out** China **Study type**	**Sample size** 52 **Ref Id** 479723 **Characteristics** Gastric cancer **Inclusion criteria**	**Interventions** Peripheral or central vein PN Omega-3 fatty acid supplemented PN, N=26 versus Standard PN, N=26	**Details** Timing:POD 1-6 Approach: Peripheral or central vein PN	**Results** See Forest plots	**Limitations** Random sequence generation (selection bias)? Allocation concealment (selection bias)- Blinding of participants and personnel (performance bias) ?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
RCT **Aim of the study** trial comparing immunonutrition with standard nutrition in the perioperative period					Blinding of outcome assessment (detection bias) ? Incomplete outcome data (attrition bias) ? Selective reporting (reporting bias) ? KEY: + is low risk, - high risk, ? unclear risk
Full citation Yildiz, S. Y., Yazicioglu, M. B., Tiryaki, C., Ciftci, A., Boyacioglu, Z., Ozyildiz, M., Coskun, M., Subasi, O., The effect of enteral immunonutrition in upper gastrointestinal surgery for cancer: A prospective study, Turkish Journal of Medical Sciences, 46, 393, 2016	**Sample size** 41 **Ref Id** 471741 **Characteristics** Oesophageal (24%), gastric (59%) and pancreatic (17%) cancer	**Interventions** HMB, Arginine and Glutamine + high protein, N=21 versus Standard EN, N=20	**Details** Timing: Preop 7 days, POD 1-7 Approach: Oral (preop), nasojejunal tube	**Results** See Forest plots	**Limitations** Random sequence generation (selection bias)? Allocation concealment (selection bias)? Blinding of participants and

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out Turkey **Study type** RCT **Aim of the study** trial comparing immunonutrition with standard nutrition in the perioperative period	**Inclusion criteria**				personnel (performance bias) + Blinding of outcome assessment (detection bias) ? Incomplete outcome data (attrition bias) ? Selective reporting (reporting bias) ? KEY: + is low risk, - high risk, ? unclear risk
Full citation Barlow, R., Price, P., Reid, T. D., Hunt, S., Clark, G. W., Havard, T. J., Puntis, M. C., Lewis, W. G., Prospective multicentre randomised controlled trial of early enteral nutrition for patients undergoing major upper gastrointestinal surgical resection,	**Sample size** 111 **Ref Id** 471580 **Characteristics**	**Interventions** Jejunostomy, N=64 versus IV fluids, N=57	**Details** Timing & duration: POD 1-12	**Results** See Forest plot	**Limitations** Random sequence generation (selection bias)+ Allocation concealment (selection bias)+

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Clinical NutritionClin Nutr, 30, 560-6, 2011 **Country/ies where the study was carried out** UK **Study type** RCT **Aim of the study** Trials comparing early enteral nutrition with IV fluids after surgery.	Oesophageal (45%), gastric (31%) or pancreatic cancer (24%)				Blinding of participants and personnel (performance bias) - Blinding of outcome assessment (detection bias) - Incomplete outcome data (attrition bias) + Selective reporting (reporting bias) + KEY: + is low risk, - high risk, ? unclear risk
Full citation Farreras, N., Artigas, V., Cardona, D., Rius, X., Trias, M., Gonzalez, J. A., Effect of early postoperative enteral immunonutrition on wound	**Sample size** 60 **Ref Id** 471608	**Interventions** Arginine, Omega-3 fatty acids and RNA, N=30 versus Isocaloric, isonitrogenous N=30	**Details** Timing and duration: POD 1-7	**Results** See Forest plot	**Limitations** Random sequence generation (selection bias)+

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
healing in patients undergoing surgery for gastric cancer, Clinical NutritionClin Nutr, 24, 55-65, 2005 **Country/ies where the study was carried out** Spain **Study type** RCT **Aim of the study** trial comparing immunonutrition with standard nutrition in the perioperative period	**Characteristics** Gastric cancer				Allocation concealment (selection bias)? Blinding of participants and personnel (performance bias) + Blinding of outcome assessment (detection bias) + Incomplete outcome data (attrition bias) + Selective reporting (reporting bias) + KEY: + is low risk, - high risk, ? unclear risk
Full citation	**Sample size** 164	**Interventions**	**Details**	**Results**	**Limitations**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Fujita, T., Daiko, H., Nishimura, M., Early enteral nutrition reduces the rate of life-threatening complications after thoracic esophagectomy in patients with esophageal cancer, European surgical research. Europäische chirurgische Forschung. Recherches chirurgicales européennes, 48, 79-84, 2012 **Country/ies where the study was carried out** Japan **Study type** RCT **Aim of the study** To comparie early enteral nutrition with parenteral nutrition after surgery	**Ref Id** 471611 **Characteristics** Oesophageal cancer	Nasojejunal feeding tube, N=76 versus Peripheral vein PN, N=88	Duration of nutrition support: POD 1-6	See Forest plots	Random sequence generation (selection bias)? Allocation concealment (selection bias)? Blinding of participants and personnel (performance bias) ? Blinding of outcome assessment (detection bias) ? Incomplete outcome data (attrition bias) ? Selective reporting (reporting bias) ? KEY: + is low risk, - high risk, ? unclear risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					Other information This was a retrospective study, where patients were 'randomly assigned' to EN or PN with not description on how this was done. No details are given on the PN intervention, except that the 'liquid balance' was managed through a peripheral line. Likely that they were given IV fluid, not PN as stated in the paper.
Full citation	**Sample size** 60	**Interventions**	**Details**	**Results**	**Limitations**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Fujitani, K., Tsujinaka, T., Fujita, J., Miyashiro, I., Imamura, H., Kimura, Y., Kobayashi, K., Kurokawa, Y., Shimokawa, T., Furukawa, H., Osaka Gastrointestinal Cancer Chemotherapy Study, Group, Prospective randomized trial of preoperative enteral immunonutrition followed by elective total gastrectomy for gastric cancer, British Journal of SurgeryBr J Surg, 99, 621-9, 2012 **Country/ies where the study was carried out** Japan **Study type** RCT **Aim of the study** trial comparing immunonutrition with standard nutrition in the perioperative period	**Ref Id** 471612 **Characteristics** Gastric cancer	Arginine, Omega-3 fatty acids and RNA, N=30 versus Isocaloric, isonitrogenous N=30	Timing and duration: Preop 5 days Nutrition approach: oral	See Forest Plots	Random sequence generation (selection bias)+ Allocation concealment (selection bias)+ Blinding of participants and personnel (performance bias) + Blinding of outcome assessment (detection bias) ? Incomplete outcome data (attrition bias) + Selective reporting (reporting bias) + KEY: + is low risk, - high risk, ? unclear risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Liu, H., Ling, W., Shen, Z. Y., Jin, X., Cao, H., Clinical application of immune-enhanced enteral nutrition in patients with advanced gastric cancer after total gastrectomy, Journal of Digestive DiseasesJ Dig Dis, 13, 401-6, 2012 **Country/ies where the study was carried out** China **Study type** RCT **Aim of the study** Trial comparing immunonutrition with standard nutrition in the perioperative period	**Sample size** 42 **Ref Id** 471652 **Characteristics** Gastric cancer	**Interventions** Glutamine, Arginine, N=28 versus Standard EN, N=24	**Details** Timing: POD 1-7 Approach: nasojejunal tube	**Results** See forest plots	**Limitations** Random sequence generation (selection bias)+ Allocation concealment (selection bias)? Blinding of participants and personnel (performance bias) ? Blinding of outcome assessment (detection bias) + Incomplete outcome data (attrition bias) + Selective reporting (reporting bias) + KEY: + is low risk, - high risk, ? unclear risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Miyata, H., Yano, M., Yasuda, T., Hamano, R., Yamasaki, M., Hou, E., Motoori, M., Shiraishi, O., Tanaka, K., Mori, M., Doki, Y., Randomized study of clinical effect of enteral nutrition support during neoadjuvant chemotherapy on chemotherapy-related toxicity in patients with esophageal cancer, Clinical NutritionClin Nutr, 31, 330-6, 2012 **Country/ies where the study was carried out** Japan **Study type** RCT **Aim of the study** trial of additional nutritional support during chemotherapy or chemoradiotherapy	**Sample size** 91 **Ref Id** 471673 **Characteristics** Oesophageal cancer	**Interventions** Omega-3 fatty acid rich enteral supplement plus parenteral nutrition, N=47 versus Parenteral nutrition only, N=44	**Details** Timing: During chemotherapy for 14 days Approach: Oral, or transnasal tube	**Results** See Forest plots	**Limitations** Random sequence generation (selection bias)+ Allocation concealment (selection bias)? Blinding of participants and personnel (performance bias) - Blinding of outcome assessment (detection bias) - Incomplete outcome data (attrition bias) + Selective reporting (reporting bias) + KEY: + is low risk, - high risk, ? unclear risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Okamoto, Y., Okano, K., Izuishi, K., Usuki, H., Wakabayashi, H., Suzuki, Y., Attenuation of the systemic inflammatory response and infectious complications after gastrectomy with preoperative oral arginine and omega-3 fatty acids supplemented immunonutrition, World Journal of SurgeryWorld J Surg, 33, 1815-21, 2009 **Country/ies where the study was carried out** Japan **Study type** RCT **Aim of the study** trial comparing immunonutrition with standard nutrition in the perioperative period	**Sample size** 44 **Ref Id** 471683 **Characteristics** Gastric cancer	**Interventions** Arginine, Omega-3 fatty acids and RNA, N=30 versus Isocaloric, N=14	**Details** Timing: Preop 7 days Approach: oral	**Results** See Forest plots	**Limitations** Random sequence generation (selection bias)+ Allocation concealment (selection bias)? Blinding of participants and personnel (performance bias) ? Blinding of outcome assessment (detection bias) ? Incomplete outcome data (attrition bias) + Selective reporting (reporting bias) +

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					KEY: + is low risk, - high risk, ? unclear risk
Full citation Page, R. D., Oo, A. Y., Russell, G. N., Pennefather, S. H., Intravenous hydration versus naso-jejunal enteral feeding after esophagectomy: a randomised study, European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery, 22, 666-72, 2002 **Country/ies where the study was carried out** UK **Study type** RCT **Aim of the study**	**Sample size** 40 **Ref Id** 471686 **Characteristics** Oesophageal cancer	**Interventions** Nasojejunal feeding tube, N=20 versus IV support, N=20	**Details** Duration of nutrition support: POD 1-6	**Results** See Forest plots	**Limitations** Random sequence generation (selection bias) ? Allocation concealment (selection bias) + Blinding of participants and personnel (performance bias) ? Blinding of outcome assessment (detection bias) ? Incomplete outcome data (attrition bias) +

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
trial comparing early enteral nutrition with IV fluids after surgery					Selective reporting (reporting bias) + KEY: + is low risk, - high risk, ? unclear risk
Full citation Rajabi Mashhadi, M. T., Bagheri, R., Ghayour-Mobarhan, M., Zilaee, M., Rezaei, R., Maddah, G., Majidi, M. R., Bahadornia, M., Early Post Operative Enteral Versus Parenteral Feeding after Esophageal Cancer Surgery, Iranian journal of otorhinolaryngologyIran, 27, 331-6, 2015 **Country/ies where the study was carried out** Iran **Study type** Trial comparing early enteral nutrition with parenteral nutrition after surgery	**Sample size** 40 **Ref Id** 471697 **Characteristics** Oesophageal cancer	**Interventions** Jejunostomy, N=20 versus PN, N=20	**Details** Duration of nutrition support: POD 1-7	**Results** See Forest plots	**Limitations** Random sequence generation (selection bias)+ Allocation concealment (selection bias)? Blinding of participants and personnel (performance bias) - Blinding of outcome assessment (detection bias) -

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study trial comparing early enteral nutrition with parenteral nutrition after surgery					Incomplete outcome data (attrition bias) ? Selective reporting (reporting bias) + KEY: + is low risk, - high risk, ? unclear risk
Full citation Sakurai, Y., Masui, T., Yoshida, I., Tonomura, S., Shoji, M., Nakamura, Y., Isogaki, J., Uyama, I., Komori, Y., Ochiai, M., Randomized clinical trial of the effects of perioperative use of immune-enhancing enteral formula on metabolic and immunological status in patients undergoing esophagectomy, World Journal of SurgeryWorld J Surg, 31, 2150-7; discussion 2158-9, 2007 **Country/ies where the study was carried out** Japan	**Sample size** 30 **Ref Id** 471703 **Characteristics** **Inclusion criteria**	**Interventions** Arginine, Omega-3 fatty acids and RNA, N=16 versus Isocaloric, N=14	**Details** Timing: Preop 3 days, POD 14 Approach: Oral (preop), jejunostomy	**Results** See Forest plots	**Limitations** Random sequence generation (selection bias)+ Allocation concealment (selection bias)? Blinding of participants and personnel (performance bias) - Blinding of outcome

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type RCT **Aim of the study** trial comparing immunonutrition with standard nutrition in the perioperative period					assessment (detection bias) - Incomplete outcome data (attrition bias) ? Selective reporting (reporting bias) + KEY: + is low risk, - high risk, ? unclear risk
Full citation Sand, J., Luostarinen, M., Matikainen, M., Enteral or parenteral feeding after total gastrectomy: prospective randomised pilot study, European Journal of SurgeryEur J Surg, 163, 761-6, 1997 **Country/ies where the study was carried out** Finland **Study type** RCT	**Sample size** 29 **Ref Id** 505919 **Characteristics** Gastric cancer	**Interventions** Nasojejunal feeding tube, N=13 versus PN, N=16	**Details** Duration of nutrition support: NR	**Results** See Forest plots	**Limitations** Random sequence generation (selection bias)? Allocation concealment (selection bias)? Blinding of participants and personnel (performance bias) ?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study Trial comparing early enteral nutrition with IV fluids after surgery					Blinding of outcome assessment (detection bias) ? Incomplete outcome data (attrition bias) ? Selective reporting (reporting bias) ? KEY: + is low risk, - high risk, ? unclear risk
Full citation Sultan, J., Griffin, S. M., Di Franco, F., Kirby, J. A., Shenton, B. K., Seal, C. J., Davis, P., Viswanath, Y. K., Preston, S. R., Hayes, N., Randomized clinical trial of omega-3 fatty acid-supplemented enteral nutrition versus standard enteral nutrition in patients undergoing oesophagogastric cancer surgery,	**Sample size** 129 **Ref Id** 471715 **Characteristics** Gastric cancer	**Interventions** Omega-3 fatty acid supplemented EN, N=66 Standard EN (Osmolite), N=63	**Details** Timing: Preop 7 days, POD 1-7 Approach: Oral (preop), jejunostomy or nasojejunal tube	**Results** See Forest plots	**Limitations** Random sequence generation (selection bias)+ Allocation concealment (selection bias)? Blinding of participants and personnel (performance

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
British Journal of SurgeryBr J Surg, 99, 346-55, 2012 **Country/ies where the study was carried out** UK **Study type** RCT **Aim of the study** trial comparing immunonutrition with standard nutrition in the perioperative period					bias) + Blinding of outcome assessment (detection bias) + Incomplete outcome data (attrition bias) + Selective reporting (reporting bias) + KEY: + is low risk, - high risk, ? unclear risk
Full citation Sunpaweravong, S., Puttawibul, P., Ruangsin, S., Laohawiriyakamol, S., Sunpaweravong, P., Sangthawan, D., Pradutkanchana, J., Raungkhajorn, P., Geater, A., Randomized study of antiinflammatory and immune-modulatory effects of enteral	**Sample size** 71 **Ref Id** 471718 **Characteristics** Oesophageal cancer	**Interventions** Arginine, glutamine and Omega-3 fatty acid EN, N=35 versus isocaloric and isonitrogenous EN, N=36	**Details** Timing: During chemo-radiotherapy for 28 days Approach: Percutaneous endoscopic gastrostomy	**Results** See Forest plots	**Limitations** Random sequence generation (selection bias)? Allocation concealment (selection bias)? Blinding of participants and

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
immunonutrition during concurrent chemoradiotherapy for esophageal cancer, Nutrition and Cancer, 66, 1-5, 2014 **Country/ies where the study was carried out** Thailand **Study type** RCT **Aim of the study** trial of additional nutritional support during chemotherapy or chemoradiotherapy					personnel (performance bias) ? Blinding of outcome assessment (detection bias) ? Incomplete outcome data (attrition bias) ? Selective reporting (reporting bias) ? KEY: + is low risk, - high risk, ? unclear risk
Full citation Carey, S., Ferrie, S., Ryan, R., Beaton, J., Young, J., Allman-Farinelli, M., Long-term nutrition intervention following major upper gastrointestinal surgery: a prospective randomized controlled trial, European Journal of Clinical Nutrition, 67, 324-329, 2013	**Sample size** 27 **Ref Id** 506231 **Characteristics** Oesophageal (37%), gastric (37%) or pancreatic (26%) cancer	**Interventions** Regular phone review by the clinical dietitian on a fortnightly basis for the following 6 months, and face-to-face follow-up if needed, N=14 versus No dietician follow-up, N=13	**Details** Timing: Starting at discharge from hospital, for six months	**Results** See Forest plots	**Limitations** Random sequence generation (selection bias)+ Allocation concealment (selection bias)?

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out Australia **Study type** RCT **Aim of the study** trial of continued dietitian follow up after discharge from hospital					Blinding of participants and personnel (performance bias) - Blinding of outcome assessment (detection bias) - Incomplete outcome data (attrition bias) + Selective reporting (reporting bias) + KEY: + is low risk, - high risk, ? unclear risk
Full citation Froghi, F, Sanders, G, Berrisford, R, Wheatley, T, Peyser, P, Rahamim, J, Lewis, S, A randomised trial of post-discharge enteral feeding following surgical resection of an upper gastrointestinal malignancy,	**Sample size** 41 **Ref Id** 590268 **Characteristics**	**Interventions** Enteral feeds (600 kcal/day) via jejunostomy,N=20 versus Discontinuation of jejunostomy feeds (restarted only if	**Details** Timing: starting at discharge from hospital, for six weeks	**Results** See Forest plots	**Limitations** Random sequence generation (selection bias)+

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Clinical nutrition. (no pagination), 2016, Date of Publication: September 12, 2017 **Country/ies where the study was carried out** UK **Study type** RCT **Aim of the study** trial of continued nutrition support via jejunostomy after discharge from hospital	Oesophageal (73%) or gastric (27%) cancer	deemed necessary) N=21			Allocation concealment (selection bias)? Blinding of participants and personnel (performance bias) - Blinding of outcome assessment (detection bias) - Incomplete outcome data (attrition bias) + Selective reporting (reporting bias) + KEY: + is low risk, - high risk, ? unclear risk
Full citation	**Sample size**	**Interventions**	**Details**	**Results**	**Limitations**
Miyata, H., Yano, M., Yasuda, T., Yamasaki, M., Murakami, K., Makino, T., Nishiki, K., Sugimura,	61 **Ref Id**	Omega-3 fatty acid rich enteral supplement plus	Timing: During chemotherapy for 12 days	See Forest plots	Random sequence

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
K., Motoori, M., Shiraishi, O., Mori, M., Doki, Y., Randomized study of the clinical effects of omega-3 fatty acid-containing enteral nutrition support during neoadjuvant chemotherapy on chemotherapy-related toxicity in patients with esophageal cancer, Nutrition, 33, 204-210, 2017 **Country/ies where the study was carried out** Japan **Study type** RCT **Aim of the study** trial of additional nutritional support during chemotherapy or chemoradiotherapy	589185 **Characteristics** Oesophageal cancer	parenteral nutrition N=31 versus Omega-3 fatty acid poor enteral supplement plus parenteral nutrition, N=30	Approach: Oral or transnasal tube		generation (selection bias)+ Allocation concealment (selection bias)? Blinding of participants and personnel (performance bias) - Blinding of outcome assessment (detection bias) - Incomplete outcome data (attrition bias) + Selective reporting (reporting bias) + KEY: + is low risk, - high risk, ? unclear risk
Full citation	**Sample size** 20	**Interventions**	**Details**	**Results**	**Limitations**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Okada, T., Nakajima, Y., Nishikage, T., Ryotokuji, T., Miyawaki, Y., Hoshino, A., Tokairin, Y., Kawada, K., Nagai, K., Kawano, T., A prospective study of nutritional supplementation for preventing oral mucositis in cancer patients receiving chemotherapy, Asia Pacific Journal of Clinical NutritionAsia Pac J Clin Nutr, 26, 42-48, 2017 **Country/ies where the study was carried out** Japan **Study type** RCT **Aim of the study** trial of additional nutritional support during chemotherapy or chemoradiotherapy	**Ref Id** 589802 **Characteristics** Oesophageal cancer	Elemental diet supplement (Elental), N=10 versus Regular diet, N=10	Timing:During chemotherapy for 14 days Approach: Oral	See Forest plots	Random sequence generation (selection bias)? Allocation concealment (selection bias)? Blinding of participants and personnel (performance bias) - Blinding of outcome assessment (detection bias) - Incomplete outcome data (attrition bias) ? Selective reporting (reporting bias) ? KEY: + is low risk, - high risk, ? unclear risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Ida, S., Hiki, N., Cho, H., Sakamaki, K., Ito, S., Fujitani, K., Takiguchi, N., Kawashima, Y., Nishikawa, K., Sasako, M., Aoyama, T., Honda, M., Sato, T., Nunobe, S., Yoshikawa, T., Randomized clinical trial comparing standard diet with perioperative oral immunonutrition in total gastrectomy for gastric cancer, British Journal of SurgeryBr J Surg, 104, 377-383, 2017 **Country/ies where the study was carried out** Japan **Study type** RCT **Aim of the study** To evaluate whether perioperative administration of an eicosapentaenoic acid-enriched supplement can prevent	**Sample size** 123 **Ref Id** 618297 **Characteristics** gastric cancer: stage I (40%), stage II (32%), stage III (28%) age median 65 years (range 30 to 80 years) **Inclusion criteria** Histologically proven adenocarcinoma of the stomach; clinical T1–T4a and M0 disease; R0 resection possible by total gastrectomy; sufficient oral intake; adequate organ function; and age ranging between 20 and 80 years.	**Interventions** Immunonutirion: standard diet plus eicosapentaenoic acid (ProSure; N=63) versus standard diet (N=60)	**Details** Timing: 7 days before and 21 days after surgery Approach: oral	**Results** See Forest plots	**Limitations** Random sequence generation (selection bias)+ Allocation concealment (selection bias)? Blinding of participants and personnel (performance bias) - Blinding of outcome assessment (detection bias) - Incomplete outcome data (attrition bias) + Selective reporting (reporting bias) + KEY: + is low risk, - high risk, ? unclear risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
bodyweight loss after total gastrectomy for gastric cancer. **Study dates** 2011 - 2014					
Full citation Klek, S., Scislo, L., Walewska, E., Choruz, R., Galas, A., Enriched enteral nutrition may improve short-term survival in stage IV gastric cancer patients: A randomized, controlled trial, NutritionNutrition, 36, 46-53, 2017 **Country/ies where the study was carried out** Poland **Study type** RCT **Aim of the study** To determine whether the postoperative use of enteral nutrition enriched with arginine,	**Sample size** 145. 99 included in ITT analysis **Ref Id** 618298 **Characteristics** Gastric cancer: stage I (8%), stage II (22%), stage III (23%), stage IV (46%) Age 33 to 80 years (median 65) **Inclusion criteria**	**Interventions** Immunonutrition (Reconvan; N=76) versus standard nutrition (Peptisorb; N=69)	**Details** Timing: POD 1 to 7 Approach: enteral tube (not specified)	**Results** Overall survival reported (follow up 5 years in survivors) See Forest plots	**Limitations** Random sequence generation (selection bias)+ Allocation concealment (selection bias)+ Blinding of participants and personnel (performance bias) + Blinding of outcome assessment (detection bias) +

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
glutamine, and omega-3 fatty acids influences survival in patients diagnosed with stomach cancer. **Study dates** 2003 to 2009	Patients with stomach who were malnourished, as defined by unintentional weight loss of at least 10% or body mass index (BMI) less than 18 kg/m 2, being referred for surgical resection; BMI of at least 17 kg/m 2 ; serum albumin concentration of at least 2.5 g/dL; and total lymphocyte count of at least 1200 cells/mm 3 .				Incomplete outcome data (attrition bias) - Selective reporting (reporting bias) + KEY: + is low risk, - high risk, ? unclear risk

1

2

F.183 Palliative care

4 **What is the effectiveness of nutritional interventions in adults with oesophago-gastric cancer receiving palliative care?**

5 No evidence was available for this review.

F.191 Routine follow-up

2 **In adults who have undergone treatment for oesophago-gastric cancer with curative intent, with no symptoms or evidence of residual**
3 **disease, what is the optimal method(s), frequency, and duration of routine follow-up for the detection of concurrent disease?**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Full citation Hahn, Kyu Yeon, Park, Jun Chul, Kim, Eun Hye, Shin, Suji, Park, Chan Hyuk, Chung, Hyunsoo, Shin, Sung Kwan, Lee, Sang Kil, Lee, Yong Chan, Incidence and impact of scheduled endoscopic surveillance on recurrence after curative endoscopic resection for early gastric cancer,	**Sample size** N=1347 **Characteristics** Mean age approx. 62 years Approx. 75% male The mean follow-up period after ESD was 32.12 months (interquartile range, 14.60-44.73). **Inclusion Criteria** Patients with initial-onset gastric cancers who met expanded indications for ESD underwent gastric ESD at Severance Hospital	**Tests** N/A	**Methods** Treatment Course All ESDs were performed by 5 experienced endoscopists with a standard single-channel endoscope (GIF-Q260J or GIF-H260Z; Olympus, Tokyo, Japan). All patients were under moderate sedation (modified observer assessment of alertness/sedation at 2 to w3, responds only after mild prodding or shaking or responds only after name is called loudly and/or repeatedly) that was achieved with intravenous midazolam and/or propofol. After identifying the target lesion, dots were marked circumferentially at about 5-mm lateral to the margin of the lesion using a needleknife (KD-10Q; Olympus) or argon plasma coagulation (Erbe Elektromedizin, Tübingen, Germany). Epinephrine (1:10,000 dilution) was then injected into the submucosal layer using a 21-gauge needle to lift the lesion from the muscle layer. Finally, direct dissection of the submucosal layer was performed	**Results** Overall recurrence rate 141/ 1347 39= recurrence at ESD site 102= synchronous or metachronous lesions During the 60-month surveillance period, the annual incidence was .84% for recurrence at a previous ESD site and 2.48% for recurrence in the stomach other than at the ESD site Overall survival 5-year Recurrent group: 94.0% Non-recurrent group: 91.5% Disease-free survival 5-year Recurrent group: 100% Non-recurrent group: 98.2%	**Limitations** 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results Yes 1.2 Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias Yes 1.3 The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias Yes 1.4 The outcome of interest is adequately measured in study participants, sufficient to limit potential bias Yes 1.5 Important potential confounders are appropriately

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Gastrointestinal Endoscopy Gastrointest Endosc, 84, 628-638.e1, 2016 **Ref Id** 512547 **Country/ies where the study was carried out** Korea **Study type** Retrospective cohort study **Aim of the study** The aim of this study was to identify the incidence of recurrent lesions after endoscopic	**Exclusion Criteria** 148 patients who underwent noncurative resection and 43 patients who never underwent follow-up endoscopy were excluded from this study		using an insulated-tip knife (IT knife, KD-610L; Olympus). Endoscopic hemostasis with specialized hemostatic forceps (FD-410LR; Olympus) was performed as needed. Follow-up Protocol Patients underwent an EGD with or without biopsy sampling at 3, 6, 12, 18, and 24 months after ESD for detecting residual or recurrent tumors. After 24 months of surveillance EGD was performed every 12 months. A biopsy was performed to exclude the presence of a recurrent tumor at the endoscopist's discretion. Abdomen CT was performed every 6 months for the first year or second year and annually thereafter to detect lymph node metastasis or distant metastasis.		accounted for, limiting potential bias with respect to the prognostic factor of interest Yes 1.6 The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results Yes **Other information**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
submucosal dissection (ESD) and to determine whether scheduled endoscopic surveillance might control their development and treatment. **Study dates** 2007-2014 **Source of funding** Not reported					
Full citation Cazin, J. L., Gambier, L., Gosselin, P.,	**Sample size** N=38 **Characteristics** 17 women, 21 men	**Tests** Index test: Serum samples Venous blood was drawn by venipuncture 1 week prior to surgery and then 3, 7 and 14 days after gastrectomy and every 3	**Methods** **Follow-up process** The clinical evaluation was done every. 3 months during the first 2 years and every 6 months thereafter, until the fifth year, with alternating echographic and scanning investigations.	**Results** **CEA marker** PD or R: NED or NEP: Total	**Limitations** QUADAS-2 a quality assessment tool for diagnostic accuracy studies: Overall quality: high risk of bias. **Patient Selection**

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>Boniface, B., Cornillie, F., Quandalle, P., Diagnostic, prognostic and monitoring value of CA 72.4 in gastric cancer. A prospective study including CA 19.9 and CEA, Immuno-Analyse et Biologie Specialisee, 13, 141-150, 1998

Ref Id

512737

Country/ies where the study was carried out

France

Study type</td>
<td>Mean age= 59 (range 31-78)
Gastric carcinoma
Radical surgery= 21; palliative surgery= 17; cryoreductive surgery + chemotherapy= 12

Inclusion Criteria
with clinical diagnosis of localized or metastatic, histologically confirmed primary gastric carcinoma were consecutively enrolled into this prospective two-year study.

Exclusion Criteria
Patients with neoadjuvant treatment, with concurrent malignancy or a previous history of malignancy or without adequate serial serum sampling during the follow-up were excluded.</td>
<td>months during clinical follow-up. All sera were promptly separated, aliquotted and stored frozen at -80 °C. Samples were thawed only at the time of assay.
Radioimmunoassays
A total of 821 determinations of tumour markers were performed, according to the manufacturer's instructions. Serum levels of CA 72.4 were determined using the Centocor (Malvern, PA, USA) CA 72.4 IRMA kit, a forward sandwich solid phase radioimmunoassay. Signal detection was done with t
Reference test:
Clinical outcome</td>
<td>Antigen cut-off levels
The cut-offlevel resulting in 95 % tumour specificity, allo- wing the comparison of the three antigens under the same conditions, were, according to the classical method, 29.4 U mL -1 for CA 19.9 and 10.6 U mL -1 for CEA.</td>
<td>
<table>
<tr><td>CEA +</td><td>6</td><td>2</td><td></td></tr>
<tr><td>CEA -</td><td>5</td><td>13</td><td></td></tr>
<tr><td>Total</td><td></td><td></td><td>26</td></tr>
</table>
PD= progressive disease; R= recurrence; NED= no evidence of disease; NEP= no evidence of progression
Unclear why follow-up only includes 26 patients
Diagnostic test results calculated by NGA technical team:
Sensitivity (95% CI)= 54.55 (23.38- 83.25)
Specificity (95% CI)= 86.67 (59.54- 98.34)
Positive likelihood ratio= 4.09 (1.01- 16.56)
Negative likelihood ratio= 0.52 (0.27-1.03)
Positive predictive value= 75.00 (42.56 - 92.39)
Negative predictive value= 72.22 (56.92 - 83.65)

CA 19-9 marker
<table>
<tr><td></td><td>PD or R</td><td>NED or NEP</td><td>Total</td></tr>
<tr><td>C19-9 +</td><td>5</td><td>4</td><td></td></tr>
<tr><td>C19-9 -</td><td>6</td><td>11</td><td></td></tr>
<tr><td>Total</td><td></td><td></td><td>26</td></tr>
</table>
</td>
<td>A. Risk of Bias
Was a consecutive or random sample of patients enrolled? Yes.
Was a case-control design avoided? Yes.
Did the study avoid inappropriate exclusions? Unclear (inclusion criteria not well defined)
Could the selection of patients have introduced bias? Unclear risk.
B. Concerns regarding applicability:
Are there concerns that the included patients and setting do not match the review question? Low concern.
Index Test
A. Risk of Bias
Were the index test results interpreted without knowledge of the results of the reference standard? Yes.
If a threshold was used, was it pre-specified?
Yes. (Diagnostic criteria was defined.)
Could the conduct or interpretation of the index test have</td>
</tr>
</table>

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Prospective cohort study **Aim of the study** The diagnostic, prognostic and monitoring value of CA 72.4 in gastric cancer was prospectively studied, in parallel with CA 19.9 and CEA. **Study dates** NR **Source of funding** This work was supported by the Comitd du Nord and the comitd du Pas-de-				Diagnostic test results calculated by NGA technical team: Sensitivity (95% CI)= 45.45 (16.75-76.62) Specificity (95% CI)= 73.33 (44.90- 92.21) Positive likelihood ratio= 1.70 (0.59- 4.92) Negative likelihood ratio= 0.74 (0.40- 1.38) Positive predictive value= 55.56 (30.22- 78.30) Negative predictive value= 64.71 (49.66- 77.31) **Patient Anxiety** Not reported	introduced bias? Low risk. B. Concerns regarding applicability: Are there concerns that the index test, its conduct, or interpretation differ from the review question? Low concern. **Reference Standard** A. Risk of Bias Is the reference standards likely to correctly classify the target condition? Yes. Were the reference standard results interpreted without knowledge of the results of the index tests? Yes. Clinical outcome recorded blinded to tumour assays. Could the reference standard, its conduct, or its interpretation have introduced bias? Low risk. B. Concerns regarding applicability Are there concerns that the target condition as defined by the reference standard does not match the

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Calais de la Ligue nationale franqaise contre le cancer.					question? Low concern. **Flow and Timing** A. Risk of Bias Was there an appropriate interval between index test and reference standard? Unclear Did all patients receive the same reference standard? No- clinical follow-up as needed Were all patients included in the analysis? No- 12 patients missing from follow-up data (reasons for loss of follow-up not reported) Could the patient flow have introduced bias? High risk. **Other information**
Full citation D'Angelica, M., Gonen, M., Brennan, M. F., Turnbull, A.	**Sample size** N= 1172 **Characteristics** Median age= 62 (range 21-92) 70% male	**Tests** N/A	**Methods** Diagnosis of Recurrence Work-up required inclusion of complete radiologic imaging of the chest, abdomen, and pelvis as well as a complete history and physical examination. In patients whose recurrence was	**Results** **Recurrence at 2 years:** 290/1172 **Recurrence at 4 years:** 345/ 1172 **Overall survival** Not reported	**Limitations** 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results Yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
D., Bains, M., Karpeh, M. S., Patterns of initial recurrence in completely resected gastric adenocarcinoma, Annals of SurgeryAnn Surg, 240, 808-816, 2004 **Ref Id** 512826 **Country/ies where the study was carried out** US **Study type** Retrospective cohort study **Aim of the study** To review recurrence	**Inclusion Criteria** Utilizing a prospectively maintained gastric cancer database, all patients from July 1985 to June 2000 who underwent a curative gastrectomy at Memorial Sloan-Kettering Cancer Center were identified. **Exclusion Criteria** Patients who had involved histologic margins (R1) or who had gross disease left behind during surgery (R2) were excluded.		documented at an abdominal operation, some imaging of the chest was required. Serial imaging or biopsy was required to conclusively document recurrence. In some patients, no attempt was made to confirm recurrence, and these patients were excluded. Patients who developed what appeared to be anastomotic recurrences greater than 5 years after a gastrectomy for gastric adenocarcinoma were considered to have a new primary tumor.	**Disease-free survival** median time to recurrence= 11.8 months for those with recurrence (N=382)* **Stage of disease at recurrence:** Not reported Characteristics of those with recurrence (N=382):* 283 symptomatic; 99 asymptomatic * Extracted from Benette, 2005	1.2 Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias Unclear (patients with inadequate follow-up excluded- numbers not reported) 1.3 The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias Yes 1.4 The outcome of interest is adequately measured in study participants, sufficient to limit potential bias Yes 1.5 Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest Yes 1.6 The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results Yes

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td>in completely resected gastric adenocarcinoma.

Study dates

July 1985 through June 2000

Source of funding
NR</td><td></td><td></td><td></td><td></td><td>Other information

Patients in whom complete information on their recurrence could not be obtained were not included in the final analysis</td></tr>
<tr><td>Full citation

De Potter, T., Flamen, P., Van Cutsem, E., Penninckx, F., Filez, L., Bormans, G., Maes, A., Mortelmans, L., Whole-</td><td>Sample size

Characteristics

Inclusion Criteria

Exclusion Criteria</td><td>Tests
PET imaging was performed with a CTI-Siemens 931 or an HR+ scanner (Knoxville, Tenn.), with an axial field of view of 10.1 cm or 15 cm, respectively, and a spatial reso- lution of 8 or 6 mm, respectively. All patients fasted for 6 h pre- ceding tracer administration. Sixty minutes after the</td><td>Methods</td><td>Results<table><tr><td></td><td>Recurrence +</td><td>Recurrence -</td><td>Totals</td></tr><tr><td>PET+</td><td>14</td><td>4</td><td>18</td></tr><tr><td>PET -</td><td>6</td><td>9</td><td>15</td></tr><tr><td>Totals</td><td>20</td><td>13</td><td>33</td></tr></table></td><td>Limitations
QUADAS-2 a quality assessment tool for diagnostic accuracy studies:
Overall quality: low risk of bias.
Patient Selection
A. Risk of Bias
Was a consecutive or random sample of patients enrolled? Yes.
Was a case-control design avoided? Yes.</td></tr>
</table>

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
body PET with FDG for the diagnosis of recurrent gastric cancer, European Journal of Nuclear Medicine, 29, 525-529, 2002 **Ref Id** 512835 **Country/ies where the study was carried out** **Study type** Retrospective cohort study **Aim of the study** **Study dates**		intravenous injection of 6.5 MBq/kg 18F-FDG (to a maximum of 555 MBq), a whole-body emission scan was performed. The raw imaging data were reconstructed in a 128×128 matrix with use of an in-house iterative reconstruction algorithm without attenuation correction.		Diagnostic test results calculated by NGA technical team: Sensitivity (95% CI)= 70.00 (45.72- 88.11) Specificity (95% CI)= 69.23 (38.57 - 90.91) Positive likelihood ratio= 2.27 (0.96 to 5.40) Negative likelihood ratio= 0.43 (0.20 to 0.93) Positive predictive value= 77.78 (59.58 to 89.26) Negative predictive value= 60.00 (41.20 to 76.26) **Patient Anxiety** Not reported	Did the study avoid inappropriate exclusions? Yes. Could the selection of patients have introduced bias? Low risk. B. Concerns regarding applicability: Are there concerns that the included patients and setting do not match the review question? Low concern. **Index Test** A. Risk of Bias Were the index test results interpreted without knowledge of the results of the reference standard? Yes. If a threshold was used, was it pre-specified? Yes. (Diagnostic criteria of recurrence was defined.) Could the conduct or interpretation of the index test have introduced bias? Low risk. B. Concerns regarding applicability: PET images reviewed by two experienced

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Source of funding					nuclear medicine physicians. Are there concerns that the index test, its conduct, or interpretation differ from the review question? Low concern. **Reference Standard** A. Risk of Bias Is the reference standards likely to correctly classify the target condition? Yes. Were the reference standard results interpreted without knowledge of the results of the index tests? Yes. Could the reference standard, its conduct, or its interpretation have introduced bias? Low risk. B. Concerns regarding applicability Are there concerns that the target condition as defined by the reference standard does not match the question? Low concern. **Flow and Timing** A. Risk of Bias Was there an appropriate interval

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					between index test and reference standard? Yes. Did all patients receive the same reference standard? Yes. Were all patients included in the analysis? Yes Could the patient flow have introduced bias? Low risk. **Other information** See Li, 2016 Systematic review for additional study details.
Full citation Mariette, C., Balon, J. M., Piessen, G., Fabre, S., Van Seuningen, I., Triboulet, J. P., Pattern of recurrence following complete	**Sample size** N=439 **Characteristics** • all patients received subtotal esophagectomy with	**Tests** Test type N/A	**Methods** Followed for evidence of recurrence over a mean interval of 37.3 (range, 1–207) months <u>Surgical Approach</u> The detailed resection techniques have been described elsewhere.3 Surgical resection consisted, in a transthoracic esophagectomy for tumor of the middle third or lower	**Results** **Overall recurrence rate:** 230/439 Local recurrence: 53/439 Regional recurrence: 90/439 Distant metastasis: 87/439 **Recurrence rate at 1 year:** 105/439 **1-year overall survival:** Events= 39, N=439 **3-year overall survival:** Events= 202, N=439 **5-year overall survival:** Events= 259, N= 439	**Limitations** 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results Yes 1.2 Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
resection of esophageal carcinoma and factors predictive of recurrent disease, CancerCancer, 97, 1616-1623, 2003 **Ref Id** 507855 **Country/ies where the study was carried out** France **Study type** Retrospective cohort study **Aim of the study** The current study was undertaken to evaluate the pattern of	two-field lymphadenectomy and R0 resection. • The male to female ratio was 7.8:1 • median age 57.6 (SD, 9.4; range 32–77) years. • Squamous cell carcinoma (SCC) was the predominant histologic subtype compared with adenocarcinoma with a ratio of 4.7:1. **Inclusion Criteria** Patients receiving R0 oesophagectomy with 2-field		third of the esophagus, completed with a cervical incision for anastomosis in case of tumor of the upper third of the thoracic esophagus. The surgical approach included an abdominal lymphadenectomy and an extended en bloc mediastinal lymphadenectomy (two-field lymphadenectomy). No cervical lymphadenectomy was undertaken. Abdominal lymphadenectomy comprised en bloc removal of all lymphatic tissue in the lower posterior mediastinum, in the left and right paracardial regions, along the lesser curve, and along the left gastric artery. <u>Recurrence Identification</u> All patients surviving operation were followed until death or the time of writing at the end of the first month, at six-month intervals in years one and two, and annually thereafter. Clinical review consisted of history and abdominal examination. Abdominal ultra sonography was realized twice a year, chest X-ray, endoscopy, and indirect	**1-year disease-free survival:** Events= 39, N=439 **3-year disease-free survival:** Events= 206, N=439 **5-year disease-free survival:** Events= 277, N=439 **Stage of disease at recurrence:** Not reported	to limit potential bias Yes 1.3 The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias Yes 1.4 The outcome of interest is adequately measured in study participants, sufficient to limit potential bias Yes 1.5 Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest Yes 1.6 The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results Yes **Other information** The survival status of patients was ascertained in July 2002. Followup was

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
recurrence after curative esophagectomy for cancer of the thoracic esophagus and to identify factors predictive of recurrent disease. **Study dates** resection between January 1982 and July 2002 **Source of funding** NR	lymphadenectomy at one institution. **Exclusion Criteria** Patients who had rare tumors were excluded.		laryngoscopy once a year. If recurrence was suspected, patients underwent barium-swallow, ultrasonography, chest X-rays, thoracoabdominal computed tomography (CT), and endoscopic examination with biopsies. More selective investigations such as cervical ultrasonography, bone scintigraphy, and cerebral CT were carried out based on specific symptomatology, clinical examination and biochemical profile. Diagnosis of Recurrence Follow-up was complete for all patients. By definition, the timing of recurrence was always above six months after surgery. Before six months, evidence of tumor was considered as persistent neoplastic disease. Histologic, cytologic, or unequivocal radiologic proof was required before a diagnosis of recurrence was made. Recurrence supported by clinical impression alone was not included.		complete for all 439 patients.
Full citation	**Sample size**	**Tests** FDG-PET (n 1⁄4 47) or PET/CT (n 1⁄4 45) scans were per- formed after	**Methods**	**Results**	**Limitations** QUADAS-2 a quality assessment tool for

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>Nakamoto, Y., Togashi, K., Kaneta, T., Fukuda, H., Nakajima, K., Kitajima, K., Murakami, K., Fujii, H., Satake, M., Tateishi, U., Kubota, K., Senda, M., Clinical value of whole-body FDG-PET for recurrent gastric cancer: A multicenter study, Japanese Journal of Clinical OncologyJpn J Clin Oncol, 39, 297-302, 2009

Ref Id

513410</td>
<td>Characteristics

Inclusion Criteria

Exclusion Criteria</td>
<td>patients had fasted for at least 4 h. Sixty minutes after intravenous administration of 250 – 370 MBq FDG, imaging of the trajectory of the upper thigh to skull base was performed using a dedicated full-ring BGO-based dedicated PET scanner (Advance, GE Healthcare), a BGO PET/CT scanner (Discovery LS/ST, GE Healthcare), an LSO PET/CT scanner (Biograph, CTI/Siemens) and a GSO PET/ CT scanner (Gemini, Philips Medical Systems). PET images were reconstructed with attenuation correction by the ordered-subsets expectation maximization algorithm, but specific parameters for image reconstruction were dependent on each institutional method. All PET studies were con-ducted under the guidelines issued by the Japanese Society of Nuclear Medicine.</td>
<td></td>
<td>
<table>
<tr><td></td><td>Recurrence (+)</td><td>Recurrence (-)</td><td>Total</td></tr>
<tr><td>PET (+)</td><td>34</td><td>5</td><td></td></tr>
<tr><td>PET (-)</td><td>10</td><td>43</td><td></td></tr>
<tr><td>Total</td><td>44</td><td>48</td><td>92</td></tr>
</table>
5 patients with new primary cancer identified by PET/CT are included the analysis (2 lung, 3 colon cancer)

Diagnostic accuracy calculated by the NGA technical team:
Sensitivity (95% CI)= 77.27 (62.16 to 88.53)
Specificity (95% CI)= 89.58 (77.34 to 96.53)
Positive likelihood ratio= 7.42 (3.19 to 17.27)
Negative likelihood ratio= 0.25 (0.15 to 0.44)
Positive predictive value= 87.18 (74.50 to 94.06)
Negative predictive value= 81.13 (71.20 to 88.20)

Patient Anxiety
Not reported</td>
<td>diagnostic accuracy studies:
Overall= low risk of bias
Patient Selection
A. Risk of Bias
Was a consecutive or random sample of patients enrolled? Yes.
Was a case-control design avoided? Yes.
Did the study avoid inappropriate exclusions? Yes.
Could the selection of patients have introduced bias? Low risk.
B. Concerns regarding applicability:
Are there concerns that the included patients and setting do not match the review question? Low concern.
Index Test
A. Risk of Bias
Were the index test results interpreted without knowledge of the results of the reference standard? Yes.
If a threshold was used, was it pre-specified?
Yes. (Diagnostic</td>
</tr>
</table>

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Country/ies where the study was carried out **Study type** Retrospective cohort study **Aim of the study** **Study dates** **Source of funding**					criteria of recurrence was defined.) Could the conduct or interpretation of the index test have introduced bias? Low risk. B. Concerns regarding applicability: Are there concerns that the index test, its conduct, or interpretation differ from the review question? Low concern. **Reference Standard** A. Risk of Bias Is the reference standards likely to correctly classify the target condition? Yes. Were the reference standard results interpreted without knowledge of the results of the index tests? Unclear Could the reference standard, its conduct, or its interpretation have introduced bias? Unclear risk. B. Concerns regarding applicability Are there concerns that the target condition as defined by the reference standard

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>does not match the question? Low concern.
Flow and Timing
A. Risk of Bias
Was there an appropriate interval between index test and reference standard? Yes.
Did all patients receive the same reference standard? Yes.
Were all patients included in the analysis? No. (15 patients with inadequate follow up were excluded)
Could the patient flow have introduced bias? Low risk.

Other information
See Li, 2016 systematic review for additional study details.</td></tr>
<tr><td>Full citation

Ohtsuka, T., Nakafusa,</td><td>Sample size
N= 161 (gastric cancer)</td><td>Tests
Index Tests
The tumor markers assessed in this study were serum carcinoembryonic</td><td>Methods
Follow-up
These two markers were also examined preoperatively in all patients and the follow-up schedule of the tumor markers</td><td>Results
CEA tumour marker<table><tr><td></td><td>Recurrence +</td><td>Recurrence -</td><td></td></tr></table></td><td>Limitations
QUADAS-2 a quality assessment tool for diagnostic accuracy studies:</td></tr>
</table>

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>Y., Sato, S., Kitajima, Y., Tanaka, M., Miyazaki, K., Different roles of tumor marker monitoring after curative resections of gastric and colorectal cancers, Digestive Diseases and Sciences, 53, 1537-1543, 2008

Ref Id

513450

Country/ies where the study was carried out

Japan

Study type

Retrospective cohort study</td>
<td>Characteristics
Median age= 68 (range 26-88)
106 male/ 55 female
Median follow-up= 29.4 (range 6.4-61.3)

Inclusion Criteria
The medical records of 211 patients who underwent curative resection for gastric cancer between 2002 and 2005 at the Department of Surgery, Saga University Hospital, were retrospectively reviewed (gastric cancer stage I–III according to the Japanese Classification of Gastric Carcinoma, 13th edition, 1999). All patients showed no residual cancer macroscopically as well as histologically.

Exclusion Criteria
NR</td>
<td>antigen (CEA, a Latex immunoassay, Mitsubishi Chemical Ltd., Japan, normal £5.0 ng/ml) and/or carbohydrate antigen 19-9 (CA19-9, a Latex immunoassay, Mitsubishi Chemical Ltd., Japan, normal £37 ng/ml).
Reference tests
Clinical follow-up</td>
<td>and physical examination after the operation were: every 1–3 months during the initial 6 months after the operation, every 3–6 months from 6 months to 2 years, and every 6–12 months during 2–5 years after the operation. Radiological examinations including abdominal ultrasonography, computed tomography (CT), chest X-ray, gastrointestinal series, and/or endoscopic evaluation were performed every 6–12 months during the follow-up period. Marker evaluations and physical/radiological examinations were performed at shorter-term intervals than those described above in patients with suspected recurrence, those undergoing chemotherapy, or in those demonstrating marker elevations.
Cut-off levels
CEA > 5 ng/mL; CA 19-9 > 37 ng/mL</td>
<td>
<table>
<tr><td>CEA +</td><td>10</td><td>18</td><td></td></tr>
<tr><td>CEA -</td><td>12</td><td>121</td><td></td></tr>
<tr><td></td><td>22</td><td>139</td><td>161</td></tr>
</table>
Diagnostic test results calculated by NGA technical team:
Sensitivity (95% CI)= 45.45 (24.39- 67.79)
Specificity (95% CI)= 87.05 (80.31- 92.14)
Positive likelihood ratio= 3.51 (1.87 - 6.58)
Negative likelihood ratio= 0.63 (0.43 - 0.92)
Positive predictive value= 35.71 (22.85 - 51.02)
Negative predictive value= 90.98 (87.26 - 93.69)

CA19-9 tumour marker
<table>
<tr><td></td><td>Recurrence +</td><td>Recurrence -</td><td></td></tr>
<tr><td>CA 19-9 +</td><td>4</td><td>17</td><td></td></tr>
<tr><td>CA 19-9 -</td><td>18</td><td>122</td><td></td></tr>
<tr><td></td><td>22</td><td>139</td><td>161</td></tr>
</table>
Diagnostic test results calculated by NGA technical team:
Sensitivity (95% CI)= 18.18 (5.19- 40.28)
Specificity (95% CI)= 87.77 (81.14 -92.71)
Positive likelihood ratio= 1.49 (0.55 - 4.01)
Negative likelihood ratio= 0.93 (0.76 - 1.15)
</td>
<td>Overall quality: high risk of bias.
Patient Selection
A. Risk of Bias
Was a consecutive or random sample of patients enrolled? unclear
Was a case-control design avoided? Yes.
Did the study avoid inappropriate exclusions? unclear
Could the selection of patients have introduced bias? unclear
B. Concerns regarding applicability:
Are there concerns that the included patients and setting do not match the review question? Low concern.
Index Test
A. Risk of Bias
Were the index test results interpreted without knowledge of the results of the reference standard? Yes.
If a threshold was used, was it pre-specified?
Yes. (Diagnostic criteria was defined.)</td>
</tr>
</table>

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Aim of the study We previously demonstrated that false-positive findings for tumor markers are frequently observed, and that the sensitivity of marker monitoring for early detection of the recurrence is low after curative resection of gastric cancer. The aim of this study was to investigate whether such characters are specific to gastric cancer.				Positive predictive value= 19.05 (8.03 - 38.82) Negative predictive value= 87.14 (84.65- 89.28)	Could the conduct or interpretation of the index test have introduced bias? Low risk. B. Concerns regarding applicability: Are there concerns that the index test, its conduct, or interpretation differ from the review question? Low concern. **Reference Standard** A. Risk of Bias Is the reference standards likely to correctly classify the target condition? Yes. Were the reference standard results interpreted without knowledge of the results of the index tests? Unclear Could the reference standard, its conduct, or its interpretation have introduced bias? Low risk. B. Concerns regarding applicability Are there concerns that the target condition as defined by the reference standard does not match the

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td>Study dates
2002-2005

Source of funding
NR</td><td></td><td></td><td></td><td></td><td>question? Low concern.
Flow and Timing
A. Risk of Bias
Was there an appropriate interval between index test and reference standard? Unclear
Did all patients receive the same reference standard? Unclear
Were all patients included in the analysis? Yes
Could the patient flow have introduced bias? Unclear risk.

Other information
Colorectal cancer also included in analysis but not excluded.</td></tr>
<tr><td>Full citation

Park, M. J., Lee, W. J., Lim, H. K., Park, K. W., Choi, J. Y., Kim, B. T., Detecting recurrence</td><td>Sample size

Characteristics

Inclusion Criteria</td><td>Tests
In all patients, blood glucose level was checked, and PET/CT examination was performed after a normal blood glucose level was ensured. All patients fasted for at least 6 h prior to PET/CT examination. Patients</td><td>Methods</td><td>Results<table><tr><td></td><td>Recurrence +</td><td>Recurrence -</td><td></td></tr><tr><td>PET/CT +</td><td>56</td><td>7</td><td></td></tr></table></td><td>Limitations
QUADAS-2 a quality assessment tool for diagnostic accuracy studies:
Overall quality: high risk of bias.
Patient Selection
A. Risk of Bias</td></tr>
</table>

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
of gastric cancer: The value of FDG PET/CT, Abdominal ImagingAbdom Imaging, 34, 441-447, 2009 **Ref Id** 513500 **Country/ies where the study was carried out** **Study type** Retrospective cohort study **Aim of the study** **Study dates** **Source of funding**	**Exclusion Criteria**	received an intravenous injection of 370 MBq (10 mCi) of FDG, and then rested for approximately 45 min before image acquisition. Image acquisition was performed with an integrated PET/CT device (Discovery LS; GE Medical Systems, Milwaukee, Wis) that consisted of a PET scanner (Advance NXi; GE Medical Systems) and an eight-slice helical CT scanner (LightSpeed Plus; GE Medical Systems). The axes of both systems were mechanically aligned to coincide perfectly so that the patient could be moved from the CT gantry into the PET gantry by shifting the patient table. CT scanning was first performed from the head to the pelvic floor with the following standardized protocol; 140 kV, 80 mA, a tube rotation time of 0.5 s, a pitch of 6, and a section thickness of 5.0 mm which corresponded to the PET image section thickness. All patients were allowed shallow		PET/CT - 19 23 Diagnostic test results calculated by NGA technical team: Sensitivity (95% CI)= 74.67 (63.30-84.01) Specificity (95% CI)= 76.67 (57.72-90.07) Positive likelihood ratio= 3.20 (1.65-6.20) Negative likelihood ratio= 0.33 (0.21-0.51) Positive predictive value= 88.89 (80.50-93.34) Negative predictive value= 54.76 (43.91-65.18)	Was a consecutive or random sample of patients enrolled? Yes. Was a case-control design avoided? Yes. Did the study avoid inappropriate exclusions? Unclear (84 of 189 screened were not included due to follow-up of less than one year) Could the selection of patients have introduced bias? Unclear risk. B. Concerns regarding applicability: Are there concerns that the included patients and setting do not match the review question? High concern. **Index Test** A. Risk of Bias Were the index test results interpreted without knowledge of the results of the reference standard? Yes. If a threshold was used, was it pre-specified? Yes. (Diagnostic criteria was defined.) Could the conduct or interpretation of the

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
		respiration during CT scanning, and no contrast material was administered. Subsequently, PET scanning was performed without changing the patient position. Five to eight table positions were used for adequate coverage from head to pelvic floor with an acquisition time of 5 min per table position. PET image data were reconstructed iteratively by using an ordered set expectation maximization algorithm. CT data were used for attenuation correction. Viewing of coregistered images was conducted with a dedicated software (eN-TEGRA; GE Medical Systems).			index test have introduced bias? Low risk. B. Concerns regarding applicability: Are there concerns that the index test, its conduct, or interpretation differ from the review question? Low concern. **Reference Standard** A. Risk of Bias Is the reference standards likely to correctly classify the target condition? Yes. Were the reference standard results interpreted without knowledge of the results of the index tests? Unclear Could the reference standard, its conduct, or its interpretation have introduced bias? Unclear risk. B. Concerns regarding applicability Are there concerns that the target condition as defined by the reference standard does not match the question? Low concern. **Flow and Timing**

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>A. Risk of Bias
Was there an appropriate interval between index test and reference standard? Unclear
Did all patients receive the same reference standard? No- clinical follow-up as needed (pathology, imaging or clinical follow-up)
Were all patients included in the analysis? Yes
Could the patient flow have introduced bias? High risk

Other information
For additional details see Li 2016 MA</td></tr>
<tr><td>Full citation

Setoyama, T., Natsugoe, S., Okumura, H., Matsumoto, M., Uchikado,</td><td>Sample size
N=106

Characteristics

• 93 males/ 13 females</td><td>Tests
Index Test: CEA tumour antigen- serum and mRNA

In the present study, we investigated CEA mRNA expression of patients after surgery in the outpatient clinic during follow-up. Blood samples</td><td>Methods

Follow-up

Twelve patients underwent neoadjuvant chemoradiation therapy using low-dose cisplatin (7 mg/m^2) plus 5-fluorouracil (350 mg/m^2) and 40-Gy radiation. After discharge, all patients were</td><td>Results
mRNA CEA<table><tr><th></th><th>Recurrence + (Imaging)</th><th>Recurrence - (Imaging)</th><th>Total</th></tr><tr><td>CEA +</td><td>26</td><td>11</td><td></td></tr><tr><td>CEA -</td><td>8</td><td>61</td><td></td></tr><tr><td>Total</td><td>34</td><td>72</td><td>106</td></tr></table></td><td>Limitations
QUADAS-2 a quality assessment tool for diagnostic accuracy studies:
Overall quality: unclear risk of bias.
Patient Selection
A. Risk of Bias
Was a consecutive or random sample of</td></tr>
</table>

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>Y., Ishigami, S., Owaki, T., Takao, S., Aikou, T., Carcinoembryonic antigen messenger RNA expression in blood predicts recurrence in esophageal cancer, Clinical Cancer ResearchClin Cancer Res, 12, 5972-5977, 2006

Ref Id

513643

Country/ies where the study was carried out

Japan

Study type</td>
<td>mean age= 63.3 (range 39-87)
21 upper tumours/51 middle/34 lower
Inclusion Criteria
oesophageal squamous cell carcinoma
underwent R0 resection
Exclusion Criteria
Not reported</td>
<td>were obtained from the peripheral vein every 3 months. The first 6 mL of blood were discarded to prevent epidermal contamination.

Patients whose serum levels were > 5 ng/mL CEA, were usually considered to be CEA positive.

Cutoff value of CEA mRNA expression in blood. CEA mRNA expression was detected in 10 of 28 (35.7%) healthy volunteers and the mean corrected CEA mRNA score was 0.2 (range, 0-1.6). In 22 patients with inflammatory bowel disease (11 Crohn’s disease and 11 ulcerative colitis), CEA mRNA was detected in 5 (22.7%) patients and the mean corrected CEA mRNA score was 1.71 (range, 0-8.4). In 20 patients with benign disease who underwent laparotomy (7 cholecystectomy, 4 myoma uteri, 2 abdominal aortic aneurysm, 6 ileus, and 1 ischemic colitis), CEA</td>
<td>followed up with radiography and serum tumor marker (SCC and CEA) examination, computed tomography every 3 months, and ultrasonography every 6 months. Bronchoscopic and endoscopic examination and bone scintigraphy were done when necessary. Usually, most recurrent diseases were detected by computed tomography examination. Cervical nodal recurrence is useful for ultrasound, local recurrence for bronchoscopic and endoscopic examination, and scintigraphy for bone metastasis. Thus, because most recurrences such as mediastinal lymph node, lung, or liver recurrence were detected by computed tomography, there was little effect of ultrasound examination on recurrent disease. Biopsy examination was not routinely done to determine the histologic conformation. New lesions detected by imaging means were regarded as relapse in comparison with previous examination. All imagings were evaluated by two or three independent observers, including radiologists.

The median follow-up period was 27.9 months (range, 5-72.0 months).</td>
<td>Diagnostic test results calculated by NGA technical team:
Sensitivity (95% CI)= 76.47 (58.83- 89.25)
Specificity (95% CI)= 84.72 (74.31 - 92.12)
Positive likelihood ratio= 5.01 (2.82 - 8.90)
Negative likelihood ratio= 0.28 (0.15- 0.51)
Positive predictive value= 70.27 (57.08 - 80.77)
Negative predictive value= 88.41 (80.50 - 93.37)

Serum CEA
<table>
<tr><th></th><th>Recurrence + (Imaging)</th><th>Recurrence - (Imaging)</th><th>Total</th></tr>
<tr><td>CEA +</td><td>12</td><td>15</td><td></td></tr>
<tr><td>CEA -</td><td>22</td><td>57</td><td></td></tr>
<tr><td>Total</td><td>34</td><td>72</td><td>106</td></tr>
</table>
Diagnostic test results calculated by NGA technical team:
Sensitivity (95% CI)= 35.29 (19.75- 53.51)
Specificity (95% CI)= 79.17 (67.98- 87.84)
Positive likelihood ratio= 1.69 (0.89 - 3.21)
Negative likelihood ratio= 0.82 (0.62 - 1.08)
Positive predictive value= 44.44 (29.66 to 60.28)
Negative predictive value= 72.15 (66.31 to 77.33)</td>
<td>patients enrolled? Yes. Consecutive sample
Was a case-control design avoided? Yes.
Did the study avoid inappropriate exclusions? Unclear (exclusion criteria not defined)
Could the selection of patients have introduced bias? Unclear risk.
B. Concerns regarding applicability:
Are there concerns that the included patients and setting do not match the review question? Low concern.
Index Test
A. Risk of Bias
Were the index test results interpreted without knowledge of the results of the reference standard? Yes.
If a threshold was used, was it pre-specified?
Yes. (Diagnostic criteria was defined.)
Could the conduct or interpretation of the index test have introduced bias? Low risk.</td>
</tr>
</table>

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Prospective cohort study **Aim of the study** The clinical significance of isolated tumor cells (ITC) in blood has not been clearly established, particularly during follow-up in cancer patients.We conducted a longitudinal analysis of the relationship between ITC in blood during follow-up and clinicopathologic findings in patients		mRNA was detected in 6 (30%) patients and the mean corrected CEA mRNA score was 2.15 (range, 0-8.6). Because the maximum value of CEA mRNA in patients without malignancy was 8.6, a cutoff value of 9.0 was used in the present study. **Reference Test** Diagnosis of recurrence based on clinical follow-up and imaging.			B. Concerns regarding applicability: Are there concerns that the index test, its conduct, or interpretation differ from the review question? Low concern. **Reference Standard** A. Risk of Bias Is the reference standards likely to correctly classify the target condition? Yes. Were the reference standard results interpreted without knowledge of the results of the index tests? Unclear Could the reference standard, its conduct, or its interpretation have introduced bias? Unclear risk. B. Concerns regarding applicability Are there concerns that the target condition as defined by the reference standard does not match the question? Low concern. **Flow and Timing** A. Risk of Bias Was there an appropriate interval

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
with esophageal squamous cell carcinoma. **Study dates** 1999-2004 **Source of funding** Grants-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture, Japan.					between index test and reference standard? Unclear Did all patients receive the same reference standard? Unclear (most had CT to diagnosed recurrence) Were all patients included in the analysis? yes Could the patient flow have introduced bias? Unclear risk. **Other information**
Full citation Teyton, P., Metges, J.	**Sample size** N=41	**Tests** **Index Test**	**Methods** **Clinical Follow-Up**	**Results** **PET study** **All recurrence (by patient analysis)** Sensitivity: 100% Specificity: 85.5%	**Limitations** QUADAS-2 a quality assessment tool for diagnostic accuracy studies:

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
P., Atmani, A., Jestin-Le Tallec, V., Volant, A., Visvikis, D., Bail, J. P., Pradier, O., Lozac, H. P., Cheze Le Rest, C., Use of positron emission tomography in surgery follow-up of esophageal cancer, Journal of Gastrointestinal SurgeryJ Gastrointest Surg, 13, 451-458, 2009 **Ref Id** 513757 **Country/ies where the study was carried out** France	**Characteristics** 38 male/3 female median age= 59 (range 43-83) Site: 2 upper/20 middle/18 lower Histology: 31 SCC/ 10 AC Treatment Surgery alone 25 (61%) Surgery+adjuvant CT±RT 7 (17%) Surgery+neoadjuvant CT+RT 9 (22%) Pathological stage I 6 (14%) IIa 15 (37%) IIb 5 (12%) III 15 (37)	All FDGPET examinations were performed using an Allegro dedicated PET scanner (Philips Medical Systems). Emission data were corrected for scatter, random events, and dead time losses and images were reconstructed both with and without attenuation correction using a previously optimized 3D RAMLA reconstruction protocol. Baseline PET images were reported by two experienced nuclear physicians unaware of the CT, endoscopic ultrasound findings, and histological results. Images were analyzed visually and semiquantitatively. Regional lymph node involvement and distant metastatic disease were assessed as present or absent. Lymph nodes and metastases were considered as FDG-positive if focal-prominent 18FFDG uptake compared to normal mediastinal activity was found at least in two consecutive	After initial treatment, each patient was monitored regularly every 4–6 months during the first 2 years and every year after the second year in case of no recurrence. Every follow-up evaluation included a complete clinical examination. Thoracoabdominal CT, abdominal ultrasonography, and endoscopy were performed every 6 months or more frequently depending on the clinical situation. FDG-PET examinations were added to this routine follow-up procedure, every 6 months during the first 2 years and every year after the second year. Comparative CT and PET scans were performed within 1 month from each other.	NPV: 100% **Locoregional recurrence** Sensitivity: 93.3% Specificity: 97.4% NPV: 97.4% **Distant recurrence** Sensitivity: 100% Specificity: 89.4% NPV: 100% **CT study** **All recurrence (by patient analysis)** Sensitivity: 65% Specificity: 91.2% NPV: 81.5% **Locoregional recurrence** Sensitivity: 60% Specificity: 100% NPV: 86.7% **Distant recurrence** Sensitivity: 66.6% Specificity: 92.1% NPV: 87.5% * Diagnostic accuracy measures as reported by study	Overall quality: unclear risk of bias. **Patient Selection** A. Risk of Bias Was a consecutive or random sample of patients enrolled? Yes. Was a case-control design avoided? Yes. Did the study avoid inappropriate exclusions? Unclear (inclusion criteria not well defined) Could the selection of patients have introduced bias? Unclear risk. B. Concerns regarding applicability: Are there concerns that the included patients and setting do not match the review question? Low concern. **Index Test** A. Risk of Bias Were the index test results interpreted without knowledge of the results of the reference standard? Yes. If a threshold was used, was it pre-specified? Yes. (Diagnostic criteria was defined.)

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Study type Prospective cohort study **Aim of the study** This prospective study compared the ability of FDG-PET and conventional imaging to detect early recurrence of esophageal cancer after initial surgery in asymptomatic patients. **Study dates** 2003-2006	**Inclusion Criteria** 41 consecutive patients with esophageal cancer were included in the present study after they underwent esophagectomy with curative intention. **Exclusion Criteria** NR	transaxial slices. In identified lesions, the maximum standardized uptake values (SUVmax) corrected for the body weight of each patient were calculated performing region of interest analysis on the transaxial slice of the attenuation **Reference Test** Regional and distant recurrences were established by biopsy, if feasible, or by clinical follow-up and repeated examinations.		**Patient Anxiety** NR	Could the conduct or interpretation of the index test have introduced bias? Low risk. B. Concerns regarding applicability: Are there concerns that the index test, its conduct, or interpretation differ from the review question? Low concern. **Reference Standard** A. Risk of Bias Is the reference standards likely to correctly classify the target condition? Yes. Were the reference standard results interpreted without knowledge of the results of the index tests? Unclear Could the reference standard, its conduct, or its interpretation have introduced bias? unclear risk. B. Concerns regarding applicability Are there concerns that the target condition as defined by the reference standard does not match the

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Source of funding NR					question? Low concern. **Flow and Timing** A. Risk of Bias Was there an appropriate interval between index test and reference standard? Unclear Did all patients receive the same reference standard? No- biopsy if feasibly, clinical follow-up as needed Were all patients included in the analysis? Yes Could the patient flow have introduced bias? Unclear risk. **Other information** Unable to extract 2x2 data; not reported as TP, FN, TN, FP; uncertainty not reported
Full citation Versteijne, E., van Laarhoven, H. W. M.,	**Sample size** N= 184 **Characteristics** 69% male	**Tests** N/A	**Methods** <u>dCRT protocol</u> The protocol for dCRT consisted of external beam radiotherapy of 50.4 Gray in 28 fractions,	**Results** mean follow up of 22.8 months (range 0.4–89.8 months, median FU 15 months) **Locoregional recurrence-free rate**	**Limitations** 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
van Hooft, J. E., van Os, R. M., Geijsen, E. D., van Berge Henegouwen, M. I., Hulshof, M. C. C. M., Definitive chemoradiation for patients with inoperable and/or unresectable esophageal cancer: locoregional recurrence pattern, Diseases of the Esophagus Dis Esophagus, 28, 453-459, 2015 **Ref Id** 513825 **Country/ies where the study**	Median age= 66 years (Range 24-88) 44% adenocarcinoma/ 52% squamous cell carcinomca Tumour site: 21% proximal/ 33% mid/ 46% lower dCRT indication: T4 disease 31% M1a/b 24% Co-morbidity 23% Technical unresectable 8% Local recurrence 10% Patient choice 3% Other 1% **Inclusion Criteria**		administered 5 days/week and weekly administration of concurrent paclitaxel (50 mg/m^2) and carboplatin (area under the curve [AUC] = 2). The conformal clinical target volume (CTV) consisted of GTV plus at least the peri-esophageal lymph node area extended in cranio-caudal direction by a 3.5 cm margin – because of old field margins of 5 cm (minus 0.5 cm toward the 95% isodose and minus 1.0 cm for CTV-planning target volume [PTV]) with limitation of the margin into the cardia up to 2.3 cm because of toxicity and based on the guidelines of the CROSS study. The PTV consisted of the CTV expanded with 1.0 cm in all directions. <u>Follow up</u> A CT scan was carried out 8 weeks after completion of dCRT to assess response, which also served as baseline for further follow up. All patients were reviewed clinically every 3 months for 1 year, every 6 months in second and third year and thereafter once yearly. Follow up	Median locoregional recurrence-free survival was 21.3 months **1-year** Events= 65, N=184 **3-year** Events= 101, N= 184 AC group Events= 64, N=81 SCC group Events= 51, N=103 **5-year** Events= 109, N=198 **Overall locoregional recurrence rate** 76/184 **Overall distant recurrence rate** 76/184 **Combination locoregional and distant recurrence rate** 37/184 **Overall survival** 16.8 months for all patients. SCC with a median of 20.5 months compared with 14.7 months for AC **1-year** Events= 64, N=184 **3-year** Events= 132, N= 184 **5-year** Events= 145, N=184 **Stage of disease at recurrence** Not reported	potential bias to the results Unclear (11% undergoing dCRT for recurrent disease) 1.2 Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias Yes 1.3 The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias Yes 1.4 The outcome of interest is adequately measured in study participants, sufficient to limit potential bias Yes 1.5 Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest Yes 1.6 The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results Yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
was carried out The Netherlands **Study type** Retrospective cohort study **Aim of the study** The aim of this study was to determine the pattern of locoregional recurrence and its prognostic factors after dCRT in order to search for improvements in radiation treatment.	Patients were defined as unresectable when they had extended disease (T4), technical unresectable tumor (high cervical localization), and a locoregional recurrence after previous curative treatment or M1a/M1b disease (6th edition of TNM classification of the Union International Contre le Cancer [TNM UICC]). Patients were defined inoperable when co-morbidity excluded them from surgery. **Exclusion Criteria** NR		consisted of clinical evaluation and physical examination; CT scan, PET scan, or endoscopic examination were performed on indication only. <u>Recurrent disease</u> Locoregional recurrences were defined by clinical signs (e.g. progressive dysphagia, losing weight, retrosternal pain, or symptoms of possible distant disease) of recurrent or progressive disease (expansion of the tumor), combined with progression on CT scan or PET/CT scan, or suspicious endoscopic findings and/or histological proof of recurrence. Histological confirmation was only achieved if a local recurrence was not clearly suspect at PET/CT or endoscopy. Locoregional failures were classified as located at the site of the primary tumor and/or at the site or regional lymph nodes (up to supraclavicular and truncus celiac nodes). The sites of locoregional recurrence were reconstructed to the radiation fields and scored as in-field or out-field (related to the 95%		**Other information** 89% surgery for primary tumour, 11% surgery for recurrence

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td>Study dates

May 2003 to August 2011

Source of funding
NR</td><td></td><td></td><td>isodose line/PTV). Distant metastases were scored separately. The date of recurrence was taken as the date of proven histology (if present) or date of imaging of recurrent or progressive disease.</td><td></td><td></td></tr>
<tr><td>Full citation

Bilici, A., Ustaalioglu, B. B., Seker, M., Kefeli, U., Canpolat, N., Tekinsoy, B., Ozugur, S., Gumus, M., The role of 18F-FDG PET/CT in the assessment of suspected</td><td>Sample size

Characteristics

Inclusion Criteria

Exclusion Criteria</td><td>Tests
Chest and abdomen/pelvis diagnostic CT imaging were performed using the MS CT scanner (Siemens Somatom Sensation, 40-slice CT system). Images with 40×0.72 mm collimation were obtained. Axial, coronal and sagittal reformations with different thicknesses were acquired using maximum intensity projection (MIP)+multiplanar reforma- tion (MPR) before and after</td><td>Methods</td><td>Results<table><tr><th></th><th>Recurrence +</th><th>Recurrence -</th><th>Total</th></tr><tr><td>PET/CT +</td><td>23</td><td>0</td><td>23</td></tr><tr><td>PET/CT -</td><td>1</td><td>10</td><td>11</td></tr><tr><td>Total</td><td>24</td><td>10</td><td>34</td></tr></table>Diagnostic accuracy measures calculated by NGA technical team:
Sensitivity (95% CI)= 95.83 (78.88 to 99.99)
Specificity (95% CI)= 100.00 (69.15 to 100.00)
Positive likelihood ratio= infinite</td><td>Limitations
QUADAS-2 a quality assessment tool for diagnostic accuracy studies:
Overall= high risk of bias
Patient Selection
A. Risk of Bias
Was a consecutive or random sample of patients enrolled? Yes.
Was a case-control design avoided? Yes.
Did the study avoid inappropriate exclusions? Yes.
Could the selection of patients have</td></tr>
</table>

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>recurrent gastric cancer after initial surgical resection: can the results of FDG PET/CT influence patients' treatment decision making?, European Journal of Nuclear Medicine & Molecular ImagingEur J Nucl Med Mol Imaging, 38, 64-73, 2011

Ref Id

514046

Country/ies where the study was carried out

Tukey</td>
<td></td>
<td>administration of iomeprol contrast medium 1 ml/kg (60–100 ml) from the xiphoid process to the pubic symphysis with i.v. early arterial and portal phases for the abdomen and pelvis. For the thorax, axial images with 40 × 0.72 mm collimation and coronal and sagittal reformations using MIP + MPR before and after administration of 1 ml/kg (60–100 ml) iomeprol contrast medium were obtained from the thoracic inlet to inferior of the surrenal glands.
The median interval between diagnostic CT and FDG PET/CT was 2 weeks (range 1–4 weeks). The patients fasted for at least 6 h prior to imaging and their blood glucose levels were obtained prior to tracer injection. The blood glucose levels of all patients were below 200 mg/dl at the time of FDG injection. Each patient received 10– 15 mCi (370–550 Mbq) of FDG as a tracer intravenously. Following this, the patients rested</td>
<td></td>
<td>Negative likelihood ratio= 0.04 (0.01 to 0.28)
Positive predictive value= 100.00%
Negative predictive value= 90.91% (59.48 to 98.55%)

<table>
<tr><td></td><td>Recurrence +</td><td>Recurrence -</td><td>Total</td></tr>
<tr><td>CT +</td><td>15</td><td>9</td><td></td></tr>
<tr><td>CT-</td><td>9</td><td>1</td><td></td></tr>
<tr><td>Total</td><td></td><td></td><td>34</td></tr>
</table>
Diagnostic accuracy measures calculated by NGA technical team:
Sensitivity (95% CI)= 62.50 (40.59% to 81.20%)
Specificity (95% CI)= 10.00 (0.25% to 44.50%)
Positive likelihood ratio= 0.69 (0.48 to 1.01)
Negative likelihood ratio= 3.75 (0.54 to 25.83)
Positive predictive value= 62.50 (53.45% to 70.75%)
Negative predictive value= 10.00 (1.59% to 43.35%)
Patient Anxiety
Not reported</td>
<td>introduced bias? Low risk.
B. Concerns regarding applicability:
All patients were suspected of having recurrence. Suspicion based on CT or endoscopy
Are there concerns that the included patients and setting do not match the review question? High concern.
Index Test
A. Risk of Bias
Were the index test results interpreted without knowledge of the results of the reference standard? Yes.
If a threshold was used, was it pre-specified?
Yes. (Diagnostic criteria of recurrence was defined.)
Could the conduct or interpretation of the index test have introduced bias? Low risk.
B. Concerns regarding applicability:
Are there concerns that the index test, its conduct, or</td>
</tr>
</table>

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Study type Retrospective cohort study **Aim of the study** **Study dates** **Source of funding**		on a comfortable chair for 1 h to allow FDG biodistribution. For the optimal delineation of bowel structures, 400–600 ml of contrast material diluted to 2.4% (v/v) with water was ingested 1 h before CT imaging. No urinary bladder catheterization was performed, and no diuretics were administered at this time. Whole-body imaging was performed 1 h after radiotracer injection using a Siemens Biograph Duo PET/CT scanner with lutetium orthosilicate (LSO) detectors. First, low-dose CT was performed with 140 kV, 50 mA, a table speed of 22.5 mm/s and without any specific breath-holding instruc-tions. Scanning from the top of the skull down to the upper thighs was performed in a single step with the patients in the supine position. CT data were used for attenuation correction (5 mm contiguous axial cuts). Immediately afterwards, a PET emission scan was			interpretation differ from the review question? Low concern. **Reference Standard** A. Risk of Bias Is the reference standards likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index tests? Unclear Could the reference standard, its conduct, or its interpretation have introduced bias? Unclear risk. B. Concerns regarding applicability Are there concerns that the target condition as defined by the reference standard does not match the question? Low concern. **Flow and Timing** A. Risk of Bias Was there an appropriate interval between index test and reference standard? Yes. Did all patients receive the same reference

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td>obtained without changing the patient’s position. Six to eight bed positions were used with an acquisition time of 5 min for each bed position. The PET scan was acquired in a three-dimensional mode over the same anatomical regions, starting at the level of the mid-thighs. The PET image data sets were reconstructed iteratively using the CT data for attenuation correction and coregistered images were displayed on a workstation.</td><td></td><td></td><td>standard? No-histopathology after laparotomy or biopsy or clinical follow-up of 6 months
Were all patients included in the analysis? Yes
Could the patient flow have introduced bias? High risk.

Other information
See Li, 2016</td></tr>
<tr><td>Full citation

Clark, G. W., Ireland, A. P., Hagen, J. A., Collard, J. M., Peters, J. H., DeMeester, T. R., Carcinoembryonic antigen</td><td>Sample size
N=83

Characteristics
One hundred patients undergoing surgical resection of esophageal cancer had serum CEA levels measured (Figure 1). There were 83 men and 17 women, with a median age 64 years</td><td>Tests
Index test: CEA
Measurement
Serum CEA levels were determined by the CEA-Roche enzyme immunoassay (Roche, Montclair, New Jersey), which uses a highly specific monoclonal mouse antibody to CEA. In this process, the patient’s sample and CEA standards are incubated with beads coated with monoclonal</td><td>Methods
Follow-Up
Hospital survivors were followed up with laboratory studies, a chest roentgenogram, and a thoracic and abdominal CT scan at 3-month intervals for the first 3 years, then every 6 months. Objective evidence of recurrence was determined in the presence of biopsy-positive findings on endoscopy, en-larging abdominal or thoracic nodes on sequential CT scans, or unequivocal systemic metastases on roentgenogram or CT.</td><td>Results<table><tr><td></td><td>Recurrence +</td><td>Recurrence -</td><td>Total</td></tr><tr><td>CEA +</td><td>29</td><td>3</td><td>32</td></tr><tr><td>CEA -</td><td>34</td><td>27</td><td></td></tr><tr><td></td><td>53</td><td>30</td><td>83</td></tr></table></td><td>Limitations
QUADAS-2 a quality assessment tool for diagnostic accuracy studies:
Overall quality: unclear risk of bias.
Patient Selection
A. Risk of Bias
Was a consecutive or random sample of patients enrolled? Unclear
Was a case-control design avoided? Yes.</td></tr>
</table>

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
measurements in the management of esophageal cancer: an indicator of subclinical recurrence, American Journal of SurgeryAm J Surg, 170, 597-600; discussion 600-1, 1995 **Ref Id** 514100 **Country/ies where the study was carried out** US **Study type** Prospective cohort study **Aim of the study**	(range 36 to 82). Eighty patients had adenocarcinoma (48 with Barrett's esophagus); 18 squamous cell carcinoma; and 2 adenosquamous carcinoma. Only 83 of these 100 went on to follow-up study. **Inclusion Criteria** NR **Exclusion Criteria** NR	mouse anti-CEA and with a second monoclonal mouse anti-CEA conjugated to horseradish peroxidase. Levels >5 ng/mL were considered to be elevated for the purpose of this study.	The median follow-up of the 83 patients in the postoperative study was 21 months (range 4 to 81).	Diagnostic test results calculated by NGA technical team: Sensitivity (95% CI)= 46.03 (33.39- 59.06) Specificity (95% CI)= 90.00 (73.47- 97.89) Positive likelihood ratio= 4.60 (1.52- 13.92) Negative likelihood ratio= 0.60 (0.46- 0.78) Positive predictive value= 90.63 (76.18- 96.69) Negative predictive value= 44.26 (38.04 - 50.67) **Patient Anxiety** Not reported	Did the study avoid inappropriate exclusions? Unclear (eligibility criteria not well defined) Could the selection of patients have introduced bias? Unclear risk. B. Concerns regarding applicability: Are there concerns that the included patients and setting do not match the review question? Low concern. **Index Test** A. Risk of Bias Were the index test results interpreted without knowledge of the results of the reference standard? Yes. If a threshold was used, was it pre-specified? Yes. (Diagnostic criteria was defined.) Could the conduct or interpretation of the index test have introduced bias? Low risk. B. Concerns regarding applicability: Are there concerns that the index test, its

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
BAcKGRouNDD:etection of subclinical recurrence after surgical resection of esophageal cancer would allow earlier treatment of recurrent dise8se and potentially offer a better outcome for rescue therapy. **Study dates** NR **Source of funding** NR					conduct, or interpretation differ from the review question? Low concern. **Reference Standard** A. Risk of Bias Is the reference standards likely to correctly classify the target condition? Yes. Were the reference standard results interpreted without knowledge of the results of the index tests? Unclear Could the reference standard, its conduct, or its interpretation have introduced bias? Unclear risk. B. Concerns regarding applicability Are there concerns that the target condition as defined by the reference standard does not match the question? Low concern. **Flow and Timing** A. Risk of Bias Was there an appropriate interval between index test and reference standard? Unclear

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>Did all patients receive the same reference standard? No- clinical follow-up and imaging as needed
Were all patients included in the analysis? Yes
Could the patient flow have introduced bias? Unclear risk

Other information
study includes preoperative CEA analysis; data only extracted for post-operative</td></tr>
<tr><td>Full citation

Graziosi, L., Bugiantella, W., Cavazzoni, E., Cantarella, F., Porcari, M., Baffa, N., Donini, A., Role of FDG-PET/CT in follow-up of</td><td>Sample size

Characteristics

Inclusion Criteria

Exclusion Criteria</td><td>Tests
Patients undergoing 18FDG-PET/CT were asked to com- ply with a hypoglycemic diet the day before the study and to fast for at least 6 hours before the examination; 18FDG was then administered based on patient’s weight (4.5 MBq/Kg) and basal glycemia (<150 mg/dl). Data acquisition was performed 60 minutes after the injection by an</td><td>Methods</td><td>Results<table><tr><td></td><td>Recurrence +</td><td>Recurrence -</td><td>Total</td></tr><tr><td>PET +</td><td>25</td><td>4</td><td>29</td></tr><tr><td>PET -</td><td>3</td><td>18</td><td>21</td></tr><tr><td>Total</td><td>28</td><td>22</td><td>50</td></tr></table>Diagnostic accuracy measures calculated by the NGA technical team:</td><td>Limitations
QUADAS-2 a quality assessment tool for diagnostic accuracy studies:
Overall= unclear risk of bias
Patient Selection
A. Risk of Bias
Was a consecutive or random sample of patients enrolled? Yes.
Was a case-control design avoided? Yes.</td></tr>
</table>

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
patients treated with resective gastric surgery for tumour, Annali Italiani di ChirurgiaAnn Ital Chir, 82, 125-9, 2011 **Ref Id** 514194 **Country/ies where the study was carried out** **Study type** Retrospective cohort study **Aim of the study** **Study dates**		integrated Positron Emission Tomography and CT scan system (Discovery ST, GE Healthcare, Chalfont St. Giles, United Kingdom; General Electric Company, Fairfield, CT, USA). CT scan was performed after the PET with 5-millimeters-thick sections, at 350-380 mA and 140 Kw, from the neck to the perineum.		Sensitivity (95% CI)= 89.29 (71.77 to 97.73) Specificity (95% CI)= 81.82 (59.72 to 94.81) Positive likelihood ratio= 4.91 (2.01 to 12.03) Negative likelihood ratio= 0.13 (0.04 to 0.39) Positive predictive vale= 86.21 (71.85 to 93.87) Negative predictive value= 85.71 (66.92 to 94.68) **Patient Anxiety:** Not reported	Did the study avoid inappropriate exclusions? Yes. Could the selection of patients have introduced bias? Low risk. B. Concerns regarding applicability: Are there concerns that the included patients and setting do not match the review question? High concern. **Index Test** A. Risk of Bias Were the index test results interpreted without knowledge of the results of the reference standard? Unclear If a threshold was used, was it pre-specified? Unclear (Diagnostic criteria of recurrence not defined.) Could the conduct or interpretation of the index test have introduced bias? Unclear risk. B. Concerns regarding applicability: Are there concerns that the index test, its conduct, or

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Source of funding					interpretation differ from the review question? Unclear concern. **Reference Standard** A. Risk of Bias Is the reference standards likely to correctly classify the target condition? Unclear- reference standard not well defined. Were the reference standard results interpreted without knowledge of the results of the index tests? Unclear Could the reference standard, its conduct, or its interpretation have introduced bias? Unclear risk. B. Concerns regarding applicability Are there concerns that the target condition as defined by the reference standard does not match the question? Unclear concern. **Flow and Timing** A. Risk of Bias Was there an appropriate interval between index test and

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					reference standard? Unclear Did all patients receive the same reference standard? Unclear Were all patients included in the analysis? Yes Could the patient flow have introduced bias? Unclear risk. **Other information** See Li, 2016 SR for additional study details.
Full citation Kato, M., Nishida, T., Yamamoto, K., Hayashi, S., Kitamura, S., Yabuta, T., Yoshio, T., Nakamura, T., Komori, M., Kawai, N., Nishihara,	**Sample size** N= 1258 **Characteristics** Mean age= 70.5 953 male/ 305 female **Inclusion Criteria** Consecutive patients with gastric cancer who underwent	**Tests** N/A	**Methods** Treatment course ESD procedure not described Follow-up The follow-up protocols after ESD among the participating hospitals are shown in table 1. Oesophagogastroduodenoscopy (OGD) was started within 1, 3 and 6 months after the initial ESD in 30%, 41% and 100% of the subjects, respectively. Surveillance OGD was performed every 6–12 months. Abdominal CT was added for a final pathological diagnosis in the expanded guideline group.	**Results** Local recurrence: n=5 incident rate= 0.40% Metachronous cancers: 2-year: n=43 cumulative incident rate= 3.7% 3-year: n=80 cumulative incident rate= 6.9% 5-year: n= 185 cumulative incident rate= 16% Overall survival: 3-year: Events= 37	**Limitations** 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results Unclear (query applicability of Eastern population to UK setting) 1.2 Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
A., Nakanishi, F., Nakahara, M., Ogiyama, H., Kinoshita, K., Yamada, T., Iijima, H., Tsujii, M., Takehara, T., Scheduled endoscopic surveillance controls secondary cancer after curative endoscopic resection for early gastric cancer: a multicentre retrospective cohort study by Osaka University ESD study group, GutGut, 62, 1425-1432, 2013	curative ESD in the 12 hospitals between April 1999 and December 2010 were included in the study. The curability of the initial ESD was classified into the following three groups proposed by Gotoda et al16 based on the characteristics of the initially detected tumour: 'guideline group', 'expanded guideline group' and 'non-curative group'. The guideline group was defined as mucosal differentiated cancer with the largest diameter measuring <20 mm. In Japan, ER is definitely indicated for this group. The expanded guideline group was defined as the following: (1) mucosal differentiated cancer measuring >20 mm in diameter, (2) mucosal differentiated cancer with ulceration and measuring <30 mm in the largest				to limit potential bias Yes 1.3 The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias Yes 1.4 The outcome of interest is adequately measured in study participants, sufficient to limit potential bias Yes 1.5 Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest Yes 1.6 The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results Yes **Other information**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Ref Id 490692 **Country/ies where the study was carried out** Japan **Study type** Retrospective cohort study **Aim of the study** To elucidate the time at which multiple cancers develop and to determine whether scheduled endoscopic surveillance might control their	diameter and (3) differentiated cancer measuring <30 mm in the largest diameter with a submucosal invasion depth of <500 μm. If the lesions did not meet these criteria, they were classified as the non-curative group **Exclusion Criteria** The noncurative group was advised to undergo additional gastrectomy with lymph node dissection and was excluded from the data analysis, whereas both the guideline and expanded guideline groups were enrolled in the study. Moreover, the patients whose initial ESD was incomplete (piecemeal, margin-positive or unclear) were excluded from the study.				

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td>developme nt.

Study dates

From April 1999 to December 2010

Source of funding

NR</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Full citation

Kim, D. H., Oh, S. J., Oh, C. A., Choi, M. G., Noh, J. H., Sohn, T. S., Bae, J. M., Kim, S., The relationships between perioperativ</td><td>Sample size
N=479

Characteristics
NR

Inclusion Criteria

who tested for perioperative tumor markers, and</td><td>Tests
Index Test: Serum Tumour Antigens

The measurements of serum CEA, CA 19-9, were conducted by radioimmunoassay (RIA) analysis. Serum CEA, CA 19-9, tests were performed preoperatively, and were repeated every year after surgery. The normal</td><td>Methods
Follow-up

Follow-up observations were performed at 3 months, 6 months, and 1 year after surgery, after which patients were followed up every year. Complete blood count, liver function test, tumor markers, chest radiography, abdominal CT, and endoscopy were used as follow-up test. The patients who had been diagnosed positivity of the tumor marker without the</td><td>Results
Overall CEA<table><tr><th></th><th>Recurrence +</th><th>Recurrence -</th><th>Total</th></tr><tr><td>CEA +</td><td>14</td><td>3</td><td></td></tr><tr><td>CEA -</td><td>34</td><td>428</td><td></td></tr></table></td><td>Limitations
QUADAS-2 a quality assessment tool for diagnostic accuracy studies:
Patient Selection
A. Risk of Bias
Was a consecutive or random sample of patients enrolled? Yes.
Was a case-control design avoided? Yes.
Did the study avoid inappropriate exclusions? Unclear</td></tr>
</table>

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>e CEA, CA 19-9, and CA 72-4 and recurrence in gastric cancer patients after curative radical gastrectomy, Journal of Surgical OncologyJ Surg Oncol, 104, 585-91, 2011

Ref Id

514316

Country/ies where the study was carried out

Korea

Study type

Retrospective cohort study

Aim of the study</td>
<td>who were available for minimum 4-year follow-up or followed up

until recurrence, out of 1,117 patients who had been diagnosed as gastric cancer and underwent surgery from January 2003 to June 2005 at Samsung Medical Center

Exclusion Criteria
Less than 4 years follow-up</td>
<td>values of CEA, CA 19-9, were set at less than 7 ng/ml, 35 U/ml, respectively.

Reference Test

Recurrences were evaluated by physical examination, ultrasonic inspection, chest radiography, CT, PET-CT, MRI, endoscopy, or histological biopsy. Recurrence was classified into five kinds: locoregional recurrence, hematogenous recurrence, distant lymph node metastasis, peritoneal metastasis, and combined metastasis. Locoregional recurrence was defined as remnant stomach, anastomotic site, stump, or regional lymph node metastasis; hematogenous recurrence was defined as distant organ recurrence such as liver, lungs, brain, bone, and organ metastasis; peritoneal recurrence was defined as peritoneal</td>
<td>evidence of recurrence were monitored tumor markers and after three months. Radiologic study was conducted to the patients with positive tumor markers in the re-examination. Average follow-up period was 59.6 12.7 months (9.8–84.8 months), and the median follow-up was 60.7 months.</td>
<td>
<table>
<tr><td></td><td></td><td></td><td>479</td></tr>
</table>
Diagnostic test results calculated by NGA technical team:
Sensitivity (95% CI)= 29.17 (16.95-44.06)
Specificity (95% CI)= 99.30 (97.98- 99.86)
Positive likelihood ratio= 41.90 (12.49-140.63)
Negative likelihood ratio= 0.71 (0.59-0.86)
Positive predictive value= 82.35 (58.17-94.00)
Negative predictive value= 92.64 (91.30-93.79)

Overall CA19-9
<table>
<tr><td></td><td>Recurrence +</td><td>Recurrence -</td><td>Total</td></tr>
<tr><td>CA 19-9 +</td><td>16</td><td>24</td><td></td></tr>
<tr><td>CA 19-9 -</td><td>32</td><td>407</td><td></td></tr>
<tr><td></td><td></td><td></td><td>479</td></tr>
</table>
Diagnostic test results calculated by NGA technical team:
Sensitivity (95% CI)= 33.33 (20.40-48.41)
Specificity (95% CI)= 94.43 (91.83-96.40)
Positive likelihood ratio= 5.99 (3.43-10.46)
Negative likelihood ratio= 0.71 (0.58-0.86)
Positive predictive value= 40.00 (27.62-53.80)
Negative predictive value= 92.71 (91.23- 93.96)

CEA locoregional recurrence
</td>
<td>(patients followed less than 4 years were excluded after screening)
Could the selection of patients have introduced bias? Unclear risk.
B. Concerns regarding applicability:
Are there concerns that the included patients and setting do not match the review question? Low concern.
Index Test
A. Risk of Bias
Were the index test results interpreted without knowledge of the results of the reference standard? Yes.
If a threshold was used, was it pre-specified?
Yes. (Diagnostic criteria was defined.)
Could the conduct or interpretation of the index test have introduced bias? Low risk.
B. Concerns regarding applicability:
Are there concerns that the index test, its conduct, or</td>
</tr>
</table>

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>The aim of this study was to investigate the relationships between perioperative CEA, CA 19-9, and CA 72-4 and recurrence of gastric cancer

Study dates

underwent surgery from January 2003 to June 2005

Source of funding
NR</td>
<td></td>
<td>carcinomatosis or Krukenberg’s tumor; distant lymph node recurrence was defined as retroperitoneal lymph node metastasis, para-aortic lymph node metastasis, or extraperitoneal lymph node metastasis; and combined metastasis was defined as diagnosis of more than two kinds of metastases.</td>
<td></td>
<td>
<table>
<tr><th></th><th>Recurrence +</th><th>Recurrence -</th><th>Total</th></tr>
<tr><td>CEA +</td><td>0</td><td>17</td><td></td></tr>
<tr><td>CEA -</td><td>3</td><td>459</td><td></td></tr>
<tr><td></td><td></td><td></td><td>479</td></tr>
</table>
Diagnostic test results calculated by NGA technical team:
Sensitivity (95% CI)= 0 (0-70.76)
Specificity (95% CI)= 96.43 (94.34-97.91)
Positive likelihood ratio= 0
Negative likelihood ratio= 1.04 (1.02-1.06)
Positive predictive value= 0
Negative predictive value= 99.35 (99.34-99.36)

CEA distant lymph node recurrence
<table>
<tr><th></th><th>Recurrence +</th><th>Recurrence -</th><th>Total</th></tr>
<tr><td>CEA +</td><td>2</td><td>15</td><td></td></tr>
<tr><td>CEA -</td><td>3</td><td>459</td><td></td></tr>
<tr><td></td><td></td><td></td><td>479</td></tr>
</table>
</td>
<td>interpretation differ from the review question? Low concern.
Reference Standard
A. Risk of Bias
Is the reference standards likely to correctly classify the target condition? Yes.
Were the reference standard results interpreted without knowledge of the results of the index tests? Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias? Unclear risk.
B. Concerns regarding applicability
Are there concerns that the target condition as defined by the reference standard does not match the question? Low concern.
Flow and Timing
A. Risk of Bias
Was there an appropriate interval between index test and reference standard? Unclear
Did all patients receive the same reference</td>
</tr>
</table>

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>Diagnostic test results calculated by NGA technical team:
Sensitivity (95% CI)= 40.00 (5.27- 85.34)
Specificity (95% CI)= 96.84 (94.83-98.22)
Positive likelihood ratio= 12.64 (3.87-41.28)
Negative likelihood ratio= 0.62 (0.30-1.27)
Positive predictive value= 11.76 (3.92-30.33)
Negative predictive value= 99.35 (98.68-99.68)

CEA hemtagenous recurrence
<table>
<tr><td></td><td>Recurrence +</td><td>Recurrence -</td><td>Total</td></tr>
<tr><td>CEA +</td><td>4</td><td>13</td><td></td></tr>
<tr><td>CEA -</td><td>9</td><td>453</td><td></td></tr>
<tr><td></td><td></td><td></td><td>479</td></tr>
</table>
Diagnostic test results calculated by NGA technical team:
Sensitivity (95% CI)= 30.77 (9.09-61.43)
Specificity (95% CI)= 97.21 (95.28-98.51)
Positive likelihood ratio= 11.03 (4.16-29.26)
Negative likelihood ratio= 0.71 (0.50-1.02)
Positive predictive value= 23.53 (10.39-44.95)
Negative predictive value= 98.05 (97.22-98.64)

CA 19-9 locoregional recurrence
<table>
<tr><td></td><td>Recurrence +</td><td>Recurrence -</td><td>Total</td></tr>
</table></td><td>standard? No- clinical diagnosis of recurrence as appropriate (imaging, biopsy, physical exam)
Were all patients included in the analysis? Yes
Could the patient flow have introduced bias? High risk.

Other information</td></tr>
</table>

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>
<table>
<tr><td>CA 19-9 +</td><td>0</td><td>40</td><td></td></tr>
<tr><td>CA 19-9 -</td><td>3</td><td>436</td><td></td></tr>
<tr><td></td><td></td><td></td><td>479</td></tr>
</table>
Diagnostic test results calculated by NGA technical team:
Sensitivity (95% CI)= 0 (0-70.76)
Specificity (95% CI)= 91.60 (88.73-93.93)
Positive likelihood ratio= 0
Negative likelihood ratio= 1.09 (1.06-1.12)
Positive predictive value= 0
Negative predictive value= 99.32 (99.30-99.33)

CA 19-9 hematogenous recurrence
<table>
<tr><td></td><td>Recurrence +</td><td>Recurrence -</td><td>Total</td></tr>
<tr><td>CA 19-9 +</td><td>5</td><td>35</td><td></td></tr>
<tr><td>CA 19-9 -</td><td>8</td><td>431</td><td></td></tr>
<tr><td></td><td></td><td></td><td>479</td></tr>
</table>
Diagnostic test results calculated by NGA technical team:
Sensitivity (95% CI)= 38.46 (13.86-68.42)
Specificity (95% CI)= 92.49 (89.71-94.71)
</td><td></td></tr>
</table>

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>Positive likelihood ratio= 5.12 (2.40- 10.93)
Negative likelihood ratio= 0.67 (0.43-1.02)
Positive predictive value= 12.50 (6.28- 23.36)
Negative predictive value= 98.18 (97.22-98.81)

CA19-9 distant lymph node recurrence
<table>
<tr><td></td><td>Recurrence +</td><td>Recurrence -</td><td>Total</td></tr>
<tr><td>CA 19-9 +</td><td>1</td><td>39</td><td></td></tr>
<tr><td>CA 19-9 -</td><td>4</td><td>435</td><td></td></tr>
<tr><td></td><td></td><td></td><td></td></tr>
</table>
Diagnostic test results calculated by NGA technical team:
Sensitivity (95% CI)= 20.00 (0.51-71.64)
Specificity (95% CI)= 91.77 (88.92-94.08)
Positive likelihood ratio= 2.43 (0.41-14.39)
Negative likelihood ratio= 0.87 (0.56-1.35)
Positive predictive value= 2.50 (0.43-13.18)
Negative predictive value= 99.09 (98.59-99.41)</td><td></td></tr>
<tr><td>Full citation

Kim, D. W., Park, S. A., Kim, C. G., Detecting the</td><td>Sample size

Characteristics</td><td>Tests
All follow-up CECT scans were performed with multi-detector row CT scanners (Somatom Volume Zoom, Siemens AG, Enlan- gen,</td><td>Methods</td><td>Results
<table>
<tr><td></td><td>Recurrence +</td><td>Recurrence -</td><td>Total</td></tr>
</table></td><td>Limitations
QUADAS-2 a quality assessment tool for diagnostic accuracy studies:
Overall: high risk of bias.</td></tr>
</table>

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
recurrence of gastric cancer after curative resection: comparison of FDG PET/CT and contrast-enhanced abdominal CT, Journal of Korean Medical ScienceJ Korean Med Sci, 26, 875-80, 2011 **Ref Id** 514317 **Country/ies where the study was carried out** **Study type** Retrospective cohort study **Aim of the study**	**Inclusion Criteria** **Exclusion Criteria**	Germany), spanning from the liver dome to the pelvic floor. Each patient drank 200 mL of water just before undergoing CECT. Scanning was started 45 sec after the intravenous injection of 100-120 mL of iopromide (Ultravist 300, Schering Korea, Seoul, Korea) at a rate of 3 mL/sec. A slice collimation of 1.2 mm and a table pitch of 1:1 were used. Images were reconstructed at 5 mm intervals. FDG was prepared using a cyclotron (RDS-111, CTI Cyclo- tron Systems, Inc., Daejeon, Korea) and automated synthesis apparatus. The radiochemical and chemical purity of the prod- uct was assayed by analytic high-performance liquid chroma- tography and thin-layer chromatography and was consistently > 99% by both assays. The measured specific activity of the FDG was > 740 GBq/mM at the end of synthesis. Patients fasted for at least 8 hr		PET + | 15 | 17 | PET - | 13 | 94 | Total | 28 | 111 | 139 Diagnostic accuracy measured calculated by the NGA technical team: Sensitivity (95% CI)= 53.57 (33.87 to 72.49) Specificity (95% CI)= 84.68 (76.61 to 90.82) Positive likelihood ratio= 3.50 (2.00 to 6.11) Negative likelihood ratio= 0.55 (0.37 to 0.82) Positive predictive value= 46.87 (33.58 to 60.63) Negative predictive value= 87.85 (82.82 to 91.56) Accuracy of locoregional recurrence diagnosis: Sensitivity: 42.9% Specificity: 88.6% (Unable to construct 2x2 table and estimate uncertainty) Accuracy of distant recurrence diagnosis: Sensitivity: 100% Specificity: 98.5% (Unable to construct 2x2 table and estimate uncertainty) Accuracy of contrast-enhanced CT | | Recurrence + | Recurrence - | CT + | 18 | 15 |	**Patient Selection** A. Risk of Bias Was a consecutive or random sample of patients enrolled? Yes. Was a case-control design avoided? Yes. Did the study avoid inappropriate exclusions? Yes. Could the selection of patients have introduced bias? Low risk. B. Concerns regarding applicability: Are there concerns that the included patients and setting do not match the review question? Low concern. **Index Test** A. Risk of Bias Were the index test results interpreted without knowledge of the results of the reference standard? Yes. If a threshold was used, was it pre-specified? Yes. (Diagnostic criteria of recurrence was defined.) Could the conduct or interpretation of the index test have

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Study dates **Source of funding**		and drank 300 mL of water just before undergoing FDG PET/CT. The PET/CT scan was started 55-60 min after the administration of 296-444 MBq FDG using an integrated PET/ CT system (Biograph Sensation 16, Siemens Medical Systems, Munich, Germany). The axes of both systems are mechanically aligned to coincide optimally. CT data were acquired first and the following parameters were used: tube rotation time 0.5 sec per revolution, 120 kV, 140 mAs, reconstructed slice thickness 5 mm. No contrast medium was used for the CT examination. Af- ter the CT data had been completely acquired, the table top with the patient automatically advanced into the PET sensitive field of view and acquisition of PET data was started in three-dimen- sional mode with the patient in exactly the same position on the table. Scanning was		CT - 10 96 Total 28 111 Diagnostic accuracy measured calculated by the NGA technical team: Sensitivity (95% CI)= 64.29 (44.07% to 81.36%) Specificity (95% CI)= 86.49 (78.69% to 92.23%) Positive likelihood ratio= 4.76 (2.76 to 8.21) Negative likelihood ratio= 0.41 (0.25 to 0.68) Positive predictive value= 54.55 (41.02% to 67.44%) Negative predictive value= 90.57 (85.31% to 94.07%) Accuracy of locoregional recurrence diagnosis: Sensitivity: 42.9% Specificity: 94.7% (Unable to construct 2x2 table and estimate uncertainty) Accuracy of distant recurrence diagnosis: Sensitivity: 71.4% Specificity: 95.5% (Unable to construct 2x2 table and estimate uncertainty) **Patient Anxiety:** Not reported	introduced bias? Low risk. B. Concerns regarding applicability: 2 experienced nuclear medicine physicians examined the images. Are there concerns that the index test, its conduct, or interpretation differ from the review question? Low concern. **Reference Standard** A. Risk of Bias Is the reference standards likely to correctly classify the target condition? Yes Were the reference standard results interpreted without knowledge of the results of the index tests? Unclear Could the reference standard, its conduct, or its interpretation have introduced bias? Unclear risk. B. Concerns regarding applicability Are there concerns that the target condition as defined by the reference standard does not match the

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
		performed in one bed position for 3 min. The attenuation correction was automatically completed using corresponding CT data.			question? Low concern. **Flow and Timing** A. Risk of Bias Was there an appropriate interval between index test and reference standard? Yes. Did all patients receive the same reference standard? No (25 had histopathology and 114 based on clinical and radiologic follow-up) Were all patients included in the analysis? Yes Could the patient flow have introduced bias? High risk. **Other information** See Li, 2016 SR for additional study details.
Full citation Lee, D. Y., Lee, C. H., Seo, M. J., Lee, S. H., Ryu, J. S.,	**Sample size** **Characteristics**	**Tests** 18F-FDG PET/CT imaging Before 18F-FDG PET/CT, all patients fasted for C6 h prior to the injection of 18F-FDG. Venous blood glucose	**Methods**	**Results** Recurrence + Recurrence -	**Limitations** QUADAS-2 a quality assessment tool for diagnostic accuracy studies: Overall: low risk of bias **Patient Selection** A. Risk of Bias

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Lee, J. J., Performance of (18)F-FDG PET/CT as a postoperative surveillance imaging modality for asymptomatic advanced gastric cancer patients, Annals of Nuclear MedicineAnn Nucl Med, 28, 789-95, 2014 **Ref Id** 514371 **Country/ies where the study was carried out** **Study type** Retrospective cohort study	**Inclusion Criteria** **Exclusion Criteria**	was \140 mg/dL. All patients were instructed to drink 500 mL water before 18F-FDG injection. Patients were injected with 370–555 MBq (10–15 mCi) 18F-FDG, and *60 min after the injection 18F-FDG PET scans were acquired from the base of the skull to the upper thigh for 2–3 min per each bed position using a total of 5–6 bed positions. Delayed scan was not performed. Discovery STE (GE Healthcare, Milwaukee, WI, USA), Discovery 690 (GE Healthcare), Biograph Sensation16 (Siemens, Knoxville, TN, USA), or Biograph TruePoint 40 scanners (Siemens) were used. All PET images were reconstructed using an iterative algorithm with attenuation correction. Each scanner was routinely calibrated against the dose calibrators and well counters. The measured standardized uptake value (SUV) of the phantoms was within the acceptable range of 90–		PET+ | 4 | 5 | 9 PET- | 0 | 37 | 37 Total | 4 | 42 | 46 Diagnostic accuracy calculated by NGA technical team: Sensitivity (95% CI)= 100% (39.76 to 100%) Specificity (95% CI)= 88.1 (74.37 to 96.02) Positive likelihood ratio= 8.40 (3.69 to 19.12) Negative likelihood ratio= 0.00 Positive predictive value= 44.44 (26.00 to 64.56) Negative predictive value= 100% **Local recurrence:** | Recurrence + | Recurrence - | PET+ | 1 | 3 PET- | 0 | 42 Total | 1 | 45 | 46 Diagnostic accuracy calculated by NGA technical team: Sensitivity (95% CI)= 100% (2.5 to 100%) Specificity (95% CI)= 93.33 (81.73 to 98.60)	Was a consecutive or random sample of patients enrolled? Yes. Was a case-control design avoided? Yes. Did the study avoid inappropriate exclusions? Yes. Could the selection of patients have introduced bias? Low risk. B. Concerns regarding applicability: Are there concerns that the included patients and setting do not match the review question? Low concern. **Index Test** A. Risk of Bias Were the index test results interpreted without knowledge of the results of the reference standard? Yes. Nuclear medicine physicians were blinded to patient information. If a threshold was used, was it pre-specified? Yes. (Diagnostic criteria of recurrence was defined.) Could the conduct or interpretation of the

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>Aim of the study

Study dates

Source of funding</td>
<td></td>
<td>110 %. Routine calibration and PET scanner normalization were conducted (at least quarterly) using GE-68 cylinders (which were changed annually). Cross-calibration of each scanner against the dose calibrator (performed annually along with GE-68 cylinder replacement) and well counters (quarterly) was routinely performed.</td>
<td></td>
<td>Positive likelihood ratio= 15.00 (5.03 to 44.76)
Negative likelihood ratio= 0.00
Positive predictive value= 25.00 (10.05 to 49.87)
Negative predictive value= 100%

Distant recurrence:
<table>
<tr><td></td><td>Recurrence +</td><td>Recurrence -</td><td>Total</td></tr>
<tr><td>PET +</td><td>3</td><td>3</td><td></td></tr>
<tr><td>PET -</td><td>0</td><td>40</td><td></td></tr>
<tr><td>Total</td><td>3</td><td>43</td><td></td></tr>
</table>
Diagnostic accuracy calculated by NGA technical team:
Sensitivity (95% CI)= 100% (29.24 to 100%)
Specificity (95% CI)= 93.02 (80.94 to 98.54)
Positive likelihood ratio= 14.33 (4.81 to 42.69)
Negative likelihood ratio= 0.00
Positive predictive value= 50.00 (25.14 to 74.86)
Negative predictive value= 100%

Patient Anxiety:
Not reported</td>
<td>index test have introduced bias? Low risk.
B. Concerns regarding applicability:
Are there concerns that the index test, its conduct, or interpretation differ from the review question? Low concern.
Reference Standard
A. Risk of Bias
Is the reference standards likely to correctly classify the target condition? Yes.
Were the reference standard results interpreted without knowledge of the results of the index tests? Yes.
Could the reference standard, its conduct, or its interpretation have introduced bias? Low risk.
B. Concerns regarding applicability
Are there concerns that the target condition as defined by the reference standard does not match the question? Low concern.
Flow and Timing</td>
</tr>
</table>

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>A. Risk of Bias
Was there an appropriate interval between index test and reference standard? Yes.
Did all patients receive the same reference standard? No- confirmation of recurrence was a combination of tumour markers, chest CT, endoscopy as indicated
Were all patients included in the analysis? Yes
Could the patient flow have introduced bias? Unclear risk.

Other information
For additional study details see Li, 2016 SR.</td></tr>
<tr><td>Full citation

Lee, E. C., Yang, J. Y., Lee, K. G., Oh, S. Y., Suh, Y. S.,</td><td>Sample size
N= 1304

Characteristics

881 male/433 female</td><td>Tests

Index Test: Serum CEA and CA 19-9

Serum levels of CEA and CA19-9 were measured using the</td><td>Methods
Follow-up

Patient follow-up included measurement of serum CEA and CA19-9 levels, along with physical examination, abdomino pelvic CT or abdominal sonography, and</td><td>Results
CEA<table><tr><td></td><td>Recurrence +</td><td>Recurrence -</td><td>Total</td></tr></table></td><td>Limitations
QUADAS-2 a quality assessment tool for diagnostic accuracy studies:
Overall quality: high risk of bias.
Patient Selection</td></tr>
</table>

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>Kong, S. H., Yang, H. K., Lee, H. J., The value of postoperative serum carcinoembryonic antigen and carbohydrate antigen 19-9 levels for the early detection of gastric cancer recurrence after curative resection, Journal of Gastric CancerJ, 14, 221-8, 2014

Ref Id

514372

Country/ies where the study was carried out

Korea</td>
<td>Mean age= 57.0 (11.6)
<table><tr><td>Tumor stage*</td><td></td></tr><tr><td>I</td><td>835 (63.</td></tr><tr><td>II</td><td>233 (16.</td></tr><tr><td>III</td><td>246 (17.</td></tr></table>The number of patients who underwent a partial gastrectomy and total gastrectomy were 1,038 (79.0%) and 276 (21.0%), respectively. There were 835 (63.5%) patients with stage I disease, 233 (16.5%) with stage II disease, and 246 (17.7%) with stage III disease.

Inclusion Criteria

Patients who underwent curative (R0) gastric cancer surgery from January 1, 2005 to December</td>
<td>immunoradiometric method (the ‘sandwich’ method) with iodine-125. Cut-off values were 5.0 ng/ml for CEA and 37 U/ml for CA19-9. In patients with recurrence, confirmed by imaging or pathologic findings, during the follow-up period, postoperative tumor marker levels measured ＜3 months before or after the time of recurrence were considered. For those without recurrence, the postoperative tumor marker levels considered were the highest levels measured during the follow-up period.

Reference test

Recurrence confirmed by imaging or pathology.</td>
<td>gastrofiberoscopy, conducted every 6 months. Because disease recurrence in most cases occurs within the first 2 years after surgery, the follow-up period for this study was 2 years.</td>
<td><table><tr><td>CEA +</td><td>52</td><td>99</td><td></td></tr><tr><td>CEA -</td><td>76</td><td>843</td><td></td></tr><tr><td></td><td></td><td></td><td>1070</td></tr></table>Diagnostic test results calculated by NGA technical team:
Sensitivity (95% CI)= 40.62 (32.04-49.66)
Specificity (95% CI)= 89.49 (87.35- 91.38)
Positive likelihood ratio= 3.87 (2.92- 5.12)
Negative likelihood ratio= 0.66 (0.57- 0.77)
Positive predictive value= 34.44 (28.41 to 41.01)
Negative predictive value= 91.73 (90.56 to 92.77)
CA 19-9
<table><tr><td></td><td>Recurrence +</td><td>Recurrence -</td><td>Total</td></tr><tr><td>CA 19-9 +</td><td>40</td><td>57</td><td></td></tr><tr><td>CA 19-9 -</td><td>77</td><td>828</td><td></td></tr><tr><td></td><td></td><td></td><td>1002</td></tr></table>Diagnostic test results calculated by NGA technical team:
Sensitivity (95% CI)= 34.19 (25.67- 43.53)</td>
<td>A. Risk of Bias
Was a consecutive or random sample of patients enrolled? Yes.
Was a case-control design avoided? Yes.
Did the study avoid inappropriate exclusions? Yes
Could the selection of patients have introduced bias? Low risk.
B. Concerns regarding applicability:
Are there concerns that the included patients and setting do not match the review question? Low concern.
Index Test
A. Risk of Bias
Were the index test results interpreted without knowledge of the results of the reference standard? Yes.
If a threshold was used, was it pre-specified?
Yes. (Diagnostic criteria was defined.)
Could the conduct or interpretation of the index test have introduced bias? Low risk.</td>
</tr>
</table>

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>Study type

Retrospective cohort study

Aim of the study

This study aimed to evaluate the value of serum carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) levels to detect gastric</td>
<td>31, 2006 at Seoul National University Hospital.

Exclusion Criteria

Patients who underwent gastric cancer surgery for recurrence or metastasis were excluded.</td>
<td></td>
<td></td>
<td>Specificity (95% CI)= 93.56 (91.74- 95.09)
Positive likelihood ratio= 5.31 (3.72- 7.57)
Negative likelihood ratio= 0.70 (0.62 - 0.80)
Positive predictive value= 41.24 (32.97- 50.03)
Negative predictive value= 91.49 (90.41- 92.46)
CEA or CA 19-9
<table>
<tr><td></td><td>Recurrence +</td><td>Recurrence -</td><td>Total</td></tr>
<tr><td>CEA or CA 19-9 +</td><td>69</td><td>141</td><td></td></tr>
<tr><td>CEA or CA 19-9 -</td><td>58</td><td>740</td><td></td></tr>
<tr><td></td><td></td><td></td><td>1008</td></tr>
</table>
Diagnostic test results calculated by NGA technical team:
Sensitivity (95% CI)= 54.33 (45.26-63.19)
Specificity (95% CI)= 84.00 (81.40-86.36)
Positive likelihood ratio= 3.39 (2.72- 4.23)
Negative likelihood ratio= 0.54 (0.45- 0.66)
Positive predictive value= 32.86 (28.20-37.88)
Negative predictive value= 92.73 (91.33 to 93.92)
CEA AND CA 19-9
<table>
<tr><td></td><td>Recurrence +</td><td>Recurrence -</td><td>Total</td></tr>
</table>
</td>
<td>B. Concerns regarding applicability:
Are there concerns that the index test, its conduct, or interpretation differ from the review question? Low concern.
Reference Standard
A. Risk of Bias
Is the reference standards likely to correctly classify the target condition? Yes.
Were the reference standard results interpreted without knowledge of the results of the index tests? Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias? Unclear risk.
B. Concerns regarding applicability
Are there concerns that the target condition as defined by the reference standard does not match the question? Low concern.
Flow and Timing
A. Risk of Bias
Was there an appropriate interval</td>
</tr>
</table>

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
cancer recurrence. **Study dates** January 1, 2005 to December 31, 2006 **Source of funding** This study was supported by research grant from Cancer Research Institute, Seoul National University (2012) and by a grant from the National R&D Program for Cancer				CEA and CA 19-9 + 23 15 CEA and CA 19-9 - 97 929 1064 Diagnostic test results calculated by NGA technical team: Sensitivity (95% CI)= 19.17 (12.56-27.36) Specificity (95% CI)= 98.41 (97.39 - 99.11) Positive likelihood ratio= 12.06 (6.47- 22.47) Negative likelihood ratio= 0.82 (0.75 - 0.90) Positive predictive value= 60.53 (45.15 - 74.07) Negative predictive value= 90.55 (89.77 - 91.27)	between index test and reference standard? Unclear Did all patients receive the same reference standard? No- imaging or histophathology Were all patients included in the analysis? No- 201 patients included were lost to follow up Could the patient flow have introduced bias? High risk. **Other information** 1505 patients were initially included but 201 were lost to follow-up over the 2 years.

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td>Control, Ministry of Health & Welfare, Republic of Korea (1320270)</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Full citation

Lee, J. E., Hong, S. P., Ahn, D. H., Jeon, T. J., Kang, M. K., Kwon, C. I., Ko, K. H., Hwang, S. G., Park, P. W., Rim, K. S., The role of 18F-FDG PET/CT in the evaluation of gastric cancer recurrence after curative gastrectomy, Yonsei Medical JournalYon</td><td>Sample size

Characteristics

Inclusion Criteria

Exclusion Criteria</td><td>Tests
18F-FDG PET/CT scan The patients fasted at least 4 h prior to intravenous injection of 370-666 MBq [10-18 mCi (0.14 mCi/kg)] 18F-FDG Blood glucose levels were checked in patients with diabe- tes and patients who did not know their blood glucose lev- els prior to the injection of 18F-FDG. A PET/CT scan was performed only when blood glucose levels did not exceed 150 mg/dL (8.3 mmol/L). Data acquisition was done by an integrated PET/CT system (Philips Gemini, DA Best, the Netherlands) 1 h after the 18F-FDG injections. CT scanning was performed prior to the PET scan from the head</td><td>Methods</td><td>Results
<table>
<tr><td></td><td>Recurrence +</td><td>Recurrence -</td><td></td></tr>
<tr><td>PET/Ct +</td><td>9</td><td>29</td><td></td></tr>
<tr><td>PEt/CT -</td><td>12</td><td>43</td><td></td></tr>
<tr><td></td><td></td><td></td><td></td></tr>
</table>
Diagnostic test results calculated by NGA technical team:
Sensitivity (95% CI)= 42.86 (21.82-65.98)
Specificity (95% CI)= 59.72 (47.50-71.12)
Positive likelihood ratio= 1.06 (0.60 - 1.88)
Negative likelihood ratio= 0.96 (0.63 - 1.45)
Positive predictive value= 23.68 (14.95- 35.40)
Negative predictive value= 78.18 (70.27-84.45)
<table>
<tr><td></td><td>Recurrence +</td><td>Recurrence -</td><td>Total</td></tr>
</table></td><td>Limitations
QUADAS-2 a quality assessment tool for diagnostic accuracy studies:
Overall quality: high risk of bias.
Patient Selection
A. Risk of Bias
Was a consecutive or random sample of patients enrolled? Yes.
Was a case-control design avoided? Yes.
Did the study avoid inappropriate exclusions? Yes
Could the selection of patients have introduced bias? Low risk.
B. Concerns regarding applicability:
Are there concerns that the included patients and setting do not match the review</td></tr>
</table>

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>sei Med J, 52, 81-8, 2011

Ref Id

514377

Country/ies where the study was carried out

Study type

Retrospective cohort study

Aim of the study

Study dates

Source of funding</td>
<td></td>
<td>to the pelvic floor with 120 kVp, 250 mA, and a 5.3 mm section thickness. Next, the PET scan was performed with a 5-min emission acquisition per imaging level and the images were reconstructed. PET image data was acquired by imaging re-construction using a Row Action Maximum Likelihood Al- gorithm (RAMLA). A board certified nuclear radiologist re- viewed the 18F-FDG PET/CT scans. Strong and focal FDG uptake combined with a delayed image was indicative of a recurring malignant lesion, but diffuse or segmental pat-terns without focally increased accumulation were inter- preted as physiologic uptakes.
Abdominopelvic contrast CT scan
The patients fasted at least 6 h prior to the CT scan, and in- gested 600-800 mL of oral contrast. Scanning from above the diaphragm to the greater trochanter was performed using a 16-row multi-slice CT unit</td>
<td></td>
<td>
<table>
<tr><td>CT +</td><td>18</td><td>9</td><td></td></tr>
<tr><td>CT -</td><td>3</td><td>62</td><td></td></tr>
<tr><td>Total</td><td>21</td><td>71</td><td></td></tr>
</table>
Diagnostic test results calculated by NGA technical team:
Sensitivity (95% CI)= 85.71 (63.66% to 96.95%)
Specificity (95% CI)= 87.32 (77.30% to 94.04%)
Positive likelihood ratio= 6.76 (3.58 to 12.76)
Negative likelihood ratio= 0.16 (0.06 to 0.47)
Positive predictive value= 66.67 (51.45% to 79.05%)
Negative predictive value= 95.38 (87.84% to 98.34%)
</td>
<td>question? Low concern.
Index Test
A. Risk of Bias
Were the index test results interpreted without knowledge of the results of the reference standard? Yes.
If a threshold was used, was it pre-specified?
Yes. (Diagnostic criteria was defined.)
Could the conduct or interpretation of the index test have introduced bias? Low risk.
B. Concerns regarding applicability:
Are there concerns that the index test, its conduct, or interpretation differ from the review question? Low concern.
Reference Standard
A. Risk of Bias
Is the reference standards likely to correctly classify the target condition? Yes.
Were the reference standard results interpreted without knowledge of the</td>
</tr>
</table>

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
		(Sensation 16; Siemens Medical Solutions, Erlangen, Germany), with 120 kVp, 300 mA, and 5 mm section thickness at 7 mm/sec table speed.			results of the index tests? Unclear (unlikely) Could the reference standard, its conduct, or its interpretation have introduced bias? Unclear risk. B. Concerns regarding applicability Are there concerns that the target condition as defined by the reference standard does not match the question? Low concern. **Flow and Timing** A. Risk of Bias Was there an appropriate interval between index test and reference standard? Unclear Did all patients receive the same reference standard? No-histopathology, other imaging or clinical follow-up Were all patients included in the analysis? Yes Could the patient flow have introduced bias? High risk.

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>Other information
For other information see Li 2016 SR.</td></tr>
<tr><td>Full citation

Lee, J. W., Lee, S. M., Son, M. W., Lee, M. S., Diagnostic performance of FDG PET/CT for surveillance in asymptomatic gastric cancer patients after curative surgical resection, European Journal of Nuclear Medicine and Molecular Imaging, 43, 881-888, 2016

Ref Id</td><td>Sample size
N= 190

Characteristics
Age 61 years (29-80)
66% male
Operation type: total gastrectomy (83%), subtotal (16.8%)
Stage: T1 (60.5%), T2 (25.8%), T3 (10.5%), T4 (3.2%)

FDG PET/CT at 12 months: 91 patients
FDG PET/CT at 24 months: 99 patients

Inclusion Criteria

(1) underwent curative surgical resection for histopathologically confirmed gastric cancer,</td><td>Tests
PET/CT

FDG PET/CT scans were performed with using a Gemini PET/CT scanner (Philips, Milpitas, CA, USA) or a Biograph mCT 128 scanner (Siemens Healthcare, Knoxville, TN, USA). All patients fasted for at least 6 h before the scans. Patients were intravenously injected with 5.18MBq/kg (Gemini PET/CT scanner) or 4.07 MBq/kg (Biograph mCT 128 scanner) of FDG approximately 60 min before the imaging. The blood glucose level in every patient was <150.0 mg/dL before FDG injection [22]. Prior to PET/CTscanning, patients were instructed to drink at least 500 ml of water. Each PET/CT scan was acquired from the skull base to the</td><td>Methods

Patients

The institutional review board of our university approved this retrospective study, and the requirement to obtain informed consent was waived. We retrospectively reviewed the medical records of all patients with gastric cancer who had undergone curative surgical resection at our medical center between 2007 and 2012. Of these patients, we recruited asymptomatic gastric cancer patients who underwent 1- or 2-year postoperative FDG PET/CT surveillance after surgical resection, in addition to a routine followup program.

Data analyses</td><td>Results
<table><tr><td></td><td>Recurrence (+)</td><td>Recurrenc</td></tr><tr><td>PET (+)</td><td>16</td><td>21</td></tr><tr><td>PET (-)</td><td>3</td><td>150</td></tr><tr><td>Totals</td><td>19</td><td>171</td></tr></table>Sensitivity (95% CI): 84.21 (60.42-96.62)
Specificity (95% CI): 87.72 (81.84-92.23)
Positive likelihood ratio: 6.86 (4.39-10.70)
Negative likelihood ratio: 0.18 (0.06 to 0.51)
Positive predictive value: 43.24 (32.80 to 54.33)
Negative predictive value: 98.04 (94.64 to 99.30)

Diagnostic tests calculated by NGA technical team .

Patient Anxiety
not reported</td><td>Limitations
QUADAS-2 a quality assessment tool for diagnostic accuracy studies:
Overall= Low risk of bias.
Patient Selection
A. Risk of Bias
Was a consecutive or random sample of patients enrolled? Yes.
Was a case-control design avoided? Yes.
Did the study avoid inappropriate exclusions? Yes.
Could the selection of patients have introduced bias? Low risk.
B. Concerns regarding applicability:
Are there concerns that the included patients and setting do not match the review question? Low concern.
Index Test
A. Risk of Bias</td></tr>
</table>

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
488084 **Country/ies where the study was carried out** Korea **Study type** Retrospective cohort study **Aim of the study** The present study evaluated the diagnostic performance of 2-[18F] fluoro-2-deoxy-D-glucose (FDG) positron emission tomography /computed	(2) underwent surveillance FDG PET/CT in addition to follow-up examinations at 1 year (second follow-up examination) or 2 years (fourth follow-up examination) after surgical resection, (3) absence of symptoms or signs of recurrence at the time of FDG PET/ CT scan, and (4) no evidence of recurrence by conventional follow-up examinations performed before the FDG PET/CT scan at 6 months (first follow-up examination) or 18 months (third follow-up examination) after surgery. **Exclusion Criteria** Patients who had a history of another	proximal thigh in one bed position for 2.5 min for the Gemini PET/CT scanner and 1.5 min for the Biograph mCT 128 scanner. At first, a CT scan was performed without contrast enhancement. Subsequently, a PET scan was performed in the three-dimensional (3D) mode. PET images were reconstructed with an iterative reconstruction algorithm with attenuation correction. All the PET/CT images of enrolled patients were interpreted by a board-certified nuclear medicine physician. **Diagnosis of cancer recurrence** For patients who showed abnormal findings on FDG PET/CT and routine follow-up examinations, histopathological confirmation or clinical follow-up for more than	The findings of FDG PET/CT were compared with the histopathological findings and the results of the follow-up studies. The diagnostic performance of FDG PET/CT in all patients was evaluated in terms of sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Additionally, patients were classified into two groups according to the T stage, early gastric cancer (histopathologically T1 stage, irrespective of lymph node metastasis) and advanced gastric cancer (histopathologically T2-T4 stage), and according to the time interval between operation and FDG PET/CT scan, 1-year postoperative and 2-year postoperative FDG PET/CT. The diagnostic performance of FDG PET/CTin each group was further assessed and compared using the chi-square test and Fisher's exact test. The statistical analyses were performed using MedCalc version 15.6 (MedCalc software, Mariakerke, Belgium).		Were the index test results interpreted without knowledge of the results of the reference standard? Yes. If a threshold was used, was it pre-specified? Yes. (Diagnostic criteria of recurrence was defined by PET criteria and clinical and histopathological criteria) Could the conduct or interpretation of the index test have introduced bias? Low risk. B. Concerns regarding applicability: Are there concerns that the index test, its conduct, or interpretation differ from the review question? Low concern. **Reference Standard** A. Risk of Bias Is the reference standards likely to correctly classify the target condition? Yes. Were the reference standard results interpreted without knowledge of the

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
tomography (PET/CT) for surveillance in asymptomatic gastric cancer patients after curative surgical resection. **Study dates** Patients underwent resection between 2007 and 2012 and subsequent 1 and 2 year follow-up. **Source of funding** This work was supported	malignancy or who were lost to follow-up after FDG PET/CT surveillance were excluded from the study.	12 months with tumor markers and imaging studies was performed to confirm gastric cancer recurrence. For patients who showed elevated serum tumor marker level without abnormal findings on imaging studies or gastroduodenoscopy, the recurrence of gastric cancer was determined by clinical follow-up for more than 12 months with tumor marker follow-up and diagnostic studies including FDG PET/CT and contrast-enhanced CT.			results of the index tests? Yes. Could the reference standard, its conduct, or its interpretation have introduced bias? Low risk. B. Concerns regarding applicability Are there concerns that the target condition as defined by the reference standard does not match the question? Low concern. **Flow and Timing** A. Risk of Bias Was there an appropriate interval between index test and reference standard? Yes. Did all patients receive the same reference standard? Yes. Were all patients included in the analysis? Yes Could the patient flow have introduced bias? Low risk **Other information**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
in part by the Soonchunhyang University Research Fund.					
Full citation Lee, J. Y., Choi, I. J., Cho, S. J., Kim, C. G., Kook, M. C., Lee, J. H., Ryu, K. W., Kim, Y. W., Routine follow-up biopsies after complete endoscopic resection for early gastric cancer may be unnecessary, Journal of Gastric CancerJ, 12, 88-98, 2012	**Sample size** N= 372 **Characteristics** NR for population overall. **Inclusion Criteria** Between January 2002 and April 2008, ERs were performed to treat 536 EGCs in 500 consecutive patients at the National Cancer Center, Goyang, Korea. Patients were followed-up to examine for recurrence until April 2011.	**Tests** N/A	**Methods** <u>ER Technique</u> ER was performed by ESD or EMR, either by a cap-fitted endoscope and suction method (EMR-C) or a circumferential mucosal incision and snaring method (EMR-P). Patients were sedated with midazolam (2.5~5.0 mg) and meperidine (25~50 mg) administered intravenously. EMR-C was performed with a single or two-channel endoscope (GIF-Q240 or GIF-2T240; Olympus Co. Ltd, Tokyo, Japan), transparent hoods (MH-594 or MAJ-665; Olympus Co. Ltd), and a crescent-shaped snare (SD-7P-1; Olympus Co. Ltd) as previously described.(14) The EMR-P was performed with a two-channel endoscope (GIF-2T240) as previously reported. (15) After making a circumferential mucosal incision with a needle papillotome (MTW Endoscopy, Wesel, Germany), the lesion was	**Results** <u>Recurrence Rate</u> The 5-years cumulative recurrence rate was 4.8%. Recurrence was found in 12 of the 17 cases of local recurrence (71%) within 12 months, while local recurrence was detected in the other five cases (29%) after 12 months (range: 17-49 months).	**Limitations** 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results Unclear (Eastern setting and population) 1.2 Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias Unclear (23 patients with follow-up less than 6 months excluded) 1.3 The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias Yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Ref Id 514381 **Country/ies where the study was carried out** Korea **Study type** Retrospective cohort study **Aim of the study** The aims of this study are to evaluate the predictive factors for local recurrence, and suggest an appropriate follow-up biopsy strategy.	The criteria for ER were: histologically confirmed well- or moderately-differentiated adenocarcinoma with an endoscopic diagnosis of mucosal cancer, a lesion with diameter ＜3 cm, and no ulcerative findings. The following cases were excluded from risk factor analysis: cases without follow-up endoscopic examination or surgical resection; cases with argon plasma coagulation immediately after ER to eradicate possible residual cancer; cases with less than 6 months of follow-up; and cases with surgical resection immediately after ER. **Exclusion Criteria** Those with follow-up of less than 6 months.		resected by direct snaring with an oval-shaped device (SD-16L-1; Olympus Co. Ltd). ESD was performed with a single-channel endoscope (GIF-H260; Olympus Co. Ltd) as previously described.(16) After making a circumferential incision, the submucosal layer was dissected with an ESD-knife (MTW Endoscopy) and/or a fixed flexible snare (Kachu Technology, Seoul, Korea). Follow-up Patients with complete resections and patients with incomplete resections who declined additional surgery were examined endoscopically 3, 6, and 12 months after ER and annually thereafter. To evaluate local recurrence, two to four biopsy specimens were routinely obtained from the ER ulcer scar during each examination with standard fenestrated open-cup forceps (FB- 25K-1; Olympus Co. Ltd) or ellipsoid fenestrated cup forceps with needle (FB-24K-1; Olympus Co. Ltd). Local recurrence was defined as the cancer detected at the ER ulcer scar in the follow-up biopsy regardless of period from ER.		1.4 The outcome of interest is adequately measured in study participants, sufficient to limit potential bias Yes 1.5 Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest Yes 1.6 The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results Yes **Other information**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Study dates January 2002 and April 2008 **Source of funding** This work was supported by a grant from the National Cancer Center, Korea (1210230).					
Full citation Lou, F., Sima, C. S., Adusumilli, P. S., Bains, M. S.,	**Sample size** N= 1147 **Characteristics** 77.4% male Mean age= 63 (range 21-89)	**Tests** N/A	**Methods** <u>Retrospective Methodology</u> Details on recurrences were obtained from medical records from MSKCC and outside institutions, when available, and	**Results** <u>Recurrence rate</u> Overall recurrence: 435/1147 Distant and locoregional: 73/1147 Distant: 241/1147 Locoregional: 121/1147 <u>Disease-free survival</u> 2 year recurrence rate: 326/1147	**Limitations** 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results Yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Sarkaria, I. S., Rusch, V. W., Rizk, N. P., Esophageal cancer recurrence patterns and implications for surveillance, Journal of Thoracic Oncology: Official Publication of the International Association for the Study of Lung CancerJ Thorac Oncol, 8, 1558-62, 2013 **Ref Id** 514430 **Country/ies where the study was carried out**	17.9% SCC/ 82.1% adenocarcinoma Induction therapy Chemotherapy 67 (5.8%) Chemoradiation therapy 656 (57.2%) None 424 (37.0%) **Inclusion Criteria** Patients who had undergone esophagectomy for pathologic stage I to III esophageal adenocarcinoma or squamous cell carcinoma at Memorial Sloan-Kettering Cancer Center (MSKCC) between 1996 and 2010.		from documented patient communications. In some instances, questionnaires regarding recurrences and long-term complications were mailed every 2 to 3 years to patients who were not receiving follow-up at MSKCC. <u>Follow-up</u> After surgery, patients received regular follow-up from their surgeon and/or medical oncologist. Clinic visits took place every 4 to 6 months for the first 2 years after surgery and then yearly thereafter. Each visit consisted of a medical history, physical examination, and chest and abdominal CT scan. In general, surveillance upper endoscopy was performed every 6 months for 2 years and then yearly thereafter by either the primary surgeon or a gastroenterologist. <u>Definition of Recurrence</u> Once a recurrence was suspected, patients underwent further workup that included PET/CT scan, endoscopic ultrasound, upper endoscopy, biopsy, or other modalities	The median time to recurrence was 5.5 years (95% confidence interval [CI], 3.8–8.1 years) <u>Overall survival</u> Unable to extract data- only reported graphically.	1.2 Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias Unclear (follow-up from difference sources- MSKCC institution and others) 1.3 The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias Yes 1.4 The outcome of interest is adequately measured in study participants, sufficient to limit potential bias Yes 1.5 Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest Yes 1.6 The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results Yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
US **Study type** Retrospective cohort study **Aim of the study** We investigated posttreatment recurrence patterns and methods of detection in survivors of esophageal cancer. **Study dates** 1996 and 2010 **Source of funding**	**Exclusion Criteria** Exclusion criteria were histologic type other than squamous cell carcinoma or adenocarcinoma (*n* = 36), Barrett's esophagus or carcinoma in situ (*n* = 64), R2 resection (*n* = 95), stage IV disease (*n* = 25), primary resection not performed at MSKCC (*n* = 4), and nonesophageal primary cancer (*n* = 2).		specific to the suspected site of recurrence. The date of detection of recurrence was defined as the date at which the initial abnormal surveillance study or symptomatic presentation led to further workup and diagnosis of recurrence. Diagnosis of recurrence was adjudicated by pathologic confirmation or by findings by other study modalities that led to changes in treatment. Locoregional recurrence was defined as a recurrence isolated to the area of the anastomosis (perianastomotic) or in lymph nodes in the mediastinum and upper abdomen (supraceliac). Distant recurrence was defined as any spread of disease beyond a locoregional recurrence.		**Other information**

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td>NIH/NCI Cancer Center Support Grant P30 CA008748.</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Full citation

Marrelli, D., Pinto, E., De Stefano, A., Farnetani, M., Garosi, L., Roviello, F., Clinical utility of CEA, CA 19-9, and CA 72-4 in the follow-up of patients with resectable gastric cancer, American Journal of SurgeryAm J Surg, 181, 16-9, 2001</td><td>Sample size
N=133

Characteristics
80 male/ 53 female
Mean age= 66 (range 30-82)

Inclusion Criteria
Patients resected for primary cancer of the stomach.

Exclusion Criteria
Patients who underwent noncurative surgery, those who died of causes not associated with tumor recurrence, those with second</td><td>Tests
Index test: tumour markers
Blood samples were taken from patients upon admission to the hospital, 1 week after surgery, and at every follow-up examination. Assay for the markers CEA, CA 19-9, and CA 72-4 was performed using enzyme immunoassay commercial kits (Cobas Core EIA, Roche, Basel, Switzerland). Pathological cut-off levels were established as 5 ng/mL for CEA, 37 U/mL for CA 19-9, and 6 U/mL for CA 72-4, as previously reported.
Reference test:
Diagnosis of recurrence based on clinical follow-up</td><td>Methods
Follow-up
All patients were included in a follow-up program; follow-up examinations were performed 1 month after surgery, once per trimester for the first 2 years, and every semester for the years thereafter. The follow-up program included clinical examination, hematological analyses, and tumor marker assay (at each checkup), abdominal ultrasound and chest radiograph (every 6 months), and endoscopy of the upper digestive tract (once a year). Abdominal computed tomography (CT) scan was performed in cases of suspected recurrence, as well as after diagnosis of recurrence, in order to complete staging. Mean follow-up period for the entire patient population was 41 6 33 months, and 71 6 27 months for patients classified as disease-free.</td><td>Results
CEA marker
<table><tr><td></td><td>Recurrence +</td><td>Recurrence -</td><td></td></tr><tr><td>CEA +</td><td>33</td><td>12</td><td></td></tr><tr><td>CEA -</td><td>42</td><td>46</td><td></td></tr><tr><td></td><td>75</td><td>58</td><td>133</td></tr></table>Diagnostic test results calculated by NGA technical team:
Sensitivity (95% CI)= 44.00 (32.55-55.94)
Specificity (95% CI)= 79.31 (66.65-88.83)
Positive likelihood ratio= 2.13 (1.21 to 3.74)
Negative likelihood ratio= 0.71 (0.56 to 0.90)
Positive predictive value= 73.33 (60.99 to 82.87)
Negative predictive value= 52.27 (46.29 to 58.20)

CA 19-9 marker</td><td>Limitations
QUADAS-2 a quality assessment tool for diagnostic accuracy studies:
Overall quality: unclear risk of bias.
Patient Selection
A. Risk of Bias
Was a consecutive or random sample of patients enrolled? Unclear
Was a case-control design avoided? Yes.
Did the study avoid inappropriate exclusions? Yes.
Could the selection of patients have introduced bias? Unclear risk.
B. Concerns regarding applicability:
Are there concerns that the included patients and setting do</td></tr>
</table>

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>Ref Id

514451

Country/ies where the study was carried out

Italy

Study type

Retrospective cohort study

Aim of the study
The aim of this longitudinal study was to evaluate the effectiveness of the serum tumor markers CEA, CA 19-9, and CA 72-4 in the early diagnosis of recurrence of gastric cancer.</td>
<td>primaries, and survivors with a follow-up time less than 4 years were excluded.</td>
<td></td>
<td></td>
<td>
<table>
<tr><td></td><td>Recurrence +</td><td>Recurrence -</td><td></td></tr>
<tr><td>CA 19-9 +</td><td>42</td><td>15</td><td></td></tr>
<tr><td>CA 19-9 -</td><td>33</td><td>43</td><td></td></tr>
<tr><td></td><td>75</td><td>58</td><td>133</td></tr>
</table>
Diagnostic test results calculated by NGA technical team:
Sensitivity (95% CI)= 56.00 (44.06 to 67.45)
Specificity (95% CI)= 74.14 (60.96 to 84.74)
Positive likelihood ratio= 2.17 (1.34 to 3.50)
Negative likelihood ratio= 0.59 (0.44 to 0.80)
Positive predictive value= 73.68 (63.41 to 81.90)
Negative predictive value= 56.58 (49.19 to 63.69)

Patient Anxiety
Not reported
</td>
<td>not match the review question? Low concern.
Index Test
A. Risk of Bias
Were the index test results interpreted without knowledge of the results of the reference standard? Yes.
If a threshold was used, was it pre-specified?
Yes. (Diagnostic criteria was defined.)
Could the conduct or interpretation of the index test have introduced bias? Low risk.
B. Concerns regarding applicability:
Are there concerns that the index test, its conduct, or interpretation differ from the review question? Low concern.
Reference Standard
A. Risk of Bias
Is the reference standards likely to correctly classify the target condition? Yes.
Were the reference standard results interpreted without</td>
</tr>
</table>

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Study dates 1988- 1995 **Source of funding** This work was supported by the Ministero Universita` Ricerca Scientifica e Tecnologica, PAR University of Siena, Siena, Italy					knowledge of the results of the index tests? Unclear Could the reference standard, its conduct, or its interpretation have introduced bias? Unclear risk. B. Concerns regarding applicability Are there concerns that the target condition as defined by the reference standard does not match the question? Low concern. **Flow and Timing** A. Risk of Bias Was there an appropriate interval between index test and reference standard? Yes. Did all patients receive the same reference standard? No- clinical follow-up Were all patients included in the analysis? Yes Could the patient flow have introduced bias? Low risk. **Other information**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Full citation Min, B. H., Kim, E. R., Kim, K. M., Park, C. K., Lee, J. H., Rhee, P. L., Kim, J. J., Surveillance strategy based on the incidence and patterns of recurrence after curative endoscopic submucosal dissection for early gastric cancer, Endoscopy Endoscopy, 47, 784-93, 2015 **Ref Id** 514465	**Sample size** N=1306 (included in long-term follow-up) **Characteristics** Mean age= approx. 62 80% male **Inclusion Criteria** Patients who underwent their first ESD for differentiated-type early gastric cancer (well or moderately differentiated early gastric cancer or papillary early gastric cancer) at Samsung Medical Center between November 2003 and May 2011 were enrolled in this study. Those undergoing curative endoscopic resection.	**Tests** N/A	**Methods** ESD procedure In brief, ESD consists of three steps: (i) injecting fluid into the submucosal layer to separate it from the proper muscle layer; (ii) circumferential cutting of the mucosa surrounding surrounding the lesion; and (iii) submucosal dissection of the connective tissue under the lesion with an electrosurgical knife. Follow-up Esophagogastroduodenoscopy (EGD) with a biopsy was performed 2months after ESD, to confirmhealing of the ESD-induced artificial ulcer and to exclude the presence of any residual tumor. EGD with a biopsy and abdominal CT were performed every 6 months thereafter for 3 years, to detect local, metachronous, or extragastric recurrence. From the 4th to 5th years after ESD, EGD with a biopsy and abdominal CTwere performed annually.	**Results** Overall survival 5-year survival Overall: Events=38, N=1306 absolute indication: Events= 28, N= 1032 expanded indication: Events=10, N=274 P-log rank P=0.236 (15 patients with patient indication included under expanded indication) Recurrence rate Local recurrence: 1/1306 Metachronous recurrence: 47/1306 44 early gastric cancer 3 advanced gastric cancer Distant recurrence: 2/1306	**Limitations** 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results Unclear (Eastern setting and population) 1.2 Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias Unclear (154 patients with inadequate follow-up excluded) 1.3 The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias Yes 1.4 The outcome of interest is adequately measured in study participants, sufficient to limit potential bias Yes 1.5 Important potential confounders are

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Country/ies where the study was carried out Korea **Study type** Retrospective cohort study **Aim of the study** To suggest an appropriate surveillance strategy after curative endoscopic submucosal dissection (ESD) for early gastric cancers, based on incidence and patterns of local, metachronous, and	**Exclusion Criteria** Patients were excluded from the study population when the pathologic examination of the ESD specimen gave a diagnosis of poorly differentiated or signet ring cell early gastric cancer. In cases of multiple early gastric cancers, patients were excluded from the study population if at least one lesion was finally diagnosed as poorly differentiated or signet ring cell early gastric cancer. Patients with less than 1 year follow-up excluded from long-term follow up.		<u>Diagnosis of Recurrence</u> A cancer detected at the primary resection site during the first or second follow-up EGD within 12 months after curative resection was regarded as a residual lesion. Local recurrence was defined when the cancer was detected at the primary resection site after at least two negative follow-up EGDs after curative ESD of the primary lesion. A new gastric cancer lesion detected at a location other than the primary resection site within 12 months after curative resection was regarded as a synchronous lesion. Metachronous recurrence was defined when a new gastric cancer lesion was detected at a location other than the primary resection site at least 12 months after curative ESD of the primary lesion.		appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest Yes 1.6 The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results Yes **Other information**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
extragastric recurrence. **Study dates** 2003 and 2011 **Source of funding** NR					
Full citation Moorcraft, S. Y., Fontana, E., Cunningham, D., Peckitt, C., Waddell, T., Smyth, E. C., Allum, W., Thompson, J., Rao, S., Watkins, D., Starling,	**Sample size** N=360 (Gastric= 146, oesophageal/GOJ= 214) **Characteristics** <u>Oesophageal/GOJ</u> 88% male Median age= 64 (33-83) <u>Gastric</u> 67% male median age= 70 (24-89)	**Tests** N/A	**Methods** <u>Treatment paradigm</u> 2001-2006: Oesophageal and type I/II GOJ adenocarcinoma: 2 cycles neoadjuvant CF followed by surgery Gastric and type III GOJ adenocarcinoma: Surgery 2006-2010: Oesophageal, GOJ and gastric: 3 cycles ECF/X followed by surgery and 3 cycles ECF/X Nodal dissection tended to be D2 throughout the study period.	**Results** **<u>Recurrence rate</u>** **Oeso/junction cancer** overall: 100/214 1 year: 53/214 2 year: 82/214 3 year: 94/214 Local recurrence: 7/214 Distant recurrence: 79/214 Both local and distant recurrence: 14/214 **Gastric cancer** overall: 47/ 146 1 year: 22/146 2 year: 34/146 3 year: 41/146 Local recurrence: 4/146 Distant recurrence: 37/146 Both local and distant recurrence: 6/146	**Limitations** 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results Yes 1.2 Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias Yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
N., Chau, I., Characterising timing and pattern of relapse following surgery for localised oesophagogastric adenocarcinoma: a retrospective study, BMC CancerBMC Cancer, 16, 112, 2016 **Ref Id** 514481 **Country/ies where the study was carried out** UK **Study type** Retrospective cohort study **Aim of the study**	**Inclusion Criteria** We searched the Royal Marsden (RM) electronic medical record system for patients with a diagnosis of oesophageal, gastrooesophageal junction (GOJ) or gastric adenocarcinoma who had undergone surgery with radical intent between January 2001 and December 2010. **Exclusion Criteria** Patients who were followed up in another hospital, patients for whom no data was available apart from the date of surgery and patients who were found to have unresectable metastatic disease at		<u>Follow-up paradigm</u> 2001-2006: Oesophageal and type I/II GOJ adenocarcinoma: clinical review and tumour markers, 3 monthly in year 1 and then 6 monthly Gastric and type III GOJ adenocarcinoma: No specific recommendations 2006-2010: Oesophageal, GOJ and gastric: clinical review and tumour markers, 3 monthly in year 1 and then 6 monthly	ECOG performance status at relapse: Oeso/junction cancer 0= 12; 1=13; 2=4; 3-4= 8; unknown=63 Gastric cancer 0=3; 1=7; 2=2; 3-4=4; unknown=31	1.3 The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias Yes 1.4 The outcome of interest is adequately measured in study participants, sufficient to limit potential bias Yes 1.5 Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest Yes 1.6 The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results Yes **Other information**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
We conducted a retrospective analysis to investigate patterns of relapse following resection for OGA to assist in formulating an optimal surveillance strategy for these patients. **Study dates** January 2001 and December 2010 **Source of funding**	the time of surgery were excluded.				

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
We acknowledge support from the NIHR RM/ICR Biomedical Research Centre.					
Full citation Nakajima, T., Oda, I., Gotoda, T., Hamanaka, H., Eguchi, T., Yokoi, C., Saito, D., Metachronous gastric cancers after endoscopic resection: how effective is annual endoscopic surveillance?, Gastric CancerGastric Cancer,	**Sample size** N=633 **Characteristics** The average follow-up period after ER for the 633 study patients was 4.4 ± 2.8 years (range, 1.0–13.9 years), the average age of the subjects was 66.5 ± 9.0 years (range, 35–93 years) and the male-to-female ratio was 4:1 (510 men and 123 women). **Inclusion Criteria** Patients treatment with endoscopic	**Tests** N/A	**Methods** Treatment course At the beginning of this series of consecutive ERs, most of ERs were performed by the so-called “strip biopsy method,” a relatively simple technique described previously [13]. Since 1997, however, a new ER procedure using an insulation-tipped diathermic knife [14] has been used in most patients at our institution. In this study, we evaluated patients with EGC consistent with the pre-ER indications	**Results** Overall recurrence rate 52/633 (8.2%) 3-year recurrence rate 5.9% Overall survival Not reported	**Limitations** 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results Unclear (inclusion criteria not well defined) 1.2 Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias Unclear (180 patient with follow-up less than 1 year were excluded) 1.3 The prognostic factor of interest is adequately measured

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
9, 93-8, 2006 **Ref Id** 514500 **Country/ies where the study was carried out** Japan **Study type** Retrospective cohort study **Aim of the study** we investigated the incidence of MGC after ER and assessed our annual endoscopic surveillance program after ER. **Study dates**	resection for gastric cancer for gastric cancer. **Exclusion Criteria** We excluded 158 patients who underwent additional surgery due to noncurative ERs, 180 patients whose surveillance periods were less than 1 year, 1 patient with hereditary nonpolyposis colorectal cancer (HNPCC), and 1 patient with gastric tube cancer.				in study participants, sufficient to limit potential bias Yes 1.4 The outcome of interest is adequately measured in study participants, sufficient to limit potential bias Yes 1.5 Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest Yes 1.6 The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results Yes **Other information**

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td>1987 to 2002

Source of funding
Not reported</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Full citation

Roedl, J. B., Harisinghani, M. G., Colen, R. R., Fischman, A. J., Blake, M. A., Mathisen, D. J., Mueller, P. R., Assessment of treatment response and recurrence in esophageal carcinoma based on tumor</td><td>Sample size
N=47

Characteristics
35 male/ 12 female
mean age= 66
Site: 5 upper/10 middle/11 lower/ 21 GEJ
Histology: 11 SCC/ 36 AC
TNM stage: II 23/ III 24

Inclusion Criteria

Consecutive patients with squamous cell carcinoma and adenocarcinoma of the esophagus who underwent</td><td>Tests
Index test: PET-CT

The third scan was 18.4 5.2 months after surgery. The third PET-CT scan was earlier if tumor recurrence was indicated by suggestive symptoms, equivocal or suspicious findings on clinical examination, radiologic studies, or endoscopy.

Subjects received an intravenous injection of 15 mCi (555 MBq) of FDG. Data were acquired 60 minutes after injection using an integrated PET-CT system (Biograph 16; Siemens Medical Solutions, Erlangen, Germany). Low-dose CT</td><td>Methods
Follow-up

After surgical resection, patients were followed up at 3-month intervals during the first year, and at 6-month intervals during the second year. The median follow-up time was 25.0 months, with a range of 10.0 to 39.0 months.</td><td>Results
Patient-based/ Overall recurrence
<table><tr><td></td><td>Recurrence +</td><td>Recurrence -</td><td></td></tr><tr><td>PET/CT +</td><td>24</td><td>5</td><td></td></tr><tr><td>PET/CT -</td><td>3</td><td>15</td><td></td></tr><tr><td></td><td>27</td><td>20</td><td>47</td></tr></table>Diagnostic test results calculated by NGA technical team:
Sensitivity (95% CI)= 88.89 (70.84 to 97.65)
Specificity (95% CI)= 75.00 (50.90 to 91.34)
Positive likelihood ratio= 3.56 (1.65 to 7.68)
Negative likelihood ratio= 0.15 (0.05 to 0.44)
Positive predictive value= 82.76 (68.95 to 91.21)
Negative predictive value= 83.33 (62.55 to 93.74)

Patient Anxiety
Not reported</td><td>Limitations
QUADAS-2 a quality assessment tool for diagnostic accuracy studies:
Overall quality: unclear risk of bias.
Patient Selection
A. Risk of Bias
Was a consecutive or random sample of patients enrolled? Yes.
Was a case-control design avoided? Yes.
Did the study avoid inappropriate exclusions? Unclear (inclusion criteria not well defined)
Could the selection of patients have introduced bias? Unclear risk.
B. Concerns regarding applicability:</td></tr>
</table>

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
length and standardized uptake value on positron emission tomography-computed tomography, Annals of Thoracic SurgeryAnn Thorac Surg, 86, 1131-8, 2008 **Ref Id** 514589 **Country/ies where the study was carried out** USA **Study type** Nested case-control study **Aim of the study**	neoadjuvant chemoradiotherapy followed by surgery were included in the study. The clinical stage of all patients before neoadjuvant therapy was stage II or stage III. **Exclusion Criteria** NR	for attenuation correction was performed first with the 16- slice multidetector CT component of the combined PET-CT. Immediately after CT, the PET emission scan was obtained with a high-resolution lutetium oxyorthosilicate–based PET scanner in a three-dimensional mode. The transverse field of view was identical to the CT scan. Subsequently, patients received a diagnostic contrast-enhanced CT with 100 mL of 300 mg iodine per milliliter injected along with 20 mL saline. The parameters were as follows: table feed, 15 mm/s; pitch, 1.5; tube voltage, 140 kV; and tube current, 170 mA. Images were reconstructed with a 2-mm or 2.5-mm slice thickness. **Reference test** Suspicious sites of recurrence and tumor			Are there concerns that the included patients and setting do not match the review question? Low concern. **Index Test** A. Risk of Bias Were the index test results interpreted without knowledge of the results of the reference standard? Yes. If a threshold was used, was it pre-specified? Yes. (Diagnostic criteria was defined.) Could the conduct or interpretation of the index test have introduced bias? Low risk. B. Concerns regarding applicability: Are there concerns that the index test, its conduct, or interpretation differ from the review question? Low concern. **Reference Standard** A. Risk of Bias Is the reference standards likely to correctly classify the target condition? Yes.

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
We therefore evaluated the additional value of combined PET–computed tomography (CT) over PET in the assessment of tumor recurrence after surgery in patients with esophageal carcinoma. **Study dates** NR **Source of funding** NR		progression (suspected on PET-CT) were proved by biopsy. A tumor/recurrence-free status at the 18 month follow-up PET-CT scan was confirmed by EUS and follow-up.			Were the reference standard results interpreted without knowledge of the results of the index tests? unclear Could the reference standard, its conduct, or its interpretation have introduced bias? Unclear risk of bias B. Concerns regarding applicability Are there concerns that the target condition as defined by the reference standard does not match the question? Low concern. **Flow and Timing** A. Risk of Bias Was there an appropriate interval between index test and reference standard? Yes Did all patients receive the same reference standard? Yes-histopathology Were all patients included in the analysis? Yes Could the patient flow have introduced bias? low risk.

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>Other information
Sensitivity and specificity not reported for site-based analysis</td></tr>
<tr><td>Full citation

Sim, S. H., Kim, Y. J., Oh, D. Y., Lee, S. H., Kim, D. W., Kang, W. J., Im, S. A., Kim, T. Y., Kim, W. H., Heo, D. S., Bang, Y. J., The role of PET/CT in detection of gastric cancer recurrence, BMC CancerBMC Cancer, 9, 73, 2009

Ref Id

514645

Country/ies where</td><td>Sample size

Characteristics

Inclusion Criteria

Exclusion Criteria</td><td>Tests
All scans were performed by PET/CT system (Philips Gemini, DA best, Netherlands). The patients were asked to fast for at least 4 hours before undergoing PET/CT and 555–740 MBq (15–20 mCi; 0.22 mCi/kg body weight) of FDG was administered intravenously 1 hour prior to imaging. CT was performed prior to PET, and the resulting data were used to generate an attenuation correction map for PET. Five-millimeter-thick sections were obtained at 50 mA (but adjusted for body thickness) and 120 kVp from the skull base to the mid-thigh. Next, PET was per- formed with a 5-min emission acquisition per imaging level and the images were reconstructed.</td><td>Methods</td><td>Results
<table><tr><td></td><td>Recurrence +</td><td>Recurrence -</td><td></td></tr><tr><td>PET/CT+</td><td>26</td><td>4</td><td></td></tr><tr><td>PET/CT-</td><td>12</td><td>10</td><td></td></tr><tr><td></td><td>38</td><td>14</td><td>52</td></tr></table>Diagnostic accuracy measures calculated by the NGA technical team:
Sensitivity (95% CI)= 68.42 (51.35% to 82.50%)
Specificity (95% CI)= 71.43 (41.90% to 91.61%)
Positive likelihood ratio= 2.39 (1.02 to 5.64)
Negative likelihood ratio= 0.44 (0.25 to 0.78)
Positive Predictive Value= 86.67 (73.42% to 93.86%)
Negative Predictive Value= 45.45 (31.96% to 59.65%)

Diagnostic Accuracy of contrast CT
<table><tr><td></td><td>Recurrence +</td><td>Recurrence -</td><td></td></tr></table></td><td>Limitations
QUADAS-2 a quality assessment tool for diagnostic accuracy studies:
Overall risk of bias= unclear due to poor definition of reference standard.
Patient Selection
A. Risk of Bias
Was a consecutive or random sample of patients enrolled? Yes.
Was a case-control design avoided? Yes.
Did the study avoid inappropriate exclusions? Yes.
Could the selection of patients have introduced bias? Low risk.
B. Concerns regarding applicability:
Are there concerns that the included patients and setting do not match the review question? low concern.</td></tr>
</table>

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
the study was carried out **Study type** Retrospective cohort study **Aim of the study** **Study dates** **Source of funding**				<table><tr><td>CT +</td><td>34</td><td>5</td><td></td></tr><tr><td>CT -</td><td>4</td><td>9</td><td></td></tr><tr><td></td><td>38</td><td>14</td><td>52</td></tr></table>Diagnostic accuracy measures calculated by the NGA technical team: Sensitivity (95% CI)= 89.47 (75.20% to 97.06%) Specificity (95% CI)= 64.29 (35.14% to 87.24%) Positive likelihood ratio= 2.51 (1.23 to 5.10) Negative likelihood ratio= 0.16 (0.06 to 0.45) Positive Predictive Value= 87.18 (76.95% to 93.27%) Negative Predictive Value= 69.23 (45.14% to 86.02%) **Patient Anxiety:** Not reported	**Index Test** A. Risk of Bias Were the index test results interpreted without knowledge of the results of the reference standard? Yes. If a threshold was used, was it pre-specified? Yes. (Diagnostic criteria of recurrence was defined.) Could the conduct or interpretation of the index test have introduced bias? Low risk. B. Concerns regarding applicability: Are there concerns that the index test, its conduct, or interpretation differ from the review question? Low concern. **Reference Standard** A. Risk of Bias Is the reference standards likely to correctly classify the target condition? Unclear Were the reference standard results interpreted without knowledge of the

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					results of the index tests? Unclear- method of confirming recurrence not well defined. Could the reference standard, its conduct, or its interpretation have introduced bias? Unclear risk. B. Concerns regarding applicability Are there concerns that the target condition as defined by the reference standard does not match the question? Unclear concern. **Flow and Timing** A. Risk of Bias Was there an appropriate interval between index test and reference standard? Unclear Did all patients receive the same reference standard? Unclear Were all patients included in the analysis? No. (patients with suspected recurrence based on other diagnostic tests were excluded). Could the patient flow have introduced bias? Unclear risk

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>Other information
For additional study details, see Li 2016 SR</td></tr>
<tr><td>Full citation

Sun, L., Su, X. H., Guan, Y. S., Pan, W. M., Luo, Z. M., Wei, J. H., Wu, H., Clinical role of 18F-fluorodeoxyglucose positron emission tomography/computed tomography in post-operative follow up of gastric cancer: initial results, World Journal of GastroenterologyWorld</td><td>Sample size

Characteristics

Inclusion Criteria

Exclusion Criteria</td><td>Tests
18FDG PET/CT technique
The patients were asked to fast for at least 4 h before undergoing 18F-FDG PET/CT. Their blood glucose level should be within the normal range (70-120 mg/dL) prior to intravenous injection of 18F-FDG. The patients received an intravenous injection of 370-666 MBq (10-18 mCi) of 18F-FDG. Data acquisition by an integrated PET/CT system (Discovery STE; GE Medical Systems, Milwaukee, WI, USA) was performed within 60 min after injection. The data acquisition procedure was as follows: CT scanning was first performed, from the head to the pelvic floor, with 110 kV, 110 mA, a tube rotation time of 0.5</td><td>Methods</td><td>Results
<table><tr><td></td><td>Recurrence +</td><td>Recurrence -</td><td>Total</td></tr><tr><td>PET +</td><td>12</td><td>2</td><td>14</td></tr><tr><td>PET -</td><td>2</td><td>7</td><td>9</td></tr><tr><td>Total</td><td>14</td><td>9</td><td>23</td></tr></table>Diagnostic test results calculated by NGA technical team:
Sensitivity (95% CI)= 85.71 (57.19 - 98.22)
Specificity (95% CI)= 77.78 (39.99- 97.19)
Positive likelihood ratio= 3.86 (1.12 to 13.34)
Negative likelihood ratio= 0.18 (0.05 to 0.69)
Positive predictive value= 85.71 (63.43 to 95.40)
Negative predictive value= 77.78 (48.08 to 92.97)

Patient Anxiety
Not reported</td><td>Limitations
QUADAS-2 a quality assessment tool for diagnostic accuracy studies:
Overall quality: low risk of bias.
Patient Selection
A. Risk of Bias
Was a consecutive or random sample of patients enrolled? Yes.
Was a case-control design avoided? Yes.
Did the study avoid inappropriate exclusions? Yes.
Could the selection of patients have introduced bias? Low risk.
B. Concerns regarding applicability:
Are there concerns that the included patients and setting do not match the review question? Low concern.
Index Test</td></tr>
</table>

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
J Gastroenterol, 14, 4627-32, 2008 **Ref Id** 514676 **Country/ies where the study was carried out** **Study type** Retrospective cohort study **Aim of the study** **Study dates** **Source of funding**		s, and a 3.3-mm section thickness which was matched to the PET section thickness. Immediately after CT scanning, a PET emission scan that covered the identical transverse field of view was obtained. Acquisition time was 3 min per table position. PET image data sets were reconstructed iteratively by applying the CT data for attenuation correction, and coregistered images were displayed on a workstation.			A. Risk of Bias Were the index test results interpreted without knowledge of the results of the reference standard? Yes. If a threshold was used, was it pre-specified? Yes. (Diagnostic criteria of recurrence was defined.) Could the conduct or interpretation of the index test have introduced bias? Low risk. B. Concerns regarding applicability: PET images reviewed by two independent reviewers Are there concerns that the index test, its conduct, or interpretation differ from the review question? Low concern. **Reference Standard** A. Risk of Bias Is the reference standards likely to correctly classify the target condition? Yes. Were the reference standard results interpreted without

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					knowledge of the results of the index tests? Unclear Could the reference standard, its conduct, or its interpretation have introduced bias? Unclear risk. B. Concerns regarding applicability Are there concerns that the target condition as defined by the reference standard does not match the question? Low concern. **Flow and Timing** A. Risk of Bias Was there an appropriate interval between index test and reference standard? Yes. Did all patients receive the same reference standard? No- clinical follow-up or histopathological confirmation . Were all patients included in the analysis? Yes Could the patient flow have introduced bias? Low risk.

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>Other information
For additional study details see Li, 2016 SR.</td></tr>
<tr><td>Full citation

Tanaka, K., Yano, M., Motoori, M., Kishi, K., Miyashiro, I., Shingai, T., Gotoh, K., Noura, S., Takahashi, H., Ohue, M., Yamada, T., Ohigashi, H., Yamamoto, T., Yamasaki, T., Doki, Y., Ishikawa, O., CEA-antigen and SCC-antigen mRNA expression in</td><td>Sample size
N=244

Characteristics Treatment course

We performed neoadjuvant therapy for the clinically lymph node positive patients. A total of 106 received neoadjuvant therapy. Among them, 85 patients received chemotherapy consisting of 5-fluorouracil/cisplatin/ Adriamycin or 5-fluorouracil/cisplatin, and 21 patients received radiotherapy with or without chemotherapy.[10] In our hospital,</td><td>Tests
Index Test: mRNA CEA

Purified RNA was quantified and assessed for purity by ultraviolet (UV) spectrophotometry. Complementary DNA (cDNA) was generated with a transcriptor first-strand cDNA synthesis kit (Roche Diagnostics, Mannheim, Germany), according to the protocol provided by the manufacturer.

Cut-off values not reported.

Reference Test

Clinical follow-up and diagnosed of recurrence.</td><td>Methods

Patient Follow-Up After Resection

Patients were followed every 1–3 months in outpatient clinics and monitored for recurrence based on the presence of serum tumor markers (SCC and CEA) and by imaging studies (radiography and computed tomography) every 3 months. Endoscopic examination, PET-CT, and ultrasonography were performed when necessary. The median follow-up period after resection was 24.3 months.</td><td>Results
Lymph node recurrence
<table><tr><td></td><td>Recurrence +</td><td>Recurrence -</td><td>Total</td></tr><tr><td>CEA mRNA+</td><td>13</td><td>20</td><td></td></tr><tr><td>CEA mRNA -</td><td>54</td><td>157</td><td></td></tr><tr><td>Total</td><td></td><td></td><td></td></tr></table>Diagnostic test results calculated by NGA technical team:
Sensitivity (95% CI)= 19.40 (10.76-30.89)
Specificity (95% CI)= 88.70 (83.09-92.96)
Positive likelihood ratio= 1.72 (0.91-3.25)
Negative likelihood ratio= 0.91 (0.90-1.03)
Positive predictive value= 39.39 (25.54 to 55.19)
Negative predictive value= 74.41 (71.88 to 76.78)

Haematogenous recurrence</td><td>Limitations
QUADAS-2 a quality assessment tool for diagnostic accuracy studies:
Overall quality: low risk of bias.
Patient Selection
A. Risk of Bias
Was a consecutive or random sample of patients enrolled? Yes.
Was a case-control design avoided? Yes.
Did the study avoid inappropriate exclusions? Yes
Could the selection of patients have introduced bias? Low risk.
B. Concerns regarding applicability:
Are there concerns that the included patients and setting do not match the review question? Low concern.
Index Test
A. Risk of Bias</td></tr>
</table>

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>peripheral blood predict hematogenous recurrence after resection in patients with esophageal cancer, Annals of Surgical OncologyAnn Surg Oncol, 17, 2779-86, 2010

Ref Id

514704

Country/ies where the study was carried out

Japan

Study type

Prospective cohort study

Aim of the study</td>
<td>esophagectomy with 2- to 3-field lymph node dissection is the standard treatment for esophageal carcinoma when the neoplasms are considered resectable.

Inclusion Criteria

To avoid any influence of residual tumor or epithelial cells on the CEA mRNA and SCCA mRNA levels, patients were enrolled in the study based on the following criteria: (1) no history of malignant disease, (2) no history of dermatologic disease, and (3) resection with no residual neoplasm.

Exclusion Criteria</td>
<td></td>
<td></td>
<td>
<table>
<tr><th></th><th>Recurrence +</th><th>Recurrence -</th><th>Total</th></tr>
<tr><td>CEA mRNA+</td><td>12</td><td>21</td><td></td></tr>
<tr><td>CEA mRNA -</td><td>39</td><td>172</td><td></td></tr>
<tr><td>Total</td><td></td><td></td><td></td></tr>
</table>
Diagnostic test results calculated by NGA technical team:
Sensitivity (95% CI)= 23.53 (12.79- 37.49)
Specificity (95% CI)= 89.12 (83.85-93.14)
Positive likelihood ratio= 2.16 (1.14- 4.10)
Negative likelihood ratio= 0.86 (0.73- 1.01)
Positive predictive value= 36.36 (23.18-51.97)
Negative predictive value= 81.52 (78.98- 83.81)

Local recurrence
<table>
<tr><th></th><th>Recurrence +</th><th>Recurrence -</th><th>Total</th></tr>
<tr><td>CEA mRNA+</td><td>7</td><td>26</td><td></td></tr>
<tr><td>CEA mRNA -</td><td>27</td><td>184</td><td></td></tr>
</table>
</td>
<td>Were the index test results interpreted without knowledge of the results of the reference standard? Yes.
If a threshold was used, was it pre-specified?
Yes. (Diagnostic criteria was defined.)
Could the conduct or interpretation of the index test have introduced bias? Low risk.
B. Concerns regarding applicability:
Are there concerns that the index test, its conduct, or interpretation differ from the review question? Low concern.
Reference Standard
A. Risk of Bias
Is the reference standards likely to correctly classify the target condition? Yes.
Were the reference standard results interpreted without knowledge of the results of the index tests? Unclear
Could the reference standard, its conduct,</td>
</tr>
</table>

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
The aim of this study was to prospectively examine the correlation between CTC and outcome in a large number of patients who underwent esophagectomy. **Study dates** 2002-2007 **Source of funding** NR	Excluded were 8 patients with a history of malignant disease and 7 patients who had undergone resection with macroscopic or microscopic residual neoplasm			Total Diagnostic test results calculated by NGA technical team: Sensitivity (95% CI)= 20.59 (8.70-37.90) Specificity (95% CI)= 87.62 (82.39 to 91.75) Positive likelihood ratio= 1.66 (0.78-3.53) Negative likelihood ratio= 0.91 (0.76 to 1.08) Positive predictive value= 21.21 (11.26 to 36.35) Negative predictive value= 87.20 (85.08 to 89.07) **Patient Anxiety** Not reported	or its interpretation have introduced bias? Unclear risk. B. Concerns regarding applicability Are there concerns that the target condition as defined by the reference standard does not match the question? Low concern. **Flow and Timing** A. Risk of Bias Was there an appropriate interval between index test and reference standard? Unclear Did all patients receive the same reference standard? No- clinical follow-up as needed Were all patients included in the analysis? Yes Could the patient flow have introduced bias? Unclear risk. **Other information** Overall 2x2 data not reported for CEA (data pooled with SCC antigen)

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Full citation Abe, S., Oda, I., Suzuki, H., Nonaka, S., Yoshinaga, S., Nakajima, T., Sekiguchi, M., Mori, G., Taniguchi, H., Sekine, S., Katai, H., Saito, Y., Long-term surveillance and treatment outcomes of metachronous gastric cancer occurring after curative endoscopic submucosal dissection, Endoscopy Endoscopy, 47, 1113-8, 2015	**Sample size** N=1526 **Characteristics** median age= 67.0 (27-93) 1180 male/346 female **Inclusion Criteria** A total of 1537 consecutive patients with 1879 EGC lesions underwent curative resection by ESD between 1999 and 2006.Curative resection was defined as an R0 resection that had a negligible riskof lymphnodemetastasis,basedonhistological criteria. All lesions met the absolute and expanded histological criteria outlined by the Japanese Gastric Cancer Treatment Guidelines for curative resection [2].	**Tests** N/A	**Methods** Treatment course ESD not described Follow-up Patients werefollowedupatthe National CancerCenterHospital or by the referring endoscopists. The majorityof patients underwentesophagogastroduodenoscopy(EGD)surveillanceonanannualorbiannualbasis,atthediscretionoftheendoscopist.Inaddition, abdominal computed tomography (CT), ultrasound, or endoscopic ultrasound (EUS) was carried out every 6 months or 1 year to identify lymph node and distant metastases in patients who met the expanded criteria of Japanese Gastric Cancer Treatment Guidelines[2]. Surveillance endoscopy was performed using GIF-Q240, GIFQ240Z, GIF-Q260, GIF-H260, or GIFH260Z endoscopes (Olympus Medical, Tokyo,Japan). Ifa suspicious lesionwas detectedduring white-light endoscopy, chromoendoscopy using 0.2% indigo carmine was performed to evaluate the tumor margin and a biopsy specimen was taken from the lesion. Tumor size, depth of invasion,andthepresenceofulcerationwereestimatedandrecorded either during the surveillance EGD or an additional preoperative EGD. Magnification endoscopy	**Results** Metachronous lesions Overall rate: 228/1526 5-year: n=145 cumulative incidence= 9.5% 10-year: n=346 cumulative incidence= 22.7%	**Limitations** 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results Unclear (unclear applicability of eastern setting and population to UK) 1.2 Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias Yes 1.3 The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias Yes 1.4 The outcome of interest is adequately measured in study participants, sufficient to limit potential bias Yes 1.5 Important potential confounders are appropriately accounted for, limiting potential bias with respect to the

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Ref Id 506920 **Country/ies where the study was carried out** Japan **Study type** Retrospective cohort study **Aim of the study** The aim of this study was to evaluate the long-term surveillance and treatment outcomes of MGC aftercurative gastric ESD. **Study dates**	**Exclusion Criteria** There were 11 patients whowere excluded as they underwent prescheduled surgery for synchronous esophageal or gastric cancer after their ESD.		and EUS were used if clinically necessary.		prognostic factor of interest Yes 1.6 The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results Yes **Other information**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Underwent curative resection by ESD between 1999 and 2006 **Source of funding** NR					
Full citation Bennett, J. J., Gonen, M., D'Angelica, M., Jaques, D. P., Brennan, M. F., Coit, D. G., Is detection of asymptomatic recurrence after curative resection associated with improved survival in	**Sample size** **Characteristics** **Inclusion Criteria** **Exclusion Criteria**	**Tests**	**Methods**	**Results**	**Limitations** **Other information** Same study as Dangelica- additional analysis; results reported under Dangelisa

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
patients with gastric cancer?, Journal of the American College of SurgeonsJ Am Coll Surg, 201, 503-510, 2005 **Ref Id** 514921 **Country/ies where the study was carried out** **Study type** Nested case-control study **Aim of the study** **Study dates**					

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Source of funding					
Full citation Dittmar, Y., Schule, S., Koch, A., Rauchfuss, F., Scheuerlein, H., Settmacher, U., Predictive factors for survival and recurrence rate in patients with node-negative gastric cancer-a European single-centre experience, Langenbecks Archives of SurgeryLangenbecks Arch Surg,	**Sample size** N=228 **Characteristics** 63.2 % men median age= 63 years (range: 25-92) **Inclusion Criteria** We included all patients who underwent elective gastric resection for gastric adenocarcinoma with curative intent, had no evidence of lymph node metastases, as well as clear resection margins. **Exclusion Criteria** Patients who underwent emergency surgery for gastric cancer or were under medical	**Tests** N/A	**Methods** Data collected in a prospectively maintained database. Treatment Course We performed 85 total gastrectomies (37 %) and 83 partial gastric resections (37 %, 72 distal and 11 proximal resections). The remaining patients received either an extended gastrectomy (36 cases, 11 %), a stump gastrectomy (9 cases, 4 %), a multivisceral resection (14 cases, 6 %), a thoracoabdominal resection (3 cases, 1 %) or an endoscopic mucosa resection (8 cases, 4 %). Since our study group comprises lymph-node-negative patients, chemotherapy was performed only in few cases (25 cases, 11 %). Twenty-one patients underwent neoadjuvant chemotherapy. In four cases, adjuvant chemotherapy was administered for a locally advanced tumour stage. Chemotherapy protocols have undergone substantial changes during the observation period with ECF being the most commonly used protocol (n=11). Follow-up	**Results** **Overall survival** 5-year Events= 35, N= 207 10-year Events= 51, N= 207 15-year Events= 56, N=207 **Disease-free survival** 5-year Events= 46, N= 207 10-year Events= 56, N= 207 15-year Events= 56, N=207 **Recurrence rate** Overall 43/207 Local recurrence: 16/207 Peritoneal recurrence: 14/207 Distance recurrence: 9/207 1-year 16/207 2-year 27/207 5-year 37/207	**Limitations** 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results Yes 1.2 Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias Unclear (patients with inadequate follow-up excluded- numbers not reported) 1.3 The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias Yes 1.4 The outcome of interest is adequately measured in study participants, sufficient to limit potential bias Yes

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
400, 27-35, 2015 **Ref Id** 515104 **Country/ies where the study was carried out** Germany **Study type** Retrospective cohort study **Aim of the study** The aim of this study was to determine if a subgroup with higher risk for tumour recurrence exists in patients with node negative gastric cancer. Furthermore, we	immunosuppression were excluded from the analysis		Duration of follow-up ranged from 1 to 212 months, with a median follow-up time of 59 months. Standard procedures during follow-up were clinical examination including body weight, abdominal ultrasound and chest X-ray in order todetect distant metastases, as well as upper gastrointestinal endoscopy for intraluminal local recurrence. During the first postoperative year, we performed a follow-up every 3 months, followed by half-yearly sessions in the second and third year of observation and yearly controls afterwards.		1.5 Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest Yes 1.6 The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results Yes **Other information** For the calculation of survival data, recurrence rate and factors with possible impact on survival, all patients who died during the immediate postoperative period were excluded (n1=207). For all other calculations, these cases were included in the analysis (n2=228).

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
aimed to identify prognostic factors and recurrence patterns for this subgroup. **Study dates** 1994- 2011 **Source of funding** NR					
Full citation Jin, L. X., Moses, L. E., Squires, M. H., Poultsides, G. A., Votanopoulos, K., Weber, S. M., Bloomston, M., Pawlik, T. M.,	**Sample size** N= 317 **Characteristics** 56% male mean age= 66 (12) **Inclusion Criteria** All patients who underwent resection for GAC via an abdominal approach between January	**Tests** N/A	**Methods** <u>Treatment course</u> With respect to operative characteristics, no significant differences existed in the type of operation, extent of nodal dissection, mean or median number of total nodes examined, or the likelihood of having had more than 15 nodes examined between the 2 groups. In general, the majority of patients received either a subtotal or total gastrectomy (44% and 37%, respectively) and 56% of patients	**Results** **Recurrence rate** Overall: 54/317 2-year: 36/317 5-year: 48/317 Local recurrence: 18/317 Regional recurrence: 16/317 Distant recurrence: 38/317 **Overall survival** 5-year: Events= 149, N=317 Of those with recurrence: Events= 46, N=54 Of those without recurrence: Events= 82, N=263	**Limitations** 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results Yes 1.2 Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Hawkins, W. G., Linehan, D. C., Strasberg, S. M., Schmidt, C., Worhunsky, D. J., Acher, A. W., Cardona, K., Cho, C. S., Kooby, D. A., Levine, E., Winslow, E. R., Saunders, N. D., Spolverato, G., Maithel, S. K., Fields, R. C., Factors Associated With Recurrence and Survival in Lymph Node-negative Gastric Adenocarcinoma A 7-Institution Study of the	2000 and December 2012 at participating institutions were included. Patients with lymph-node negative disease. **Exclusion Criteria** patients undergoing palliative resection, patients with zero nodes retrieved, those with known metastatic disease (AmericanJoint Committee on Cancer stage IV), and 30-day preoperative mortalities were excluded from analysis.		underwent at least a D2 lymphadenectomy.		to limit potential bias Yes 1.3 The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias Yes 1.4 The outcome of interest is adequately measured in study participants, sufficient to limit potential bias Yes 1.5 Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest Yes 1.6 The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results Yes **Other information**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
US Gastric Cancer Collaborative, Annals of SurgeryAnn Surg, 262, 999-1005, 2015 **Ref Id** 515336 **Country/ies where the study was carried out** US **Study type** Retrospective cohort study **Aim of the study** To determine pathologic features associated with recurrence and survival in patients with lymph node–					

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td>negative gastric adenocarcinoma.

Study dates
2000-2012

Source of funding
NR</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Full citation

Joypaul, B., Browning, M., Newman, E., Byrne, D., Cuschieri, A., Comparison of Serum Ca-72-4 and Ca-19-9 Levels in Gastric-Cancer Patients and</td><td>Sample size
N= 52

Characteristics
Thirty patients were followed for a median postopera tive period of 38 months (range 10 to 105).
Fifty-two patients (31 males, 21 females) aged 49 to 74 years (median 61) who had undergone surgery for primary gastric adenocarcinomas were also assessed. Each cancer patient’s</td><td>Tests
Index test: Tumour Markers
Serum CA 72-4 and CA 19-9 levels were measured by a one-step solid-phase sandwich enzyme-linked immuno-sorbent assay with streptavidin-biotin technologyi6Jg (Enzymun-Test CA 72-4 and Enzymun-Test CA 19-9, Boehringer Mannheim GmbH, Mannheim, Germany). For each tumor marker, samples were analyzed singly at 25°C on the fully automated ES 300</td><td>Methods
Follow-up
Outpatient visits were scheduled every 3 months for the first year and every 6 months thereafter. At each visit, the patient was evaluated by full physical examination, standard biochemical and hematological blood profiles, chest ra-diographs, upper gastrointestinal endoscopic assessment, and computed tomographic scan of the abdomen and pelvis.</td><td>Results
<table><tr><th></th><th>Recurrence+</th><th>Recurrence -</th><th>Total</th></tr><tr><td>CA 19-9 +</td><td>9</td><td>7</td><td></td></tr><tr><td>CA 19-9 -</td><td>4</td><td>10</td><td></td></tr><tr><td>Total</td><td>13</td><td>17</td><td>30</td></tr></table>Diagnostic test results calculated by NGA technical team:
Sensitivity (95% CI)= 69.23 (38.57-90.91)
Specificity (95% CI)= 58.82 (32.92-81.56)
Positive likelihood ratio= 1.68 (0.86 - 3.30)</td><td>Limitations
QUADAS-2 a quality assessment tool for diagnostic accuracy studies:
Overall quality: high risk of bias.
Patient Selection
A. Risk of Bias
Was a consecutive or random sample of patients enrolled? Unclear
Was a case-control design avoided? Yes.
Did the study avoid inappropriate exclusions? Unclear-inclusion and exclusion not reported</td></tr>
</table>

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Correlation with Recurrence , American Journal of SurgeryAm J Surg, 169, 595-599, 1995 **Ref Id** 515346 **Country/ies where the study was carried out** UK **Study type** Prospective cohort study **Aim of the study** This longitudinal prospective study evaluates the serum levels of the tumor markers CA 72-4 and	disease was classified ac- cording to the tumor node metastasis (TNM) system18 as stage I (n = 7), stage II (n = 5), stage III (n = 1 l), or stage IV (n = 29). **Inclusion Criteria** NR **Exclusion Criteria** NR	Enzymun-Test System. The recommended cut-off points (95% confi- dence limits) for normal CA 72-4 and CA 19-9 assay re- sults are 6.7 kU/L and 22 kU/L respectively (confirmed by our own unpublished results). **Reference test: clinical follow-up** Recurrence was diagnosed based on the evaluation of symptoms, signs of recurrence, and the results of the investigations		Negative likelihood ratio= 0.52 (0.21 - 1.30) Positive predictive value= 56.25 (39.59 to 71.61) Negative predictive value= 71.43 (50.23 to 86.10) **Patient Anxiety** Not reported	Could the selection of patients have introduced bias? High risk. (unclear drop outs from gastric cancer group) B. Concerns regarding applicability: Are there concerns that the included patients and setting do not match the review question? Low concern. **Index Test** A. Risk of Bias Were the index test results interpreted without knowledge of the results of the reference standard? Yes. If a threshold was used, was it pre-specified? Yes. (Diagnostic criteria of recurrence was defined.) Could the conduct or interpretation of the index test have introduced bias? Low risk. B. Concerns regarding applicability: Are there concerns that the index test, its conduct, or interpretation differ

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
CA 19-9, alone or in combination, in gastric cancer patients. **Study dates** NR **Source of funding** NR					from the review question? Low concern. **Reference Standard** A. Risk of Bias Is the reference standards likely to correctly classify the target condition? Yes. Were the reference standard results interpreted without knowledge of the results of the index tests? Yes. Could the reference standard, its conduct, or its interpretation have introduced bias? Low risk. B. Concerns regarding applicability Are there concerns that the target condition as defined by the reference standard does not match the question? Low concern. **Flow and Timing** A. Risk of Bias Was there an appropriate interval between index test and reference standard? Yes. Did all patients receive the same reference

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>standard? No- clinical follow up
Were all patients included in the analysis? No
Could the patient flow have introduced bias? High risk

Other information
Only 30 patients follow-up post-surgically. Reason not specified.
Benign disease also included in the study but not included in the extracted.</td></tr>
<tr><td>Full citation

Kato, H., Miyazaki, T., Nakajima, M., Fukuchi, M., Manda, R., Kuwano, H., Value of positron emission tomography</td><td>Sample size
N=55

Characteristics
48 male/ 7 female
The median age of the patients was 61·2 (range 36–74) years.

site: 10 upper/29 middle/16 lower

Tumour stage</td><td>Tests
Index test: PET or CT

PET images were obtained with a SET 2400Wscanner (Shimadzu Corporation, Kyoto, Japan) with a 59·5-cm transaxial field of view and a 20-cm axial field of view. This produced 63 image planes spaced 3·125 mm apart.</td><td>Methods
Follow-up
Asymptomatic patients underwent PET twice per year, CT three times yearly and endoscopy once per year during the first 2 years. Symptomatic patients with suspicion of recurrent disease underwent earlier and additional evaluations.

The mean (s.d.) follow-up period was 26·9(15·8) (range 7–58) months.</td><td>Results
<u>PET Study</u>
Any recurrence
<table>
<tr><th></th><th>Recurrence +</th><th>Recurrence -</th><th></th></tr>
<tr><td>PET +</td><td>26</td><td>9</td><td></td></tr>
<tr><td>PET -</td><td>1</td><td>19</td><td></td></tr>
</table></td><td>Limitations
QUADAS-2 a quality assessment tool for diagnostic accuracy studies:
Overall quality: low risk of bias.
Patient Selection
A. Risk of Bias
Was a consecutive or random sample of patients enrolled? Yes.
Was a case-control design avoided? Yes.
Did the study avoid inappropriate</td></tr>
</table>

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>in the diagnosis of recurrent oesophageal carcinoma, British Journal of SurgeryBr J Surg, 91, 1004-1009, 2004

Ref Id

515365

Country/ies where the study was carried out

Japan

Study type

Retrospective cohort study

Aim of the study
Positron emission tomography (PET) with [18F]fluorodeoxyglucose (FDG) might be</td>
<td>T1 21

T2 5

T3 23

T4 6

Lymph node stage

N0 23

N1 32

Metastasis

M0 46

M1 9

Inclusion Criteria
consecutive patients who had undergone oesophageal resection were studied

Exclusion Criteria
NR</td>
<td>All patients underwent CT of the neck, chest and abdomen. Ten-millimetre continuous scans were obtained from the neck to the bottom of the liver. CTwas performed after administration of intravenous contrast medium. Lymph nodes were considered positive for metastasis if the long axis was greater than 1 cm. Hard-copy images were interpreted by two radiologists who were blinded to the PET results. Comparative CT and PET scans were performed within 1 month.

Reference test

Recurrent disease was assessed by physical examination, histological findings, clinical follow-up and specific imaging. If recurrent disease was not diagnosed by histology, clinical follow-up or radiological</td>
<td></td>
<td>
<table>
<tr><td></td><td>27</td><td>28</td><td>55</td></tr>
</table>
Diagnostic test results calculated by NGA technical team:
Sensitivity (95% CI)= 96.30 (81.03 - 99.91)
Specificity (95% CI)= 67.86 (47.65- 84.12)
Positive likelihood ratio= 3.00 (1.74 - 5.16)
Negative likelihood ratio= 0.05 (0.01- 0.38)
Positive predictive value= 74.29 (62.66 - 83.26)
Negative predictive value= 95.00 (73.19- 99.25)
Locoregional recurrence
<table>
<tr><td></td><td>Recurrence +</td><td>Recurrence -</td><td></td></tr>
<tr><td>PET +</td><td>19</td><td>9</td><td></td></tr>
<tr><td>PET -</td><td>0</td><td>27</td><td></td></tr>
<tr><td></td><td>19</td><td>36</td><td>55</td></tr>
</table>
Diagnostic test results calculated by NGA technical team:
Sensitivity (95% CI)= 100 (82.35-100)
Specificity (95% CI)= 75.00 (57.80- 87.88)
Positive likelihood ratio= 4.00 (2.27-7.04)
Negative likelihood ratio= not estimable
Positive predictive value= 67.86 (54.52 to 78.80)
Negative predictive value= 100%
Distant recurrence
</td>
<td>exclusions? Unclear (inclusion criteria not well defined)
Could the selection of patients have introduced bias? Unclear risk.
B. Concerns regarding applicability:
Are there concerns that the included patients and setting do not match the review question? Low concern.
Index Test
A. Risk of Bias
Were the index test results interpreted without knowledge of the results of the reference standard? Yes.
If a threshold was used, was it pre-specified?
Yes. (Diagnostic criteria was defined.)
Could the conduct or interpretation of the index test have introduced bias? Low risk.
B. Concerns regarding applicability:
Are there concerns that the index test, its conduct, or interpretation differ</td>
</tr>
</table>

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>useful for staging oesophageal squamous cell carcinoma (SCC). FDG-PET may be more accurate than computed tomography (CT) in diagnosing lymph node metastasis. This retrospective study compared the ability of FDG-PET and CT to diagnose recurrent oesophageal carcinoma.

Study dates
1998-2002</td>
<td></td>
<td>imaging, investigations were repeated within 6 months.

Recurrent disease was described as either locoregional (affecting the operative field) or distant (involving remote organs including liver, lung and bone, or lymph nodes outside the operative field).</td>
<td></td>
<td>
<table>
<tr><td></td><td>Recurrence +</td><td>Recurrence -</td><td></td></tr>
<tr><td>PET +</td><td>13</td><td>2</td><td></td></tr>
<tr><td>PET -</td><td>2</td><td>38</td><td></td></tr>
<tr><td></td><td>15</td><td>40</td><td>55</td></tr>
</table>
Diagnostic test results calculated by NGA technical team:
Sensitivity (95% CI)= 86.67 (59.54- 98.34)
Specificity (95% CI)= 95.00 (83.08 - 99.39)
Positive likelihood ratio= 17.33 (4.43- 67.90)
Negative likelihood ratio= 0.14 (0.04-0.51)
Positive predictive value= 86.67 (62.40-96.22)
Negative predictive value= 95.00 (83.92 to 98.57)
<u>CT Study</u>

Any recurrence
<table>
<tr><td></td><td>Recurrence +</td><td>Recurrence -</td><td></td></tr>
<tr><td>CT +</td><td>24</td><td>6</td><td></td></tr>
<tr><td>CT -</td><td>3</td><td>22</td><td></td></tr>
</table>
</td>
<td>from the review question? Low concern.
Reference Standard
A. Risk of Bias
Is the reference standards likely to correctly classify the target condition? Yes.
Were the reference standard results interpreted without knowledge of the results of the index tests? Yes.
Could the reference standard, its conduct, or its interpretation have introduced bias? Low risk.
B. Concerns regarding applicability
Are there concerns that the target condition as defined by the reference standard does not match the question? Low concern.
Flow and Timing
A. Risk of Bias
Was there an appropriate interval between index test and reference standard? Yes
Did all patients receive the same reference</td>
</tr>
</table>

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>Source of funding

This work was supported in part by a Grant-in-Aid for Cancer Research (13-18) from the Japanese Ministry of Health, Labour and Welfare.</td>
<td></td>
<td></td>
<td></td>
<td>
<table>
<tr><td></td><td>27</td><td>28</td><td>55</td></tr>
</table>

Diagnostic test results calculated by NGA technical team:

Sensitivity (95% CI)= 88.89 (70.84 - 97.65)

Specificity (95% CI)= 78.57 (59.05 - 91.07)

Positive likelihood ratio= 4.15 (2.02 to 8.54)

Negative likelihood ratio= 0.14 (0.05 to 0.42)

Positive predictive value= 80.00 (66.03 to 89.17)

Negative predictive value= 88.00 (71.26 to 95.59)

Locoregional recurrence
<table>
<tr><td></td><td>Recurrence +</td><td>Recurrence -</td><td></td></tr>
<tr><td>CT +</td><td>16</td><td>5</td><td></td></tr>
<tr><td>CT -</td><td>3</td><td>31</td><td></td></tr>
<tr><td></td><td>19</td><td>36</td><td>55</td></tr>
</table>
</td>
<td>standard? No- clinical follow-up as needed
Were all patients included in the analysis? Yes
Could the patient flow have introduced bias? high risk

Other information</td>
</tr>
</table>

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td>Diagnostic test results calculated by NGA technical team:

Sensitivity (95% CI)= 84.21 (60.42- 96.62)

Specificity (95% CI)= 86.11 (70.50 - 95.33)

Positive likelihood ratio= 6.06 (2.63 - 13.99)

Negative likelihood ratio= 0.18 (0.06 - 0.52)

Positive predictive value= 76.19 (58.10 - 88.07)

Negative predictive value= 91.18 (78.39 - 96.71)

Distant recurrence

<table><tr><td></td><td>Recurrence +</td><td>Recurrence -</td><td></td></tr><tr><td>CT +</td><td>13</td><td>1</td><td></td></tr><tr><td>CT -</td><td>2</td><td>39</td><td></td></tr><tr><td></td><td>15</td><td>40</td><td>55</td></tr></table>
Diagnostic test results calculated by NGA technical team:

Sensitivity (95% CI)= 86.67 (59.54 to 98.34)</td><td></td></tr>
</table>

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
				Specificity (95% CI)= 97.50 (86.84 to 99.94) Positive likelihood ratio= 34.67 (4.95 to 242.57) Negative likelihood ratio= 0.14 (0.04 to 0.50) Positive predictive value= 92.86 (65.01 to 98.91) Negative predictive value= 95.12 (84.28 to 98.61)	
Full citation Li, P. L., Liu, Q. F., Wang, C., Wang, T. B., Liu, J. J., Huang, G., Song, S. L., Fluorine-18-fluorodeoxyglucose positron emission tomography to evaluate recurrent gastric cancer after surgical resection: a systematic review and meta-	**Sample size** Studies= 12, N= 711 **Characteristics** **Bilici 2011** N= 34 Country= Turkey Age= 58.5 (32-79) years Stage: 1-4 Histology: adenocarcinoma, signet ring carcinoma **Graziosi 2011** N= 50 Country= Italy Age= 68.4 years Stage: 1-4 Histology: NA **Jadvar 2003** N= 18 Country= USA Age= 37-79 years Stage: NA Histology: NA	**Tests** **Bilici 2011** Index test: PET/CT Reference test: Histological and clinical follow-up **Graziosi 2011** Index test: PET/CT Reference test: Histological and clinical follow-up **Jadvar 2003** Index test: PET Reference test: clinical follow-up **Kim 2011** Index test: PET/CT Reference test: Histological and clinical follow-up **Lee 2014** Index test: PET/CT Reference test: Histological and clinical follow-up **Lee 2011** Index test: PET/CT	**Methods** All included studies were retrospective design.	**Results** **2X2 tables to be extracted from individual studies including false negative, false positive, true negative, true positive **Bilici 2011** Sensitivity: 0.958 Specificity: 1.00 **Graziosi 2011** Sensitivity: 0.897 Specificity: 0.857 **Jadvar 2003** Sensitivity: 0.778 Specificity: 0.667 **Kim 2011** Sensitivity: 0.536 Specificity: 0.847 **Lee 2014** Sensitivity: 1.00 Specificity: 0.881 **Lee 2011** Sensitivity: 0.429 Specificity: 0.597 **Nakamoto 2009** Sensitivity: 0.773 Specificity: 0.724 **Potter 2002** Sensitivity: 0.70	**Limitations** **Quality of SR:** Assessed using ROBIS checklist. ROBIS tool for bias risk assessment in systematic reviews: Study Eligibility Criteria 1.Did the review adhere to pre-defined objectives and eligibility criteria? Y 2.Were the eligibility criteria appropriate for the review question? Y 3.Were the eligibility criteria unambiguous? Y 4.Were all the restrictions on eligibility criteria based on study characteristics appropriate? Y 5.Were any restrictions in eligibility criteria based on sources of

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
analysis, Annals of Nuclear MedicineAnn Nucl Med, 30, 179-187, 2016 **Ref Id** 515528 **Country/ies where the study was carried out** **Study type** Systematic review **Aim of the study** We aimed to explore the diagnostic accuracy of ^{18}F-fluorodeoxyglucose positron emission tomograp	**Kim 2011** N= 139 Country= Korea Age= 61.5 years Stage: NA Histology: adenocarcinoma, signet ring carcinoma, mucinous cell carcinoma **Lee 2014** N= 46 Country= Korea Age= 60.6 years Stage: 1-3 Histology: adenocarcinoma, signet ring carcinoma, mucinous cell carcinoma **Lee 2011** N= 89 Country= Korea Age= 56.4 years Stage: 1-4 Histology: adenocarcinoma, signet ring carcinoma, mucinous cell carcinoma **Nakamoto 2009** N= 92 Country= Japan Age= 67 (31-87) years Stage: NA Histology: adenocarcinoma, signet ring	Reference test: Histological and clinical follow-up **Nakamoto 2009** Index test: PET/CT Reference test: Histological and clinical follow-up **Potter 2002** Index test: PET Reference test: Histological and clinical follow-up **Park 2009** Index test: PET/CT Reference test: clinical follow-up **Sharma 2012** Index test: PET/CT Reference test: Histological and clinical follow-up **Sim 2009** Index test: PET/CT Reference test: Histological and clinical follow-up **Sun 2008** Index test: PET/CT Reference test: Histological and clinical follow-up **Yun 2005** Index test: PET Reference test: Histological and clinical follow-up		Specificity: 0.69 **Park 2009** Sensitivity: 0.75 Specificity: 0.77 **Sharma 2012** Sensitivity: 0.959 Specificity: 0.795 **Sim 2009** Sensitivity: 0.894 Specificity: 0.714 **Sun 2008** Sensitivity: 0.857 Specificity: 0.778 **YUn 2005** Sensitivity: 0.941 Specificity: 0.692	information available? Y 6.Concern regarding specification of study eligibility criteria: Low Identification and Selection of Studies 1.Did the search include an appropriate range of databases/electronic sources for published and unpublished reports? Y 2.Were the methods additional to database searching used to identify relevant reports? Y 3 .Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible? PY 4.Were restrictions based on date, publication format or language appropriate? PY 5.Were efforts made to minimise error in selection of studies? Y 6.Concern regarding methods used to identify or select studies: LOW Data Collection and Study Appraisal

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
hy (^{18}F-FDG PET) for detection of gastric cancer recurrence after surgical resection through a systematic review and meta-analysis. **Study dates** Search from 2002 to 2015 **Source of funding** Funded by the National Natural Science Foundation of China	carcinoma, mucinous cell carcinoma **Potter 2003** N= 33 Country= Belgium Age= 60 years Stage: NA Histology: adenocarcinoma, signet ring carcinoma, **Park 2009** N= 105 Country= Korea Age= 58 (34-83) years Stage: NA Histology: adenocarcinoma, signet ring carcinoma, mucinous cell carcinoma **Sharma 2012** N= 72 Country= India Age= 52.8 (28-86) years Stage: NA Histology: NA **Sim 2009** N= 52 Country= Korea Age= 55.4 (27-84) years Stage: 1-4 Histology: adenocarcinoma, signet ring carcinoma,				1.Were efforts made to minimise error in data collection? Y 2.were sufficient study characteristics available? Y 3.Were all relevant study results collected for use and synthesis? Y 4.Was risk of bias formally assessed using appropriate criteria? Y 5.Were efforts made to minimise error in risk of bias assessment? Y 6.Concern: LOW Synthesis and Findings 1.Did the synthesis include all studies it should? Y 2.Were all pre-defined analyses reported and departures explained? Y 3.Was the synthesis appropriate given the nature and similarity in the research questions? Y 4.Was heterogeneity minimal or addressed? Y 5.Were the findings robust as demonstrated though funnel plot or sensitivity analysis? Y

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
(Grants No. 81471708), Shanghai Jiao Tong University Medical Engineering Cross research fund (No. YG2012MS 13) and Shanghai Pujiang Program (No. 11PJD018)	**Sun 2008** N= 23 Country= China Age= 55.4 (27-84) years Stage: NA Histology: NA **Yun 2005** N= 30 Country= Korea Age= 58.3 (27-80) years Stage: 1-4 Histology: adenocarcinoma, signet ring carcinoma, **Inclusion Criteria** **The inclusion criteria of the SR were as follows:** (a) 18F-FDG PET/CT was used to detect gastric cancer recurrence after surgical resection; (b) for per-patient level statistics, the primary data were sufficient to calculate totals of				6.Were biases in primary studies minimal or addressed in the synthesis? Y 7.Concern= LOW Risk of bias in the review 1.Did the interpretation of findings address all the concerns identifies in 1-4? Y 2.Was the relevance of identified studies to the review's research question appropriately considered? Y 3.Did the reviewers avoid emphasizing results on the basis of their statistical significance? Y 4. Risk of bias= LOW **Other information** 1 studies included in the meta-analysis is not relevant to this review. MA 2009 is Chinese language. **Quality of individual diagnostic studies:** Extracted from individual studies.

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
	truepositives, false-positives, true-negatives, and false-negatives; (c) the selected studies included at least 10 patients in this meta-analysis; (d) histopathology analysis and/or clinical and imaging follow-up were used as the reference standard; (e) when data were presented in more than one article, the article with the most details or the latest articles was chosen; (f) abstracts, case report, letters, editorials, and comments were excluded. **Exclusion Criteria** No additional				

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>Full citation

Qiu, M. Z., Lin, J. Z., Wang, Z. Q., Wang, F. H., Pan, Z. Z., Luo, H. Y., Li, Y. H., Zhou, Z. W., He, Y. J., Xu, R. H., Cutoff value of carcinoembryonic antigen and carbohydrate antigen 19-9 elevation levels for monitoring recurrence in patients with resectable gastric adenocarcinoma, International Journal of Biological Markers, 24, 258-264, 2009</td>
<td>Sample size
N=181

Characteristics
120 male/ 61 female
median age= 58 (range 20-82)
Median follow-up 37.8 months
All patients received surgery (160 received adjuvant chemotherapy).

Inclusion Criteria
- patients admitted for radical surgery for gastric adenocarcinoma

Exclusion Criteria
NR</td>
<td>Tests
Index test
CEA and CA 19-9 assayed using commercial enzyme immunoassay kits (Cobas Core EIA, Roche, Switzerland).
Reference test
Clinical follow-up.
Recurrent disease defined as local relapse and/or distant metastasis.</td>
<td>Methods
Follow-up
Every 3 months after surgery. TO exclude false elevation of tumour markers, a rise in CEA and CA19-9 was confirmed 2 weeks later.
Cut-offs
CEA 5 ng/mL and CA 19-9 35 U/mL.</td>
<td>Results
CEA tumour marker
<table>
<tr><td></td><td>Recurrence +</td><td>Recurrence -</td><td></td></tr>
<tr><td>CEA +</td><td>26</td><td>11</td><td>36</td></tr>
<tr><td>CEA -</td><td>40</td><td>104</td><td></td></tr>
<tr><td></td><td>66</td><td>115</td><td>181</td></tr>
</table>
Diagnostic test results calculated by NGA technical team:
Sensitivity (95% CI)= 39.39 (27.58- 52.19)
Specificity (95% CI)= 90.43 (83.53- 95.13)
Positive likelihood ratio= 4.12 (2.18 - 7.78)
Negative likelihood ratio= 0.67 (0.55- 0.82)
Positive predictive value= 70.27 (55.56- 81.71)
Negative predictive value= 72.22 (67.96 to 76.11)

CA 19-9 tumour marker
<table>
<tr><td></td><td>Recurrence +</td><td>Recurrence -</td><td></td></tr>
<tr><td>CA 19-9 +</td><td>24</td><td>9</td><td>33</td></tr>
</table>
</td>
<td>Limitations
QUADAS-2 a quality assessment tool for diagnostic accuracy studies:
Overall quality: low risk of bias.
Patient Selection
A. Risk of Bias
Was a consecutive or random sample of patients enrolled? Unclear
Was a case-control design avoided? Yes.
Did the study avoid inappropriate exclusions? Unclear (inclusion/exclusion not well define)
Could the selection of patients have introduced bias? Unclear risk
B. Concerns regarding applicability:
Are there concerns that the included patients and setting do not match the review question? Low concern.
Index Test
A. Risk of Bias
Were the index test results interpreted without knowledge of the results of the</td>
</tr>
</table>

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Ref Id 515779 **Country/ies where the study was carried out** China **Study type** Prospective cohort study **Aim of the study** Aim of this study is to try and improve the specificity of CEA and CA19-9 in monitoring tumour recurrence in patients with resectable gastric adenocarcinoma by setting suitable				<table><tr><td>CA 19-9 -</td><td>42</td><td>106</td><td></td></tr><tr><td></td><td>66</td><td>115</td><td>181</td></tr></table>Diagnostic test results calculated by NGA technical team: Sensitivity (95% CI)= 36.36 (24.87-49.13) Specificity (95% CI)= 92.17 (85.66- 96.36) Positive likelihood ratio= 4.65 (2.30 - 9.39) Negative likelihood ratio= 0.69 (0.57- 0.83) Positive predictive value= 72.73 (56.88- 84.35) Negative predictive value= 71.62 (67.61- 75.32)	reference standard? Yes. If a threshold was used, was it pre-specified? Yes. (Diagnostic criteria was defined.) Could the conduct or interpretation of the index test have introduced bias? Low risk. B. Concerns regarding applicability: Are there concerns that the index test, its conduct, or interpretation differ from the review question? Low concern. **Reference Standard** A. Risk of Bias Is the reference standards likely to correctly classify the target condition? Yes. Were the reference standard results interpreted without knowledge of the results of the index tests? Unclear Could the reference standard, its conduct, or its interpretation have introduced bias? Unclear risk.

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
elevation levels. **Study dates** 2004-2007 **Source of funding** None reported					B. Concerns regarding applicability Are there concerns that the target condition as defined by the reference standard does not match the question? Low concern. **Flow and Timing** A. Risk of Bias Was there an appropriate interval between index test and reference standard? Yes. Did all patients receive the same reference standard? No-diagnosis of recurrence based on clinical follow-up. Were all patients included in the analysis? Yes Could the patient flow have introduced bias? High risk. **Other information** Diagnostic accuracy analysis also completed for additional cut off values.

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr>
<td>Full citation

Sharma, P., Singh, H., Suman, S. K. C., Sharma, A., Reddy, R. M., Thulkar, S., Bal, C., Malhotra, A., Kumar, R., F-18-FDG PET-CT for detecting recurrent gastric adenocarcinoma: results from a Non-Oriental Asian population, Nuclear Medicine CommunicationsNucl Med Commun, 33, 960-966, 2012

Ref Id

515857</td>
<td>Sample size

Characteristics

Inclusion Criteria

Exclusion Criteria</td>
<td>Tests
Imaging studies were conducted using a dedicated PET-CT scanner (Biograph 2, Siemens). All patients fasted for at least 4 hours. Blood glucose was less than 140 mh/dl. A dose of 370 MBq of 18F-FDG was injected intravenously. No intravenous contrast was used for the CT portion. Patients were given water or oral contrast to distend the stomach. CT acquisition was performed on a spiral dual slice CT with 130 kV, 60 mAs, slice thickness of 4 mm using a matrix of 512x512. 3D PET acquisition was performed for 2-3 min per bed position. PET data were acquired using a matrix of 128X128.</td>
<td>Methods</td>
<td>Results
Data extracted from Sharma 2012*:
<table>
<tr><th></th><th>Recurrence +</th><th>Recurrence -</th><th>Total</th></tr>
<tr><td>PET+</td><td>47</td><td>9</td><td>56</td></tr>
<tr><td>PET -</td><td>2</td><td>35</td><td>37</td></tr>
<tr><td>Total</td><td>49</td><td>44</td><td>93</td></tr>
</table>
Reported per PET/CT (No studies=93) not per patient (N=72).
Diagnostic test results calculated by NGA technical team:
Sensitivity (95% CI)= 95.92 (86.02-99.50)
Specificity (95% CI)= 79.55 (64.70-90.20)
Positive likelihood ratio= 4.69 (2.61- 8.42)
Negative likelihood ratio= 0.05 (0.01- 0.20)
Positive predictive value= 83.93 (74.41- 90.37)
Negative predictive value= 94.59 (81.71- 98.56)

Lesion-wise diagnostic accuracy as reported in study (unable to extract 2x2 data):
Local:
Sensitivity= 94.5% (81.7 to 99.1); Specificity= 85.7% (73.7-93.6); PPV= 81.4 (66.5-91.5); NPV= 96% (86.2-99.4)
Lymph node:
Sensitivity= 87.5% (67.6-97.2); Specificity= 97.1% (89.9-99.5); PPV= 91.3 (71.9- 98.6); NPV= 95.7% (87.9 - 99)</td>
<td>Limitations
Quality of Sharma, 2012:
QUADAS-2 a quality assessment tool for diagnostic accuracy studies:
Overall quality: unclear risk of bias.
Patient Selection
A. Risk of Bias
Was a consecutive or random sample of patients enrolled? Unclear whether consecutive sample enrolled.
Was a case-control design avoided? Yes.
Did the study avoid inappropriate exclusions? Unclear
Could the selection of patients have introduced bias? Unclear risk.
B. Concerns regarding applicability:
Are there concerns that the included patients and setting do not match the review question? Low concern.
Index Test
A. Risk of Bias
Were the index test results interpreted</td>
</tr>
</table>

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Country/ies where the study was carried out India **Study type** Retrospective cohort study **Aim of the study** **Study dates** **Source of funding**				Liver: Sensitivity= 77.8% (40-96.5); Specificity= 98.8 (93.5-99.8); PPV= 87.5 (47.3 - 97.9); NPV= 97.6% (91.7-99.6) Lung: Sensitivity= 80% (22.8-96.7); Specificity= 97.7 (92-99.6); PPV= 66.6 (22.8-94.6); NPV= 98.8 (93.7-99.8) Bone: Sensitivity= 100 (47.9-100); Specificity= 98.8 (93.8-99.8); PPV= 83.3 (36.1-97.2); NPV= 100 (95.8-100) Other Sites: Sensitivity= 100 (54-100); Specificity= 98.8 (93.7-99.8); PPV= 85.7 (42.2-97.6); NPV= 100 (95.7-100) **Patient Anxiety** Not reported	without knowledge of the results of the reference standard? Yes. If a threshold was used, was it pre-specified? Yes. (Diagnostic criteria of recurrence was defined.) Could the conduct or interpretation of the index test have introduced bias? Low risk. B. Concerns regarding applicability: PET images reviewed by two experienced nuclear medicine physicians. Are there concerns that the index test, its conduct, or interpretation differ from the review question? Low concern. **Reference Standard** A. Risk of Bias Is the reference standards likely to correctly classify the target condition? Yes. Were the reference standard results interpreted without knowledge of the

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					results of the index tests? Unclear- unlikely Could the reference standard, its conduct, or its interpretation have introduced bias? Unclear risk. B. Concerns regarding applicability Are there concerns that the target condition as defined by the reference standard does not match the question? Low concern. **Flow and Timing** A. Risk of Bias Was there an appropriate interval between index test and reference standard? Yes. Did all patients receive the same reference standard? No- clinical follow-up, imaging follow-up or histopathology. Were all patients included in the analysis? Yes Could the patient flow have introduced bias? High risk. **Other information**

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					For additional details see Li, 2016 SR.
Full citation Spolverato, G., Ejaz, A., Kim, Y., Squires, M. H., Poultsides, G. A., Fields, R. C., Schmidt, C., Weber, S. M., Votanopoulos, K., Maithel, S. K., Pawlik, T. M., Rates and Patterns of Recurrence after Curative Intent Resection for Gastric Cancer: A United States Multi-Institutional Analysis,	**Sample size** N=817 **Characteristics** Median age= 65.8 (IQR 56.4-74.7) 56.6% male **Inclusion Criteria** Patients undergoing curative intent resection for gastric cancer between 2000 and 2012 at 1 of 7 major academic institutions participating in the US Gastric Cancer Collaborative. **Exclusion Criteria** Patients who underwent a palliative operation,	**Tests** N/A	**Methods** <u>Treatment course</u> At the time of surgery, the majority of patients underwent a partial gastrectomy (n ¼ 481, 59.2%); the remaining 332 (40.8%) patients underwent a total gastrectomy. A complete R0 resection was achieved in 91.6% (n ¼ 748) of patients; the remaining 8.4% (n ¼ 69) of patients had at least 1 microscopically positive margin (R1). No patients had any evidence of macroscopic disease (R2) at the completion of surgery. Most patients underwent a D2 lymphadenectomy (n ¼ 484, 59.2%), while 293 patients (35.9%) underwent a D1 lymphadenectomy. <u>Follow-up</u> Follow-up protocol not reported. <u>Definition of recurrence</u>	**Results** <u>Overall recurrence rate</u> 244/817 Hematogenous recurrence: n= 57 Peritoneal recurrence: n=47 Locoregional recurrence: n=59 Multiple site reccurence: n=81 <u>Overall survival</u> 1-year Events= 154, N=817 3-year Events= 401, N=817 5-year Events= 496, N=817 <u>Disease-free survival</u> Median overall: 27.7 months (IQR 23.2-35.5) Median time to recurrence= 10.8 (IQR 8.9-12.8), among those experiences recurrence.	**Limitations** 1.1 The study sample represents the population of interest with regard to key characteristics, sufficient to limit potential bias to the results Yes 1.2 Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias Yes 1.3 The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias Unclear (follow-up protocol not described/defined) 1.4 The outcome of interest is adequately measured in study participants, sufficient to limit potential bias Yes 1.5 Important potential confounders are appropriately

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Journal of the American College of SurgeonsJ Am Coll Surg, 219, 664-675, 2014 **Ref Id** 515902 **Country/ies where the study was carried out** US **Study type** Retrospective cohort study **Aim of the study** The aim of this study was to determine incidence and pattern of recurrence	had known metastatic disease preoperatively, or experienced perioperative mortality within 30 days of surgery were excluded from analysis. Only patients with a gastric adenocarcinoma were included in this study; patients with other gastric tumors (eg, carcinoid, gastrointestinal stromal tumor, etc) were not included.		Recurrence was defined as the presence of a biopsy-proven tumor showing adenocarcinoma cells or the presence of imaging highly suspicious of tumor recurrence. Recurrences were classified as locoregional (nodal or gastric), peritoneal, or hematogenous (eg, liver, lung, bone, etc).		accounted for, limiting potential bias with respect to the prognostic factor of interest Yes 1.6 The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results Yes **Other information** Same database as Jin 2015; all patient undergoing curative resection covered here.

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
after curative intent surgery for gastric cancer. **Study dates** patients undergoing curative intent resection for gastric cancer between 2000 and 2012. **Source of funding** Not reported					
Full citation Yoon, H. H., Khan,	**Sample size** N=796	**Tests** N/A	**Methods** <u>Treatment course</u> Most surgery performed were transthoracic or transhiatal esophagectomies. 124 cases	**Results** Overall survival 1-year Events= 183; N=796 3-year	**Limitations** 1.1 The study sample represents the population of interest with regard to key

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
M., Shi, Q. A., Cassivi, S. D., Wu, T. T., Quevedo, J. F., Burch, P. A., Sinicrope, F. A., Diasio, R. B., The Prognostic Value of Clinical and Pathologic Factors in Esophageal Adenocarcinoma: A Mayo Cohort of 796 Patients With Extended Follow-up After Surgical Resection, Mayo Clinic Proceedings Mayo Clin Proc, 85, 1080-1089, 2010 **Ref Id**	**Characteristics** median age= 65 (IQR 57.2-71.5) **Inclusion Criteria** • 18 years or older at time of sugery • tissue-confirmed adenocarcinoma of the oesophagus, GOJ or gastric cardia • surgery with curative intent at the mayo clinic **Exclusion Criteria** • patients whose status or staging precluded surgery with curative intent		(16%) that were not: thoracoabdominal or tri-incisional esophagectomies. Follow-up Follow-up schedule not reported.	Events= 462; N=796 5-year Events= 549; N=796 Disease-free survival 1-year Events= 310; N=796 3-year Events= 517; N=796 5-year Events= 573; N=796	characteristics, sufficient to limit potential bias to the results Yes 1.2 Loss to follow-up is unrelated to key characteristics (that is, the study data adequately represent the sample), sufficient to limit potential bias Unclear (retrospective study- only those with follow-up data included) 1.3 The prognostic factor of interest is adequately measured in study participants, sufficient to limit potential bias Yes 1.4 The outcome of interest is adequately measured in study participants, sufficient to limit potential bias Yes 1.5 Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest Yes 1.6 The statistical analysis is appropriate for the design of the study, limiting potential

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516115 **Country/ies where the study was carried out** USA **Study type** Retrospective cohort study **Aim of the study** To identify and describe clinicopathologic prognostic factors in patients with oesophageal adenocarcinoma who underwent surgical resection with curative intent.	• patients whose records were unavailable • patients in whom surgery with curative intent was not performed				for the presentation of invalid results Yes **Other information**

<table>
<tr><th>Bibliographic details</th><th>Participants</th><th>Tests</th><th>Methods</th><th>Outcomes and results</th><th>Comments</th></tr>
<tr><td>Study dates
surgery from 1980 to 1997

Source of funding
Program for clinical-translational research at the mayo clinic; national cancer institute</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Full citation

Yun, M., Choi, H. S., Yoo, E., Bong, J. K., Ryu, Y. H., Lee, J. D., The role of gastric distention in differentiating recurrent tumor from</td><td>Sample size

Characteristics
Most evaluated for lesions suspected on CT (n=23).

Inclusion Criteria

Exclusion Criteria</td><td>Tests
All patients were instructed to fast for at least 4 h before the intravenous injection of 18F-FDG. The mean interval between the injection and the beginning of whole-body scanning was 66 min (range, 50–76 min). Images were obtained on either an Advance PET scanner (GE Healthcare) or an Allegro PET system (Philips- ADAC</td><td>Methods</td><td>Results<table><tr><th></th><th>Recurrence +</th><th>Recurrence -</th><th>Total</th></tr><tr><td>PET +</td><td>16</td><td>4</td><td>20</td></tr><tr><td>PET -</td><td>1</td><td>9</td><td>10</td></tr><tr><td>Total</td><td>17</td><td>13</td><td>30</td></tr></table></td><td>Limitations
QUADAS-2 a quality assessment tool for diagnostic accuracy studies:
Overall quality: low risk of bias.
Patient Selection
A. Risk of Bias
Was a consecutive or random sample of patients enrolled? Yes.
Was a case-control design avoided? Yes.</td></tr>
</table>

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
physiologic uptake in the remnant stomach on 18F-FDG PET, Journal of Nuclear MedicineJ Nucl Med, 46, 953-7, 2005 **Ref Id** 575625 **Country/ies where the study was carried out** **Study type** Retrospective cohort study **Aim of the study** **Study dates**		Medical Systems). The Advance obtained images in 2-di- mensional mode, and the Allegro in 3-dimensional mode. Trans- mission scans using 68Ge or 137Cs point sources were obtained to correct for nonuniform attenuation. After initial whole-body im- aging, the patients were asked to drink as much water as possible (at least 300 mL). The mean interval between whole-body scan- ning and the beginning of regional scanning after water ingestion was 6.7 min (range, 3–13 min). Regional imaging of the stomach was performed at a mean interval of 113 min (range, 89 –128 min) after the injection of 18F-FDG. The images were reconstructed using an iterative reconstruction algorithm: ordered-subset expec- tation maximization for the Advance or low-action maximal like- lihood for the Allegro. The adequacy of gastric distention after water ingestion was confirmed		Diagnostic test results calculated by NGA technical team: Sensitivity (95% CI)= 94.12 (71.31 to 99.85) Specificity (95% CI)= 69.23 (38.57 - 90.91) Positive likelihood ratio= 3.06 (1.34 to 6.97) Negative likelihood ratio= 0.08 (0.01 to 0.59) Positive predictive value= 80.00 (63.70 to 90.12) Negative predictive value= 90.00 (56.50 to 98.42) **Patient Anxiety** Not reported	Did the study avoid inappropriate exclusions? Yes. Could the selection of patients have introduced bias? Low risk. B. Concerns regarding applicability: Are there concerns that the included patients and setting do not match the review question? Low concern. **Index Test** A. Risk of Bias Were the index test results interpreted without knowledge of the results of the reference standard? Yes. If a threshold was used, was it pre-specified? Yes. (Diagnostic criteria of recurrence was defined.) Could the conduct or interpretation of the index test have introduced bias? Low risk. B. Concerns regarding applicability: PET images reviewed by two experienced

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
Source of funding		if the remnant stomach appeared circular or as an elongated tube with a convex margin. No or only minimal 18F-FDG uptake along the gastric wall was expected in well-distended cases.			nuclear medicine physicians. Are there concerns that the index test, its conduct, or interpretation differ from the review question? Low concern. **Reference Standard** A. Risk of Bias Is the reference standards likely to correctly classify the target condition? Yes. Were the reference standard results interpreted without knowledge of the results of the index tests? Unclear-unlikely. Could the reference standard, its conduct, or its interpretation have introduced bias? Unclear risk. B. Concerns regarding applicability Are there concerns that the target condition as defined by the reference standard does not match the question? Low concern. **Flow and Timing** A. Risk of Bias

Bibliographic details	Participants	Tests	Methods	Outcomes and results	Comments
					Was there an appropriate interval between index test and reference standard? Unclear Did all patients receive the same reference standard? No- clinical follow-up, endoscopic biopsy or histopathology. Were all patients included in the analysis? Yes Could the patient flow have introduced bias? High risk **Other information** See Li, 2016 SR for additional details.

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