Ovarian cancer: the recognition and initial management of ovarian cancer

Evidence Review

Contents

Chapter 2: Detection in primary care

2.1 Awareness of symptoms and signs

"*What are the symptoms and signs of ovarian cancer?*"

Short Summary:

Women with ovarian cancer are more likely to experience certain symptoms and signs in the year before their diagnosis than women without ovarian cancer. These symptoms include abdominal pain, abdominal distension, urinary symptoms, abdominal mass and postmenopausal/abnormal bleeding. The prevalence of ovarian cancer in women is low, hence in spite of the relatively high likelihood ratios for individual symptoms; their positive predictive value is low.

The symptoms with the highest positive predictive value are abdominal mass and postmenopausal/abnormal bleeding. These warrant urgent referral according to the NICE referral guidelines for suspected cancer. There is some evidence that combining symptoms can increase positive predictive value (e.g. Hamilton *et al.,* 2009).

Review Protocol:

Question

What are the symptoms and signs of ovarian cancer?

Objectives

To identify which symptoms and signs are associated with ovarian cancer, to potentially allow earlier recognition of ovarian cancer in primary care.

Study inclusion criteria

- **Participants:** Women with possible ovarian cancer in primary care
- **Interventions:** Assessment of symptoms and signs
- **Outcomes:** Definitive diagnosis of ovarian cancer

Search strategy

The searches included the following databases: Medline, PreMEDLINE, EMBASE, Cochrane Library, CINAHL, BNI, PsycINFO, Web of Science and Biomed central. Case control or cohort studies will be included. To calculate the positive predictive value of the various symptoms in primary care, an estimate of the population prevalence of undiagnosed ovarian cancer was also needed.

Review strategy

The likelihood ratios of each symptom for ovarian cancer were estimated from individual studies. These were combined with pre-test probability (prevalence) to estimate the positive predictive value of the individual symptom or sign.

The benefit of combining different symptoms was also considered (for example whether symptom indices have better positive predictive value than the individual symptoms).

The titles and abstracts of the studies identified in the literature search were screened for potential relevance by two reviewers (LSA and KF). Two reviewers (LSA and NB) extracted data. Study quality was assessed using the QUADAS checklist for diagnostic studies. The definitions of symptoms were taken from the studies themselves, and differences in between studies in these definitions were noted.

Search results:

Literature searches identified 141 potentially relevant studies. After reading study titles and abstracts, 16 studies were included.

Evidence summary:

Evidence about symptoms and signs of ovarian cancer came from case control studies. For practical reasons these studies were retrospective and prone to recall bias. For example if women with ovarian cancer can recall their symptom history better than controls, the predictive value of symptoms would be inflated.

A systematic review by Bankhead *et al.* (2005) estimated that 93% [95%CI: 92% to 94%] of women experienced symptoms before diagnosis. Evidence from case control studies shows that abdominal pain, abdominal distension, urinary symptoms, abdominal mass and postmenopausal/abnormal bleeding are more likely to be reported by women before a diagnosis of ovarian cancer than in women without ovarian cancer (see Table 2.1 and Figure 2.1 below).

Table 2.1 Individual symptoms for ovarian cancer

Symptom	Sensitivity	Specificity	Positive predictive value*	Negative predictive value*	References
Abdominal pain	17% to 64%	70% to 95%	0.07% to 0.33%	99.97% to 99.99%	Friedman *et al.,* 2005; Goff *et al.,* 2004; Hamilton *et al.,* 2009; Kim *et al.,* 2009; Lurie *et al,* 2009; Olson *et al.,*2001; Rossing *et al.,* 2010 and Vine *et al.,* 2001.
Abdominal bloating	5% to 68%	62% to 98%	0.01% to 0.30%	99.95% to 99.98%	Bankhead *et al.,* 2008; Goff *et al.,* 2004; Friedman *et al.,* 2005 and Hamilton *et al.,* 2009.
Abdominal distension	22% to 86%	53% to 99%	0.07% to 2.26%	99.97% to 99.99%	Bankhead *et al.,* 2008 and Goff *et al.,* 2004; Friedman *et al.*, 2005; Hamilton *et al.,* 2009 and Lurie *et al.*, 2009,
Abdominal mass/swelling	16% to 33%	99% to 100%	0.48% to 11%	99.97% to 99.98%	Hamilton *et al.,* 2009 and Lurie *et al.,* 2009
Urinary frequency or urgency	11% to 43%	78% to 97%	0.05% to 0.17%	99.97% to 99.98%	Friedman *et al.*, 2005; Hamilton *et al.,* 2009; Lurie *et al.,* 2009; Olson *et al.,* 2001; Rossing *et al.*, 2010 and Vine *et al.,* 2001.
Abnormal or postmenopausal bleeding	13% to 20%	96% to 99%	0.13% to 0.42%	99.97%	Bankhead *et al.,* 2008; Friedman *et al.,* 2005; Hamilton *et al.*, 2009; Lurie *et al.,* 2009 and Vine *et al.,* 3003,

Loss of appetite	14% to 39%	70% to 98%	0.05% to 0.49%	99.97%	Bankhead *et al.,* 2008, Lurie *et al.,* 2009, Olson *et al.,* 2001, Friedman *et al.,* 2005 and Hamilton *et al.,* 2009

*Assuming a prior probability of undiagnosed ovarian cancer of 0.04% (Hamilton *et al,* 2009)

Box 2.1 Definitions of terms used in this section

Sensitivity is the proportion of women with ovarian cancer who experienced the symptom in the year prior to diagnosis.

Specificity is the proportion of women without ovarian cancer who did not experience the symptom within the last year

The ***prior probability*** or ***pre-test probability*** is the background risk that a woman has undiagnosed ovarian cancer, regardless of her symptoms. Hamilton *et al.* (2009) estimated the prior probability of undiagnosed ovarian cancer in women presenting to primary care (for symptoms experienced within the previous year) at 0.036%, using UK national incidence data for ovarian cancer. However, as Hamilton *et al.* (2009) point out, not all women will present to primary care in a given year. In Hamilton's study, 10.8% of the control group had not consulted in primary care over the one year period of the study. For women consulting in primary care the prior probability of ovarian cancer was estimated at 0.04%.

The ***positive predictive value*** (PPV) of a given symptom for ovarian cancer is the proportion of women with that symptom who have ovarian cancer. For example if a symptom had a PPV of 0.2% for ovarian cancer, 1 in 500 women with that symptom would have ovarian cancer. The PPV of a symptom for ovarian cancer in those presenting to primary care depends both on the sensitivity/specificity of the symptom and the background risk of ovarian cancer in this population.

The ***negative predictive value*** (NPV) of a given symptom for ovarian cancer is the proportion of women without that symptom who do not have ovarian cancer.

The positive predictive value of bloating as a symptom of ovarian cancer showed great variability, probably due to various definitions of bloating used in the studies (from intermittent temporary bloating to permanent or continued abdominal distension).

While the sensitivity of individual symptoms for ovarian cancer is low it can be improved by combining the symptoms (see Table 2.2 and Figure 2.2). Hamilton *et al.* (2009) and Rossing *et al*. (2010) noted that 85% of women with ovarian cancer reported at least one symptom during the year before diagnosis.

The Goff symptom index (Goff *et al.,* 2007) uses a more restrictive definition of symptoms which incorporates symptom frequency and onset. This improves specificity at the expense of sensitivity.

Table 2.2 Combining symptoms to improve sensitivity

Symptom	Sensitivity	Specificity	Positive predictive value*	Negative predictive value*	References
Any symptom†	85%	74% to 85%	0.13% to 0.21%	More than 99.99%	Hamilton *et al.,* 2009 and Rossing *et al.,* 2010
Goff symptom index‡	64% to 69%	88% to 97%	0.20% to 0.94%	99.99%	Rossing *et al.,* 2010; Goff *et al.,* 2007; Andersen (2010) and Kim *et al.,* 2009

* Assuming a prior probability of undiagnosed ovarian cancer of 0.04% (Hamilton *et al.*, 2009)

† Any of the following symptoms for at least a week during the previous year: urinary frequency/urgency, abdominal distension, abdominal bloating, pelvic/abdominal pain or loss of appetite. Hamilton *et al.* (2009) also included postmenopausal or rectal bleeding. Rossing *et al.* (2010) also included nausea and diarrhoea/constipation.
‡ Any of the following symptoms at least 12 times a month (but present for less than one year): pelvic/abdominal pain, urinary urgency/frequency, increased abdominal size/bloating and difficulty eating/feeling full (Goff *et al.*, 2007).

Evidence tables:

Author(s): Bankhead *et al.* (2005)

Design: Systematic review
Country: United Kingdom

Included population: Women with all stages of ovarian cancer.

Included studies:

Papers investigating the symptoms experienced by women before having been diagnosed with ovarian cancer and ranging in design from retrospective case-control studies, longitudinal studies, questionnaires and surveys. One prospective study was identified and included.

Excluded studies:

Papers describing treatment or palliative care, screening, prevention or risk factors; Papers describing women with other conditions; Diagnostic or prognostic studies; Case studies, non-research articles, conference proceedings, letters, abstracts and others.

Population: N~2,800. Ages ranged between 15 and 90 years. Early and late stage disease.

Intervention(s) and comparator(s): N/A

Outcomes:

To identify the percentage of women who were asymptomatic before the time of diagnosis of ovarian cancer and to determine the prevalence of symptoms reported from quantitative studies.

Results:

- **Outcome:** Proportion of women with ovarian cancer without symptoms before diagnosis (using quantitative data directly from patients; N=8 studies (see below)) = 0.07 (95% C.I: 0.06-0.08). Between studies heterogeneity was not significant: X^2 (Q) = 11.3; df = 7; P=0.013 (Q statistic equivalent, I^2 = 38%).
    - Flam *et al.* (1988): Retrospective questioning. 362 cancers (172 stages IA or IB & 190 stages IIB-IV). Patients recently diagnosed and questioned before treatment.
    - Olson *et al.* (2001): Retrospective case-control study. Interviewer-led symptom checklist. 37 stages I/II and 118 stages II/IV. Patients diagnosed within a median of 4.7 months.
    - Vine *et al.* (2001): Case-control study. Standardised interview with symptoms checklist. 767 ovarian cancer cases comprising 616 invasive and 151 borderline cancers.
    - Vine *et al.* (2003): Case-control study. Interviewer-led symptom checklist. 267 ovarian cancer cases comprising 200 invasive and 67 borderline cancers.
    - Chan *et al.* (2003): Open ended questionnaire study. 87 patients (43 stages I/II and 37 stages II/IV). Newly diagnosed cancer patients.
    - Koldjeski *et al.* (2003): Retrospective symptom checklist, part of a longitudinal study on the impact of ovarian cancer. 20 patients (6 stages I/II and 13 stages III/IV).

Cancer diagnosed within previous 2-3 weeks.

- Webb *et al.* (2004): Part of a case-control study. Open-ended questions regarding up to four symptoms later categorised into 8 broader groups. 811 cancers (218 stages I/II and 447 stages III/IV and 146 borderline cancers. Newly diagnosed cases.

- Goff *et al.* (2004): Case-control study. Prospective symptom checklist of experiences in the previous year. 44 cancers (11 stages I/II and 33 stages II/IV). Women going through diagnosis.

- **Outcome:** Proportion of women with ovarian cancer without symptoms before diagnosis (using data collected from hospital records; N=3 studies (see below)) = 0.23 (95% C.I: 0.18-0.27). Between studies heterogeneity was not significant: X^2 (Q) = 1.76; df = 2; P=0.42 (Q statistic equivalent, I^2 = 0%).

  Petignat *et al.* (1997): Retrospective cancer registry data. Symptoms were recorded from all available sources. 119 cancers diagnosed from 1989-1995; stages IA-IB and 92 stages IC-IV.

  Eltabbakh *et al.* (1999): Retrospective case note review. Symptoms recorded at the time of presentation. 72 cancers diagnosed from 1984-1999; 50 stage I/II and 22 borderline.

  Nelson *et al.* (1999): Retrospective data from hospital notes. Symptoms recorded at the time of presentation. 72 cancers diagnosed from 1989-1991; 91 stages I/II and 59 stages III/IV.

- **Outcome:** Frequencies of symptoms reported from quantitative studies when comparing cases with controls. Data from symptom checklists according to Goff *et al.* (2004) Olson *et al.* (2001) or Vine *et al.* (2003).

  - Bloating (including fullness and pressure in the abdomen/pelvis OR = 25.3 (95% C.I:15.6-40.9)
  - Bloating or feeling of fullness OR = 14.6 (95% C.I: 9.4-22.8)
  - Bloating OR = 3.6 (95% C.I: 1.8-7.0) with clinic controls
  - Bloating OR = 3.5 (95% C.I: 1.5-8.2) with clinic controls
  - Distended/hard abdomen OR = 29.2 (95% C.I: 16.5-51.8)
  - Increased abdominal size OR = 7.4 (95% C.I: 3.8-14.2) with clinic controls

  - Abdominal/lower back pain OR = 6.2 (95% C.I: 4.0-9.6)
  - Pelvic/abdominal discomfort or pain OR = 16.4 (95% C.I: 10.3-25.3)

  - Abdominal mass OR = 5.4 (95% C.I: 2.4-12.0) with clinic controls
  - Urinary urgency OR = 3.5 (95% C.I: 1.6-8.2) with benign tumour controls
  - Constipation OR = 3.5 (95% C.I: 1.5-8.1) with benign tumour controls
  - Lack of appetite OR =8.8 (95% C.I: 4.3-18.2)

Follow-up: N/A

Notes:

This high quality systematic review combined data from 24 papers on the symptoms of ovarian cancer. Selection was made after searching for studies (including those in a non-English language) dated between 1984 and 2004 from Medline, EMBASE and CINAHL databases as well as hand searches of several other (named) journals. The search strategy was described and resulted in the identification of 220 potentially relevant papers. After the titles and abstracts were read and papers selected, data were extracted independently by two of the review authors. During this process two papers were excluded because the source of data was unclear and one because the study did not distinguish between symptoms of women with malignant or benign conditions.

Data were pooled to identify the percentage of women who were asymptomatic at the time of diagnosis. The methodology followed the methodology of inverse variance and the results were shown as a forest plot. Separate analyses were conducted according to whether data were collected from study participants or were taken from hospital notes. Where practicable, data were also combined across studies to try and identify those symptoms which had a significantly higher prevalence in women with ovarian cancer compared with matched controls.

Points to consider from these results:

1. The results from the meta-analysis showed that the overall proportion of asymptomatic women with ovarian cancer was 7.2%.
2. The results also showed that women with late stage cancer were more symptomatic than women with early or borderline cancer.
3. The authors have concluded that salient predictive symptoms have not been identified because of the retrospective nature of the study, recall bias, inherent patient bias, long duration between interview and diagnosis, under-estimation of patient experiences in medical records.
4. The systematic review was well conducted with the available data and is of high quality.

References used in the meta-analyses:

Chan YM., Ng TY., Lee PW., Ngan HY and Wong LC (2003) Symptoms, coping strategies, and timing of presentations in patients with newly diagnosed ovarian cancer. *Gynecol Oncol* **90:** 651-656.

Eltabbakh GH., Yadav PR and Morgan A (1999) Clinical picture of women with early stage ovarian cancer. *Gynecol Oncol* **75:** 476-479.

Flam F., Einhorn N and Sjovall K (1988) Symptomatology of ovarian cancer. *Eur J Obstet Gynecol Reprod Biol* **27:** 53-57.

Goff BA., Mandel LS., Melancon CH and Muntz HG (2004) Frequency of symptoms of ovarian cancer in women presenting to primary care clinics. *JAMA* **291:** 2705-2712.

Koldjeski D., Kirkpatrick MK., Swanson M., Everett L and Brown S (2003) Ovarian cancer: early symptom patterns. *Oncol Nurs Forum* **30:** 927-933.

Nelson L., Ekbom A and Gerdin E (1999) Ovarian cancer in young women in Sweden, 1989-1991. *Gynecol Oncol* **74:** 472-476.

Olson SH., Mignone L., Nakraseive C., Caputo TA., Barakat RR and Harlap S (2001) Symptoms of ovarian cancer. *Obstet Gynecol* **98:** 212-217.

Petignat P., Gaudin G., Vajda D., Joris F and Obrist R (1997) [Ovarian cancer: the symptoms and pathology. The cases of the Cantonal Cancer Registry (1989-1995)]. *Schweiz Med Wochenschr* **127:** 1993-1999.

Vine MF., Ness RB., Calingaert B., Schildkraut JM and Berchuck A (2001) Types and duration of symptoms prior to diagnosis of invasive or borderline ovarian tumor. *Gynecol Oncol* **83:** 466-471.

Vine MF., Calingaert B., Berchuck A and Schildkraut JM (2003) Characterization of prediagnostic symptoms among primary epithelial ovarian cancer cases and controls. *Gynecol Oncol* **90:** 75-82.

Webb PM., Purdie DM., Grover S., Jordan S., Dick ML and Green AC (2004) Symptoms and diagnosis of borderline, early and advanced epithelial ovarian cancer. *Gynecol Oncol* **92:** 232-239.

Author(s): Attanucci *et al.* (2004).

Design: Retrospective case-control study
Country: United States of America.

Inclusion criteria:

Cases: Women with invasive and borderline ovarian cancer.

Controls: Women with an adnexal mass subsequently found to have a benign ovarian neoplasm.

Exclusion criteria:

Cases: Women whose tumours had been incompletely surgically staged (N=35).

Controls: Women without a pathology report confirming an adnexal mass (N=77), women who already had cancer (N=6), women who had not been treated within the study period (N=11) and women with a germ cell tumour (N=2).

Population:
Cases: N=147. Mean age of women with invasive disease: 62 years (range: 21-85); mean age of women with borderline tumours: 50 years (range: 20-86).
Controls: N=76. Mean age: 49 years (range: 15-81).

Intervention(s) and comparator(s): N/A

Outcomes:

To compare the symptoms experienced by women with early stage ovarian cancer with women having late stage, borderline and benign ovarian neoplasms.

Results:

33/147 women were diagnosed with early stage disease (I and II), 81 women were diagnosed with late stage disease (III and IV) and 33 women had borderline disease. All women in the control group had a benign ovarian neoplasm.

- **Outcome: comparison of symptoms:**

  Early stage cancer patients were significantly more likely to report symptoms of mass effect (frequency, constipation, palpable mass, pelvic pressure) compared to patients having benign, borderline or invasive cancers:

  Early stage vs. benign cancers: 67% vs. 15% (P<0.001)
  Early stage vs. invasive cancers: 67% vs. 40% (P=0.008)
  Early stage vs. borderline cancers: 67% vs. 33% (P=0.007)

  There was no significant difference in the reporting of pain, gastrointestinal or gynaecological symptoms between women with early stage ovarian cancer and women with benign and borderline cancers.

  Compared to women having late stage disease, women with early stage ovarian cancer were less likely to report gastrointestinal symptoms (30% vs. 63%, P=0.002) and more likely to report gynaecological symptoms i.e. irregular vaginal bleeding, vaginal discharge, dyspareunia, post-coital bleeding or changes in the menstrual cycle (46% vs. 24%, P=0.02). However, there were no significant between group differences

in the reporting of pain or constitutional symptoms i.e. fever, fatigue, weight loss or weight gain.
Follow-up: N/A
Notes: This paper described the results of a retrospective case-control study conducted in the United States of America. All women were diagnosed between January 1st 1999 and 31st December 2001 and identified by tumour board registry and International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9) codes. Medical, operative and pathology records were reviewed to identify symptoms, verify diagnoses and stage tumours. The authors concluded that mass effect symptoms such as frequency, constipation, palpable mass and pelvic pressure were more prevalent in women with early stage ovarian cancer. They hypothesised that early stage tumours, whilst large and symptomatic, may be less likely to metastasise but tumours of late stage disease may metastasise when relatively small and hence not cause symptoms associated with their mass. Conversely, women with more advanced cancer reported more gastrointestinal symptoms than women with early stage disease. Points to be considered from these results: 1. There is an inherent bias from retrospective studies. 2. The data were retrieved from medical records reporting the patient's initial consultation, before receiving a cancer diagnosis, which might have minimised recall bias. 3. During an initial consultation, patients may have denied having symptoms, failed to report them or the symptoms may not have been recorded by the physician. 4. Women in the control group were referred to the senior author with an adnexal mass - they were not selected from a larger general population. 5. Comparing data from early stage disease with benign, borderline and late stage cancer showed consistent results.

Author(s): Smith *et al.*(2005)
Design: Population based, retrospective case-control study **Country:** United States of America
Inclusion criteria: Cases: Women diagnosed with ovarian cancer (stages IC and above) between 1994 and 1999. Controls: [1] Women with early (stages 0 or I) breast cancer and [2] women without cancer, age matched to the cases and randomly selected. All study participants had to be eligible for (if not necessarily claiming) Medicare, a national health insurance scheme, open only to people ≥65 years, those with a chronic disability or having various other (named) conditions.
Exclusion criteria: Women not entitled to Medicare A and B (insurance cover for in-patient hospital and convalescent expenses) or who had not been enrolled continuously in the 36 months prior to the date of cancer diagnosis; women in managed care plans; women with ovarian or breast cancer for whom this was not their first primary tumour; data only available from an autopsy or death certificate.

Population:

Cases: N=1,985; median age = 77 years (range: 68-101).

Controls: [1] N=6,024; median age = 75 years (range: 68-102) [2] N=10,941; median age = 78 years (range: 68-101).

Intervention(s) and comparator(s): N/A

Outcomes:

To evaluate the pattern of symptoms and the associated diagnostic tests documented in women with ovarian cancer over 36 months prior to the date of diagnosis. Each Medicare claim included at least one diagnostic code (ICD-9-CM) which could be grouped into the following categories: GI symptoms, abdominal pain, pelvic pain and abdominal swelling. Frequencies were then compared between the cases and each of the control groups and were reported as odds ratios (OR).

Results:

Of 1,985 women, 73.2% were classed as having stage III or IV disease (12.3% were unassigned) and 89.2% of tumours were identified as being epithelial (7% were unassigned).

The frequency and adjusted OR for each symptom type (claim code) experienced by women with ovarian cancer (cases) versus women with breast cancer or age-matched women without cancer are shown in the Table 1 (see Appendix A). Please note that due to the large amount of relevant data reported over three years, the results table has been reproduced directly from the original paper but will not appear in the published ovarian cancer guideline – instead the table will be substituted by a reference to the appropriate page number in the publication.

The proportion of women with ovarian cancer experiencing abdominal pain was highest in months 1-3 (30.6%), similarly abdominal swelling (16.5%) pelvic pain (5.4%) and GI symptoms (8.4%). In addition, the symptoms during this time period were also significantly more prevalent in women with ovarian cancer compared with either women with breast cancer or women with no cancer: abdominal pain (OR: 6.0 and 6.2 respectively) abdominal swelling (OR: 30.9 and 39.2 respectively) pelvic pain (OR 4.3 and 4.2 respectively) and GI symptoms (OR: 2.3 and 2.0 respectively). The increased frequency of cancer symptoms, comparative to controls, continued to be significant 7-9 months before diagnosis and one year before diagnosis, 7.4% of women with ovarian cancer reported at least one target symptom.

Follow-up: N/A

Notes:

This paper described the results of a large retrospective case control study conducted in the United States of America using data from women diagnosed with ovarian cancer (stages IC and above) between 1994 and 1999. Data were extracted from the SEER database and linked by a patient unique identifier to claims submitted to the United States health insurance program, Medicare by healthcare providers. Details for each patient also included a Common Procedure Terminology (CPT) code identifying the service rendered by the practitioner to the patient. Controls were also selected through Medicare records.

The authors concluded from their study that ovarian cancer could potentially have been diagnosed earlier in some patients, currently delayed by up to four months because health care providers ordered tests that would were not appropriate to make a definitive cancer diagnosis. They suggested that the use of tumour markers or pelvic imaging at an earlier point in the treatment pathway could have reduced this delay.

Points to consider from these results:

1. This is a retrospective study which has an inherent risk of bias since patient records were selected for inclusion.
2. The linking of patient data to health claim records may reduce the incidence of recall bias since, although symptoms were recorded up the three years before diagnosis, they were being reported at the time, not being recalled later as happens in some retrospective studies.
3. The authors made clear that the data were limited because they were extracted from databases that were designed for other purposes.
4. Since the majority of women had stage III/IV cancer, the authors excluded data from women with stages IA and IB disease.
5. All the women in this study were aged 68 years or over and hence younger women, possibly with earlier disease stages, were unrepresented.
6. There may be a bias in only including women who were eligible for Medicare.
7. Having two independent control groups, against which the cases were compared with reasonably consistent results, may have strengthened the validity of the findings.

Author(s): Yawn *et al.* (2004).

Design: Population based retrospective cohort study
Country: United States of America

Inclusion criteria: Women with a diagnosis of primary ovarian cancer.

Exclusion criteria: None stated.

Population: N=107. Mean age: 64.7 years (range: 30.5-98.1).

Intervention or comparators: N/A

Outcomes: To investigate the presenting signs, symptoms and stages of ovarian cancer in a community cohort of women.

Results:

98/107 (92%) women had epithelial ovarian cancer. 60% of tumours were stage III or IV and 60% were grade 3 or 4.

The initial symptoms reported varied with the tumour stage. Patients with early disease (stages I and II) were likely to present with crampy, abdominal pain and urinary symptoms. Alternatively, these tumours were found on routine examination. Women with late stage disease (stages III and IV) generally presented with abdominal bloating and weight loss.

- **Outcome: Symptoms prior to diagnosis:**
    - Abdominal pain: 22% in early disease vs. 35% in advanced disease (no P value)
    - Increased abdominal girth: 19% in early disease vs. 10% in advanced disease, P≥0.05 (NSD)
    - Weight loss: 0% in early disease vs. 8% in advanced disease, P≥0.05 (NSD)
    - Bowel changes: 2% in early disease vs. 10% in advanced disease, P≥0.05 (NSD)
    - Asymptomatic: 28% in early disease vs. 6% in advanced disease, P<0.01

- **Outcome: The time of onset of symptoms:**
    - <2 months: 55% of patients.
    - 2-6 months: 31% of patients
    - >6 months: 13% of patients.

Follow-up: N/A

Notes:

This paper presented findings from a small community cohort study conducted in Minnesota, USA from 1985 to 1997. Data on symptoms experienced up to two years before receiving a cancer diagnosis and on the duration of those symptoms were collected from medical records using the Rochester Epidemiology Project (REP) and SEER databases. In addition, the data abstractors, nurses who were familiar with the topic of ovarian cancer, constructed a short summary of each woman's course of symptoms and care before diagnosis**.**

Patients were divided into two groups according to time from the first documentation of signs or symptoms that were later associated with a positive diagnosis: group (1) <2 months or group (2) ≥2 months. A team of one physician and three nurses helped the authors to develop themes or domains and developed six categories to describe factors associated with the diagnostic course.

The authors concluded that the majority of symptoms were entirely abdominal and not specific to the pelvis, making diagnosis difficult. However recurrent, unresolved, or unexplained symptoms required exclusion of ovarian cancer as aetiology.

Points to be considered from these results:

1. This is a cohort study conducted with data from white, non-Hispanic women and hence the results may not be generalisable to other women with ovarian cancer.
2. The data were obtained from medical records which may have reduced recall bias
3. Women may not have described all their symptoms or the physician may not have recorded all the symptoms described by patients.

Author(s): Wynn *et al.*(2007)

Design: Population based, retrospective case-control study
Country: United States of America

Inclusion criteria:

Cases: Women diagnosed with ovarian cancer and having made at least two medical claims between 1998 and 2002. To rule-out remissions, cases had to have had surgery consistent with diagnosis or treatment of ovarian cancer within fourteen days of diagnosis.

Controls: Women with at least one medical claim and without cancer were matched to the cases for age, geographic location, Medicare eligibility and health plan. Participants were then randomly selected from this population.

All study participants had to be eligible for Medicare, a national health insurance scheme, or private employer based health insurance.

Exclusion criteria:

Cases: Women who'd had ovarian cancer diagnostic codes recorded in the year previous to the current diagnosis within the study.

All: Women who had not been continuously enrolled in a health plan for nine months preceding, and one month after, confirming surgery. Women who were pregnant in the ten-month study period.

Population:

Cases: N=920. Median age: 59 years.
Controls: [1] N=2,760 Median age: 59 years.

Intervention(s) and comparator(s): N/A

Outcomes:

To compare the pattern of symptoms, conditions and procedures documented in Medicare claims in women with ovarian cancer over nine months prior to the date of diagnosis. A predetermined list of fifteen symptoms was identified for each patient through the ICD-9-CM coding of their claims records. Frequencies were then compared between the cases and control groups and the trend pattern for each of the symptoms was plotted over the nine month study period.

Results:

- **Outcome: Frequency of symptoms (cases vs. controls):**
    - Abdominal (36.2% vs. 7.5%) P<0.0001
    - Urethra/urinary tract (12.7%vs. 6.4%) P<0.0001
    - Menopausal (12.4% vs. 7.5%) P<0.0001
    - Female genital (9.8% vs. 2.7%) P<0.0001
    - Gastrointestinal symptoms (7.7% vs. 5%) P<0.0001

The increased frequency of cancer symptoms, compared to controls, was also significant in the sixty to ninety days prior to diagnosis but diverged thereafter.

Follow-up: N/A

Notes:

This paper described the results of a large retrospective case control study conducted in the United States of America using data from women diagnosed with ovarian cancer between 1998 and 2002. Data were extracted from the Medstat's MarketScan Commercial Claims and Encounters and Medicare Supplemental database. Details for each patient also included a Common Procedure Terminology (CPT) code identifying the service rendered by the practitioner to the patient. The Charleson Comorbidity Index (CCI) was calculated using claims accumulated during the 9-month period to assess general health status. Controls were also selected through these records.

The authors concluded from their study that there were quantitative differences in symptoms in women with ovarian cancer from two to three months prior to their diagnoses.

Points to consider from these results:

1. This was a retrospective study, which has an inherent risk of bias since patient claim records were selected for inclusion.
2. As the data were not from the cancer registry they may not be representative of all women diagnosed with ovarian cancer.

3. The authors made clear that the data were limited because they were extracted from databases that were designed for other purposes.
4. Since the study excluded patients who had not had surgery within fourteen days of diagnosis, data from some women e.g. the elderly or those in ill health were not considered.
5. The linking of patient data to health claims may have reduced recall bias since, although symptoms were recorded up the three years before diagnosis, they were being recorded at the time of reporting.
6. Only women who were eligible for insurance were included in this study.
7. Claims records do not show tumour staging or histological data and these data were not otherwise available, a point noted by the authors as a major limitation.
8. The results from the study were consistent with other studies but, nonetheless, this is limited, poor quality evidence.

Author(s): Friedman *et al.* (2005).

Design: Retrospective case-control study
Country: United States of America

Inclusion criteria:

All women were in the Kaiser Permanente Medical care program, an integrated health care system.

Cases: Women diagnosed with ovarian cancer in 2001 – approximately half to have early stage disease (IA or IB) and the remainder to have advanced disease (IC-IV).

Controls: Randomly selected female subscribers matched for age, length of scheme membership and medical facility attended.

Exclusion criteria:

Cases: Incomplete follow-up; second primary cancer.

Controls: None stated.

Population: N=102. Age range: 29-87 years.

Intervention(s) and comparator(s): NA

Outcomes:

To identify the early symptoms of ovarian cancer from pre-diagnostic medical records and to compare symptoms in women with and without ovarian cancer.

Results:

Thirty-three patients had stage IA or IB disease; sixty-nine patients had stages IC-IV disease. 95/102 (93%) epithelial ovarian tumours.

One hundred and four symptoms were identified from medical records and these were compared between cases and controls. Of these, sixteen symptoms were equally reported by case and controls and were considered to be possibly unrelated to ovarian cancer. Data analyses were restricted to the remaining eighty-eight symptoms which showed case-control differences.

- **Outcome: Symptoms experienced >50% more often in cases than controls:**

  - Overall: 67/88 (76% 95% C.I: 67%-85%)
  - In the 6 months before diagnosis: 78% (95% C.I: 68%-88%)
  - In the 6 months to 1 year before diagnosis: 69% (95% C.I: 58%-80%)
  - In the 1 year to 2 years before diagnosis: 58% (95% C.I: 47%-69%)

In early cancers none of the symptoms exceeded chance expectation when compared to the incidence in controls although obesity was prominent and what the authors described as notably excessive was the occurrence of abdominal pain up to six months before diagnosis.

In advanced disease (IC-IV), the highest percentage of excess reported was 87% (95% C.I: 79%-95%) in the six months before diagnosis. For details of specific symptoms please see Table 2 (Appendix A). Please note that due to the large amount of relevant data reported, the results table has been reproduced directly from the original paper but will not appear in the published ovarian cancer guideline – instead the table will be substituted by a reference to the appropriate page number in the publication. Note that in this study, statistical significance was regarded as being $P<0.10$, which is non-standard, and was adopted because of the relatively low population number.

Over the entire study period, the predominant symptoms experienced by women with advanced ovarian cancer when compared with controls, were abdominal and gastrointestinal and also included pelvic, rectal and flank pain, dysuria, unintentional weight loss, headache, fatigue, shortness of breath and menopausal symptoms. Likelihood ratios ranged from 1.73 (shortness of breath) to 13.0 (pain in the side of trunk or flank).

Follow-up: N/A

Notes:

This paper provides only low quality evidence and describes the results of a small retrospective study conducted in California, USA using data from women diagnosed with ovarian cancer in 2001. Data were extracted from patient notes by two medical record analysts.

The authors concluded that it was not clear whether or not symptoms would be present whilst ovarian cancer was still localised and since hundreds of women would have to be investigated in order to detect one positive case, the clinical utility of symptoms was uncertain. However, they asserted that health care providers should keep ovarian cancer in mind when women presented with abdominal pain and bloating.

Points to be considered from these results:

1. There is an inherent weakness with retrospective studies and medical record analyses although recall bias may have been reduced.
2. The authors made clear that one limitation of the study was the lack of blinding of data analysts to the case-control status of each patient.
3. The study recruited a very low number of women with early stage (IA and IB) disease which may well explain the non-significant results, even with the significance cut-off set at $P<0.10$.

Author(s): Goff *et al.* (2007).

Design: Case-control study
Country: United States of America

Inclusion criteria:

Cases: Women undergoing surgery for a pelvic mass

Controls: [1] women who presented for ultrasound (USS) and [2] healthy, high-risk women enrolled in the Ovarian Cancer Early Detection study (OCEDS). None of the controls developed ovarian cancer in the six months after the study.

Exclusion criteria: None stated.

Population:

Cases: 149 with ovarian cancer (55 patients with ovarian cancer were added from another study).

Controls: 233 from the USS group and 255 from OCEDS.

All women were randomly assigned into exploratory or confirmatory groups, with the exception that all 55 patients with ovarian cancer from one author's previous study went into the exploratory group.

Intervention(s) and comparator(s): N/A

Outcomes: To evaluate symptoms in women with ovarian cancer who were surveyed prior to surgery and women at risk of having or developing cancer.

Results:

55/149 women had early stage disease, 88 women had late stage disease, 6 had unknown stage. Women with ovarian cancer were significantly older than the USS and OCEDS groups (56 years vs. 46 years and 51 years respectively, P<0.001)

Based on a correlation coefficient of ≥0.70 the following pairs of symptoms were combined into four variables: pelvic and abdominal pain, urinary frequency and urgency, increased abdominal size and bloating, difficulty eating and feeling full quickly.

- **Outcome: symptoms (cases vs. controls) occurring >12 days in each month for <6 months and <12 months (odds ratio):**
    - Pelvic/abdominal pain: OR: 19.1(95% C.I: 2.2-163.1) and OR: 23.3 (95% C.I: 3.9-163.9).
    - Urinary frequency/urgency: OR: 5.3 (95% C.I: 0.9-30.7) and OR: 5.2 (95% C.I: 1.0-25.1).
    - Increased abdominal size/bloating: OR: 11.2 (95% C.I: 2.2-58.3) and OR: 5.5 (95% C.I: 1.4-23.9).
    - Difficulty eating/feeling full quickly: OR: 1.0 (95% C.I: 0.1-9.9) and OR: 0.9 (95% C.I: 0.1-6.3).

When tested in the confirmatory group, the most sensitive model was considered to be the presence of six symptoms (the above named pairs but excluding urinary frequency/urgency) if present for >12 times per month for <1 year. This model showed a sensitivity of 56.7% for early stage disease and 79.1% for advanced stage disease with specificity of 90% for women >50 years and 86.7% for women < 50 years.

Follow-up: N/A

Notes:

This paper presented the results from a case-control study in which symptoms reported by women

with ovarian cancer were compared to those of women at high-risk of developing ovarian cancer. Study participants completed a survey on the occurrence, severity, frequency and duration of twenty-three symptoms and were surveyed either before ultrasound or histological diagnosis in order to minimise recall bias.

The exploratory group was used to determine the odds ratios of various self-reported symptoms. Those variables that were identified as significant formed a symptom index using regression modelling. The symptom index was then used with participants in the confirmatory group to test sensitivity and specificity.

The authors concluded that women who complained of pelvic and abdominal pain, urinary frequency and urgency, increased abdominal size and bloating, difficulty eating and feeling full quickly, symptoms of less than 12 month duration and occurring more than 12 times a month should be evaluated for potential ovarian cancer.

Points to be considered from these results:

1. This was a well-conducted case-control study in which the symptoms were first determined from an exploratory group and then resulting index checked with a confirmatory group.
2. One of the limitations of the study might be that the author added fifty-five ovarian cancer patients into the exploratory group whilst the other patients had been randomly selected. This may introduce a selection bias.

Author(s): Lurie *et al.* (2009)

Design: Population based case-control study.
Country: United States of America

Inclusion criteria:

Cases: Women with histologically confirmed invasive ovarian cancer.

Controls: Women of 18 years and older with no prior history of ovarian cancer and having at least one intact ovary.

Exclusion criteria: None stated.

Population:

Cases: N= 432. Controls: N=491. Age range: 19-88 years.

Intervention(s) and comparator(s): N/A

Outcomes:
To develop a symptom index that might help to diagnose ovarian cancer at an early stage and to evaluate whether there were histologically specific symptoms.

Results:

Of the 432 cases, 30% of women had local disease (stages IA-IB), 26% had regional disease (stages IC-II), 42% had distant spread (stages III-IV) and 2% were of unknown stage.

Abdominal pain was the most common symptom noted in localised ovarian cancer (sensitivity: 49%, specificity: 82%)

The following symptoms had the best predictive value for localised ovarian cancer with ROC (receiver operating curve) data in brackets:
Abdominal pain (0.81), Distended abdomen and hard abdomen (0.83), palpable abdominal mass (0.88), vaginal bleeding not associated with periods(0.88)

Women with ovarian cancer were more likely than controls to report a higher number of symptoms (Mean: 3.6 ± 0.1 vs. 2.6 ± 0.1 P<0.0001).

The authors wished to compare the various symptom indices by combining symptoms into groups. The best predictive ability was observed for a 4-symptom index that included abdominal pain, distended and hard abdomen, abdominal mass and abnormal vaginal bleeding. This index showed a sensitivity of 74% and a specificity of 77% specificity (ROC: 0.90).

When the authors compared the symptoms experienced alongside final histological diagnosis they found no statistical significance in any comparisons. The largest variation was noted in abdominal mass and distended, hard abdomen in mucinous compared with other tumours.

Follow-up: N/A

Notes:

This paper reported the results from a retrospective case-control study in which the symptom data were collected from an interview-based preset symptom questionnaire. The interviews were conducted in each participant's home by staff trained and supervised to standardise interviewing and coding techniques. All women were asked whether they had experienced any of the following 10 symptoms within 12 months prior to their diagnosis or the time of interview (controls). The duration of the symptoms were recorded:

- Persistent abdominal or pelvic pain or discomfort
- Unusual bowel irregularities such as diarrhoea or constipation, flatulence, or bloating
- Urinary frequency, difficulty emptying the bladder, or dysuria
- Persistent distended and hard abdomen
- Persistent fatigue, or loss of appetite
- Persistent flank or back pain with or without exertion
- Vaginal bleeding not associated with periods
- A palpable abdominal mass that the woman herself had noticed
- Weight gain and swelling of lower extremities
- Nausea, vomiting or heartburn.

The authors conclude that greater awareness of such symptoms, potentially related to ovarian cancer, might lead to an earlier diagnosis which might improve survival.

Points to be considered from these results:

1. There was a risk of recall bias as the interviews were conducted within a year after diagnosis.

2. Although of reasonable evidential quality, this study has all the usual disadvantages of a retrospective design.

Author(s): Lataifeh *et al.* (2005)

Design: Retrospective cohort study
Country: Australia

Inclusion criteria:

[1] Women early stage epithelial, ovarian cancer (stages IA and IB) [2] women with advanced stage epithelial, ovarian cancer (stage IIIC). Ten patients with early stage and 10 patients with advanced stage disease were selected consecutively for each of 10 years of study.

Exclusion criteria: Women with borderline and primary peritoneal cancers.

Population: N=200 (100 in groups [1] and [2])

Intervention(s) and comparator(s): N/A

Outcomes:

To determine the nature and duration of ovarian cancer symptoms, including any differences between early and advanced cancer patients.

Results:

38% of the women with early stage and 20% with advanced stage disease were <50 years of age (OR: 1.04; 95% C.I: 1.00-1.07, P=0.03). The duration of symptoms was the same regardless of cancer stage (70% early vs.60% late) presenting within 3 months of onset. All women with advanced cancer had experienced at least one symptom whilst 90% of women with early cancer were asymptomatic. The most common presenting symptom with early stage disease was vague abdominal pain (51%), also experienced by 44% of women with advanced stage disease.

- **Outcome: symptoms in early stage disease vs. advanced cancer:**
    - Abdominal swelling: 32% vs. 62% (OR 2.8: 95% C.I: 1.3-5.8, P=0.01)
    - Bloating: 10%v.s.13%
    - Abdominal pain: 51% vs. 44%
    - Abdominal pressure: 4%v.s.8%
    - Abdominal discomfort: 7% vs. 11%
    - Abnormal vaginal bleeding: 17% vs. 12%
    - Urinary symptom: 5% vs. 9%

Follow-up: N/A

General comments:

This paper reported the results of a retrospective cohort study comparing the symptomatology between early and advanced ovarian cancer. The cohort was from the Gynaecological Cancer database at Royal Hospital for Women at Australia. Data on the presenting symptoms were collected from medical records. The two groups were compared for each variable using logistic regression analysis.

Points to be considered:

- This was probably the only cohort study which compared early and advanced ovarian cancer.
- The study selectively compared stage IA and IB with IIIC but no other stages were included.
- There was a probability of bias due to recording symptoms from medical records although this may have reduced recall bias.
- Abdominal swelling, reported in advanced cancer significant more often when compared to early disease, might also have been due to ascites.
- There was no good quality evidence from this study to answer the topic question

Author(s): Bankhead *et al.* (2008)

Design: Prospective, qualitative cohort study

Country: United Kingdom

Inclusion criteria:

Women referred to hospital with suspected ovarian cancer; women recently diagnosed with ovarian cancer from hospital clinics.

Exclusion criteria: N/A

Population: Women with ovarian cancer: N=44. Mean age: 59 years. Women without ovarian cancer: N=80. Mean age: 48 years

Intervention(s) and comparator(s):

Outcomes: Symptoms in women with and without ovarian cancer.

Results:

44/124 women had malignancies (ovarian (N=40), primary peritoneal (N=2) or unknown (N=2)). 59 women had benign gynaecological pathologies and 21 had normal findings.

Multivariate analysis revealed the following symptoms as independent variable with ovarian cancer:

- **Outcome: symptoms of ovarian cancer v controls:**
    - Abdominal distension ± bloating OR: 5.2 (95% C.I: 1.3-20.5)
    - Bloating alone OR: 0.4 (95% C.I: 0.0-0.4)
    - Early satiety OR: 5.0 (95% C.I: 1.6-15.7)
    - Loss of appetite OR: 3.2 (95% C.I: 1.1-9.2)
    - Postmenopausal bleeding OR: 9.2 (95% C.I: 1.1-76.1)
    - Progression or worsening of the symptoms OR: 3.6 (95% C.I: 1.3-9.8)

The discriminatory power of the model was 81.5% which means 66% of the women with ovarian cancer and 90% of women without ovarian cancer were correctly identified.

Follow-up: N/A

Notes:

This paper described the results of a cohort study conducted in four hospitals in United Kingdom. All women were referred with suspected ovarian cancer. The study participants were interviewed before diagnosis or shortly after diagnosis and a thematic analysis of the data was conducted. The emergent symptoms were then quantitatively analysed and the symptoms for women with and without ovarian cancer were compared. 63/124 women were interviewed prior to the diagnosis and remaining women were interviewed shortly after diagnosis.

The authors concluded that change could be effected at the primary care level if general practitioners could distinguish between persistent and fluctuating distension. This is because persistent distension is an associated symptom in women with ovarian cancer and fluctuating distension or bloating is associated with women without ovarian cancer. This, they felt, would lead to more rapid and appropriate referrals for women with suspected ovarian cancer.

The authors emphasised that their qualitative study showed that the terminology used to describe symptoms did not always accurately describe the symptoms that the women experienced. They used the example of persistent and fluctuating distension which was commonly described by women as bloating.

Things to be considered from these results:

1. This study differed from other studies since medical records or a symptom checklist was not used. Instead, the authors conducted a qualitative analysis to identify symptoms and then quantified the symptoms, comparing women with and without ovarian cancer.

2. The interview was conducted before their diagnosis or shortly after diagnosis which eliminated recall and survivor bias.

3. The authors performed a subgroup analysis of the frequency of symptoms in women interviewed after diagnosis and concluded that systematic bias was not introduced.

4. The sample size was small in order to manage the qualitative analysis effectively.

5. The model was not tested on an independent set of data and needs further validation.

Author(s): Hamilton *et al.* (2009)

Design: Primary care based, retrospective case-control study

Country: United Kingdom

Inclusion criteria:

Cases: Women diagnosed with primary ovarian cancer between 2000 and 2007 and age>40 years.

Controls: Women without cancer, age and practice matched to the cases and randomly selected.

Exclusion criteria:

Women whose medical records was unobtainable, no entry in records in the year before diagnosis, women who had previous oophorectomy, or they lived outside the study area at the time of diagnosis.

Population:

Cases: N=212; median age = 67 years.

Controls: N=1060; median age = not given

Intervention(s) and comparator(s): N/A

Outcomes: To evaluate and identify symptoms of ovarian cancer in women in primary care

Results:

The data on the symptoms was collected from the medical records at primary care for one year before diagnosis. The researchers were blinded to the status of each woman. The symptoms were coded using international classification of primary care-2.

Univariate logistic regression, with P<0.1, identified symptoms for multivariate analysis. Using multivariable analysis the following seven symptoms were identified as independently associated with ovarian cancer.

Abdominal distension OR: 240 (95% CI: 46-1200),

Abdominal pain OR: 12 (95% CI: 6.1-22),

Postmenopausal bleeding OR: 24 (95% CI: 9.3-64),

Loss of appetite OR: 17 (95% CI: 6.1-50),

Urinary frequency OR: 16 (95% CI: 5.6-48),

Rectal bleeding OR: 7.6 (95% CI: 2.5-23),

Abdominal bloating OR: 5.3 (95% CI: 1.8-16).

One antagonistic interaction abdominal distension and increased urinary frequency suggesting if both symptoms are present, it is less likely to be ovarian cancer.

The calculated the positive predictive value (PPV) by combing two symptoms or same symptom reported second time. The combination of abdominal distension and loss of appetite had highest PPV of >5%, followed by abdominal distension reported twice with PPV of 4.3%.

They also calculated the odds for symptoms excluding 6months from the diagnosis. Three symptoms, abdominal distension (OR: 18, 95% CI 2.1-160), urinary frequency (OR: 3.1, 95% CI 1.3-7.3) and abdominal pain (OR: 2.6, 95% CI 1.5-4.6) was noted.

Follow-up: N/A

Notes:

This paper described the results of a retrospective case control study conducted in the United Kingdom using data from women aged more than 40 years diagnosed with ovarian cancer between 1994 and 1999. The data is from the primary care records. Data were extracted from the GP records and were not linked to the cancer registry. The controls were age and practice matched to the cases

The authors concluded from their study that symptoms of ovarian cancer in women in primary care were similar to those in hospital series. Abdominal distension with positive predictive value of 2.5% warrants rapid investigation

Points to consider from these results:

1. This is probably the only study in United Kingdom done at the primary care level and hence carries more valuable information on initial presentation.

2. The researchers have been blinded to the diagnosis and thereby reducing bias.

3. This is a retrospective study which has an inherent risk of bias since patient records were selected for inclusion.

4. All the women in this study were aged 40 years or over and hence younger women, possibly with earlier disease stages, were unrepresented.

5. There may be a bias in only including women who presented to the primary care. Some women might present directly to hospital as emergencies.

Author(s): Rossing *et al.* (2010)

Design: Case control study

Country: USA

Inclusion and exclusion criteria:

Women diagnosed with primary invasive or borderline epithelial ovarian cancer between 2002 and 2005 identified through a population based registry (SEER). Control subjects (with at least one ovary and no history of ovarian cancer) were selected by stratified random sampling from the same registry.

Population: 594 women with primary invasive ovarian cancer, 1313 healthy controls and 217 women with borderline ovarian cancer.

Intervention(s) and comparator(s):

Women were interviewed in person about their symptoms before diagnosis, which was on average 9 months before the interview. Control subjects were asked about symptoms before a reference date in the past, on average ten months before their interview.

Outcomes:

Women were asked to report five categories of symptoms: nausea; bloating or feeling of fullness; diarrhoea or constipation; pelvic or abdominal discomfort, pressure or pain; and a need to urinate more frequently or urgently than usual.

Only symptoms that were present at some point during the year before the diagnosis or reference date, at a frequency of at least daily for at least a week, were recorded.

Symptoms were analysed individually and as components of a symptom index (Goff, 2007) and consensus recommendations (Twombly *et al.*, 2007).

Results:

	Invasive ovarian cancer (N=594)	**Control (N=1313)**
Any symptom	504/594 (85%)	336/1313 (26%)

Nausea	83/594 (14%)	58/1313 (4%)
Diarrhoea or constipation	199/594 (33%)	132/1313 (10%)
Pelvic or abdominal pain	362/594 (61%)	96/1313 (7%)
Bloating or feeling full	381/594 (64%)	122/1313 (9%)
Urinary frequency or urgency	250/594 (42%)	152/1313 (12%)
Symptom index (Goff *et al.*, 2007)	400/594 (67%)	80/1313 (6%)
Consensus criteria (Twombly *et al.*, 2007)	386/594 (65%)	94/1313 (7%)

Subgroup analyses according to stage, age and symptom severity are also available

Author(s): Pavlik *et al.* (2009)

Design: Prospective case series

Country: USA

Inclusion criteria:

Subgroup of 450 women enrolled in a prospective screening study for ovarian cancer, who had abnormal transvaginal ultrasound (TVS) findings and underwent surgery. Only women who returned confident responses to the symptom index questionnaire were included (272/450).

Exclusion criteria:

Women who had died, had withdrawn from the study, who were unwilling to take the symptoms survey or who were not confident in their answers (178/450).

Population:

272 women. 32 with primary invasive ovarian cancer, 17 with low malignant potential or granulosa cell tumours, 192 with benign ovarian pathology.

Intervention(s) and comparator(s):

Women completed the Goff *et al*. (2007) symptom index questionnaire. They also had to rate their confidence in their replies (from 0 – no confidence to 5 - absolutely sure of accuracy). Only women with confidence of 3 (pretty sure) or more were included.

Transvaginal ultrasound (TVS) findings were also reported using a morphology index – the sum of the volume score (1 to 5) and the structure score (1 to 5).

Outcomes: Rate of symptoms, TVS morphology index.

Results:

	Invasive ovarian cancer (N=30)	Benign or low malignant potential ovarian pathology (N=242)
Symptom index + (Goff *et al.*, 2007)	6/30 (20%)	21/242 (9%)
TVS morphology index >3	27/20 (90%)	107/242 (44%)
TVS morphology index >4	22/30 (73%)	62/242 (27%)
Symptom index AND TVS >3	5/30 (17%)	7/242 (3%)
Symptom index AND TVS >4	5/30 (17%)	5/242 (2%)
Symptom index OR TVS >3	28/30 (93%)	121/242 (88%)
Symptom index OR TVS >4	23/30 (77%)	78/242 (32%)

Notes:

Unclear whether the questionnaire was completed as part of the screening study or following diagnosis. Combined low malignant potential tumours and benign ovarian pathology in their analysis.

Unlike the other case-control studies, all the included women had some form of ovarian pathology and had surgery. Exclude from any meta-analysis for this reason.

Author(s): Kim *et al.* 2009

Design: Case control study

Country: South Korea.

Inclusion criteria: Women visiting a single gynaecology department between 2007 and 2008. Controls had to have an intact uterus and at least one ovary.

Exclusion criteria: Women with a history of gynaecological cancer were excluded from the control group.

Population: 116 women with epithelial ovarian cancer, and 209 controls (74/209 controls had benign ovarian cysts).

Intervention(s) and comparator(s):

Women completed a questionnaire based on the Goff *et al*. (2007) symptom index. The study added an extra question about urinary symptoms.

In women with benign cysts the questionnaires were done before surgery. In women with ovarian cancer they were done during hospital stays for surgery or chemotherapy. In the remaining controls they were done during clinic visits for a routine Pap smear test. Investigators were available to help women with any questions they did not understand.

Outcomes: Individual symptoms (see below) and symptom index. The symptom index was considered positive if a woman had any of the symptoms present for less than one year but occurring more than 12 times per month.

Results:

	Ovarian cancer (N=116)	**Benign cyst (N=74)**	**Healthy control or benign cyst (N=209)**
Symptom index +	76/116	23/74	32/209
Pelvic/abdominal pain	20/116	10/74	11/209
Increased abdominal size / bloating	56/116	11/74	11/209
Urinary urgency / frequency	33/116	8/74	13/209
Difficulty eating / feeling full	42/116	10/74	14/209

Author(s): Andersen (2010)

Design: Case control study

Country: USA

Inclusion criteria:

Women with ovarian cancer. Healthy controls were identified via a screening study in high risk women.

Exclusion criteria:

Women with a history of gynaecological cancer were excluded from the control group.

Population:

74 women with ovarian cancer (6 with mucinous tumours, 6 with clear cell carcinoma, 7 with endometrioid cancer, 5 with other adenocarcinoma and 50 with serous cancer), 137 healthy controls.

Intervention(s) and comparator(s):

The target condition was the identification of ovarian cancer; the reference standard was histopathology for the women with ovarian cancer. Reference standard was not reported for the controls - it was probably negative screening tests for ovarian cancer since these women were identified via a screening study.

Outcomes: Serum samples and symptom questionnaires were collected prior to surgery (and diagnosis) in women who had surgery. Controls had serum samples and symptom questionnaires collected on a quarterly basis as part of a screening study.

Results:

Serum HE4

The HE4 threshold for positivity was the upper 95% percentile of the control group. Authors do not report the numeric value of this cut-off threshold. Using this definition fixes the specificity of HE4 at 95%.

sensitivity (95% C.I.) was 0.77 (0.66, 0.86), specificity was 0.95 (0.90, 0.98)

Serum CA125

The CA125 threshold for positivity was the upper 95% percentile of the control group. Authors do not report the numeric value of this cut-off threshold. Using this definition fixes the specificity of CA125 at 95%.

Sensitivity was 0.81 (0.70, 0.89), specificity was 0.95 (0.90, 0.98)

Symptom index (SI)

The symptom index was considered positive if the patient had at least one of the following symptoms for less than 1 year but more than 12 times per month: bloating or increased abdominal size, abdominal or pelvic pain, difficulty eating or feeling full quickly.

Sensitivity was 0.64 (0.52, 0.74), specificity was 0.88 (0.82, 0.93)

Combined tests

HE4 or CA125 positive: sensitivity was 0.89 (0.80, 0.95), specificity was 0.90 (0.83, 0.94)

HE4 or SI positive: sensitivity was 0.92 (0.83, 0.97), specificity was 0.85 (0.78, 0.90)

CA125 or SI positive: sensitivity was 0.92 (0.83, 0.97), specificity was 0.83 (0.76, 0.89)

HE4 or CA125 or SI positive: sensitivity was 0.95 (0.87, 0.99), specificity was 0.80 (0.72, 0.86)

SI and (HE4 or SI) positive: sensitivity was 0.58 (0.46, 0.70), specificity was 0.99 (0.95, 1.0)

Subgroup analyses of test accuracy according to age (<50 years versus 50 or more years), risk status and stage were also done.

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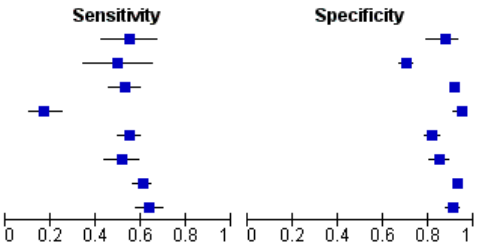
Figure 2.1 Sensitivity and specificity of individual symptoms [Back]

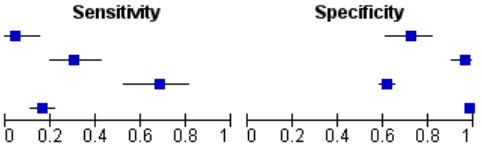
Abdominal pain

Study	TP	FP	FN	TN	Sensitivity	Specificity
Friedman 2005	38	13	31	89	0.55 [0.43, 0.67]	0.87 [0.79, 0.93]
Goff 2004	22	301	22	710	0.50 [0.35, 0.65]	0.70 [0.67, 0.73]
Hamilton 2009	112	92	100	968	0.53 [0.46, 0.60]	0.91 [0.89, 0.93]
Kim 2009	20	11	96	198	0.17 [0.11, 0.25]	0.95 [0.91, 0.97]
Lurie 2009	238	89	194	402	0.55 [0.50, 0.60]	0.82 [0.78, 0.85]
Olson 2001	87	37	81	214	0.52 [0.44, 0.60]	0.85 [0.80, 0.89]
Rossing 2010	362	96	232	1217	0.61 [0.57, 0.65]	0.93 [0.91, 0.94]
Vine 2003	171	31	96	317	0.64 [0.58, 0.70]	0.91 [0.88, 0.94]



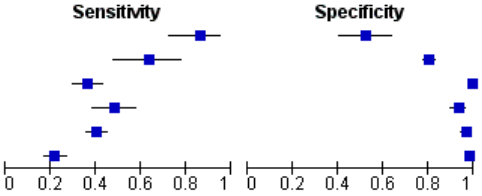
Abdominal bloating

Study	TP	FP	FN	TN	Sensitivity	Specificity
Bankhead 2008	2	22	42	58	0.05 [0.01, 0.15]	0.72 [0.61, 0.82]
Friedman 2005	21	4	48	98	0.30 [0.20, 0.43]	0.96 [0.90, 0.99]
Goff 2004	30	385	14	626	0.68 [0.52, 0.81]	0.62 [0.59, 0.65]
Hamilton 2009	35	21	177	1039	0.17 [0.12, 0.22]	0.98 [0.97, 0.99]



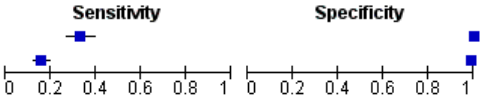
Abdominal distension

Study	TP	FP	FN	TN	Sensitivity	Specificity
Bankhead 2008	38	38	6	42	0.86 [0.73, 0.95]	0.53 [0.41, 0.64]
Goff 2004	28	197	16	814	0.64 [0.48, 0.78]	0.81 [0.78, 0.83]
Hamilton 2009	77	6	135	1054	0.36 [0.30, 0.43]	0.99 [0.99, 1.00]
Kim 2009	56	13	60	196	0.48 [0.39, 0.58]	0.94 [0.90, 0.97]
Lurie 2009	176	17	256	474	0.41 [0.36, 0.46]	0.97 [0.95, 0.98]
Vine 2003	59	5	208	312	0.22 [0.17, 0.28]	0.98 [0.96, 0.99]



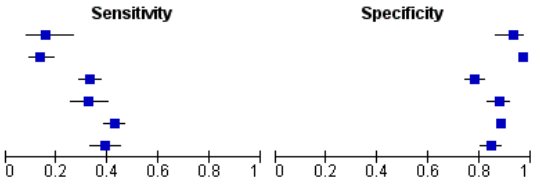
Abdominal mass

Study	TP	FP	FN	TN	Sensitivity	Specificity
Hamilton 2009	71	1	141	1059	0.33 [0.27, 0.40]	1.00 [0.99, 1.00]
Lurie 2009	70	6	362	485	0.16 [0.13, 0.20]	0.99 [0.97, 1.00]



Urinary symptoms

Study	TP	FP	FN	TN	Sensitivity	Specificity
Friedman 2005	11	7	58	95	0.16 [0.08, 0.27]	0.93 [0.86, 0.97]
Hamilton 2009	29	31	183	1029	0.14 [0.09, 0.19]	0.97 [0.96, 0.98]
Lurie 2009	143	107	289	384	0.33 [0.29, 0.38]	0.78 [0.74, 0.82]
Olson 2001	55	31	113	220	0.33 [0.26, 0.40]	0.88 [0.83, 0.91]
Rossing 2010	253	152	341	1161	0.43 [0.39, 0.47]	0.88 [0.87, 0.90]
Vine 2003	104	49	163	268	0.39 [0.33, 0.45]	0.85 [0.80, 0.88]



Abnormal vaginal or post menopausal bleeding

Study	TP	FP	FN	TN	Sensitivity	Specificity
Bankhead 2008	6	2	38	78	0.14 [0.05, 0.27]	0.97 [0.91, 1.00]
Hamilton 2009	28	12	184	1048	0.13 [0.09, 0.19]	0.99 [0.98, 0.99]
Lurie 2009	55	17	376	457	0.13 [0.10, 0.16]	0.96 [0.94, 0.98]
Vine 2003	53	12	214	305	0.20 [0.15, 0.25]	0.96 [0.93, 0.98]

Loss of appetite

Study	TP	FP	FN	TN	Sensitivity	Specificity
Bankhead 2008	17	13	27	67	0.39 [0.24, 0.55]	0.84 [0.74, 0.91]
Friedman 2005	10	2	59	100	0.14 [0.07, 0.25]	0.98 [0.93, 1.00]
Hamilton 2009	44	16	168	1044	0.21 [0.16, 0.27]	0.98 [0.98, 0.99]
Lurie 2009	166	114	266	263	0.38 [0.34, 0.43]	0.70 [0.65, 0.74]
Olson 2001	34	7	134	244	0.20 [0.14, 0.27]	0.97 [0.94, 0.99]

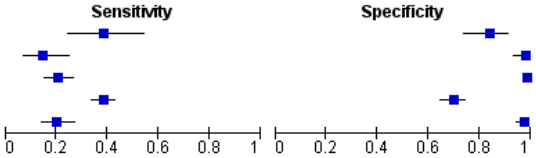
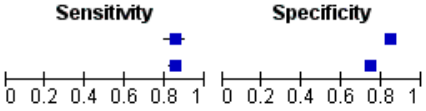


Figure 2.2 Sensitivity and specificity of combined symptoms [Back]

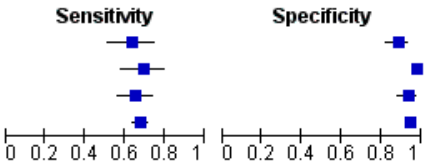
Any symptom (at least a week in previous year)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Hamilton 2009	181	164	31	896	0.85 [0.80, 0.90]	0.85 [0.82, 0.87]
Rossing 2010	504	336	90	977	0.85 [0.82, 0.88]	0.74 [0.72, 0.77]



Goff (2007) symptom index

Study	TP	FP	FN	TN	Sensitivity	Specificity
Andersen 2010	47	16	27	121	0.64 [0.52, 0.74]	0.88 [0.82, 0.93]
Goff 2007	52	45	23	1664	0.69 [0.58, 0.79]	0.97 [0.96, 0.98]
Kim 2009	76	9	40	126	0.66 [0.56, 0.74]	0.93 [0.88, 0.97]
Rossing 2010	400	70	192	1233	0.68 [0.64, 0.71]	0.95 [0.93, 0.96]



"*What is the relationship between the duration of pre-diagnostic symptoms of ovarian cancer and survival?*"

Short summary:

Limited evidence, from retrospective observational studies, suggests women presenting with advanced ovarian cancer haven't experienced their symptoms for any longer than those presenting with early stage disease.

There was insufficient evidence to say whether the duration of symptoms before diagnosis affects overall survival, quality of life or disease specific survival.

Review Protocol:

Question

What is the relationship between the duration of pre-diagnostic symptoms of ovarian cancer and survival?

Study inclusion criteria:

- **Studies:** Any study design
- **Participants:** Women with suspected ovarian cancer
- **Interventions:** Measurement of the duration of pre-diagnostic symptoms of ovarian cancer
- **Outcomes:** Overall survival, disease specific survival, disease grade and stage at diagnosis and quality of life

Search strategy:

The following electronic databases were searched: Medline, PreMEDLINE, EMBASE, Cochrane Library, CINAHL, BNI, PsycINFO, AMED, Web of Science (SCI & SSCI) and Biomed Central.

Review strategy:

The titles and abstracts of the studies identified in the literature search were screened for potentially relevant studies by one reviewer (NB).

Search results:

The literature search identified 75 studies and ten of these were included.

Description of included studies:

None of the studies were prospective: all used patients who had already been diagnosed with ovarian cancer, and obtained information about pre-diagnostic symptoms from patient interviews or medical records. The study sizes were also relatively small, except for a large postal questionnaire study of 1725 women by Goff *et al.* (2000) and an interview study of 811 women by Webb *et al.* (2004).

Four studies asked patients about their pre-diagnostic symptoms (Goff *et al.* 2000; Olsen *et al.,* 2007; Olson *et al.,* 2001 and Webb *et al.,* 2004). These interviews or questionnaires, however, were usually completed a number of months after the diagnosis of ovarian cancer and could be prone to recall bias, where patients have difficulty remembering what symptoms they experienced in the time before their diagnosis. The wording of questionnaires is also important: Tate *et al.* (2009) noted that studies using surveys with open-ended questions tended to report longer diagnostic delays than other surveys.

Six studies used medical records where symptoms should have been recorded as they were reported to doctors by patients (Fruchter *et al.,* 1981; Kirwan *et al.,* 2002; Menczer *et al.,* 2009; Neal *et al.,* 2007; Robinson *et al.,* 1984 and Wikborn *et al.,* 1996). These studies are not prone to problems with recall but can also be biased because doctors would tend to record the symptoms they feel are significant, rather than apparently minor symptoms which may in fact indicate undiagnosed ovarian cancer. The quality of individual studies are summarised in Figure 2.3.

Evidence summary:

Duration of symptoms and stage at diagnosis

Six studies compared the duration of symptoms according to disease stage at diagnosis (Fruchter *et al.,* 1981, Menczer *et al.,* 2009, Goff *et al.,* 2000, Olsen *et al.,* 2007, Robinson *et al.,* 1981 and Webb *et al.,* 2004). None of these studies found a statistically significant difference between the duration of symptoms of women presenting with early and advanced disease.

Olson *et al.* (2001) found the duration of symptoms before diagnosis was shorter in women with advanced stage (III to IV) than for early stage (I to II) ovarian cancer for all their symptom categories, except constipation. This difference was not statistically significant, however, except for diarrhoea.

Goff *et al.* (2000) reported that women with early stage disease at diagnosis were less likely to report ignoring their symptoms than women with advanced stage disease at diagnosis (74% versus 85%, P=0.002), although there was no significant difference in the time from symptom onset to diagnosis in early versus advanced stage in their study (P=0.56, t-test).

Neal *et al.* (2007) analysed the stage at diagnosis of patients with ovarian cancer according to their referral pathway. There was no significant difference between the stage at diagnosis of urgent guideline referrals and patients diagnosed through other routes (P=0.52).

Duration of symptoms and survival

Kirwan *et al.* (2002) compared patients with ovarian cancer who survived more than 18 months after the onset of symptoms with those who survived less than 18 months. There was no statistically significant difference in the time from the onset of symptoms to the first medical appointment between the two groups.

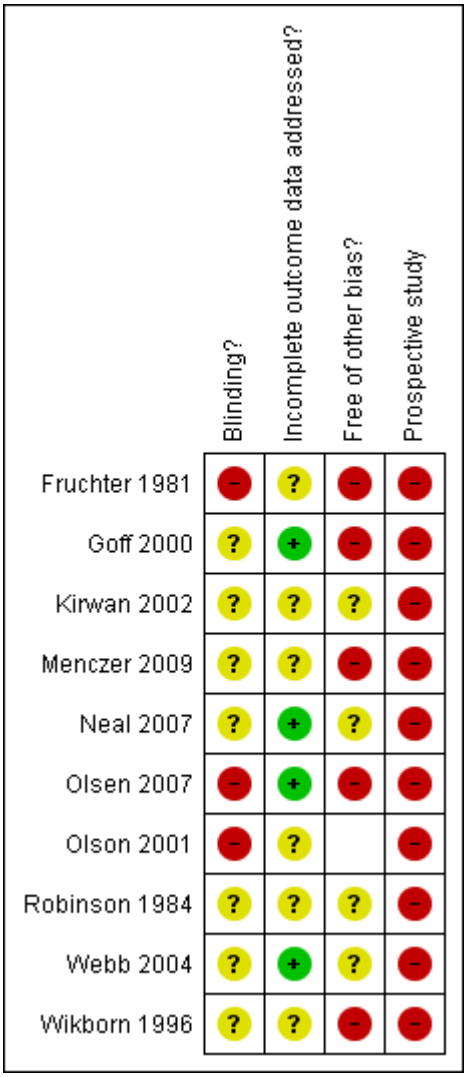
Neal *et al.* (2007) analysed the overall survival patients with ovarian cancer according to their referral pathway. Comparison of all urgent referrals with non-urgent referrals was showed no statistically significant difference (P=0.076), although Kaplan-Meier survival plots suggest poorer survival for those women who were urgently referred.

Analyses of the influence of diagnostic delay on outcome might be confounded by differences in the tumour biology between patients presenting with early and advanced disease. A patient with a fast growing tumour might experience disease progression and symptoms sooner and have quicker diagnosis but an ultimately poorer prognosis. A patient with a slow growing indolent tumour, however, might take longer to become symptomatic and to diagnose, but might have a better outcome (Neal, 2009).

Quality of life, tumour grade at diagnosis and disease specific survival

None of the studies reported these outcomes.

Figure 2.3 Summary of study quality [Back]



Evidence tables:

Author(s): Fruchter *et al.* 1981
Methods: Retrospective case series of women with diagnosed with ovarian carcinoma between 1970 and 1979 at a single institution.
Participants: 80 women. USA
Interventions: Not applicable.
Outcomes: **Diagnostic delay** Ascertained from medical records, and from interviews in some patients (between 1976 and 1978). **Disease stage** All patients were surgically staged. **Results: Delays greater than 3 months** Stage I-II: N=24, Patient delay 29%; Doctor delay 17%; Total delay 63%. Stage III, N=36, Patient delay 36%; Doctor delay 9%; Total delay 42%. Stage IV, N=20, Patient delay 36%; Doctor delay 9%;Total delay 35% Combined total, N=80, Patient delay 30%; Doctor delay 10%;Total delay 59% No statistically significant difference (using the Chi squared test) between the stage groups in terms of patient delay (P=0.45), doctor delay (P=0.40) and total delay (P=0.14)
Definition of delay: Patient delay was the interval from first symptom to first medical visit; doctor delay was the interval from first medical visit to histological diagnosis; total delay was the sum of the two. Intervals of 3 months or more were considered delayed in the analysis.

Author(s): Goff *et al.* 2000
Methods: Cross sectional study. Women who subscribed to a Canadian newsletter about ovarian carcinoma

were mailed a survey about the type and duration of pre-diagnostic symptoms in 1998.
Participants: 1725 women: 500 with early stage (I-II) disease, 1225 with advanced stage (III-IV) disease
Interventions: Postal survey, mailed after diagnosis. The delay from diagnosis to survey was not reported, but more than 50% of respondents had received a diagnosis and been treated within the last two years.
Outcomes: Duration of pre-diagnostic symptoms according to stage The mean number of months from symptom onset to diagnosis was 4.1 for early stage disease versus 4.8 for advanced stage (P=0.56, t-test). The mean number of months from first medical visit to diagnosis was 3.9 for early stage disease versus 4.6 for advanced stage (P=0.47). Women with early stage disease were less likely to report ignoring their symptoms than women with advanced stage disease (74% versus 85%, P=0.002).
Definition of delay: Women were asked to recall the dates of pre-diagnostic symptom onset, first medical visit and diagnosis of ovarian cancer.

Author(s): Kirwan *et al.* 2002
Methods: Retrospective audit of women diagnosed with epithelial ovarian cancer within a cancer UK network between 1992 and 1994
Participants: 135 women
Interventions: General practice medical records were reviewed to identify the referral pathway from primary care to hospital treatment and any primary care appointments in the year preceding the one that prompted the referral.
Outcomes:

Median diagnostic intervals, according to overall survival (OS) group

Patients were split into two groups for analysis: those surviving more than 18 months (N=81) and those surviving less than 18 months (N=54) after the onset of symptoms. Median survival times were compared using the Mann Whitney U test.

The following comparisons are for **OS > 18 months** versus **OS < 18 months:**

Patient interval: 7 days (range 1 to 395 days) versus 14 days (range 1 to 220 days), P=0.167

G.P. interval: 7 days (range 0 to 420 days) versus 1 days (range 1 to 210 days), P=0.345

G.P. to hospital interval: 7 days (range 0 to 190 days) versus 4 days (range 1 to 10 days), P=0.041

Hospital interval: 25 days (range 1 to 720 days) versus 21 days (range 1 to 400 days), P=0.167

There was no statistically significant difference between the overall survival groups in terms of diagnostic intervals, except for G.P. to hospital interval, which was significantly shorter in the group who survived less than 18 months.

G.P. to hospital interval was not an independent prognostic factor for overall survival in multivariate analysis. Independent adverse prognostic factors were age, advanced stage disease (III-IV) and presence of non-specific symptoms.

Definition of delay:

Patient interval: the duration of symptoms before attending the G.P.

G.P. interval: the time between the first presentation and subsequent referral

G.P. to hospital interval: unclear from the paper but it is probably the time between referral to and attendance at hospital.

Hospital interval: the time between attending hospital and definitive treatment.

Notes:

Authors conclude that delay by patients and G.Ps does not affect survival beyond 18 months, but this was a small study. Only significant covariates were included in the multivariate model.

Author(s): Menczer *et al.* 2009

Methods:

Population based observational study of women with histologically confirmed ovarian cancer diagnosed between 1994 and 1999 in Israel. Only women with symptoms at presentation were included.

Participants:

371 women reported symptoms, but there was only data about symptom duration from 186

women
Interventions: Clinical and symptom data were retrieved from medical records (discharge summaries and admission records). All of the 186 women included in the analysis had surgical staging of their disease.
Outcomes: **Pre-diagnostic symptom duration of 2 months or more by stage:** 18/32 (56%) of women with early stage (I-II) disease had symptom duration of 2 or more months compared with 71/154 (46%) of those with advanced stage disease. The difference is not statistically significant (P=0.39, Chi Squared test).
Definition of delay: Symptom duration defined as the interval between the earliest appearance of any of the presenting symptoms and the date of surgery.
Notes: Of the 1005 eligible patients, symptoms were recorded in 371/1005 (37%) and symptom duration in 186/1005. Some discrepancy between totals reported in the text and in tables.

Author(s): Neal, 2007
Methods: Retrospective review of hospital medical records from 2000 to 2001 from within one NHS trust for patients with lung, colorectal, prostate or ovarian cancer diagnosed either via G.P. fast track referral or through other referral pathways. Data were carefully checked for validity.
Participants: 95 patients with ovarian cancer. Survival data were available for 58 women, stage at diagnosis data were available for 82 women.
Interventions: The type of referral was noted: *urgent guideline referrals* were when patients were referred by their G.P. through the two week fast track system using locally agreed processes. Other types of referral (non-urgent GP referrals, inter-specialty referrals, accident and emergency department referrals, screening diagnoses) were grouped together. Stage at diagnosis was also noted
Outcomes: **Referral delays** 75% of women referred via the urgent guideline referral pathway had a secondary care

appointment within two weeks. This compared with 9% of non-urgent referrals.

Secondary care delays

The median secondary care delay for women referred though urgent referral guidelines was 31 days, this compared to a median of 69 days for non urgent referrals. Women referred via Accident and Emergency departments had a median delay of 18 days.

Overall survival

11 women had urgent guideline referrals, 47 were referred through other routes.There was no significant difference in survival rates between urgent guideline referrals (according to the G.P. referral guideline and those diagnosed through other routes (P = 0.21, log rank test).

Comparison of all urgent referrals (including non-guideline referral letters marked "urgent") with non-urgent referrals was showed no statistically significant difference (P=0.076), although Kaplan-Meier survival plots suggest poorer survival for those women who were urgently referred. Correction for stage at referral was not possible due to missing stage data.

Stage at diagnosis

There was no difference between the stage at diagnosis of urgent guideline referrals and patients diagnosed through other routes (P=0.52, Chi squared test). For urgent guideline referrals 26% had stage I-II disease and 74% stage III-IV. For other referrals 27% had stage I-II disease and 73% stage III-IV.

Definition of delay:

Patient delay was not reported in this study. Referral delay was the time between the date on the referral form or letter and the first hospital appointment. Secondary care delay was the time between the first hospital appointment and diagnosis.

Notes::

Small study unlikely to detect statistically significant survival differences.

Author(s): Olsen *et al.* 2007

Methods:

Observational study of women treated with surgery for an ovarian tumour between 1999 and 2002 in Queensland Australia.

Participants:

151 women with benign tumours, 61 with low malignant potential tumours and 244 with invasive ovarian cancer (89 stage I-II and 155 stages III-IV).

Interventions:

Women were contacted after their diagnosis (median 12 months after) by an interviewer using a

standard questionnaire about their pre-diagnostic symptoms.
Outcomes: **Diagnostic delay** Ascertained from patient interviews. **Disease stage** Women were surgically staged **Delay according to stage** Time from the onset of the first symptom to diagnosis was not associated with disease stage (P=0.16, t-test). Time from the onset of the first presentation to a medical practitioner was not associated with disease stage (P=0.50, t-test). There was no evidence that women with advanced disease delayed longer before presenting to their doctor: instead women with stage II-IV invasive disease reported both bowel symptoms (P=0.004) and abdominal swelling (P=0.004) to their doctor after a significantly short duration than women in the other groups.
Definition of delay: Time from symptom onset to first medical visit and time from first medical visit to diagnosis.
Notes: Women who did not receive surgery are excluded from this study.

Author(s): Olson *et al.* 2001
Methods: Case control study. Cases with ovarian cancer where recruited while attending either of two hospitals for surgery or chemotherapy.
Participants: 168 women with ovarian cancer (the data from controls are applicable to this question). 37 women had stage I-II disease, 118 had stage III-IV disease and 13 had incomplete staging.
Interventions: Women were interviewed about risk factors and pre-diagnostic symptoms. The mean time from diagnosis to interview was 4.7 months and 73% were interviewed within 9 months.

Outcomes:

Delay according to stage

The mean pre-diagnostic duration of the following symptoms was shorter in women with late disease than in early stage disease for all symptoms except unusual constipation. This difference was not statistically significant (using independent samples t-tests), except for unusual diarrhoea (P=0.009).

Unusual bloating, fullness and pressure in the abdomen or pelvis: early stage 6.4 months (SD 4.3), late stage 4.5 months (SD 4.1) P=0.08

Unusual abdominal or lower back pain: early stage 7.9 months (SD 4.5), late stage 5.6 months (SD 4.8) P=0.09.

Unusual lack of energy: early stage 6.9 months (SD 4.4), late stage 5.3 months (SD 4.5) P=0.34.

Frequent urination, urgency or burning: early stage 6.7 months (SD 5.1), late stage 4.6 months (SD 3.6) P=0.13.

Unusual constipation: early stage 5.4 months (SD 4.3), late stage 6.1 months (SD 5.7) P=0.75

Unusual lack of appetite: early stage 5.3 months (SD 2.3), late stage 3.0 months (SD 2.6) P=0.15

Unusual diarrhoea: early stage 8.1 months (SD 4.8), late stage 3.6 months (SD 3.2) P=0.009

Nausea: early stage 5.0 months (SD 4.3), late stage 2.8 months (SD 2.0) P=0.33

Other symptoms: early stage 6.0 months (SD 3.5), late stage 5.3 months (SD 4.1) P=0.65

Definition of delay:

Duration from symptom onset to diagnosis.

Author(s): Robinson *et al.* 1984

Methods:

Retrospective observational study. Patients referred to a single Israeli cancer centre in either 1974 or 1981, who had newly diagnosed cancer.

Participants:

621 patients with breast, lung, bladder, stomach or ovarian cancer. 92 women with ovarian cancer were included.

Interventions:

Not reported

Outcomes:

Diagnostic delay for ovarian cancer patients

In the 1974 audit 93% of women experienced delay, compared with 64% of women in the 1981 study.

Delay and survival for breast, lung, bladder, stomach and ovarian cancer patients combined

Survival graphs suggest that patients with delayed diagnosis had poorer overall survival than those who were not delayed, this difference was statistically significant in the 1974 audit ($P<0.01$, z-test) but not in the 1981 audit ($P>0.05$, z-test).

The overall survival data are not presented separately for ovarian cancer patients.

Delay and stage for ovarian cancer patients

There were 49 patients with diagnostic delay: stage I-II 73%, stage III 25%, unknown stage 2%

There were 43 patients who did not experience delay: stage I-II 70%, stage III 28%, unknown stage 2%

Definition of delay:

Diagnostic delay was analysed according to its patient, doctor and administrative components. Delayed diagnosis was defined as an interval of more than 6 weeks between the first symptom and final diagnosis.

Notes:

Delay was dichotomised as more or less than six weeks: this study could have analysed it as a continuous variable.

Author(s): Webb, 2004

Methods:

Observational study of women with histologically confirmed epithelial ovarian cancer between 1990 and 1993 in Queensland, New South Wales or Victoria.

Participants:

821 women. 811 (99%) has staging information and were included in the analysis.

Interventions:

Women were interviewed in person about their pre-diagnostic symptoms. The time interval between diagnosis and interview was not reported.

Outcomes:

Early invasive disease (stage III-IV)

Patient delay ≤1 month: 58%; between 1 and 3 months: 23%; more than three months: 19%

Doctor delay: ≤1 month:77%; between 1 and 3 months: 15%; more than three months: 7%

Total delay: ≤1 month 45%; between 1 and 3 months: 26%, more than three months: 29%

Advanced invasive disease (stage III-IV)

Patient delay: ≤1 month: 66%; between 1 and 3 months: 21%; more than three months: 13%

Doctor delay: ≤1 month: 67%; between 1 and 3 months: 19%; more than three months: 14%

Total delay: ≤1 month: 47%; between 1 and 3 months: 26%; more than three months: 27%

The proportion of women who waited more than 3 months before seeking medical attention was 29% for women with borderline tumours, 19% of women with early stage and 13% of women with advanced stage disease.

Definition of delay:

Time from symptom onset to first medical visit and time from first medical visit to diagnosis.

Author(s): Wikborn *et al.* 1996

Methods:

Observational study of women diagnosed with epithelial ovarian cancer between 1981 and 1986 at a single institution.

Participants:

160 women.

Interventions:

Medical records were checked for the symptoms reported at the first medical visit. Information about stage and histopathological class were also recorded.

Outcomes:

Patient related delay (duration of symptoms before medical consultation)

Patients with stage I disease had a short duration of symptoms (6 weeks on average) than those with stage II (12 weeks), stage III (15 weeks) and stage IV (10 weeks). No statistical analysis was reported, however.

Doctor related delay There was no statistically significant difference in the doctor related diagnostic delay between early and advanced stage disease (Chi Squared test, P not reported).
Definition of delay: Patient related delay - the length of time patients experienced symptoms before consulting a doctor. Doctor related delay was the time form first consultation to diagnosis.

References:

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2.2 Asking the right question – first tests

"*For women with suspected ovarian cancer, what are the most effective first tests in primary care?*"

Short summary:

There was no direct evidence comparing CA125, morphological ultrasound and pelvic examination in women with symptoms in primary care. Indirect evidence comes from systematic reviews of these tests in secondary care or in screening studies. Due to the differences in case mix between these settings it is likely that the tests will perform differently in each place. For example, as the prevalence of the ovarian cancer decreases from secondary care to primary care to screening studies, sensitivity could decrease but specificity could increase.

Assuming a prevalence of ovarian cancer in women with symptoms presenting to primary care of 0.23%, the positive predictive values of the individual tests were 0.81% for CA125 (Myers *et al.*, 2006) and 1.14% for morphological ultrasound (Liu *et al.*, 2006). This means that around 1 in every 100 women referred to secondary care with positive CA125 or ultrasound would have ovarian cancer. Negative predictive values were 0.06% for CA125 (Myers *et al.*, 2006) and 0.04% for morphological ultrasound (Liu *et al.*, 2007), suggesting around 5 in every 10,000 women with negative tests would turn out to have ovarian cancer.

The evidence suggested pelvic examination is relatively insensitive for the detection of adnexal masses. Myers *et al.,* (2006) estimated that only 45% of adnexal masses would be detected on pelvic examination. In women with palpable masses (assuming an ovarian cancer prevalence of 0.23%), pelvic examination had a positive predictive value of 2.03% for ovarian cancer and a negative predictive value of 0.07% (Myers *et al.*, 2006).

Assuming there is some disagreement between the individual tests, there is value in combining them. Tests can be combined to improve the overall sensitivity at the cost of specificity (by referring women who are positive on any of the tests). Tests can also be combined to improve specificity at the cost of sensitivity (by only referring women who are positive on all the tests).

There was no direct evidence about the performance of combined CA125, ultrasound and pelvic examination in primary care. The accuracy of combined tests was therefore estimated using the values from the meta-analyses of individual tests and assuming conditional independence between tests. Combining tests to improve sensitivity meant a reduced positive predictive value of 0.5% to 0.8% but an improved negative predictive value of 0.01 to 0.04% (depending on which combination was used). Different strategies will yield different. For example, referring if any of the combination of tests is positive is more sensitive but less specific than referring only when all the tests are positive.

Review Protocol:

Question

For women with suspected ovarian cancer, what are the most effective first tests in primary care?

Study inclusion criteria

- **Studies:** Diagnostic accuracy studies.
- **Participants:** Women with suspected ovarian cancer in primary care.
- **Index tests:** Pelvic examination, serum cancer antigen 125 (CA125) levels and ultrasound. Tests could be done individually or combined.
- **Target conditions:** The target condition is ovarian cancer.

- **Reference standards:** The reference standard diagnosis was histopathological analysis of the pelvic mass. In cases where there was no pelvic mass or malignancy was unlikely, clinical or radiological follow up would be an appropriate reference standard.

Search strategy

Review strategy

An initial list of studies was selected by the information specialist (SA). The reviewer (NB) then selected potentially relevant studies from this list on the basis of their title and abstract. These studies were ordered and each paper was checked against the inclusion criteria.

One reviewer (NB) extracted data. Only published data were included and authors were not contacted.

Study quality was assessed using the QUADAS checklist for diagnostic studies.

Search results:

The original literature search, restricted to studies in the primary care setting, did not return any studies. Terms relating to primary care were then removed from the search filter, and the search repeated.

Ultrasound

The literature search identified 234 ultrasound studies, of which five systematic reviews were included (Kinkel *et al.*, 2000; Liu *et al.,* 2007; Medeiros *et al.*, 2009a, Myers *et al.,* 2006 and Geomini *et al.,* 2009).

Pelvic examination

Searches identified one systematic review of pelvic examination (Myers *et al.*, 2006).

CA-125

The literature search identified 130 CA125 studies and two systematic reviews were included (Medeiros *et al.*, 2009b and Myers *et al.*, 2006).

Study quality:

The methodological quality of tests is summarised in Figure 2.4. Many of the studies were prospective and they shared a common reference (gold) standard test: histopathological verification of the adnexal mass. The Myers *et al.* (2006) review included some screening studies where the reference standard was ultrasound or clinical / radiological follow up.

The setting of the studies however was not well reported and it is likely that the majority of tests were done in secondary or tertiary care, prior to surgery for an adnexal mass (although the Myers *et al.* (2006) systematic review included some population based screening studies alongside secondary care studies). For this reason the applicability of the evidence is limited by the lack of primary care studies of women presenting with symptoms.

The sensitivity and specificity of a diagnostic test are often assumed to independent of prevalence. But if the test's performance is influenced by the severity of the disease, this assumption could be violated. So in practice the different case mix between primary and secondary care means that tests are likely to perform differently in the two settings. This is sometimes referred to as spectrum bias. For example diagnostic tests may have good sensitivity in secondary care, where patients have more

advanced and detectable disease whereas they may have poorer sensitivity in primary care where early stage disease is only just becoming detectable.

It was not reported in the systematic reviews whether patients had received other tests prior before the test in question. It is conceivable, for example, that women in secondary ultrasound studies had already had CA-125 tests and pelvic examination. The use of prior tests could reduce the accuracy of subsequent tests, since those women with clearly benign or clearly malignant disease might be filtered out before the index test.

Evidence summary:

Barrett *et al.* (2010) looked at G.P. records to determine the first investigations received in primary care by a woman with ovarian cancer. Their study included a cohort of 212 women diagnosed between 2000 and 2007 in Devon. Most patients (92%) had presented to their GP with at least one symptom compatible with ovarian cancer within the year before diagnosis. Most of the women (58%) were referred by their G.P. for specialist investigation as outpatients, but only around half of these referrals were to gynaecology departments. 17% were initially investigated in primary care with ultrasound and were then referred after an abnormal result. 19% presented as an emergency and a further 6% were diagnosed without any apparent primary care input. Although 21% of the women had a CA125 test in their records (all were abnormal), it was not possible to determine whether the test had been requested in primary or secondary care.

Pelvic examination for the detection of adnexal masses

Myers *et al.* (2006) summarised evidence from five studies (N=2289) of pelvic examination for the detection of adnexal masses. Two were screening studies which used ultrasound as the reference standard diagnosis. The remaining three were surgical series, and histology was the reference standard. The definition of a positive and negative test was variable, and not reported in some studies.

The pooled sensitivity was 45% (95% C.I. 28% to 68%) and pooled specificity was 90% (80% to 96%). This suggests that pelvic examination is relatively insensitive and will miss most pelvic masses, but the confidence interval is wide indicating uncertainty in the pooled estimate.

Pelvic examination for the discrimination of malignant from benign adnexal masses

Myers *et al.* (2006) included ten studies (N= 6647) of pelvic examination for the discrimination of benign from malignant adnexal masses, presumably in women with palpable masses. Three were screening studies and the remainder surgical case series. The definition of a positive pelvic examination varied, including "mass of 5cm or more in diameter" and "larger than normal". Other studies relied on clinical impression.

Pooled sensitivity was 72% (95% C.I. 49% to 88%) and pooled specificity was 92% (80% to 97%). There was a wide range of reported sensitivities (from 0% to 100%) and the pooled estimate has a wide confidence interval. If screening studies are pooled....

Ultrasound for the discrimination of benign from malignant masses

Evidence about ultrasound came from four systematic reviews (Geomini *et al.,* 2009, Kinkel *et al.,* 2000, Liu *et al.,* 2007 and Medeiros *et al.,* 2009a). Kinkel *et al.* (2000) and Liu *et al.* (2007) considered the relative accuracy of different ultrasound techniques. Medeiros *et al* (2009a) limited their review to Colour Doppler flow imaging ultrasound. Geomini *et al.* (2009) considered the relative accuracy of various models using risk scores derived from ultrasound parameters to predict malignancy in women with an adnexal mass.

The evidence suggested that the combined colour Doppler and morphometric ultrasound assessment was the most accurate technique. Using this technique and assuming a pre-test probability of ovarian cancer of 10%, a positive test would increase probability to over 40% whereas a negative test would

reduce it to less than 2%. There was some inconsistency in the sensitivity and sensitivity estimates for Colour Doppler flow imaging alone: the values reported by Medeiros *et al.* (2009a) were much higher than those of Kinkel *et al.* (2000) and Liu *et al.* (2007).

In the UKCTOCs screening trial (Menon *et al.*, 2009), abnormalities were detected at the initial ultrasound scan in 5.8% of women in the ultrasound screening arm. 34% of these abnormal initial scans were reclassified as normal following a second ultrasound test by an operator with particular expertise in gynaecological scanning. This suggests a relatively high false positive rate for ultrasound in the hands of less experienced operators. Women with whose second scan was also abnormal went for clinical assessment: and surgery was done in 42% of cases. The sensitivity and specificity for the overall strategy (screening US, repeat US and clinical assessment) were 75% and 98.3% respectively for the detection of primary invasive epithelial ovarian and tubal cancers. The diagnostic accuracy of the individual components could not be estimated.

Cancer antigen 125 (CA125)

Mederios *et al.* (2009b) conducted a systematic review and meta-analysis of serum CA125 for the discrimination of malignant/ borderline tumours from benign tumours in women with clinically suspected adnexal masses. Using a threshold CA125 level of 35 U/ml to signify malignancy and estimated the sensitivity and specificity of CA125 as 80% (95% CI 76% to 82%) and 75% (73% to 77%) respectively. Similarly in their systematic review of 46 studies, Myers *et al.* (2006) estimated the estimated the sensitivity and specificity of CA125 as 78% (95% CI 75% to 81%) and 78% (71% to 82%) respectively.

Pre-test probability (prevalence) of adnexal pathology

The test accuracy studies typically came from series of women selected for surgery and therefore had a relatively high probability of ovarian cancer. The prevalence of ovarian cancer in the included studies was around 25% or more (see Table 2.3). The prevalence of ovarian cancer in women presenting to GPs with symptoms of ovarian cancer, however, is likely to be much lower. For the economic model, prevalence was estimated at 0.23% by combining figures from Hamilton *et al.* (2009) with the yearly incidence of ovarian cancer in women over 40 from UK Cancer statistics 2005. In the Hamilton *et al.* (2009) study, 85% of the women with ovarian cancer had at least one of the following: abdominal distension, postmenopausal bleeding, loss of appetite, urinary frequency, abdominal pain, rectal bleeding or abdominal bloating in the year before presenting to primary care. These symptoms were relatively nonspecific since fifteen percent of the women without ovarian cancer in the study had also experienced such symptoms in the previous year.

Myers *et al.* (2006) reviewed evidence from 20 screening studies from the U.S.A., including 39,265 women. The screening studies menopausal or had a family history of breast, ovarian or colorectal cancer. The overall prevalence of adnexal masses referred for surgery ranged 1 to 2 percent in these studies. Approximately 10% of these masses were malignant so the prevalence of ovarian cancer was 0.2% or less.

In the American prostate, lung, colon and ovarian cancer screening trial (Hartge *et al.*, 2000) women aged 55 to 74 years were screened for ovarian cancer using bimanual ovarian palpation, transvaginal ultrasound and serum CA 125 measurement. In the 11,433 women screened 15.7% had simple cysts and 5.5% had complex cysts. This was a screening study so these women did not necessarily have symptoms, and the prevalence of cysts in women with symptoms could be different.

Effect of prevalence on test accuracy

Given that the only evidence comes from studies outside primary care it is reasonable to ask how it could be applied to primary care. Sensitivity could be lower in primary care, because there would be more difficult to detect early stage disease. But there would also be more patients with clearly benign conditions, so specificity should be better in the primary care setting. Because benign cases outnumber malignant ones by many times in primary care, overall test accuracy should be better in the primary care setting than in secondary care.

The evidence seems to support this view. In the UKCTOCs screening study (Menon *et al.*, 2009) where prevalence was 0.09%, ultrasound had a lower sensitivity (75%) but much better specificity (98%) than reported in surgical series. Similarly, pelvic examination had a lower sensitivity but higher specificity in screening studies than in surgical series in Myers *et al.* (2006).

Kinkel *et al.* (2000) and Liu *et al.* (2007) analysed the effect of ovarian cancer prevalence on the accuracy of ultrasound. Their results suggest ultrasound is more accurate in low prevalence settings than in high prevalence settings. Liu *et al.* (2007) note that this effect is likely to be due to better specificity because ultrasound is good at predicting benign status but less accurate in predicting carcinoma - especially in its early stages.

There was no direct evidence in the included studies about the effect of prevalence on the accuracy of CA125. Medieros *et al.* (2009) noted that the sensitivity of CA125 depended on the stage of the disease, with lower sensitivity for stage I disease when compared to advanced disease.

Diagnostic strategies:

Individual tests

If women with symptoms of ovarian cancer were only to receive a single test before referral, it would seem reasonable to choose the test with the optimal combination of sensitivity and specificity.

The evidence from diagnostic meta-analyses (see Table 2.4) suggests that combined Doppler and morphological ultrasound would be the most efficient. It is assumed in the literature (e.g. Myers *et al.*, 2006) that ultrasound can discriminate between women with adnexal masses and those without. Ultrasound should also be able to discriminate between benign and malignant adnexal masses in many cases, enabling targeted referral to secondary care.

Another strategy is to refer all women to a specialist without further diagnostic tests in primary care. This would only be appropriate in women with symptoms with high predictive value for malignancy. The current NICE G.P. Referral Guidelines for Suspected Cancer recommend urgent referral and investigation for women presenting with palpable masses or abnormal vaginal bleeding.

Combining tests

There were no systematic reviews about combined tests although Geomini *et al.* (2009) examined Risk of Malignancy Indices, which combine ultrasound findings with CA 125 level and menopausal status. The RMI 1 index had a similar diagnostic accuracy to combined colour Doppler and morphometric ultrasound.

Assuming there is some disagreement between CA 125, pelvic examination and US, combining their results could enhance diagnostic usefulness. If women were only referred for suspected ovarian cancer if none their test results was negative ("believe the negative"), this would increase overall specificity but decrease sensitivity . This is illustrated in the study by Shutter *et al*. (1994). The individual sensitivities and specificities of CA 125, US and pelvic examination were (93%, 80%), (88%, 64%) and (93%, 63%) respectively, but their combined sensitivity and specificity was (69%, 92%).

Menon *et al.* (2009) reported a serial screening strategy in one arm of the UKCTOCS study. All women received an initial CA125 test, those judged to be at elevated or intermediate risk of cancer went on to have an ultrasound test. This test combination had a sensitivity of 89.5% and specificity of 99.9% for primary invasive or tubal cancers within one year of the screen.

Another strategy is to refer for suspected ovarian cancer if any one of the tests is positive ("believe the positive"). This will increase the total number of women referred, decreasing specificity but increasing sensitivity, so fewer cancers would be missed. The relative importance of missed cases of

ovarian cancer versus over-investigation of women without ovarian cancer would determine the optimal strategy.

For both strategies it makes sense to do the safest and cheapest test first, since a positive or negative result on the first test can obviate further tests.

Estimating combined test accuracy:

The economic model which accompanies the guideline required an estimate of the combined test accuracy of the various combinations of CA125, ultrasound and pelvic examination. This can be estimated from the values of the individual tests if one assumes conditional independence between the tests. The individual test accuracies were taken from the reviews of Myers *et al.* (2006) and Liu *et al.* (2007).

Conditional independence is when the result on one test is not dependent upon the result of another. So if there was conditional independence between CA125 and ultrasound, the accuracy of ultrasound would be the same in women with elevated CA125 as in women with normal CA125 levels. This assumption is unlikely to be true in practice however, for example Liu *et al.* (2007) and Mederios *et al.* (2009b) suggest that patients with advanced disease are more likely to be detected on ultrasound and CA125.

Table 2.3 Accuracy of tests for diagnosis of malignancy in adnexal masses

Test	Study	N	Prevalence**	Sensitivity [95% CI]	Specificity [95% CI]	LR+	LR-	PPV	NPV
Individual tests									
CA 125 (cut-off 35 U/L)	Medeiros 2009b*	17 studies, N=2374	679/2374 (29%)	80% (76% to 82%)	75% (73% to 77%)	3.20	0.27	0.73%	0.06%
	Myers 2006*	46 studies (1 screening study), N not reported	Not reported	78% (75% to 81%)	78% (71% to 82%)	3.55	0.28	0.81%	0.06%
Ultrasound - morphologic assessment	Liu 2007*	54 studies, N=5524	24%	85% (83% to 87%)	83% (81% to 85%)	5.00	0.18	1.14%	0.04%
	Kinkel 2000*	34 studies, N=3377	24%	85% (83% to 88%)	85% (83% to 88%)	5.67	0.18	1.29%	0.04%
	Myers 2006* (Sassone criteria)	15 studies, N=not reported	Not reported	86% (79% to 91%)	77% (73% to 81%)	3.74	0.18	0.85%	0.04%
	Geomini 2009* (Sassone criteria)	18 studies, N=2670	944/2670 (35%)	84% (76% to 93%)	80% (73% to 88%)	4.20	0.20	0.96%	0.05%
Ultrasound (US) - colour Doppler	Medeiros 2009a*	12 studies, N=2398	562/2398 (23%)	87% (84% to 90%)	89% (87% to 90%)	7.90	0.15	1.79%	0.03%
	Liu 2007*	Not reported	24%	75% (72% to 77%)	73% (71% to 75%)	2.78	0.34	0.64%	0.08%
	Kinkel 2000*	10 studies, N=1408	24%	73% (58% to 87%)	73% (58% to 87%)	2.70	0.37	0.62%	0.09%
Ultrasound - combined colour Doppler and morphologic assessment	Liu 2007*	7 studies, N not reported	24%	87% (85% to 90%)	88% (85% to 91%)	7.25	0.15	1.64%	0.03%
	Myers 2006*	9 studies, N not reported	Not reported	89% (81% to 93%)	91% (80% to 96%)	9.89	0.12	2.23%	0.03%
	Kinkel 2000	7 studies, N=832	24%	92% (87% to 96%)	92% (87% to 96%)	11.50	0.09	2.58%	0.02%
Pelvic examination (PE),	Myers 2006*	2 screening studies,	Screening 173/1811	45% (28% to 68%)	90% (80% to 96%)	not applicable	not applicable	1.03%	0.14%

Test	Study	N	Prevalence**	Sensitivity [95% CI]	Specificity [95% CI]	LR+	LR-	PPV	NPV
for detection of adnexal mass		N=1811 3 other studies, N=478	(10%), Others: 235/438 (54%)						
Pelvic examination for discrimination of benign / malignant masses	Myers 2006* (all studies combined)	3 screening studies, N=5633 7 other studies N=1014	Screening: 5/5633 (0.09%) Others: 375/1014 (37%)	72% (49% to 88%)	92% (80% to 97%)	9.00	0.30	2.03%	0.07%
	Myers 2006* (screening studies)	3 studies, N=5633	5/5633 (0.09%)	58% (21% to 88%)	98% (97% to 98%)	29.00	0.43	6.27%	0.10%
Combined tests									
CA 125, US and PE all positive	Schutter 1994	228	101/228 (44%)	62% (51% to92 72%)	92% (87% to 97%)	7.75	0.41	1.76%	0.10%
PE and US positive	Schutter 1994	228	101/228 (44%)	83% (74% to 91%)	79% (72% to 86%)	3.95	0.22	0.90%	0.05%
CA 125 and PE positive	Schutter 1994	228	101/228 (44%)	67% (56% to 77%)	90% (85% to 95%)	6.7	0.37	1.52%	0.08%
US and CA 125 positive	Schutter 1994	228	101/228 (44%)	64% (53% to 74%)	89% (84% to 94%)	5.8	0.40	1.32%	0.09%

Abbreviations: LR +, likelihood ratio for a positive test result; LR -, likelihood ratio for a negative test result; NPV, negative predictive value (assuming pre-test probability of 0.23%); PE, pelvic examination; PPV, positive predictive value (assuming pre-test probability of 0.23%); RMI 1, risk of malignancy index 1; US, ultrasound;

*Systematic review and meta-analysis

**Prevalence of malignant or borderline tumours in the study.

Table 2.4 Accuracy of combined tests

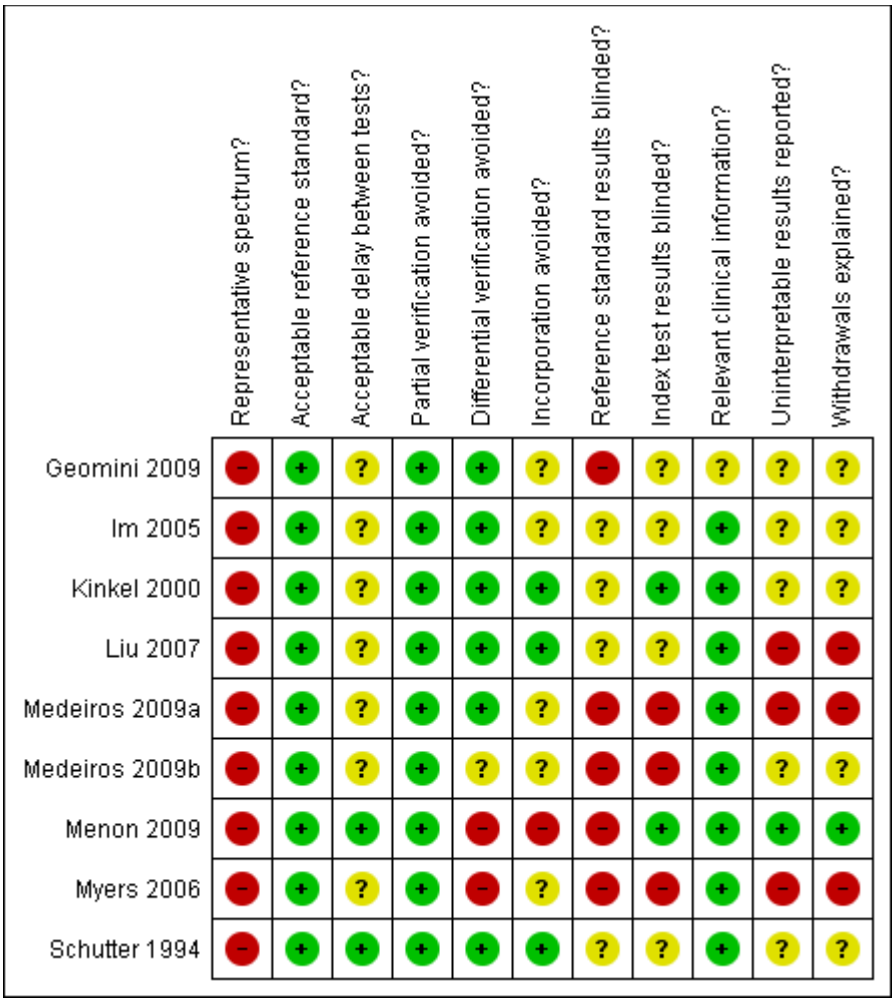
Assuming conditional independence and referring if any test is positive						
Tests	**Sensitivity [95% CI]**	**Specificity [95% CI]**	**LR+**	**LR-**	**PPV**	**NPV**
PE + CA125	88% (82 to 94%)	70% (57% to 79%)	2.93	0.17	0.67%	0.04%
PE + US	92% (88% to 96%)	75% (65% to 82%)	3.68	0.11	0.84%	0.02%
CA125 + US	97% (96% to 98%)	65% (58% to 70%)	2.77	0.05	0.63%	0.01%
PE + CA125 + US	98% (97% to 99%)	58% (46% to 67%)	2.33	0.03	0.54%	0.01%
Assuming conditional independence and referring only if all tests are positive						
Tests	**Sensitivity [95% CI]**	**Specificity [95% CI]**	**LR+**	**LR-**	**PPV**	**NPV**
PE + CA125	35% (21% to 55%)	98% (94% to 99%)	17.50	0.66	3.88%	0.15%
PE + US	38% (23% to 59%)	98% (96% to 99%)	19.00	0.63	4.20%	0.15%
CA125 + US	66% (62% to 70%)	96% (94% to 97%)	16.50	0.35	3.66%	0.08%
PE + CA125 + US	30% (17% to 48%)	100% (99% to 100%)	*	0.70	*	0.16%
Assuming tests are correlated and referring if any test is positive						
Tests	**Sensitivity [95% CI]**	**Specificity [95% CI]**	**LR+**	**LR-**	**PPV**	**NPV**
PE + CA125	78%	78%	3.55	0.28	0.81%	0.06%

PE + US	85%	83%	5.00	0.18	1.14%	0.04%
CA125 + US	85%	78%	3.86	0.19	0.88%	0.04%
PE + CA125 + US	85%	78%	3.86	0.19	0.88%	0.04%
Assuming tests are correlated and referring only if all tests are positive						
Tests	**Sensitivity [95% CI]**	**Specificity [95% CI]**	**LR+**	**LR-**	**PPV**	**NPV**
PE + CA125	45%	90%	4.50	0.61	1.03%	0.14%
PE + US	45%	90%	4.50	0.61	1.03%	0.14%
CA125 + US	78%	83%	4.59	0.27	1.05%	0.06%
PE + CA125 + US	45%	90%	4.50	0.61	1.03%	0.14%

Abbreviations: LR +, likelihood ratio for a positive test result; LR -, likelihood ratio for a negative test result; NPV, negative predictive value (assuming pre-test probability of 0.23%); PE, pelvic examination; PPV, positive predictive value (assuming pre-test probability of 0.23%); RMI 1, risk of malignancy index 1; US, ultrasound;

* Cannot calculate likelihood ratios and predictive values as specificity is 100%

Figure 2.4 Methodological quality summary [Back]



Evidence tables:

Author(s): Geomini *et al.,* 2009
Settings: Women with adnexal mass before surgery.
Participants: 109 studies were included in the review: reporting on 21750 adnexal masses: 15490 benign, 5826 malignant (27%) and 434 (2%) of borderline malignancy.
Study Design: Systematic review and meta-analysis. The included studies were observational, at least 56% were prospective, in 77% blinding of the pathologist was not mentioned and in 14% verification bias could not be excluded. Literature search included papers published up to 2008
Target Condition: The target condition was ovarian malignancy; the reference standard test was the histopathological diagnosis following surgery.
Tests: Index and comparator tests were diagnostic models predicting malignancy in ovarian masses. Models had to contain at least two parameters. 83 models were reported in the included studies: incorporating ultrasound parameters, age, menopausal status and CA 125 level. Some models relied on ultrasound parameters only (Sassone, Alcazar, Lerner, Ferrazzi, DePriest) others included additional parameters such as age, CA-125 level, and menopausal status (RMI I to IV, Tailor) The model with the optimal combination of sensitivity and specificity was the RMI I: sensitivity 78% (95% CI 71 to 85%), specificity 87% (95% CI 83 to 91%) to with a cut off value of 200). See evidence summary for the estimated accuracy of models for prediction of malignancy on ultrasound parameters.
Follow Up: Not applicable.

Author(s): Im *et al.,* 2005
Settings: Women undergoing surgical exploration for a pelvic mass at one of 6 university hospitals or a large tertiary community hospital. Exclusion criteria were age < 18 years or prior invasive gynaecologic malignancy.

Participants:

1035 women: 318 (30.7%) with primary malignancy, 50 (4.8%) with metastases to the ovaries and 667 benign masses. Women of 50 years or older were assumed to be postmenopausal. The prevalence of ovarian cancer was 77/454 (17%) in premenopausal women and 240/530 (45%) in post menopausal women.

Study Design:

Retrospective case series.

Target Condition:

Identification of ovarian malignancy. The reference standard was histopathology of the surgical specimen.

Tests:

Pelvic examination (in post-menopausal women)

Likelihood ratio for a positive test result 2.30

Likelihood ratio for a negative test result 0.50

Follow Up:

Not applicable.

Notes:

Study was designed to validate the SCO and ACOG referral guidelines for women with pelvic masses suspicious of ovarian cancer, and reports the predictive value of the various referral criteria.

Author(s): Kinkel *et al.,* 2000

Settings:

Systematic review of studies of US characterisation of adnexal masses, not discovered during screening for ovarian cancer.

Participants:

The review included a total of 46 studies with 5159 patients: The studies used the following ultrasound techniques: morphologic assessment (34 studies, N=3377), Doppler arterial resistance measurement (24 studies, N=2712), colour Doppler flow imaging (10 studies, N=1408) and combined techniques (7 studies, N=832)

Study Design:

Systematic review and meta analysis

Target Condition:

The target condition was the identification of malignancy in adnexal masses. The reference standard was histopathology.

Tests:

Ultrasound, four techniques were considered: morphologic assessment, Doppler arterial resistance measurement, colour Doppler flow imaging and combined techniques

Results - diagnostic accuracy for benign versus malignant masses

The meta-analysis calculated summary ROC curves for each of the US techniques, and obtained the Q* statistic in each case. The Q* values correspond to the point on the summary ROC curve where sensitivity and specificity are equal.

combined techniques: Q* 0.92 (95% C.I. 0.87 to 0.96)

morphologic assessment: Q* 0.85 (95% C.I. 0.83 to 0.88)

Doppler arterial resistance measurement: Q* 0.82 (95% C.I. 0.78 to 0.86)

colour Doppler flow imaging: Q* 0.73 (95% C.I. 0.58 to 0.87)

Subgroup analyses

The authors considered the following covariates: year of publication; proportion of pre-menstrual women in each study; proportion of women with mucinous tumours, endometriomas, and non-neoplastic cysts; prevalence of malignancy; stage distribution of ovarian cancer; study design (prospective versus retrospective); diagnostic criteria; US technical factors (like transabdominal versus endovaginal probes); country of publication; specialty of the person reading the US images (radiology versus gynaecology).

These factors did not have a statistically significant effect on diagnostic accuracy except in the following cases:

Prevalence of malignancy (34 studies, P=0.05) but only in US morphologic assessment studies. The accuracy of ultrasound was higher in studies with lower prevalence of malignancy.

Diagnostic criteria (89 studies, P=0.2). Accuracy of US was higher in studies which used validated diagnostic criteria.

Percentage of mucinous tumours (P=0.03, 28 studies). Accuracy of US was higher in studies with fewer cases of mucinous tumours.

Author(s): Liu *et al.,* 2007

Settings:

Women with adnexal mass (not discovered during screening for ovarian cancer), who had

ultrasound, CT or MRI before surgery.
Participants: 69 studies with 6364 patients. Ultrasound was evaluated in 65 studies with 126 data sets, of these 54 articles with 58 data sets (5524 patients) used morphologic information alone. Colour/power Doppler were used in 42 studies. Combined morphologic and colour/power Doppler were used in 7 studies. Literature search included papers published between 1990 and 2006. Menopausal status was mentioned in 34/69 studies. There were 2016/3125 (64.5%) premenopausal women in these 34 studies. At least 49% of studies were prospective, at least 53% of studies used blinded interpretation of test results but reporting of the study population was inadequate in 36% of the studies. Prevalence of malignant tumours was 24%.
Study Design: Systematic review and meta-analysis.
Target Condition: Target condition was identification of malignancy in adnexal mass, the reference standard was histopathology of the adnexal mass.
Results: Any ultrasound: sensitivity 89% (95% CI 88 to 90%), specificity 84% (82% to 86%) Morphologic assessment ultrasound: sensitivity 85% (95% CI 83 to 87%), specificity 83% (81% to 85%) Colour Doppler flow imaging: sensitivity 75% (95% CI 72 to 77%), specificity 73% (71% to 75%) Combined Doppler and morphologic US: sensitivity 87% (95% CI 85 to 90%), specificity 88% (85% to 91%) Contrast enhanced US: sensitivity 90% (95% CI 87 to 93%), specificity 89% (87% to 91%)
Follow Up: not applicable
Notes: The review does not report the setting of each study (primary, secondary or tertiary care), unclear what diagnostic tests women had already had before the ultrasound.

Author(s): Medeiros *et al.,* 2009a

Settings:

Women with clinically suspected adnexal mass, evaluated using 5 MHz transvaginal probe ultrasonography with colour Doppler, who went on to have histopathological analysis of the adnexal mass.

Participants:

12 studies included (2398 women): 7 were prospective studies, all were non-blinded. Prevalence of malignant tumours was 20% and borderline tumours 3%. Literature search included studies published between 1990 and 2007.

Study Design:

Systematic review and meta-analysis.

Target Condition:

The target condition was the identification of malignancy in adnexal masses. The reference standard was histopathology in all cases.

Tests:

Transvaginal colour Doppler ultrasound (resistance index of 0.5 or less) for malignant/borderline tumours versus benign tumours.

Pooled sensitivity was 84% (95% CI 84% to 90%)

Pooled specificity was 89% (95% CI 84% to 90%)

Follow Up:

Not applicable.

Notes:

Uncertain US results were excluded from the analysis (would inflate the estimates of diagnostic accuracy). The setting of each study is not reported (primary, secondary or tertiary care).

Author(s): Medeiros *et al.,* 2009b

Settings:

Women with clinically suspected adnexal mass, whose CA 125 levels were measured and who went on to have histopathological analysis of the adnexal mass.

Participants:

17 primary studies were included, with a total of 2374 women. The prevalence of ovarian cancer was 25.5%, and prevalence of borderline tumours was 3%. Literature search included studies

published between 1985 and 2007.
Study Design: Systematic review.
Target Condition: The target condition was ovarian cancer. Reference standard diagnosis was histopathology.
Tests: **Serum CA 125 level**, >35 U/ml cut-off value for malignancy Pooled sensitivity was 80% (95%CI 76% to 82%) for the detection of malignant/borderline tumours versus benign tumours Pooled sensitivity was 75% (95%CI 73% to 77%) for the detection of malignant/borderline tumours versus benign tumours
Follow Up: Not applicable.
Notes: Results were not analysed according to menopausal status

Author(s): Menon *et al.,* 2009
Settings: Post menopausal women aged 50-74 years, who were not at high risk of ovarian cancer.
Participants: 202638 women.
Study Design: Randomised trial of screening strategies. This paper reports the results of the prevalence (initial) screen.
Target Condition: The target condition was ovarian cancer. The reference standard was histopathology in women who had surgery or clinical/radiological follow up in others.
Tests:

Women were randomised to no screening, annual CA-125 screening with transvaginal ultrasound scan as a second test (multimodal screening) or annual screening with transvaginal ultrasound.

If initial tests (called level 1 screens) suggested intermediate or elevated risk of ovarian cancer women went for a level 2 screening test - an ultrasound scan done by an experienced gynaecologist, radiologist or senior sonographer with particular expertise in gynaecological scanning. Women with abnormal level scans were referred for clinical assessment.

Diagnostic accuracy of multimodal screening for detection of primary epithelial and tubal cancers

Sensitivity 89%, specificity not reported; for invasive cancers (within 1 year of screen) sensitivity 89.5%, specificity 99.9%

Diagnostic accuracy of ultrasound screening for detection of primary epithelial and tubal cancers

Sensitivity 85%, specificity not reported; for invasive cancers (within 1 year of screen) sensitivity 75.0%, specificity 98.3%

Author(s): Myers *et al.,* 2006

Settings:

Four clinical settings: patients with suspected adnexal masses, patients with adnexal masses, patients with suspected benign adnexal masses and patients with suspected malignant adnexal masses.

Participants:

14 studies examined pelvic examination, 153 studies ultrasound, Almost all studies were case series, although 13 population based screening studies were also included.

Study Design:

Systematic review

Target Condition:

Target condition was detection of adnexal mass, discrimination of malignant from benign adnexal masses,

Tests:

Bimanual pelvic examination, ultrasound morphology (Sassone.DePriest, Ferrazzi, Finkler or other scoring systems), ultrasound Doppler (resistance index, pulsatility index and maximum systolic velocity), combined morphology and Doppler, MRI, CT, FDG-PET, serum tumour markers (CA-125

Author(s): Schutter *et al.,* 1994

Settings:

Women presenting with a pelvic mass to gynaecology department. Inclusion criteria: age 45 or older, amenorrhoeic for at least 1 year, scheduled for surgical exploration with biopsy and/or excision of pelvic mass.

Participants:

228 women. 95 malignant tumours were found (41%) and 6 borderline tumours (2.6%).

199 of the pelvic masses were initially identified by pelvic examination and 28 by ultrasound.

Study Design:

Prospective multi centre case series.

Target Condition:

Target condition was the prediction of malignancy in pelvic masses. The reference standard was histopathology.

Tests:

Pelvic examination (PE) done by gynaecologist (clinical impression of malignant disease or not)

Sensitivity 93% (85 to 97%), specificity 63% (55 to 71%)

Transvaginal ultrasound (US) (Finkler score of 7-10 was the criteria for malignancy)

Sensitivity 88% (80 to 95%), specificity 64% (56 to 72%)

CA-125 level (>35 U/ml was the threshold for malignancy)

Sensitivity 72% (61 to 81%), specificity 80% (73 to 87%)

CA 125, US and PE all positive
Sensitivity 62% (51% to92 72%), specificity 92% (87% to 97%)

PE and US positive
Sensitivity 83% (74% to 91%), specificity 79% (72% to 86%)

CA 125 and PE positive
Sensitivity 67% (56% to 77%), specificity 90% (85% to 95%)

US and CA 125 positive
Sensitivity 64% (53% to 74%), specificity 89% (84% to 94%)

The diagnostic accuracy of other combinations of the test results were reported

Follow Up:

Not applicable
Notes: High prevalence of malignancy, patients had already had pelvic exam / ultrasound before entry into the study.

Health economic evidence (see Appendix 3)

This clinical question was highlighted as a priority for economic analysis because of the large number of patients with symptoms suggestive of ovarian cancer. In addition there are significant differences in costs and health outcomes associated with the diagnostic pathway as well as the considerable economic burden of treating ovarian cancer.

Economic evaluations of a diagnostic investigation require evidence on a number of issues, including disease prevalence and test accuracy. Furthermore, the accurate estimation of cost-effectiveness of one diagnostic strategy over another requires consideration of downstream treatment effects, health-related preferences (utilities), healthcare resource use and costs. High quality evidence on all relevant parameters is essential, however not always available. Where published evidence is sparse, expert opinion can be used to estimate relevant parameters. To test the robustness of the results of the cost-effectiveness analysis, a sensitivity analysis is undertaken.

A decision tree was constructed outlining seven strategies of interest: three of the strategies consisted of a single test (pelvic examination, ultrasound and serum CA125) and the remaining four strategies were comprised of a combination of tests (pelvic examination + serum CA125; pelvic examination + ultrasound; serum CA125 + ultrasound and pelvic examination + serum CA125 + ultrasound). A Markov process was embedded in the decision tree to model the recurrence of disease and survival based on the results of the diagnostic tests and the subsequent management of women presenting with symptom(s) of ovarian cancer in a primary care setting.

The clinical evidence required to populate the model was obtained from a number of different sources. Prevalence of the disease in primary care was assumed to comprise of linear summation of the prevalence of ovarian and colorectal malignancies and benign gynaecological problems. The estimates of the prevalence of ovarian and colorectal malignancies were obtained from published literature (CancerResearchUK, 2007; Hamilton *et al*., 2009).

The accuracy of the diagnostic procedures, in terms of the corresponding sensitivity and specificity values, were obtained from the systematic reviews of the clinical evidence conducted for this guideline (see clinical evidence in sections 2.2 and 2.3) (Hunink and Glasziou 2001; Bell *et al*., 1998). There was no consistent reporting of the proportion of patients in each treatment arm, as defined by the model structure, in the published literature. Therefore, the estimates of proportion were elicited from the GDG. Effectiveness of treatment in terms of survival and morbidity rates were obtained from published literature (Kosary 1994; Chien *et al*., 2005; Gerestein *et al*., 2009; Loft *et al*., 1991; Venesmaa and Ylikorkala 1992; International Collaborative Ovarian Neoplasm Group 2002). In addition, healthcare resource use associated with providing supportive care and follow-up monitoring were also obtained via GDG consensus.

Utility weights were required to estimate quality adjusted life years (QALYs). Estimates of health state utilities specific to ovarian cancer patients were obtained from published studies (Swart et al., 2007; Tappenden et al., 2007; Drummond et al., 2005) .

The costs considered in the analysis were those relevant to the UK NHS, and included costs of diagnostic investigations (both in primary and secondary care); costs of therapy (surgery, drug acquisition costs and administration costs) and costs associated with healthcare resource use for provision of supportive care and follow-up monitoring. Unit costs were based on NHS Reference Costs 2008-09 or the Unit Costs of Health and Social Care (PSSRU, 2009).

Within health economic evaluation, discounting of costs and health outcomes is standard practice – where costs and benefits that accrue in the future are given less weight to those which occur in the present. Following methodological guidance published by NICE, all costs and health outcomes are discounted at 3.5% per year (PSSRU, 2009).

A summary of expected cost and expected effectiveness estimates associated with each diagnostic strategy in the model is presented in Table 2.4. The cost of the strategies varies widely, ranging from the least expensive strategy (serum CA125) at just over £1,500 to the most expensive (combination of pelvic examination plus serum CA125 plus ultrasound) at £3,160 per patient. Health outcomes, measured in terms of QALYs, ranged from 20.391 for the serum CA125 strategy to 19.524 for the pelvic examination plus serum CA125 plus ultrasound combination strategy. Serum CA125 (single test) strategy on average generates 20.391 QALYs and ultrasound (single test) generates 20.387 – a difference of 0.004 QALYs is an equivalent (on average) of an additional 1.5 days of perfect health.

Table 2.4 Base case total expected cost and QALYs

Strategy	Cost (£)	Effectiveness (QALY)	ICER†
Serum CA125	1,532.32	20.391	
Ultrasound	1,604.24	20.387	(Dominated)
Pelvic examination + serum CA125	1,809.06	20.316	(Dominated)
Pelvic examination + ultrasound	1,864.16	20.298	(Dominated)
Pelvic examination	2,112.49	20.177	(Dominated)
Serum CA125 + ultrasound	2,850.49	19.681	(Dominated)
Pelvic examination + ultrasound + serum CA125	3,160.73	19.524	(Dominated)

†ICER – incremental cost-effectiveness ratio

All strategies in this analysis are dominated by the serum CA125 strategy. A strategy is said to be dominated if it is both more costly and less effective than its comparator.

A series of one-way sensitivity analyses were conducted to assess the robustness of the study results. One-way sensitivity analysis describes the process of changing one parameter in the model and re-running the model to see how a change in this parameter influences overall results.

Five scenarios were considered and are detailed below:

- nationally-agreed drug discounts
- a decrease in prevalence of ovarian malignancy in primary care
- the prevalence of benign gynaecological problem varied over an agreed range (20% - 30%)
- a decrease in the proportion of patients who are not fit for further treatment following diagnostic investigation
- an increase in age at the start of the model.

The results of the base case analysis were not sensitive to any of the five scenarios outlined above. The effect of applying nationally agreed price discounts did alter the overall expected costs but did not alter the ranking of the most cost-effective strategy. Specifying the parameters as distributions and performing a probabilistic sensitivity analysis showed that the CA125 strategy did little to alter this conclusion. Similarly, the results of the one-way sensitivity analysis in the other scenarios showed changes in the overall expected costs and health benefits but did not alter the ranking of the cost-effective diagnostic strategy.

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Chapter 3: Establishing the diagnosis in secondary care

3.1 Tumour markers: which to use?

"*For women with suspected ovarian cancer, what serum tumour marker tests should be routinely carried out to aid in diagnosis?*"

Short summary:

The evidence review considered the diagnostic accuracy of the following serum tumour markers CEA, CDX2, CA 72-4, CA 19-9, AFP, beta-hCG and HE4 in comparison to serum CA125 in women with suspected ovarian cancer. The evidence came from 39 studies of women who had surgery for pelvic tumours with histopathology to confirm their diagnosis. This means that the evidence is not directly applicable to women with symptoms of ovarian cancer in primary care.

The overall methodological quality of these studies was moderate to low - most were case series and not designed as prospective diagnostic studies. The reference standard diagnosis (histopathology) was consistently applied but the timing of the serum tumour marker tests and the use of blinding in the interpretation of tests was rarely reported.

HE4

There was consistent evidence, from five studies comparing HE4 and serum CA125 in women with pelvic masses, that HE4 is more sensitive and specific than serum CA125 for the diagnosis of ovarian cancer (Abdel-Azeez *et al.,* 2010, Huhtinen *et al.,* 2009, Moore *et al.,* 2008, Nolen *et al.,* 2010 and Shah *et al.,* 2009). These five studies included a total of 434 women with ovarian cancer and 583 with benign disease.

Summary ROC curves suggested peak sensitivity/specificity of 77% for serum CA125 compared with 83% for HE4. From these figures, for every 1000 women referred for diagnosis of a pelvic tumour, using HE4 instead of serum CA125 would identify an additional seven patients with cancer with 81 fewer false positives (assuming a 10% prevalence of undiagnosed ovarian cancer in this population (Myers et al, 2006)).

Five studies looked at the combination of HE4 and serum CA125 (Abdel-Azeez *et al.,* 2010, Huhtinen *et al.,* 2009, Moore *et al.,* 2008, Moore *et al.,* 2009 and Nolen *et al.,* 2010). The evidence suggests that the combination of HE4 and serum CA125 is more specific, but less sensitive than either marker in isolation.

CA 72.4

Ten studies, including 933 women with ovarian cancer and 1300 with benign disease, compared CA72.4 to serum CA125. The pooled results suggested CA 72.4 and serum CA125 have similar peak sensitivity/ specificity, 78% and 77% respectively. It is clear from the ROC curves, however, that (at least at the thresholds used in the studies) CA 72.4 has a lower sensitivity but higher specificity than serum CA125. Evidence from a further six studies suggests that combining the two markers could increase their specificity, but at the cost of sensitivity.

CA 19.9

Eight studies including 576 women with malignant tumours and 1432 with benign disease, compared the diagnostic accuracy of CA 19-9 and serum CA125 in women with pelvic masses .The summary ROC curve suggests CA 19.9 has relatively low sensitivity for the diagnosis of ovarian cancer, at the diagnostic thresholds used in the studies.

CEA, CDX2, AFP and beta-hCG

Eight studies including 1172 women, reported the diagnostic accuracy of CEA for the diagnosis of ovarian cancer in women with suspected ovarian cancer. Serum CEA was raised in approximately 26% of women with ovarian cancer (sensitivity 26%), but specificity varied widely between studies.

The literature searches found no studies about the use of the marker CDX2. There was a single study each about the use of serum beta-hCG and serum AFP in the diagnosis of ovarian cancer, suggesting low sensitivity for these markers. AFP and hCG are important markers for triage. However, when there is a suspicion of germ cell tumour, particularly in women younger than 40 years or where scan features suggest a germ cell tumour (for example Sturgeon *et al*., 2008).

Multiple tumour marker panels

Three of the studies (Nolen *et al.,* 2010; Moore *et al*., 2008 and Abel-Azeez *et al.,* 2010) looked at multiple tumour marker panels (combining three or more markers). There was no evidence to suggest that multiple tumour markers were much better than the two marker combination of serum CA125 and HE4.

Review Protocol:

Question

For women with suspected ovarian cancer, what serum tumour marker tests should be routinely carried out to aid in diagnosis?

Objectives

To estimate the sensitivity, specificity and positive/negative predictive values of serum tumour markers in women with suspected ovarian cancer; also, to estimate whether tumour marker levels influence treatment decisions and referral pathways in this group of women.

Study inclusion criteria

- **Participants:** Women with suspected ovarian cancer, for example with pelvic tumour or ascites.
- **Index tests:** Serum tumour markers: CA 19.9, CA 72.4, CEA, germ cell tumour markers (AFP and beta-HCG), HE4 and CDX2.
- **Target conditions:** Diagnosis of ovarian cancer, impact on referral and management.
- **Reference standards:** Histopathology (in women who had surgery) or clinical/radiological follow up in women not referred for surgery.

Search strategy

The following electronic databases were searched: Medline, PreMEDLINE, EMBASE, Cochrane Library, CINAHL, BNI, PsycINFO, AMED, Web of Science (SCI & SSCI) and Biomed Central.

Review strategy

The titles and abstracts of the studies identified in the literature search were screened for potentially relevant studies by two reviewers (LSA and NB).

One reviewer (NB) extracted the number of true and false positives and negatives for diagnostic studies. Data about the rates of serum tumour marker positivity according to disease stage and about tumour marker positivity as a prognostic factor were also recorded.

Study quality was assessed using the modified version of the QUADAS checklist for diagnostic studies included in the Cochrane Review Manager program.

Summary ROC curves and forest plots of the sensitivity and specificity of each tumour marker were plotted using the Cochrane Review Manager software program. The MetaDisc diagnostic meta-analysis software package (Zamora *et al.,* 2006) was used to pool the likelihood ratios and diagnostic odds ratios from the individual studies.

A potential source of heterogeneity (differences between the results of the studies) is the use of different cut-off thresholds to define elevated tumour markers. Cut-off values were recorded whenever studies reported them. MetaDisc was used to calculate the heterogeneity and inconsistency of the estimates of sensitivity and specificity.

Search results:

The literature search identified 229 potentially relevant studies. After reading study titles and abstracts, 39 were eventually included.

The literature searches found no studies about the use of the marker CDX2. There was a single study each about the use of serum beta-hCG and serum AFP in the diagnosis of ovarian cancer.

Study quality:

The methodological quality of the included studies is summarised in Figure 3.11. The methodological quality was moderate to low: most studies were case series and not designed as prospective diagnostic or prognostic studies. In general the reference standard diagnosis was acceptable, being histopathology in most cases. The timing of the serum tumour marker tests very poorly reported. The use of blinding in the interpretation of tests was also rarely reported.

Evidence summary:

Pooled results from studies comparing HE4, CA 19.9 or CA 72.4 to CA125 for the diagnosis of ovarian cancer in women with a pelvic mass.

	Tumour marker	N	Pooled DOR (95% C.I.)	Q* index	Pooled positive LR (95% C.I.)	Pooled negative LR (95% C.I.)
CA125 (all studies combined)	CA125	18 studies; N = 1492 with malignant and 2416 with benign disease	12.31 (9.03 to 16.77)*	77%	4.12 (3.23 to 5.27)	0.36 (0.29 to 0.44)*
HE4 versus CA125	HE4	5 studies; N = 434 with malignant and 583 with benign disease	30.97 (21.03 to 45.60)	84%	7.75 (5.45 to 11.01)	0.26 (0.19 to 0.36)*
	CA125	5 studies; N = 434 with malignant and 583 with benign disease	16.84 (11.75 to 24.14)	77%	6.42 (4.02 to 10.26)*	0.37 (0.31 to 0.45)
	HE4 or CA125	5 studies; N = 442 with malignant and 811 with benign disease	33.29 (22.16 to 50.01)	86%	7.98 (3.57 to 17.83)*	0.18 (0.12 to 0.26)
CA 72.4 versus CA125	CA 72.4	10 studies; N = 933 with malignant and 1300 with benign disease	12.64 (8.92 to 17.91)*	78%	5.51 (4.37 to 6.96)*	0.46 (0.40 to 0.52)*
	CA125	10 studies; N = 933 with malignant and 1300 with benign disease	11.56 (7.95 to 16.81)*	77%	3.39 (2.57 to 4.48)*	0.31 (0.24 to 0.41)*

	CA 72.4 or CA125	6 studies; N = 518 with malignant and 720 with benign disease	18.35 (12.50 to 26.93)*	81%	4.25 (2.92 to 6.19)*	0.25 (0.18 to 0.37)*
CA 19.9 versus CA125	CA 19.9	8 studies; N = 576 with malignant and 1432 with benign disease	2.40 (1.55 to 3.70)*	57%	1.82 (1.34 to 2.46)*	0.81 (0.72 to 0.91)*
	CA125	8 studies; N = 576 with malignant and 1432 with benign disease	11.23 (6.37 to 19.78)*	77%	3.87 (2.71 to 5.51)*	0.38 (0.26 to 0.56)*
	CA 19.9 or CA125	3 studies; N = 164 with malignant and 409 with benign disease	18.96 (11.17 to 32.16)	78%	3.13 (2.65 to 3.69)	0.17 (0.11 to 0.25)

Abbreviations: DOR, diagnostic odds ratio; LR, likelihood ratio

*significant heterogeneity in the pooled estimate (P<0.05, Cochran Q test)

Hypothetical test outcomes for 1000 women referred for diagnosis of a pelvic mass (assuming 10% have ovarian cancer). Figures were calculated using the Q* index values from pooled results table.

Tumour Marker	False negatives (cancer missed)	True positives (cancer identified)	False positives (wrongly identified as cancer)	True negatives (benign disease correctly identified)
HE4	16	84	144	756
CA125	23	77	207	693
CA 72.4	22	78	198	702
CA 19.9	73	57	387	513
CA125 OR HE4	14	86	126	774
CA125 OR CA 72.4	18	82	162	738
CA125 OR CA 19.9	12	78	198	702

This table uses the information from summary the ROC curves, and assumes the tumour marker tests could operate at the point where sensitivity and specificity are equal.

Table 3.1 Definition of terms used in tables and figures (Deeks, *et al.*, 2001)

Term	Definition
Diagnostic threshold	The cut off value (for example a tumour marker concentration) used to divide people into disease and normal categories. Changing this threshold will change the sensitivity and specificity of the test.
Sensitivity	The rate of correct identification of people with a disease.
Specificity	The rate of correct identification of people without a disease.
Summary ROC curve	This is obtained by plotting the sensitivity and specificity pairs from individual studies. This method does not yield a unique joint summary estimate: it is only possible to obtain a summary estimate of one value by specifying the value of the other.
Q* index	The point on the summary ROC curve where sensitivity and specificity are equal (the point on the curve closest to the upper left hand corner). This represents the test's maximum possible paired sensitivity and specificity according to the summary ROC curve. This sensitivity / specificity combination may not be achievable in practice.
Diagnostic odds ratio	The diagnostic odds ratio describes the odds of a positive test results in patients with disease compared with the odds of positive test results in people without disease. It is a convenient measure when combining studies in meta-analysis (but difficult to apply directly to clinical practice). It is useful in tumour marker studies as it is often reasonably constant regardless of the diagnostic threshold. A single diagnostic odds ratio corresponds to the set of sensitivities and specificities depicted by an ROC curve.

Positive likelihood ratio	The positive likelihood describes the discriminatory properties of a positive test result. As a rule of thumb, positive likelihood ratios above 10 have been noted as providing convincing evidence, whereas those above 5 provide strong diagnostic evidence.
Negative likelihood ratio	The negative likelihood describes the discriminatory properties of a negative test result. As a rule of thumb, negative likelihood ratios below 0.1 have been noted as providing convincing evidence, whereas those below 0.2 provide strong diagnostic evidence.

CA125

There were 18 studies that compared CA125 with HE4, CA 72.4 or CA 19.9 (see Figures 3.1 and 3.2). These studies included a total of 1492 women with ovarian cancer and 2416 with a benign pelvic mass. The studies used a cut-off thresholds ranging from 31 to 81 U/ml to discriminate between malignant and benign masses. Most studies (12/18) used the serum concentration cut-off of 35 U/ml (in post menopausal women). Two studies did not use discrete cut-off thresholds (Nolen *et al.,* 2010 and Moore *et al.,* 2008).

Pooling the results gave a diagnostic odds ratio of 12.31 (95% C.I. 9.03 to 16.77; significant heterogeneity) and a Q* index of 77%. This is consistent with the results of a good quality systematic review by Myers *et al.* (2006) including 46 studies. This review reported pooled sensitivity and specificity both of 78%.

HE4

There was consistent evidence, from five studies comparing HE4 and CA125 in women with pelvic masses, that HE4 is more sensitive and specific than CA125 (Abdel-Azeez *et al.,* 2010, Huhtinen *et al.,* 2009, Moore *et al.,* 2008, Nolen *et al.,* 2010 and Shah *et al.,* 2009; see Figures 3.3 and 3.4). These studies included 434 women with ovarian cancer and 583 with benign disease.

Two of the studies used cut-off thresholds ranging from 70 to 71 pM and three studies did not use discrete cut-off thresholds (Nolen *et al.,* 2010, Shah *et al.,* 2009 and Moore *et al.,* 2008).

Pooling the results for HE4 gave a diagnostic odds ratio of 30.97 (95% C.I. 21.03 to 45.60; no significant heterogeneity) and a Q* index of 84%. This compared with a diagnostic odds ratio of 16.84 (95% C.I. 11.75 to 24.14; no significant heterogeneity) and a Q* index of 77% for CA125.

Five studies looked at the combination of HE4 and CA125 (Abdel-Azeez *et al.,* 2010, Huhtinen *et al.,* 2009, Moore *et al.,* 2008, Moore *et al.,* 2009 and Nolen *et al.,* 2010). The evidence suggests that the combination of HE4 and CA125 is more specific, but less sensitive than either marker in isolation.

There was conflicting evidence, from two studies, (Nolen *et al.,* 2010; Moore *et al.,* 2008) about whether CA125, HE4 or combined CA125/HE4 was most accurate in premenopausal women or in early stage tumours.

CA 72.4

Ten studies, including 933 women with ovarian cancer and 1300 with benign disease, compared CA72.4 to CA125 (see Figures 3.5 and 3.6). The cut-off thresholds used in the studies ranged from 3 to 4.5 U/ml.

Although the pooled results suggest CA 72.4 and CA125 have similar sensitivity and specificity, the ROC curves show that at the thresholds used in the studies, CA 72.4 has a lower sensitivity but

higher specificity than CA125 (Figure 3.5). There was statistically significant heterogeneity in the pooled analysis of these studies.

Evidence from six studies suggests that combining the two markers could increase their specificity, but at the cost of sensitivity.

CA 19.9

Eight studies including 576 women with malignant tumours and 1432 with benign disease, compared the diagnostic accuracy of CA 19-9 and CA125 in women with pelvic masses (see Figures 3.7 and 3.8). Studies used diagnostic thresholds ranging from 35 to 40 U/ml.

The summary ROC curve suggests CA 19.9 has relatively low sensitivity for the diagnosis of ovarian cancer, at the diagnostic thresholds used in the studies (see Figure 3.7). There was significant heterogeneity in the pooled analysis of the study results.

Multiple serum tumour marker panels

Three studies examined the use of a panel of three or more tumour markers to diagnose ovarian cancer in women with a pelvic mass.

Nolen *et al,* (2010) examined 65 ovarian cancer-related serum tumour markers. Although they identified several multi-marker panels with good diagnostic utility, none of them outperformed the combination of CA125 and HE4 in an independent validation sample.

Similarly, Moore *et al.* (2008) examined nine tumour markers and found that the multiple biomarker panels (using three or more markers) added only a small percentage to the sensitivity of combined CA125 and HE4

Abdel-Aziz *et al.* (2010) reported that the combination of CA125, HE4 and Mesothelin was less accurate than the combination of CA125 and HE4 in the diagnosis of ovarian cancer.

CEA, beta-hCG and AFP

Eight studies including 1172 women, reported the diagnostic accuracy of CEA for the diagnosis of ovarian cancer in women with suspected ovarian cancer (see Figures 3.9 and 3.10). Serum CEA was raised in approximately 26% of women with ovarian cancer (sensitivity 26%), but specificity varied widely between studies. One reason for its low sensitivity could be an association between elevated CEA and histological type. There is some evidence that serum CEA levels higher in those patients with mucinous ovarian cancers (e.g. Tamakoshi *et al.,* 1996), although this histological type accounts for a minority of epithelial ovarian tumours.

One small study reported the use of serum CA-125/CEA in the differential diagnosis of ovarian and colorectal cancer (Yedema *et al*., 1992). A CA-125/CEA ratio greater than 25 had a sensitivity of 91% and specificity of 100% for ovarian cancer in this study.

Although it's low sensitivity means that CEA is not routinely used as a marker for early diagnosis, Sturgeon *et al.* (2008) note that CEA can be useful in determining treatment response in ovarian cancer patients.

Single studies reported the sensitivity and specificity of beta-HCG and AFP in this population cancer (see Figures 3.9 and 3.10). Both beta-hCG (Panza *et al*., 1988) and AFP (Kikuchi *et al*., 1984) had very low sensitivity for ovarian cancer. AFP and hCG are important markers for triage, however, when there is a suspicion of germ cell tumour, particularly in women younger than 40 years or where scan features suggest a germ cell tumour (e.g. Sturgeon *et al*., 2008).

Figure 3.1 Summary ROC curve for CA125 from studies comparing CA125 with HE4, CA 72.4 or CA 19.9. The pooled sensitivity and specificity from the Myers et al. (2006) systematic review is included for reference [Back]

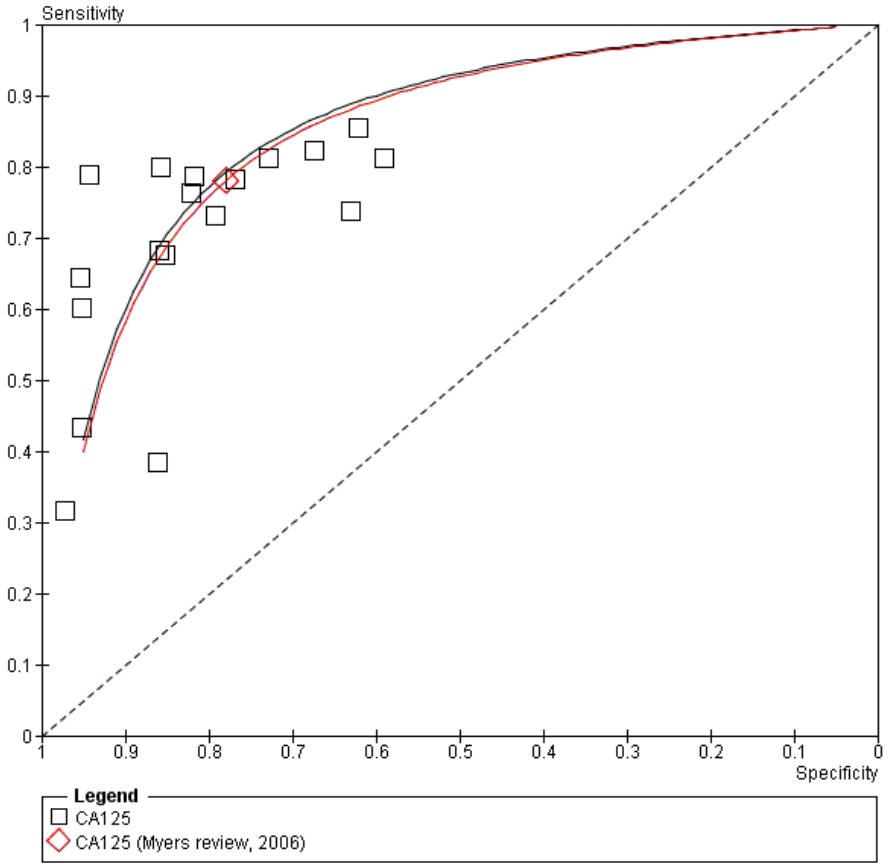


Figure 3.2 Sensitivity and specificity of CA125 in studies comparing CA125 with HE4, CA 72.4 or CA 19.9 [Back]

Study	TP	FP	FN	TN	cut-off value	Sensitivity	Specificity
Abdel Azeez 2010	30	5	11	19	35.0	0.73 [0.57, 0.86]	0.79 [0.58, 0.93]
Balbi 2001	15	7	7	43	35.0	0.68 [0.45, 0.86]	0.86 [0.73, 0.94]
Cherchi 2002	16	4	4	24	35.0	0.80 [0.56, 0.94]	0.86 [0.67, 0.96]
Fioretti 1988	27	16	13	92	65.0	0.68 [0.51, 0.81]	0.85 [0.77, 0.91]
Gadducci 1991	52	8	14	130	81.0	0.79 [0.67, 0.88]	0.94 [0.89, 0.97]
Gadducci 1992	74	83	16	171	35.0	0.82 [0.73, 0.89]	0.67 [0.61, 0.73]
Hasholzner 1996	105	14	18	23	31.0	0.85 [0.78, 0.91]	0.62 [0.45, 0.78]
Huhtinen 2009	9	6	5	123	35.0	0.64 [0.35, 0.87]	0.95 [0.90, 0.98]
Inoue 1992	25	44	40	273	65.0	0.38 [0.27, 0.51]	0.86 [0.82, 0.90]
Maggino 1995	77	23	21	103	35.0	0.79 [0.69, 0.86]	0.82 [0.74, 0.88]
Moore 2008	29	8	38	158		0.43 [0.31, 0.56]	0.95 [0.91, 0.98]
Murta 2004	6	4	13	141	35.0	0.32 [0.13, 0.57]	0.97 [0.93, 0.99]
Negishi 1993	86	23	20	33	35.0	0.81 [0.72, 0.88]	0.59 [0.45, 0.72]
Nolen 2010	129	25	40	115		0.76 [0.69, 0.83]	0.82 [0.75, 0.88]
Schutter 2002	108	35	25	94	35.0	0.81 [0.74, 0.87]	0.73 [0.64, 0.80]
Shah 2009	86	6	57	118	35.0	0.60 [0.52, 0.68]	0.95 [0.90, 0.98]
Wakahara 2001	62	77	22	131	35.0	0.74 [0.63, 0.83]	0.63 [0.56, 0.70]
Woolas 1995	150	55	42	182	35.0	0.78 [0.72, 0.84]	0.77 [0.71, 0.82]

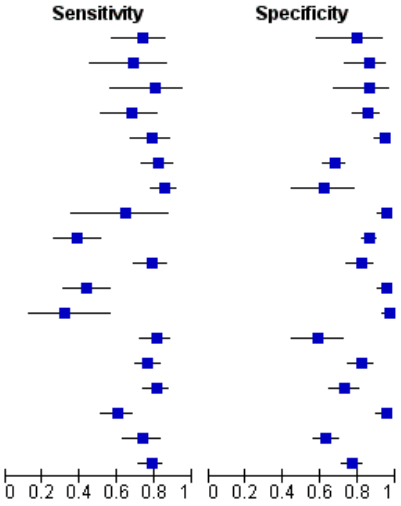


Figure 3.3 Summary ROC curves for CA125, HE4 and CA125-or-HE4 from studies comparing CA125 with HE4 [Back]

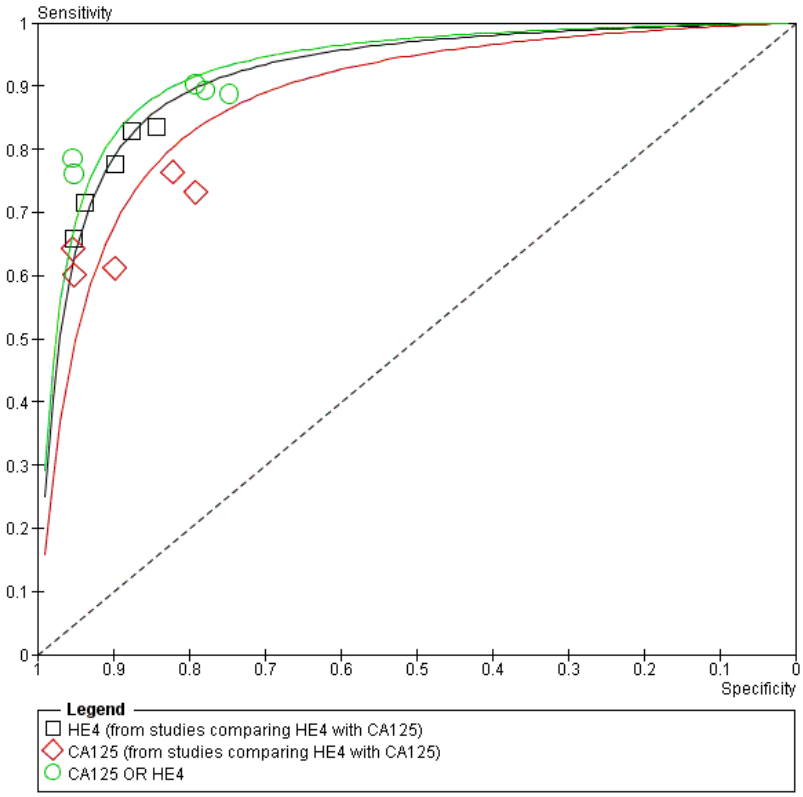
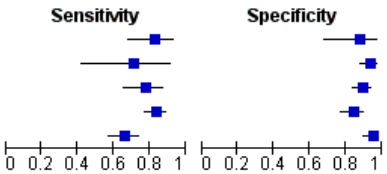


Figure 3.4 Sensitivity and specificity of CA125, HE4 and CA125-or-HE4 from studies comparing CA125 with HE4 [Back]

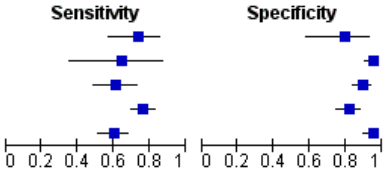
HE4 (from studies comparing HE4 with CA125)

Study	TP	FP	FN	TN	cut-off value	Sensitivity	Specificity
Abdel Azeez 2010	34	3	7	21	72.0	0.83 [0.68, 0.93]	0.88 [0.68, 0.97]
Huhtinen 2009	10	8	4	121	70.0	0.71 [0.42, 0.92]	0.94 [0.88, 0.97]
Moore 2008	52	17	15	149		0.78 [0.66, 0.87]	0.90 [0.84, 0.94]
Nolen 2010	141	22	28	118		0.83 [0.77, 0.89]	0.84 [0.77, 0.90]
Shah 2009	94	6	49	118		0.66 [0.57, 0.73]	0.95 [0.90, 0.98]



CA125 (from studies comparing HE4 with CA125)

Study	TP	FP	FN	TN	cut-off value	Sensitivity	Specificity
Abdel Azeez 2010	30	5	11	19	35.0	0.73 [0.57, 0.86]	0.79 [0.58, 0.93]
Huhtinen 2009	9	6	5	123	35.0	0.64 [0.35, 0.87]	0.95 [0.90, 0.98]
Moore 2008	41	17	26	149		0.61 [0.49, 0.73]	0.90 [0.84, 0.94]
Nolen 2010	129	25	40	115		0.76 [0.69, 0.83]	0.82 [0.75, 0.88]
Shah 2009	86	6	57	118	35.0	0.60 [0.52, 0.68]	0.95 [0.90, 0.98]



CA125 OR HE4

Study	TP	FP	FN	TN	cut-off value	Sensitivity	Specificity
Abdel Azeez 2010	37	5	4	19		0.90 [0.77, 0.97]	0.79 [0.58, 0.93]
Huhtinen 2009	11	6	3	123		0.79 [0.49, 0.95]	0.95 [0.90, 0.98]
Moore 2008	51	8	16	158		0.76 [0.64, 0.86]	0.95 [0.91, 0.98]
Moore 2009	134	89	17	263		0.89 [0.83, 0.93]	0.75 [0.70, 0.79]
Nolen 2010	151	31	18	109		0.89 [0.84, 0.94]	0.78 [0.70, 0.84]

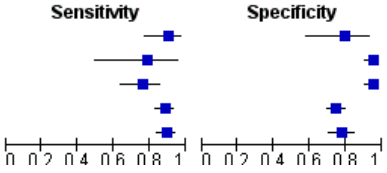


Figure 3.5 Summary ROC curves for CA125, CA 72.4 and CA125-or-CA 72.4 from studies comparing CA125 with CA 72.4 [Back]

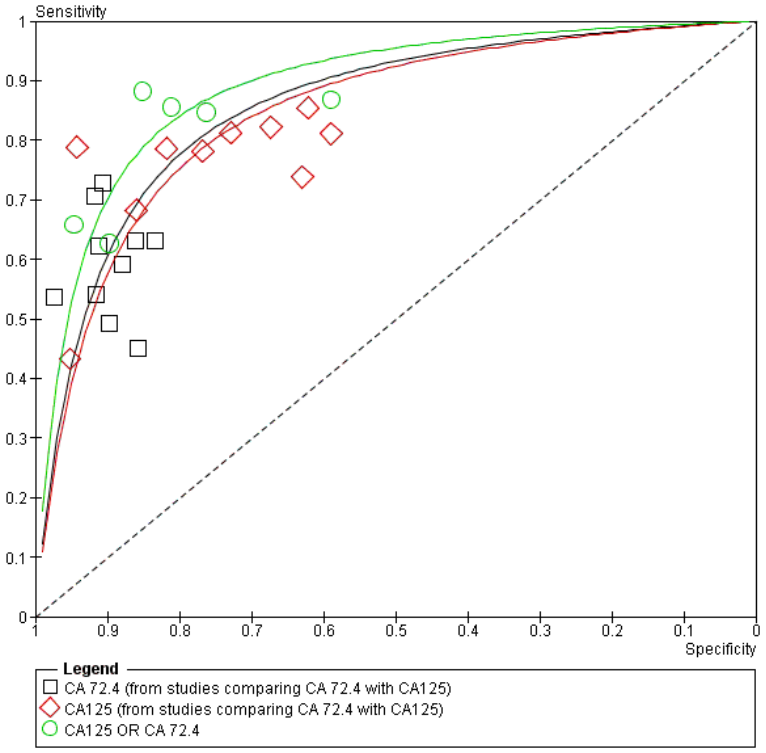
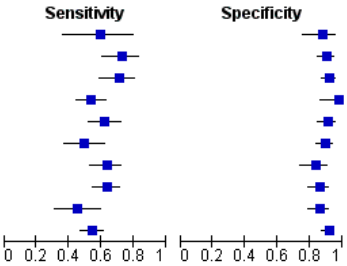


Figure 3.6 Sensitivity and specificity of CA125, CA 72.4 and CA125-or-CA 72.4 from studies comparing CA125 with CA 72.4 [Back]

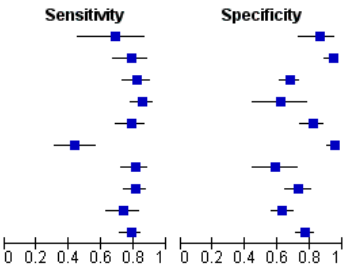
CA 72.4 (from studies comparing CA 72.4 with CA125)

Study	TP	FP	FN	TN	cut-off value	Sensitivity	Specificity
Balbi 2001	13	6	9	44	3.0	0.59 [0.36, 0.79]	0.88 [0.76, 0.95]
Gadducci 1991	48	13	18	125	3.2	0.73 [0.60, 0.83]	0.91 [0.84, 0.95]
Gadducci 1992	53	17	22	190	3.8	0.71 [0.59, 0.81]	0.92 [0.87, 0.95]
Hasholzner 1996	66	1	57	36	3.0	0.54 [0.44, 0.63]	0.97 [0.86, 1.00]
Maggino 1995	61	11	37	115	4.5	0.62 [0.52, 0.72]	0.91 [0.85, 0.96]
Moore 2008	33	17	34	149		0.49 [0.37, 0.62]	0.90 [0.84, 0.94]
Negishi 1993	67	14	39	70	4.0	0.63 [0.53, 0.72]	0.83 [0.74, 0.91]
Schutter 2002	84	18	49	111	3.5	0.63 [0.54, 0.71]	0.86 [0.79, 0.92]
Wakahara 2001	23	18	28	108	4.0	0.45 [0.31, 0.60]	0.86 [0.78, 0.91]
Woolas 1995	104	20	88	217	3.8	0.54 [0.47, 0.61]	0.92 [0.87, 0.95]



CA125 (from studies comparing CA 72.4 with CA125)

Study	TP	FP	FN	TN	cut-off value	Sensitivity	Specificity
Balbi 2001	15	7	7	43	35.0	0.68 [0.45, 0.86]	0.86 [0.73, 0.94]
Gadducci 1991	52	8	14	130	81.0	0.79 [0.67, 0.88]	0.94 [0.89, 0.97]
Gadducci 1992	74	83	16	171	35.0	0.82 [0.73, 0.89]	0.67 [0.61, 0.73]
Hasholzner 1996	105	14	18	23	31.0	0.85 [0.78, 0.91]	0.62 [0.45, 0.78]
Maggino 1995	77	23	21	103	35.0	0.79 [0.69, 0.86]	0.82 [0.74, 0.88]
Moore 2008	29	8	38	158		0.43 [0.31, 0.56]	0.95 [0.91, 0.98]
Negishi 1993	86	23	20	33	35.0	0.81 [0.72, 0.88]	0.59 [0.45, 0.72]
Schutter 2002	108	35	25	94	35.0	0.81 [0.74, 0.87]	0.73 [0.64, 0.80]
Wakahara 2001	62	77	22	131	35.0	0.74 [0.63, 0.83]	0.63 [0.56, 0.70]
Woolas 1995	150	55	42	182	35.0	0.78 [0.72, 0.84]	0.77 [0.71, 0.82]



CA125 OR CA 72.4

Study	TP	FP	FN	TN	cut-off value	Sensitivity	Specificity
Gadducci 1989	30	7	4	40		0.88 [0.73, 0.97]	0.85 [0.72, 0.94]
Gadducci 1992	77	48	13	206		0.86 [0.77, 0.92]	0.81 [0.76, 0.86]
Hasholzner 1996	81	2	42	35		0.66 [0.57, 0.74]	0.95 [0.82, 0.99]
Maggino 1995	83	38	15	122		0.85 [0.76, 0.91]	0.76 [0.69, 0.83]
Moore 2008	42	17	25	149		0.63 [0.50, 0.74]	0.90 [0.84, 0.94]
Shah 2009	92	23	14	33		0.87 [0.79, 0.93]	0.59 [0.45, 0.72]

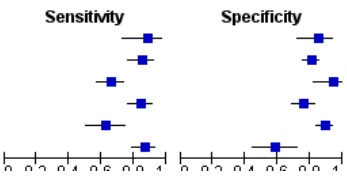


Figure 3.6 Summary ROC curves for CA125, CA 19.9 and CA125-or-CA 19.9 from studies comparing CA125 with CA 19.9 [Back]

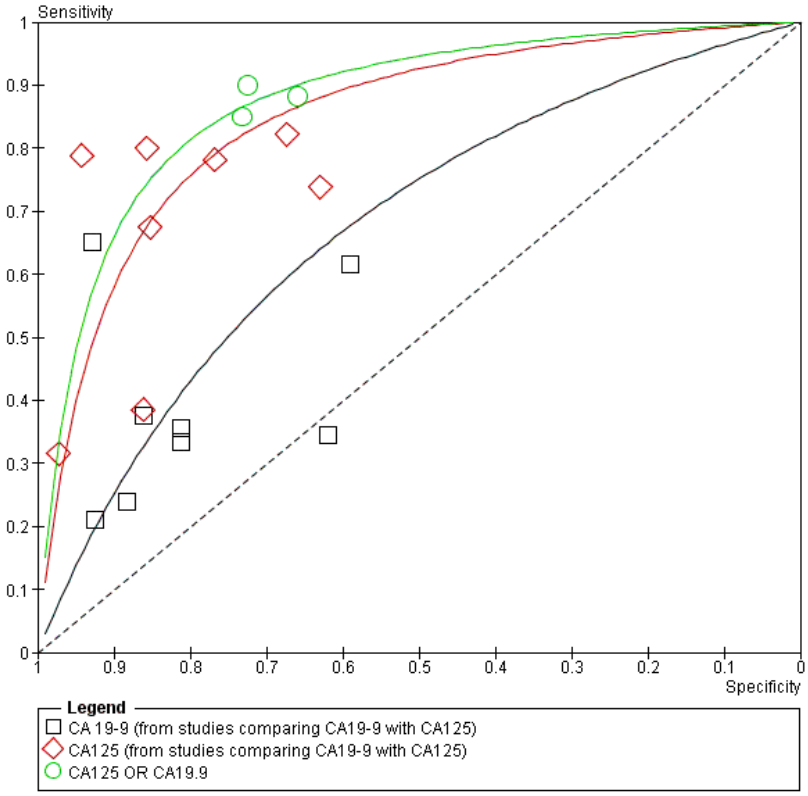
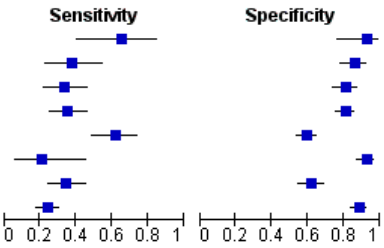


Figure 3.7 Sensitivity and specificity of CA125, CA 19.9 and CA125-or-CA 19.9 from studies comparing CA125 with CA 19.9 [Back]

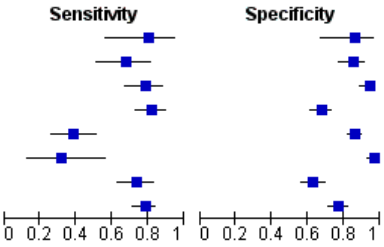
CA 19-9 (from studies comparing CA19-9 with CA125)

Study	TP	FP	FN	TN	cut-off value	Sensitivity	Specificity
Cherchi 2002	13	2	7	26	35.0	0.65 [0.41, 0.85]	0.93 [0.76, 0.99]
Fioretti 1988	15	15	25	93	40.0	0.38 [0.23, 0.54]	0.86 [0.78, 0.92]
Gadducci 1991	22	26	44	112	40.0	0.33 [0.22, 0.46]	0.81 [0.74, 0.87]
Gadducci 1992	32	48	58	206	40.0	0.36 [0.26, 0.46]	0.81 [0.76, 0.86]
Inoue 1992	40	130	25	187	37.0	0.62 [0.49, 0.73]	0.59 [0.53, 0.64]
Murta 2004	4	11	15	134	37.0	0.21 [0.06, 0.46]	0.92 [0.87, 0.96]
Wakahara 2001	29	78	55	127	37.0	0.35 [0.24, 0.46]	0.62 [0.55, 0.69]
Woolas 1995	46	28	146	209	39.0	0.24 [0.18, 0.31]	0.88 [0.83, 0.92]



CA125 (from studies comparing CA19-9 with CA125)

Study	TP	FP	FN	TN	cut-off value	Sensitivity	Specificity
Cherchi 2002	16	4	4	24	35.0	0.80 [0.56, 0.94]	0.86 [0.67, 0.96]
Fioretti 1988	27	16	13	92	65.0	0.68 [0.51, 0.81]	0.85 [0.77, 0.91]
Gadducci 1991	52	8	14	130	81.0	0.79 [0.67, 0.88]	0.94 [0.89, 0.97]
Gadducci 1992	74	83	16	171	35.0	0.82 [0.73, 0.89]	0.67 [0.61, 0.73]
Inoue 1992	25	44	40	273	65.0	0.38 [0.27, 0.51]	0.86 [0.82, 0.90]
Murta 2004	6	4	13	141	35.0	0.32 [0.13, 0.57]	0.97 [0.93, 0.99]
Wakahara 2001	62	77	22	131	35.0	0.74 [0.63, 0.83]	0.63 [0.56, 0.70]
Woolas 1995	150	55	42	182	35.0	0.78 [0.72, 0.84]	0.77 [0.71, 0.82]



CA125 OR CA19.9

Study	TP	FP	FN	TN	cut-off value	Sensitivity	Specificity
Fioretti 1988	34	29	6	79		0.85 [0.70, 0.94]	0.73 [0.64, 0.81]
Gadducci 1989	30	16	4	31		0.88 [0.73, 0.97]	0.66 [0.51, 0.79]
Gadducci 1992	81	70	9	184		0.90 [0.82, 0.95]	0.72 [0.67, 0.78]

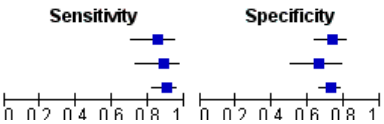


Figure 3.8 Summary ROC curves for CEA, AFP and beta-hCG [Back]

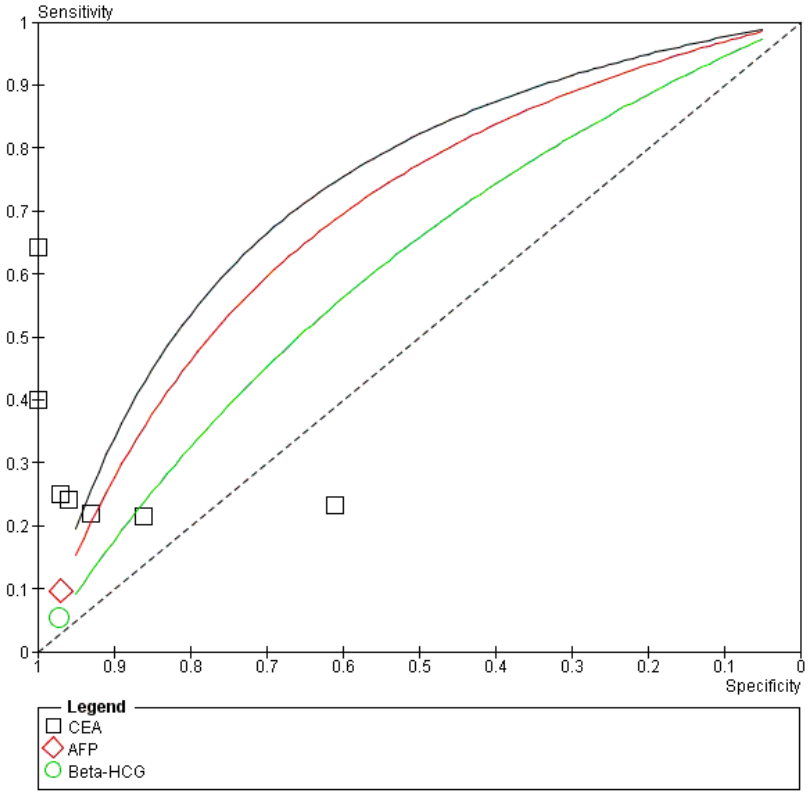


Figure 3.9 Sensitivity and specificity of CEA, AFP and beta-hCG [Back]

CEA

Study	TP	FP	FN	TN	cut-off value	Sensitivity	Specificity
Cherchi 2002	8	0	12	28	5.0	0.40 [0.19, 0.64]	1.00 [0.88, 1.00]
de Bruijn 1993	15	1	47	24	4.5	0.24 [0.14, 0.37]	0.96 [0.80, 1.00]
Inoue 1992	14	44	51	273	2.5	0.22 [0.12, 0.33]	0.86 [0.82, 0.90]
Kikuchi 1984	8	2	24	64	2.7	0.25 [0.11, 0.43]	0.97 [0.89, 1.00]
Malkin 1978	27	0	113	0	4.0	0.19 [0.13, 0.27]	Not estimable
Panza 1988	13	41	43	64	3.0	0.23 [0.13, 0.36]	0.61 [0.51, 0.70]
Parente 1981	9	0	5	25	2.5	0.64 [0.35, 0.87]	1.00 [0.86, 1.00]
Roman 1998	7	13	25	172	3.0	0.22 [0.09, 0.40]	0.93 [0.88, 0.96]

Sensitivity Specificity
0 0.2 0.4 0.6 0.8 1 0 0.2 0.4 0.6 0.8 1

AFP

Study	TP	FP	FN	TN	cut-off value	Sensitivity	Specificity
Kikuchi 1984	3	2	28	64	8.3	0.10 [0.02, 0.26]	0.97 [0.89, 1.00]

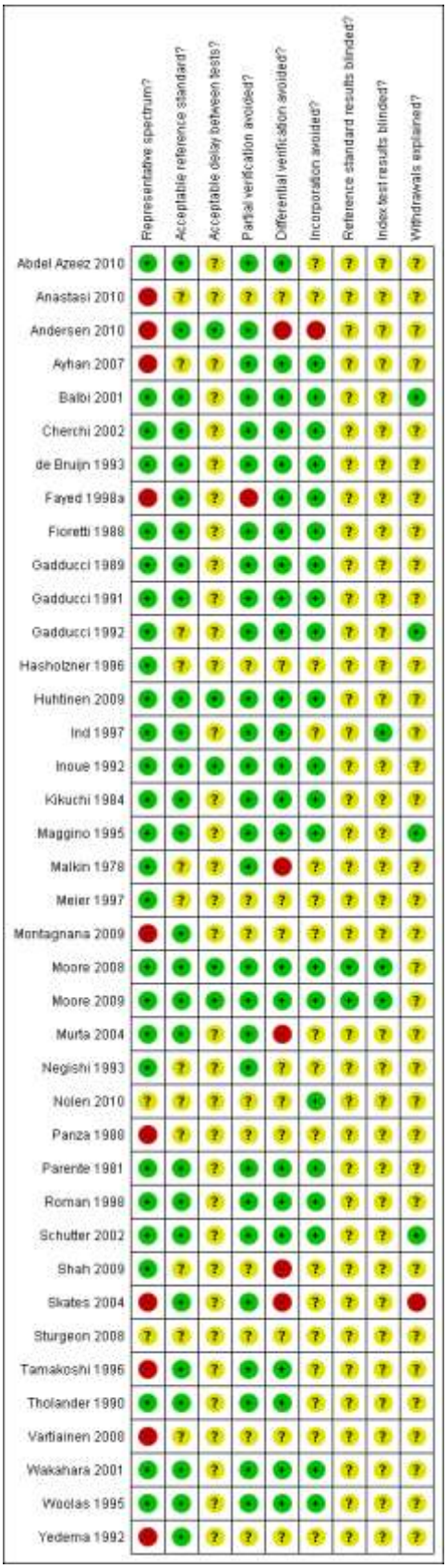
Sensitivity Specificity
0 0.2 0.4 0.6 0.8 1 0 0.2 0.4 0.6 0.8 1

Beta-HCG

Study	TP	FP	FN	TN	cut-off value	Sensitivity	Specificity
Panza 1988	3	3	53	102	9.0	0.05 [0.01, 0.15]	0.97 [0.92, 0.99]

Sensitivity Specificity
0 0.2 0.4 0.6 0.8 1 0 0.2 0.4 0.6 0.8 1

Figure 3.10 Methodological quality of included studies [Back]



Evidence tables:

Author(s): Abdel Azeez *et al.,* 2010
Settings: Women with presenting with a pelvic mass, to a single university hospital.
Participants: 65 women: 24 with benign ovarian disease and 41 with ovarian carcinoma. Egypt
Study Design: Case series
Target Condition: The target condition was ovarian carcinoma. Reference standard was histopathological diagnosis.
Tests: **Serum CA125 (cut-off level 35 U/ml).** Sensitivity 79.2%, specificity 73.2% **Serum HE4 (cut-off level 72 pM)** Sensitivity 87.5%, specificity 82.9% **Elevated serum CA125 OR HE4** Sensitivity 79.2%, specificity 90.2%

Author(s): Anastasi *et al.,* 2010
Settings: Patients with suspected cancer with serum sample available and healthy controls (blood donors). All patients were admitted to the same oncology department.
Participants: 267 patients: 32 with ovarian cancer, 7 with colorectal cancer, 16 with breast cancer, 26 with cervical cancer, 86 with benign ovarian tumours, 28 with other benign pathologies and 72 healthy controls. Italy.
Study Design:

Retrospective diagnostic accuracy study
Target Condition: Target condition was the diagnosis of ovarian cancer. The reference standard test was not reported.
Tests: The index tests were serum HE4 levels (at cut-offs of 150, 250, 350 and 450 pmol/L) and serum CA125 levels (at cut-off levels of 37, 127, 237 and 337 U/ml). At a cut-off of 150 pmol/L HE4 had sensitivity of 96.9% (31/32 patients with ovarian cancer were detected), specificity was 96.9% (5 false positives in 163 patients without ovarian cancer).
Notes: Identified in update search.

Author(s): Andersen *et al.,* 2010
Settings: Women with ovarian cancer and healthy controls (identified via screening of high risk women).
Participants 74 women with ovarian cancer (6 with mucinous tumours, 6 with clear cell carcinoma, 7 with endometrioid cancer, 5 with other adenocarcinoma and 50 with serous cancer), 137 healthy controls
Study Design: Case/control study.
Target Condition: The target condition was the identification of ovarian cancer, the reference standard was histopathology for the women with ovarian cancer. Reference standard was not reported for the controls - it was probably negative screening tests for ovarian cancer since these women were identified via a screening study.
Tests: Serum samples and symptom questionnaires were collected prior to surgery (and diagnosis) in women who had surgery. Controls had serum samples and symptom questionnaires collected on a quarterly basis as part of a screening study. Index tests were:

serum HE4

The HE4 threshold for positivity was the upper 95% percentile of the control group. Authors do not report the numeric value of this cut-off threshold. Using this definition fixes the specificity of HE4 at 95%.

sensitivity (95% C.I.) was 0.77 (0.66, 0.86), specificity was 0.95 (0.90, 0.98)

serum CA125

The CA125 threshold for positivity was the upper 95% percentile of the control group.

Authors do not report the numeric value of this cut-off threshold. Using this definition fixes the specificity of CA125 at 95%.

sensitivity was 0.81 (0.70, 0.89), specificity was 0.95 (0.90, 0.98)

symptom index (SI)

The symptom index was considered positive if the patient had at least one of the following symptoms for less than 1 year but more than 12 times per month: bloating or increased abdominal size, abdominal or pelvic pain, difficulty eating or feeling full quickly.

sensitivity was 0.64 (0.52, 0.74), specificity was 0.88 (0.82, 0.93)

combined tests

HE4 or CA125 positive: sensitivity was 0.89 (0.80, 0.95), specificity was 0.90 (0.83, 0.94]

HE4 or SI positive: sensitivity was 0.92 (0.83, 0.97), specificity was 0.85 (0.78, 0.90)

CA125 or SI positive: sensitivity was 0.92 (0.83, 0.97), specificity was 0.83 (0.76, 0.89)

HE4 or CA125 or SI positive: sensitivity was 0.95 (0.87, 0.99), specificity was 0.80 (0.72, 0.86)

SI and (HE4 or SI) positive: sensitivity was 0.58 (0.46, 0.70), specificity was 0.99 (0.95, 1.0)

Subgroup analyses of test accuracy according to age (<50 years versus 50 or more years), risk status and stage were also done.

Notes:

Identified in update search. Uses already identified cases and healthy controls - inappropriate design for diagnostic test study as it probably overestimates the diagnostic accuracy of the tests studied.

Author(s): Ayhan *et al.,* 2007

Settings:

Women with well staged borderline ovarian tumours, treated between 1994 and 2004 at a single institution.
Participants: 60 women
Study Design: Retrospective case series
Target Condition: Study reports the correlation between elevated tumour markers and stage, histological type, tumour size, cytology, lymph node metastases, age at diagnosis, parity, use of oral contraceptives, smoking, choice of surgical staging (fertility sparing or not), micropapillary architecture, implant, micro invasion and tumour bilateralism.
Tests: Serum tumour markers: CA 125, CA 19-9 (cut-off value > 37 U/ml), CA 15-3 and CEA (cut-off value >4 ng/ml)
Follow Up: Not reported (although there is no survival analysis).

Author(s): Balbi *et al.,* 2001
Settings: Women with pelvic masses originating in the ovary. Women with clearly benign or clearly malignant masses were excluded
Participants: 50 women with benign ovarian mass and 22 with malignant masses
Study Design: Case series
Target Condition: Identification of ovarian cancer in women with ovarian masses. Reference standard was histopathological diagnosis.
Tests:

Serum tumour markers: CA 125, CA 72.4 (cut-off >3 U/ml), PE and US
Notes: Reports the sensitivity and specificity of combinations of PE, US and CA-125

Author(s): Cherchi *et al.,* 2002
Settings: Women with benign or malignant pelvic pathology, before surgery. It is not reported how women were selected for this study
Participants: 20 women with cysto-adenocarcinoma of the ovary, 44 women with benign ovarian pathology (16 with functional cysts and 28 with
Study Design: Not reported.
Target Condition: Discrimination of malignant from benign ovarian pathology. Reference standard was histopathology.
Tests: Serum tumour markers Tumour markers in intracystic fluids were also studied (but are not included in this appraisal)

Author(s): de Bruijn *et al.,* 1993
Settings: Women with ovarian tumours, unclear how women were selected for the study.
Participants: 87 women with ovarian tumours: 25 with benign mucinous tumours, 10 with borderline mucinous malignancy, 24 with malignant mucinous tumours and 28 with malignant non-mucinous tumours.
Study Design: Case series

Target Condition: Identification of malignancy in women with ovarian tumours. Reference standard was not reported, although tumour histology was reported in all cases.
Tests: Serum tumour markers: CA 195, CEA (cut-off value >4.5 micrograms/mL), TATI and CA 125.
Follow Up: Not reported

Author(s): Fayed *et al.,* 1998a
Settings: Unclear how women were entered into the study
Participants: 30 women with epithelial ovarian cancer, 30 with benign ovarian pathology and 30 healthy controls.
Study Design: Not reported
Target Condition: Target condition was ovarian cancer. Reference standard was histopathology following surgery (or peritoneal cytology if there was no mass to biopsy), there was no reference standard in the healthy control group.
Tests: serum tumour markers: CA 72-4 (cut-off >8.5 U/ml), CA 125

Author(s): Fioretti *et al.,* 1988
Settings: Women undergoing laparotomy for adnexal masses in a single gynaecology department.
Participants: 148 women. 40 women had epithelial ovarian cancer, 108 had benign ovarian pathology
Study Design:

Case series, single institution
Target Condition: Identification of ovarian cancer in women with adnexal masses. Reference standard was histological diagnosis, following laparotomy
Tests: Serum tumour markers: CA 125, CA 19-9 (cut-off value >40 U/ml).
Follow Up: Not reported

Author(s): Gadducci *et al.,* 1989
Settings: Women undergoing laparotomy for adnexal mass
Participants: 81 women: 47 with benign disease and 34 with ovarian cancer (8 FIGO stage I or II and 26 FIGO stage III or IV)
Study Design: Case series, single institution
Target Condition: Identification of ovarian cancer. Reference standard was not specified, but was presumably the findings of surgery plus histopathology (the histological types of all tumours were reported).
Tests: Serum tumour markers including CA 19.9 (cut-off > 40 U/ml) and CA 72.4 (cut-off >3.8 U/ml).
Follow Up: Not reported
Notes: See Gadducci *et al.,* 1992

Author(s): Gadducci *et al.,* 1991

Settings: Women undergoing laparotomy for a clinical diagnosis of ovarian mass
Participants: 209 women: 66 women had epithelial ovarian cancer and 138 benign ovarian pathology
Study Design: Case series, single institution
Target Condition: Identification of ovarian cancer. Reference standard was laparotomy and histopathology
Tests: Serum tumour markers: Ca 125, CA 19-9 (cut off 40 U/ml or more), CA 72.4 (cut-off 3.2 U/ml or more).

Author(s): Gadducci *et al.,* 1992
Settings: Women undergoing laparotomy for ovarian mass
Participants: 344 women: 90 with malignant and 254 benign
Study Design: Case series, consecutive (possibly prospective)
Target Condition: Identification of malignancy in ovarian mass. Reference standard was findings of laparotomy - although the histopathological techniques are not reported.
Tests: Serum CA 19-9 (positive test was defined as 40 U/ml or greater). Other tumour markers were measured (CA125, CA15.4, CA72.4 and TATI).

Author(s): Hasholzner *et al.,* 1996
Settings: Unclear how women were entered into the study, possibly identified through hospital database

since this is a retrospective analysis of serum samples.
Participants: 123 women with ovarian carcinoma (54 serous, 30 mucinous and 39 others), 37 women with benign gynaecological disease.
Study Design: Retrospective study.
Target Condition: Identification of ovarian carcinoma (also reports serial tumour marker measurements in follow up). Reference standard was not reported: presumably it was the histological diagnosis since the histological sub types of ovarian carcinoma were reported.
Tests: Serum tumour markers, CA 125 and CA 72-4 (cut off values 2.9 and 3.0 U/ml are used).

Author(s): Huhtinen 2009
Settings: Women diagnosed with endometriosis, ovarian cancer or endometrial cancer - diagnosed through laparoscopy or laparotomy confirmed by histopathology.
Participants: 225 women: 66 healthy controls, 129 with endometriosis, 14 with ovarian cancer and 16 with endometrial cancer.
Study Design: Prospective diagnostic study
Target Condition: Target condition was diagnosis of malignant ovarian tumours. Reference standard was findings of laparoscopy or laparotomy plus histopathology.
Tests: serum HE4 levels (cut-off for abnormal was 70pM) **Ovarian cancer versus ovarian endometriosis** Sensitivity 71.4%, specificity 94%

Ovarian cancer versus healthy controls Sensitivity 78.6%, specificity 97%
Notes: The evidence review calculated sensitivity and specificity using data from women with endometriosis and women with ovarian cancer (excluding those with endometrial cancer and healthy controls).

Author(s): Ind *et al.,* 1997
Settings: Women with histologically confirmed epithelial ovarian carcinoma, with serum sample collected before surgery
Participants: 111 women: histological type was serous in 50% of cases, mucinous in 10%, endometrioid in 10% and 30% other histological types.
Study Design: Consecutive case series
Target Condition: Comparison of stage and survival according to marker positivity
Tests: Serum tumour markers: CA 125, CASA, free beta-hCG (cut-off value 0.2 IU), PLAP
Follow Up: 2 years
Notes: On univariate analysis free beta-hCG positivity was an adverse prognostic factor for OS (HR=2.31, 95% CI 1.31 to 4.01), but on multivariate analysis it was not statistically significant (HR=1.61 to 3.14), although stage, elevated PLAP, elevated CA 125 were all significant adverse prognostic factors.

Author(s): Inoue *et al.,* 1992

Settings: Women undergoing laparotomy for pelvic mass
Participants: 382 women, 65 with malignant ovarian tumours and 317 with benign pelvic masses.
Study Design: Case series, single institution
Target Condition: Malignancy in pelvic masses. Reference standard was histological diagnosis of the mass following laparotomy
Tests: Index tests were preoperative serum tumour markers, including CA 19-9 (cut-off for abnormal was >37 U/ml) and CEA (cut-off for abnormal was >2.5 ng/ml).
Follow Up: Not reported

Author(s): Kikuchi *et al.,* 1984
Settings: Women with benign or malignant ovarian mass, who went on to have histopathologic confirmation of their diagnosis.
Participants: 120 women: 66 women with benign ovarian tumours and 54 with ovarian cancer.
Study Design: Design not reported - observational study.
Target Condition: Malignancy in ovarian masses. Reference standard was histopathology.
Tests: 12 serum tumour markers, including AFP and CEA. The cut-off levels for positive tests were defined as the mean + 2 standard deviations of the value in the group of women with benign

masses.
Notes: The number of women with positive tests in the benign group was not reported - the positivity rate is estimated by assuming a normal distribution of tumour marker levels in the benign group

Author(s): Maggino *et al.,* 1995
Settings: Post-menopausal women referred to a gynaecologic clinic with a diagnosis of pelvic mass.
Participants: 126 women with benign ovarian pathology, 98 women with ovarian malignancy, 34 women with benign extra-ovarian pathology and 16 with malignant extra-ovarian pathology.
Study Design: Prospective multicentre study
Target Condition: Diagnosis of ovarian malignancy. Reference standard was histopathology following laparotomy.
Tests: Serum tumour markers: CA 72-4 (cut-offs of 3.9 and 4.5 U/ml) and CA 125

Author(s): Malkin *et al.,* 1978
Settings: Women with ovarian cancer or cervical dysplasia or cervical carcinoma *in-situ,*
Participants: 140 women with ovarian cancer. The paper also reports tumour markers in women with cervical cancer
Study Design: Case series
Target Condition: Target condition was ovarian malignancy. Reference standard was laparotomy plus

histopathology for the women with ovarian cancer and biopsy plus histopathology for those with cervical dysplasia/carcinoma in-situ.
Tests: Serum tumour markers: CEA (), pregnancy associated macroglobulin and PLAP

Author(s): Meier *et al.,* 1997
Settings: Women with primary ovarian cancer. Unclear how these women were eligible for inclusion in this study
Participants: 296 women with primary ovarian cancer (73% serous histology, 9% mucinous, 9% endometrioid).
Study Design: Unclear
Target Condition: Tumour marker positivity according to disease stage. Not reported how disease stage was determined
Tests: Serum tumour markers: CEA (cut-off value 3 ng/ml) and CA-125.

Author(s): Montagnana *et al.,* 2009
Settings: Women diagnosed with pelvic mass, who underwent laparoscopy or laparotomy with histopathological confirmation of their diagnosis. Healthy controls were also recruited from hospital personnel.
Participants: 18 women with benign ovarian masses, 12 healthy controls, 46 women with ovarian cancer, 22 women with endometriosis.
Study Design: Prospective case series

Target Condition: Identification of malignancy in patients with pelvic masses. Reference standard was laparoscopy or laparotomy with histopathological confirmation.
Tests: Index test was serum HE4 levels (abnormal was defined as 30pmol/l).
Follow Up: Not reported
Notes: Compared healthy volunteers with those with ovarian cancer to estimate sensitivity and specificity - likely to bias estimates.

Author(s): Moore *et al.,* 2008
Settings: Women undergoing surgery for removal of an adnexal mass
Participants: 67 women with ovarian cancer, 166 women with benign disease.
Study Design: Prospective case series
Target Condition: Diagnosis of malignancy. Reference standard was the histological diagnosis, following surgery.
Tests: Index tests were serum tumour markers, including HE4 (cut-off level for abnormality was >70 pM, although ROC analysis suggests several levels were analysed)
Follow Up: not reported
Notes: Poorly reported - although elevated HE4 is defined as >70 pM the study does not report how many women with ovarian cancer had elevated HE4, only those with benign disease. Hence

sensitivity had to estimated from their reported ROC analysis

Author(s): Moore *et al.,* 2009
Settings: Women aged 18 or older diagnosed with ovarian cyst or pelvic mass with planned surgical intervention.
Participants: 531 women: 352 with benign tumours, 129 with epithelial ovarian cancer, 22 with low malignant potential tumours, 6 with non-epithelial ovarian cancer and 22 with non-ovarian cancers.
Study Design: Prospective multicentre study
Target Condition: Target condition was identification of epithelial ovarian cancer, the aim was to classify patients into high or low risk groups. The reference standard was pathological analysis of tissue specimens of the pelvic mass or cyst (with central pathology review)
Tests: Serum tumour markers: CA-125 and HE4 combined in a predictive index (PI) for epithelial ovarian cancer Premenopausal Predictive index = -12.0 + 2.38*LN(HE4)+0.0626*LN(CA 125). Postmenopausal Predictive index = -8.09 + 1.04*LN(HE4)+0.732*LN(CA 125). Predicted probability of epithelial ovarian cancer = exp(PI)/[1+exp(PI)] **Results** in the post menopausal group, sensitivity was 92.3% (95% C.I. 85.9% to 96.4%), specificity was 75.0% (95% C.I. 66.9% to 81.4%) in the premenopausal group, sensitivity was 76.5% (95% C.I. 58.8% to 89.3%), specificity was 74.8% (95% C.I. 68.2% to 80.6%)
Notes: Study does not report the individual sensitivity and specificity of the tumour markers

Author(s): Murta *et al.,* 2004

Settings: Women referred to a pelvic mass outpatient service
Participants: 373 women. 209 were thought to have benign disease and followed up clinically. 164 underwent laparotomy: 66 had benign neoplasia, 79 had non-neoplastic benign disease (cysts etc.) and 19 patients had malignant neoplasms.
Study Design: Prospective case series, single institution
Target Condition: Identification of malignant ovarian tumours. Reference standard was laparotomy
Follow Up: Women kept on clinical follow up received gynaecological and US examinations with tumour marker assays at 2 to 3 monthly intervals. It was not reported how long follow up was continued
Notes: Tumour marker sensitivity and specificity are calculated using data from the 164 patients who had laparotomy.

Author(s): Negishi *et al.,* 1993
Settings: Women with suspected ovarian cancer.
Participants: 104 healthy controls (used to establish normal reference range for serum CA 72-4), 106 women with primary ovarian cancer, 56 women with benign ovarian tumours and 28 women with endometric cyst.
Study Design: Not reported
Target Condition: Identification of ovarian cancer. Reference standard was not reported, although histological type was reported for all tumours.

Tests:

Serum tumour marker CA 72.4 (cut-off value of >4.0 U/ml)

Notes:

Women with benign ovarian tumours, endometric cysts or ovarian cancer were included in the calculation of sensitivity and specificity.

Author(s): Nolen *et al.,* 2010

Settings:

Women with adnexal masses (excluding pelvic inflammatory disease). Women were identified through five large US cancer institutions as well as via the Gynaecological Oncology Group.

Participants:

The training set: included 264 women with ovarian cancer and 141 women with benign masses. The validation set included 169 women with ovarian cancer and 140 women with benign masses. The training and validation sets were all postmenopausal women. A small group of premenopausal women were also tested (18 benign, 58 with ovarian cancer). USA

Study Design:

Diagnostic accuracy.

Target Condition:

The target condition was ovarian cancer. The reference standard test was histopathology for women with ovarian cancer; it is unclear what the reference standard was for women diagnosed with benign masses.

Tests:

The index test was a panel of 65 serum tumour markers (for ovarian and other cancers). The study used xMAP (Luminex Corp,Texas) bead-based technology to simultaneously analyse the 65 tumour markers. This paper does not report when the serum samples were taken (but refers to an earlier paper from this study).

The training set was used to identify panels of 2, 3 or 4 biomarkers with good diagnostic accuracy. The most accurate panels were identified using the Metropolis algorithm with Monte Carlo simulation. The accuracy of these panels was then tested using the validation set (results below).

Threshold values for the five most promising individual markers

For each marker, 95% of the benign group had serum marker concentration lower than the corresponding threshold

CA125: 93.15 U/ml
HE4:18421 pg/ml
CEA: 23604 pg/ml
Cyfra 21-1: 3210 pg/ml

EGFR: 115248 pg/ml

accuracy: single markers

HE4: sensitivity 83% and specificity 84%

CA125: sensitivity 76% and specificity 82%

accuracy: 2 marker panel

CA125 and HE4: sensitivity 89% and specificity 78%

accuracy: 3 marker panels

CA125, HE4 and CEA: sensitivity 91% and specificity 77%

CA125, HE4 and Cyfra 21-1: sensitivity 86% and specificity 79%

CA125, HE4 and EGFR: sensitivity 89% and specificity 74%

accuracy: 4 marker panel

CA125, HE4, Cyfra 21-1 and EGFR: sensitivity 75% and specificity 90%

Notes:

Identified in update search.

Author(s): Panza *et al.,* 1988

Settings:

Women with epithelial ovarian cancer admitted to a single institution during an 18 month period.

Participants:

56 women with ovarian carcinoma, most (31/56) had already received treatment when they entered the study. Also included were 124 healthy controls (56 men and 68 women) used to establish reference ranges for the tumour markers, 105 patients with non-ovarian tumours

Study Design

Prospective case series, single institution

Target Condition

Identification of ovarian cancer. Reference standard was cytology or histology for the women with ovarian cancer, but not reported for the other patients.

Tests

Serum tumour markers: CA-125 (cut-off >38.5 U/ml), CEA (cut-off >3 ng/ml), beta-HCG (cut-off >

9 IU/ml), TPA (cut-off >85 mU/ml)
Follow Up Not reported
Notes The control group included patients with non-ovarian cancers, rather than benign ovarian disease.

Author(s): Parente and Greston, 1981
Settings: Women with tumours of the abdominopelvic region
Participants: 25 women with benign tumours, 14 with ovarian cancer and 36 with other malignancies
Study Design: Case series
Target Condition: Identification of ovarian cancer, reference standard was histopathology.
Tests: Serum tumour marker CEA (cut-off >2.5 ng/nl) Results (ovarian cancer versus benign tumours) sensitivity 0.64 (95% C.I. 0.35, 0.87) specificity 1.00 (95% C.I. 0.86, 1.00),

Author(s): Roman *et al.,* 1998
Settings: Women with isolated pelvic masses
Participants: 226 women: 183 women had benign disease, 17 had tumours of low malignant potential, 15 had frankly invasive epithelial tumours and there were 11 other malignancies (germ cell tumours, sarcoma or stromal cancer).
Study Design:

Prospective diagnostic study
Target Condition: Target condition was diagnosis of ovarian malignancy. Reference standard was laparoscopy or laparotomy with pathologic examination of the surgical specimen
Tests: Index test was serum CEA (levels greater than 3.0 ng/ml were considered abnormal)
Follow Up: Not reported

Author(s): Schutter *et al.,* 2002
Settings: Women with pelvic mass, before surgical exploration.
Participants: 133 women with ovarian cancer and 129 women with benign ovarian tumours
Study Design: Retrospective study, multicentre
Target Condition: Target condition was identification of ovarian cancer in women with a pelvic mass. Reference standard was surgical exploration with biopsy and/or excision of the pelvic mass with subsequent histological analysis.
Tests: Serum tumour markers: CA 125, CA 15-3 and CA 72-4 (cut-off value of >3.5 U/ml). The utility of other cut-off values was reported
Follow Up: Not reported.

Author(s): Shah *et al.,* 2009
Settings:

Women with average or high risk for ovarian cancer. Risk was ascertained using a questionnaire that covered personal and family history of cancer and BRCA gene mutation tests. High risk was defined as a lifetime risk of at least 10% for developing ovarian cancer.
Participants: 444 healthy controls, 143 women with ovarian cancer and 124 women with benign ovarian tumours.
Study Design: Prospective multicentre study
Target Condition: Identification of ovarian cancer, in women with average or high risk of the condition.
Tests: Serum tumour markers: HE4 (variable cut-off), mesothelin and CA-125. **Results for HE4 (women with ovarian cancer versus those with benign ovarian tumours)** for average risk women: sensitivity 58.8% specificity 95% for high risk women: sensitivity 63.4%, specificity 95%

Author(s): Skates *et al.,* 2004
Settings: Women with early stage ovarian cancer.
Participants: The training set consisted of 63 women with ovarian cancer (27 with early stage and 36 with late stage) and 128 healthy controls. The validation set consisted of 60 women with early stage ovarian cancer and 98 controls.
Study Design: Multicentre study
Target Condition: Target condition was ovarian cancer. Reference standard was histopathology in the women with ovarian cancer: no reference standard was reported in controls.
Tests:

Serum tumour markers: CA-125II, CA 15-3, CA 72-4 and macrophage colony stimulating factor. Markers were entered into a logistic regression, classification tree and mixture discriminant analysis models to predict malignancy.

Author(s): Sturgeon *et al.,* 2008
Settings: Laboratory medicine practice guideline for the use of tumour markers for 5 cancer sites: testicular, prostate, colorectal, breast and ovarian, although only the evidence about ovarian cancer is included in this appraisal. Published by the National Academy of Clinical Biochemistry.
Participants: Studies of tumour markers for use in ovarian cancer (for diagnosis, prognosis or tumour monitoring).
Study Design: Guideline, based on evidence review and consensus of a panel of 5 experts (for the ovarian cancer section).
Target Condition: The use of tumour markers for screening early detection of ovarian cancer, discrimination of pelvic masses and monitoring treatment is discussed.
Tests: Tumour markers: CA125, Her-2/neu, Akt-2, Inhibin, HLA-G, TATI, CASA, LPA, PAI-1, Kallikreins 5 to 11 and 13 to 15, hCG-beta-cf, prostatin, osteopontin, HE4, Mitogen-activated protein kinase, Insulin like growth factor binding protein-2 (IGFBP-2), RSF 1. NAC 1.
Notes: Members of the diagnostic industry were included in the tumour site sub-committees, although conflicts of interest are noted.

Author(s): Tamakoshi *et al.,* 1996
Settings: Women with histopathologically confirmed borderline ovarian tumour, treated within a single cancer centre or its affiliated hospitals.
Participants: 101 patients: 41 with serous tumours, 56 mucinous tumours and 4 endometrioid tumours. Stage

was I in 66% and II-III in 34%.
Study Design: Case series
Target Condition: Prediction of disease stage using tumour markers. Reference standard was staging according to FIGO classification.
Tests: Serum tumour markers: CEA, CA 19-9

Author(s): Tholander *et al.,* 1990
Settings: Women with histopathologically confirmed invasive epithelial ovarian cancer. The study entry criteria are reported in a separate paper (Tholander *et al.*, 1986)
Participants: 142 women (54% serous tumours, 12% mucinous, 20% endometrioid and 14% others).
Study Design: Case series
Target Condition: Correlation between serum tumour marker level and histological type, FIGO stage and the interaction between histology and stage. Reference standard was histopathology.
Tests: Serum tumour markers CA 125, CEA (cut off value not used), TPA and PLAP. **The correlation between serum CEA level and histological type:** R squared was 0.33, P<0.0001 (mucinous carcinomas having higher CEA levels than serous) **The correlation between serum CEA level and stage:** R squared was 0.31, P<0.0001 (in general CEA level increased with FIGO stage) **The correlation between serum CEA level and histology X stage:**

R squared was 0.42, P<0.0001 (CEA level increased with FIGO stage, in the mucinous group)

Author(s): Vartiainen *et al.,* 2008
Settings: Women with serous ovarian carcinoma, treated in a single institution between 1990 and 2000
Participants: 173 women (34% grade I-II, 66% grade III-IV). Most (86%) received platinum or platinum taxane chemotherapy. 38% had residual tumour greater than 1cm in size, following surgery.
Study Design: Consecutive case series
Target Condition: Beta-hCG as a prognostic factor for overall survival.
Tests: Serum Beta-hCG (cut-off of 2.0 pmol/L defined elevated). Tissue expression of p53 was also studied.
Follow Up: Median follow-up was 39 months (range 4.5 to 123 months) for patients still alive at the end of the study period.

Author(s): Wakahara *et al.,* 2001
Settings: Women with ovarian masses, who underwent laparotomy.
Participants: 292 women: 208 with benign ovarian tumours, 18 with low malignant potential tumours and 66 with malignant ovarian tumours.
Study Design: Case series, single institution.
Target Condition:

Diagnosis of ovarian cancer. The reference standard was findings of laparotomy, with histopathology.
Tests: Serum tumour markers: CA-125, CA 19-9 (cut-off >37 U/ml) and CA 72-4 (cut-off >4 U/ml).

Author(s): Woolas *et al.,* 1995
Settings: Women with clinically detected pelvic
Participants: 429 women, 192 with malignant pelvic masses (177 had primary ovarian cancer) and 237 with benign pelvic masses.
Study Design: Multicentre case series, single institution.
Target Condition: Target condition was identification of malignancy in pelvic masses (not ovarian cancer *per se*). Reference standard was surgery and histopathology.
Tests: Serum tumour markers, including CA 19-9 (cut-off value >39.0 U/ml) and CA 72-4 (cut-off value 3.8 U/ml). Logistic regression and CART models were developed to predict malignancy using a panel of serum tumour markers
Follow Up: Not reported.

Author(s): Yedema *et al.,* 1992
Settings: Women with advanced colorectal or ovarian cancer, before treatment
Participants: 47 women with advanced ovarian cancer and 24 with advanced colorectal cancer.
Study Design:

Study design was not reported.
Target Condition: Discrimination of ovarian from colorectal cancer. Reference standard was not reported
Tests: Serum tumour markers: CA 125 (cut-off 35 U/ml), CA 15-3, CA 19-9 (cut-off 37 U/ml), CEA (cut-off 5 ng/ml) , CA M29 and CA M26. Reports combination of CA 125 and CEA : **CA 125 > 35 U/ml and CEA 5 ng/ml or less** sensitivity 81%, specificity 100%, PPV 100% and NPV 73% **CA 125/CEA ratio greater than 25** sensitivity 91%, specificity 100%, PPV 100% and NPV 86%

References:

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3.2 Cancer pathway management: malignancy indices

"For women with suspected ovarian cancer, which malignancy index is the most effective?"

Short summary:

The evidence for this topic comprised one good quality systematic review of diagnostic studies (Geomini *et al*., 2009) in which the reviewers appraised one hundred and nine studies of eighty-three validated risk of malignancy models. By pooling data appropriately the authors concluded that the RMI I proposed by Jacobs *et al.* (1990) was superior in terms of sensitivity and specificity to the other comparators. With a cut-off score of 200, sensitivity = 78% [95%CI: 71-85%] and specificity = 87% [95%CI: 83-91%] and with a cut-off score of 50, sensitivity = 91% [95%CI: 85-97%] and specificity = 74% [95%CI: 69-80%].

Updated evidence:

Raza *et al*., (2010) published a rapid communication reporting the results of a prospective observational study that had been conducted in a UK hospital. Using Jacob's RMI I index, as modified by Tingulstad *et al.,* (1996) they referred all women with a suspicious mass and a score of ≥450 directly to the cancer clinic. All patients were first discussed at a MDT meeting and those with a lower RMI score may still have been referred if there were clinical indications of malignancy. Of 104 women in the study 27 were directly referred, of which one had benign disease. One woman with a low RMI was referred to the clinic on the basis of having had a suspicious CT scan. With a cut-off score in this very limited population, the RMI I index had sensitivity = 96.2% [95%CI: 80.4-99%] and specificity 98.7% [95%CI: 93.1-100%].

Review Protocol

Objectives

To determine which malignancy index is the more accurate in assessing the probability of malignant pathology in women with suspected ovarian cancer prior to their surgery.

Study inclusion criteria

- **Population:** Women with an adnexal mass
- **Index tests:** Malignancy indices including Risk of Malignancy Index (RMI) I & RMI II
- **Reference standard:** Histopathology of post-surgical biopsy specimens
- **Condition:** Diagnosis of ovarian cancer; impact on referral and management

Search strategy

The following electronic databases were searched: Medline, PreMedline, EMBASE, Cochrane Library, CINAHL, BNI, PsychInfo, AMED, Web of Science (SCI & SSCI) and Biomed Central. A general exclusion filter was applied (to eliminate non-reviewable material, for example notes, comments etc). No date filter was applied.

Review strategy:

The titles and abstracts of the studies identified in the literature search were screened for potential relevance by one reviewer (KF).

One reviewer (KF) extracted data for pooled sensitivity and specificity.

Study quality was assessed using the QUADAS checklist for diagnostic studies.

Search results:

The literature search identified 136 potentially relevant studies. After reading study titles and abstracts 11 papers were ordered of which 1 up to date systematic review was eventually included. Studies prior to this date (2009) were not considered further unless they reported outcomes other than those reported in the review.

Evidence summary:

The evidence base for this topic comprised one recent systematic review of diagnostic studies in which the reviewers appraised one hundred and nine studies of eighty-three validated risk of malignancy models. By pooling data appropriately the authors concluded that the RMI I proposed by Jacobs *et al.* (1990) was superior in terms of sensitivity and specificity to other comparators. For reference purposes, the components of RMI I are outlined briefly below.

Risk of Malignancy Index (RMI)

RMI combine three pre-surgical features: CA125 score, menopausal status and ultrasound score.

- Serum CA125 score provides continuous numerical data. Log transformed CA125 approximates the Normal distribution. The mean values of two groups can be compared using the Student's t-test. CA125 is measured in U(nits) per ml and can vary between 0 to hundreds or even thousands of units.

- Menopausal status provides categorical data – every woman is either pre-menopausal or post-menopausal. The Chi^2 test compares the distribution of responses between two groups to see if they are equal. The classification of 'post-menopausal' is women who have had no period for more than one year or women over the age of 50 who have had a hysterectomy.

- Ultrasound score provides non-parametric data, which are not normally distributed. The Mann Whitney U test determines if two probability distributions are equal. The ultrasound result is graded according to the presence or absence of five physiological features on the scan: multiple locus cysts, solid areas, metastases, ascites and bilateral lesions.

RMI I (Jacobs *et al.,* 1990):
Menopausal status: premenopausal scores '1' and postmenopausal scores '3'.
Ultrasound: '0' means none of the five physiological features were present, '1' indicates the presence of one of the five elements and '3' indicates the presence of two or more features.
RMI I score is the product of CA125 Uml^{-1} x ultrasound score (0, 1, 3) x menopausal status (1, 3).

RMI II (Tingulstad *et al.,* 1996):
Menopausal status: premenopausal scores '1' and post-menopausal status scores '4'.
Ultrasound: '1' means none or one of the five physiological features was present and '4' indicates the presence of two or more. RMI II score is the product of CA125 Uml^{-1} x ultrasound score (1, 4) x menopausal status (1, 4).

Author(s): Geomini *et al.* (2009)

Design: Systematic review
Country: The Netherlands

Included studies: The review included one hundred and nine studies containing data on the accuracy of an index model in predicting the risk of malignancy of an ovarian mass. To be included, a study had to combine at least two parameters, for example menopausal status and serum CA125 level, in a validated model.

Exclusion criteria: Studies in which a model was being developed rather than validated. Papers from which it was not possible to construct a two-by-two contingency table.

Population: N=21,750 adnexal masses (5,826 malignancies)

Intervention(s) and comparator(s):

Included studies reviewed a validated malignancy index. There were 83 such prediction models, the results of which were compared with histopathology as gold standard. The most commonly used indices included RMI I (see summary) RMI II (menopausal status, grayscale ultrasound and serum CA125) Tailor's regression model (age, transvaginal colour Doppler imaging and papillary projections) and other models including those by Sassone (grayscale ultrasonography, inner wall structure, wall thickness, septa and echogenecity) Alcazar (logistic regression using morphological score from Sassone) Lerner (similar to Sassone's model but replacing wall thickness with shadow) DePriest (tumour volume, wall structure and septa) and Ferrazzi (wall structure, septa, vegetations and echogenecity).

The method of meta analysis was described as a bivariate, random effects meta-regression which pooled estimates of sensitivity and specificity for risk cut off values to fit a summary receiver operating characteristic (ROC) curve or a point estimate. This model allowed for the two-dimensional nature of the sensitivity and specificity relationship and for the likelihood of variation due to the use of different cut off values employed. The random effects model allowed for heterogeneity between studies which might occur with clinical or methodological variation and the included studies were also weighted according to the distribution of malignancy within study groups. This means that, for example, patients in tertiary care are likely to have a much higher prevalence of malignancy therefore these data had more weight when pooling sensitivity and, similarly, a study in which more women had benign conditions had more weight when pooling specificity.

Outcomes: Pooled sensitivity and specificity.

Results:

sensitivity and specificity of most commonly used indices

Sassone (N=18 studies). Scale ranged from 4-15. With cut of point at 9, sensitivity = 84% (95% C.I: 76-93) and specificity = 80% (95% C.I: 73-88). ROC curve plotted.

Alcazar (N=4 studies). Sensitivity and specificity ranged too widely to allow pooling.

Lerner (N=8 studies). Scale range presumed to be similar to that of Sassone since only one variable was changed. With a cut off point of 3, sensitivity = 90% (95% C.I: 87-98) and specificity = 63% (95% C.I: 40-81). Point estimate only.

DePriest (N=10 studies). Scale ranged from 0-12. With a cut off point of 5, sensitivity = 91% (95% C.I: 85-97) and specificity = 69% (95% C.I: 60-78). Point estimate only.

Ferrazzi (N=9 studies). Scale ranged from 4-18. With a cut off point of 9, sensitivity = 88% (95% C.I: 71-96) and specificity = 74% (95% C.I: 59-89). Point estimate only.

RMI I (N=16 studies). Scale ranged from 0-∞. With a cut off point of 200, sensitivity = 78% (95% C.I: 71-85) and specificity = 87% (95% C.I: 83-91). With a cut off point of 50, sensitivity = 91% (95% C.I: 85-97) and specificity = 74% (95% C.I: 69-80).

RMI II (N=7 studies). Scale ranged from 1-∞. With a cut off point of 200, sensitivity = 79% (95% C.I: 71-87) and specificity = 81% (95% C.I: 72-90).

Taylor's regression (N=6). Scale ranged from 0-100%. With a cut off point of 50%, sensitivity = 60% (95% C.I: 20-100) and specificity = 93% (95% C.I: 82-100). With a cut off point of 25%, sensitivity = 78% (95% C.I: 33-100) and specificity = 77% (95% C.I: 35-100).

When all models were plotted together, the ROC curves for RMI I and then RMI II showed distributions closest to the optimum compared with other models i.e. the highest combination of sensitivity and specificity. These data could not be compared statistically but were judged by eye from the summary plot.

Follow-up: N/A

Notes:

This paper presents the findings of a systematic review of literature concerning the use of prediction models for pre-operative assessment of adnexal masses. Searches for literature were made from MEDLINE and EMBASE databases and details of search expressions were given. Two independent reviewers selected 109 studies from which they extracted study characteristics, study quality and test accuracy. Pooled values of sensitivity, specificity were used to fit summary receiver operating characteristic (ROC) curves.

Individual papers were assessed by the review authors and checked for quality with respect to: study type (cohort vs. case control) data collection (prospective vs. retrospective) sampling method (consecutive vs. other) blinding and verification bias. The review authors judged included studies to be of 'moderate' quality. Approximately 90% of the studies were of cohort design; just less than 60% used prospective data collection and only 40% sampled data consecutively. One general shortcoming of more than 80% of studies was that the pathologist was not blinded to the results of the index when assessing the biopsy specimens or at least this was not discussed adequately in the papers. Finally, the majority (~85%) of studies had no verification bias, which means that all patients received the gold standard test i.e. histology, regardless of the malignancy index prediction.

When RMI I was applied with a cut off score of 200, sensitivity of 78%, specificity of 87% and a post-test probability of malignancy of 10%, women with a score >200 had a probability of malignancy of 40% but women with a score <200 had a probability of malignancy of 2.7%. The authors concluded that this scoring system would be of the most value clinically.

Author(s): Raza *et al.* (2010)

Design: Observational study
Country: United Kingdom

Inclusion criteria: Women presenting at a cancer unit with an ovarian mass.

Exclusion criteria: Women for whom imaging or pathology results were not available

Population: 104 women (no further information)
Interventions and comparators: RMI I (according to the criteria of Jacobs *et al.,* 1990)
Outcomes: Sensitivity and specificity of RMI I with a cut-off score of 450 or greater.
Results: 27/104 women were referred directly to the cancer centre, of which one was referred on the basis, not of RMI I but because of a suspicious CT scan. 26/27 of these women had surgery and all were shown to have invasive ovarian cancer. The remaining woman had a benign condition, detected by imaging and biopsy. 77/104 women had surgery locally, of which 6 had borderline cancer and 2 had granulosa cell tumours. **Sensitivity and specificity of RMI I with cut-off score of 450:** Sensitivity: 96.2% (95% C.I: 80.4-99.9%) Specificity: 98.7% (95% C.I: 93.1-100%) Positive predictive value: 96.3% (95% C.I: 81.0-99.9%) Negative predictive value: 98.7% (95% C.I: 93.0-100%)
Follow-up: N/A
Notes: This paper briefly presents data from 104 women with ovarian masses who presented at a cancer unit from July 2004 to September 2006 and were assessed by a MDT (comprising a gynaecologist, radiologist, pathologist, clinical nurse specialist and co-ordinator). Those women with a RMI I score of ≥450 were referred directly to a cancer centre. Other women with a lower RMI I score may have been referred by the MDT if there was clinical suspicion of malignancy. This is a non-comparative, observational study and therefore of low evidential quality. It must be noted that although the sensitivity and specificity of the RMI I in this group is high, the population is small and highly selected. Applicability to the population as a whole may therefore by low.

References:

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3.3 Imaging in the diagnostic pathway: which procedure and where?

"*For women with suspected ovarian cancer, what is the most appropriate imaging to be done to determine future management?*"

Short summary:

Evidence from diagnostic meta-analysis suggests the accuracy of combined grey-scale/colour Doppler ultrasound, CT and MRI for the differentiation of benign and malignant ovarian masses are broadly similar. The diagnostic accuracy of colour Doppler ultrasound alone was much lower than combined grey-scale/colour Doppler, CT and MRI.

Evidence for the staging of ovarian cancer was sparse in comparison to that for diagnosis, consisting mainly CT studies. There was insufficient evidence to suggest the optimal imaging test for staging. No evidence about the use of chest X-ray was found.

Although there are several published models that predict sub-optimal cytoreduction using the preoperative CT scan, independent validation studies have failed to support any of them.

Review Protocol:

Question

For women with suspected ovarian cancer, what is the most appropriate imaging to be done to determine future management?

Objectives

To determine which imaging tests should be done in women referred to secondary care with suspected ovarian cancer.

Study inclusion criteria

- **Studies:** Any study design including 20 or more patients, reporting sufficient data to calculate true positive, true negative, false positive and false negative test results. English language publications only.
- **Participants:** Women with suspected ovarian cancer
- **Index tests:** CT, MRI, Chest X-ray, Ultrasound
- **Comparator tests:** Index tests were compared with each other
- **Target conditions:** Diagnosis of ovarian cancer, staging of ovarian cancer, operability, influence on management
- **Reference standards:** Histopathology, or clinical and radiological follow up when histology is not available

Search strategy

The following electronic databases were searched: Medline, PreMEDLINE, EMBASE, Cochrane Library, CINAHL, BNI, PsycINFO, AMED, Web of Science (SCI & SSCI) and Biomed Central.

Reference lists of included studies were checked for relevant studies. Papers could also come from other searches from the guideline or from stakeholders and guideline group members.

Review strategy

Good quality systematic reviews were identified, so studies published before the review's search date were not included unless they reported outcomes not considered in the systematic review.

Study quality was assessed using the QUADAS checklist for diagnostic studies

Search results:

The literature search identified 654 studies of which 59 were ordered for appraisal and 27 included.

There were five systematic reviews of diagnostic test for ovarian cancer: all five considered ultrasound (grey-scale, colour Doppler and combined), and three considered MRI and CT. A further 18 studies were included; these were either studies of staging or prediction of optimal cytoreduction or diagnostic studies published after the systematic reviews.

There were no systematic reviews of CT, MRI or ultrasound for staging or prediction of operability in women with ovarian cancer. The searches found no studies about the use chest X-ray in this population

Study quality:

The methodological quality of the included studies was reasonable: many studies reported that the interpretation of the diagnostic tests was done by a clinician blinded to other clinical information. The reference standard was histopathologic findings following surgery, although it is possible that the surgical protocol was influenced by the preoperative imaging which would inflate the apparent accuracy of imaging. Indeterminate test results were often not reported, and presumably excluded from some studies. Patients with ovarian cancer missed on imaging, and not scheduled for any surgery, would also be excluded from these studies.

Evidence summary:

Differentiation of benign from malignant ovarian tumours

The diagnostic accuracy of US, MRI and CT for malignancy in adnexal masses is summarised in Table 6.1. For illustration the post test probabilities of ovarian cancer following positive and negative tests are displayed for each test using an arbitrary pre-test probability of 10%. There majority of studies were of grey-scale ultrasound, with fewer MRI and colour Doppler ultrasound studies and very few CT studies.

The diagnostic accuracy of combined grey-scale/colour Doppler, CT and MRI were broadly similar with sensitivity approaching 90% and specificity exceeding 85%. The diagnostic accuracy of colour Doppler ultrasound alone was much lower than grey-scale/colour Doppler ultrasound, CT and MRI.

Women with indeterminate grey scale ultrasound results

Li *et al.* (2006) noted that ultrasound is most accurate in identifying simple cystic masses, and the ultrasound studies in their meta-analysis had a lower prevalence of complex ovarian lesions than the CT and MRI studies. It is possible that the diagnostic utility of MRI and CT is underestimated in the meta-analyses.

Kinkel *et al*. (2005) reviewed evidence for imaging in women with indeterminate masses at grey-scale ultrasound, presumably excluding those women with simple cystic masses. In this group of patients MRI had a higher positive predictive value (post test probability), than CT and combined grey-scale/colour Doppler (see Table 3.2).

Staging

The evidence about CT, MRI and US for staging was sparse, in comparison to the diagnostic studies. The evidence from staging studies is summarised according to anatomical site in Figures 3.12 to 3.25. Most evidence comes from studies using CT, with very few studies reporting staging with MRI or US. There was insufficient evidence to suggest the optimal imaging modality for staging.

The evidence suggests moderate to poor sensitivity but reasonable specificity for the detection of metastases or tumour involvement in the various sites. Thus these imaging tests are useful when they show tumour involvement/metastases as they are quite likely to be correct, but negative CT or MRI does not rule out tumour involvement or metastases. This suggests women are more likely to be under-staged than over-staged using these tests.

There was a lack of studies about chest X-rays in this patient group.

Prediction of optimal cytoreduction

The evidence is summarised in Figure 3.12 and Table 3.4. Most evidence came from studies using CT, with only one US study and two MRI studies. Five studies (Nelson *et al*., 1993; Bristow *et al*., 2000; Dowdy *et al.,* 2004; Quayyum *et al*., 2004; Meyer *et al*., 1995) reported models to predict suboptimal cytoreduction on the basis of CT features (see Table 3.4).

Although the authors of these models report reasonable sensitivity and specificity for their models, two independent studies (Axtell *et al*., 2007; Gemer *et al*., 2009) did not validate these findings. The low positive predictive values reported by Axtell *et al.* (2007) and Gemer *et al.* (2009) suggest that most patients predicted to have sub-optimal cytoreduction would in fact have optimal cytoreduction if operated on.

Table 3.2 Accuracy of tests for diagnosis of malignancy in adnexal masses [Back]

Test	Systematic review / meta-analysis	N	Sensitivity [95% CI]	Specificity [95% CI]	LR+	LR-	Probability of ovarian cancer after positive test (pre-test probability 10%)	Probability of ovarian cancer after negative test (pre-test probability 10%)
Ultrasound - morphologic assessment	Liu 2007	54 studies, N=5524	85% (83% to 87%)	83% (81% to 85%)	5.00	0.18	35.71%	1.96%
	Kinkel 2000	34 studies, N=3377	85% (83% to 88%)	85% (83% to 88%)	5.67	0.18	38.65%	1.96%
Ultrasound - colour Doppler	Liu 2007	Not reported	75% (72% to 77%)	73% (71% to 75%)	2.78	0.34	23.60%	3.64%
	Kinkel 2000	10 studies, N=1408	73% (58% to 87%)	73% (58% to 87%)	2.70	0.37	23.08%	3.95%
Ultrasound - combined colour Doppler and morphologic assessment	Liu 2007	7 studies, N not reported	87% (85% to 90%)	88% (85% to 91%)	7.25	0.15	44.62%	1.64%
	Medeiros 2009	12 studies, N=2398	87% (84% to 90%)	89% (87% to 90%)	7.90	0.15	46.75%	1.64%
	Myers 2006	9 studies	89% (81% to 93%)	91% (80% to 96%)	9.89	0.12	52.36%	1.32%
	Kinkel 2000	7 studies, N=832	92% (87% to 96%)	92% (87% to 96%)	11.50	0.09	56.10%	0.99%
	Kinkel 2005*	8 studies, N=1529	84% (81% to 87%)	82% (79% to 85%)	4.67	0.20	34.16%	2.17%

MRI	Liu 2007	11 studies, N not reported	89% (95% CI 88% to 92%)	86% (95% CI 84% to 88%)	6.36	0.13	41.41%	1.42%
	Myers 2006	15 studies, N not reported	91% (95% CI 86% to 94%)	87% (83% to 90%)	7.00	0.10	43.75%	1.10%
	Kinkel 2005*	10 studies, N=773	81% (77% to 84%)	98%(97% to 99%)	9.5	0.19	51.35%	2.07%
CT	Liu 2007	4 studies, N not reported	85% (95% CI 83% to 86%)	86% (95% CI 72% to 92%)	6.07	0.17	40.28%	1.85%
	Myers 2006	3 studies, N not reported	90% (83% to 94%)	75% (36% to 94%)	3.60	0.13	28.57%	1.42%
	Kinkel 2005*	3 studies, N=161	81% (73% to 86%)	87% (81% to 94%)	6.23	0.22	40.91%	2.39%

*Kinkel *et al.,* 2005 includes only studies of women with prior non-diagnostic grey scale ultrasound.

Abbreviations: LR +, likelihood ratio for a positive test result; LR -, likelihood ratio for a negative test result;

Table 3.3 Accuracy of models for diagnosis of ovarian malignancy on ultrasound (from Geomini *et al.,* 2009 systematic review)

Prediction model	N	Sensitivity [95% CI]	Specificity [95% CI]	LR+	LR-	Probability of ovarian cancer after positive test (pre-test probability 10%)	Probability of ovarian cancer after negative test (pre-test probability 10%)
Sassone	18 studies, N=2670	84% (76% to 93%)	83% (73% to 88%)	4.94	0.19	35.44%	2.07%
Lerner	8 studies (N not reported)	90% (87% to 98%)	63% (40% to 81%)	2.43	0.16	21.26%	1.75%
Ferrazzi	9 studies (N not reported)	88% (71% to 96%)	74% (59% to 89%)	3.38	0.16	27.30%	1.75%
DePriest	10 studies (N not reported)	91% (85% to 97%)	69% (60% to 78%)	2.94	0.29	24.62%	3.12%
Tailor (incorporates age and colour Doppler)	6 studies (N not reported)	60% (20% to 100%)	93% (82% to 100%)	8.57	0.43	48.78%	4.56%

Abbreviations: N.R., not reported.

Table 3.4 Accuracy of predictive models for suboptimal cytoreduction using CT [Back]

Model	Study	Prevalence of sub optimal cytoreduction	Sensitivity	Specificity	Accuracy	PPV	NPV
Nelson	Nelson 1993	31% (≥2cm)*	92%	79%	86%	67%	96%
	Gemer 2009	27% (>1cm)*	64%	64%	64%	40%	83%
	Axtell 2007	22% (>1cm)*	79%	45%	62%	28%	88%
Bristow	Bristow 2000	51% (>1cm)*	100%	85%	93%	88%	100%
	Gemer 2009	27% (>1cm)*	70%	64%	66%	42%	85%
	Axtell 2007	22% (>1cm)*	93%	55%	74%	36%	97%
Dowdy	Dowdy 2004	29% (>1cm)*	52%	90%	71%	57%	82%
	Gemer 2009	27% (>1cm)*	33%	86%	73%	50%	79%
	Axtell 2007	22% (>1cm)*	7%	88%	48%	14%	78%
Qayyum	Qayyum 2005	15% (>1cm)*	79%	99%	88%	92%	96%
	Gemer 2009	27% (>1cm)*	67%	57%	60%	36%	82%
	Axtell 2007	22% (>1cm)*	50%	65%	58%	28%	83%
Meyer	Meyer 1995	43% (≥2cm)*	58%	100%	79%	100%	76%
	Axtell 2007	22% (>1cm)*	57%	45%	51%	22%	79%

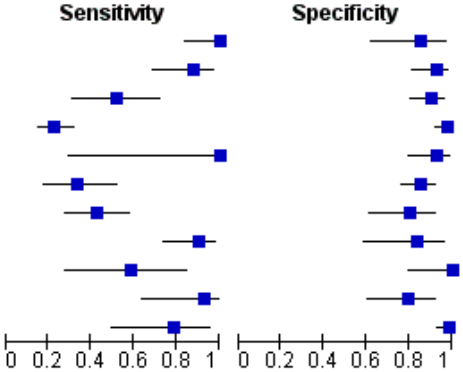
* Diameter of residual tumour deposits

Abbreviations: PPV, positive predictive value; NPV, negative predictive value

Figure 3.12 Diagnostic accuracy of CT, US and MRI for the prediction of sub-optimal cytoreductive surgery [Back]

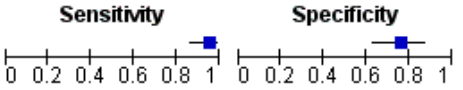
CT for prediction of suboptimal cytoreduction

Study	TP	FP	FN	TN	Sensitivity	Specificity
Bristow 2000	21	3	0	17	1.00 [0.84, 1.00]	0.85 [0.62, 0.97]
Byrom 2002	22	4	3	48	0.88 [0.69, 0.97]	0.92 [0.81, 0.98]
Dowdy 2004	13	6	12	56	0.52 [0.31, 0.72]	0.90 [0.80, 0.96]
Ferrandina 2009	25	2	84	84	0.23 [0.15, 0.32]	0.98 [0.92, 1.00]
Forstner 1995b	3	3	0	37	1.00 [0.29, 1.00]	0.93 [0.80, 0.98]
Gemer 2009	11	13	22	77	0.33 [0.18, 0.52]	0.86 [0.77, 0.92]
Jung 2010	20	6	27	24	0.43 [0.28, 0.58]	0.80 [0.61, 0.92]
Kebapci 2010	27	3	3	15	0.90 [0.73, 0.98]	0.83 [0.59, 0.96]
Meyer 1995	7	0	5	16	0.58 [0.28, 0.85]	1.00 [0.79, 1.00]
Nelson 1993	12	6	1	23	0.92 [0.64, 1.00]	0.79 [0.60, 0.92]
Qayyum 2005	11	1	3	76	0.79 [0.49, 0.95]	0.99 [0.93, 1.00]



US for prediction of suboptimal cytoreduction

Study	TP	FP	FN	TN	Sensitivity	Specificity
Testa 2006	56	13	3	42	0.95 [0.86, 0.99]	0.76 [0.63, 0.87]



MRI for prediction of suboptimal cytoreduction

Study	TP	FP	FN	TN	Sensitivity	Specificity
Forstner 1995b	10	1	1	38	0.91 [0.59, 1.00]	0.97 [0.87, 1.00]
Qayyum 2005	5	0	2	39	0.71 [0.29, 0.96]	1.00 [0.91, 1.00]

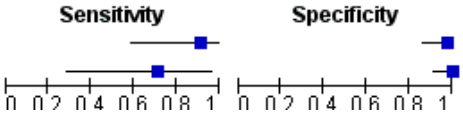


Figure 3.13 CT, US and MRI for the prediction of sub-optimal cytoreductive surgery, summary ROC curve [Back]

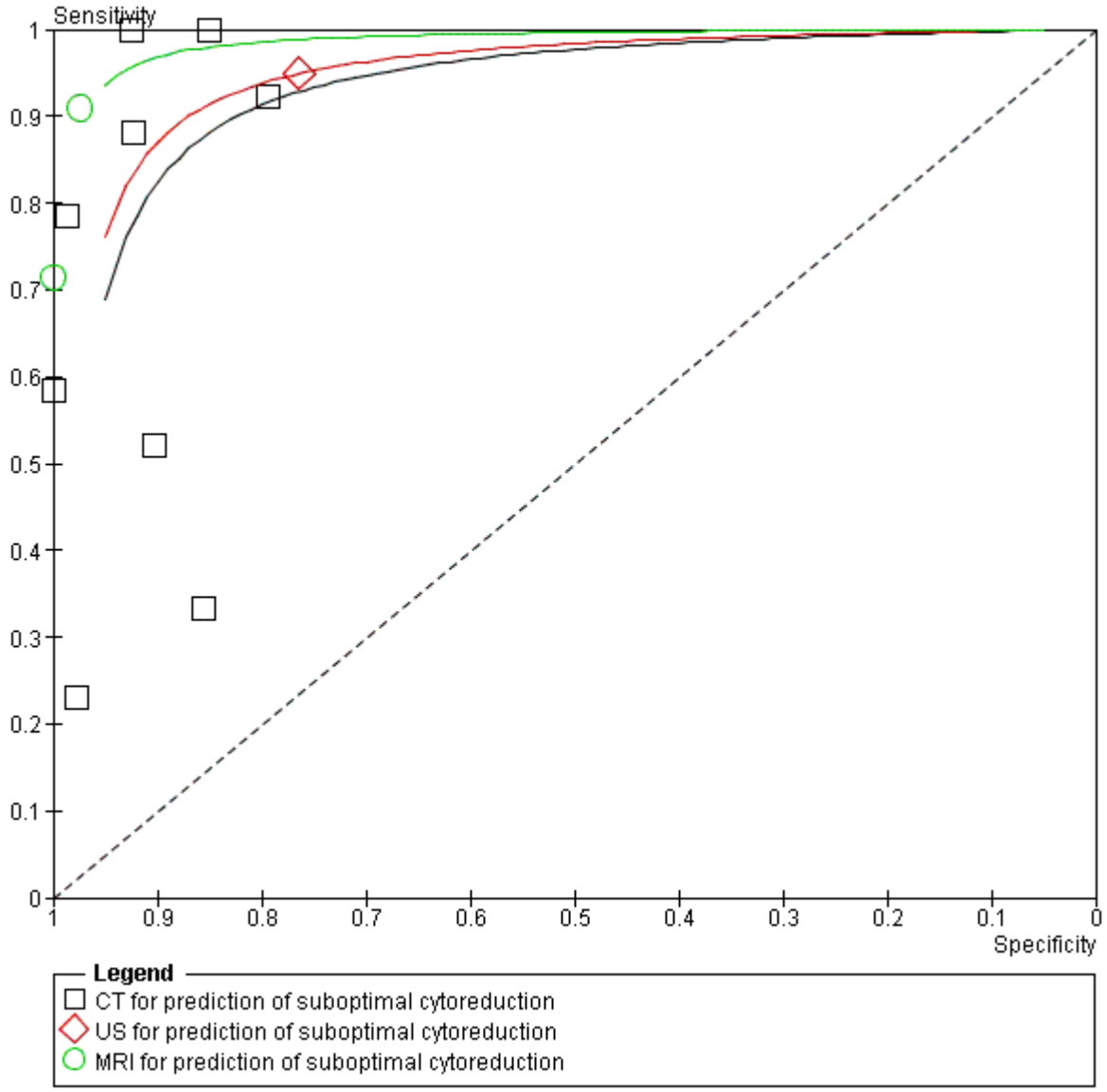
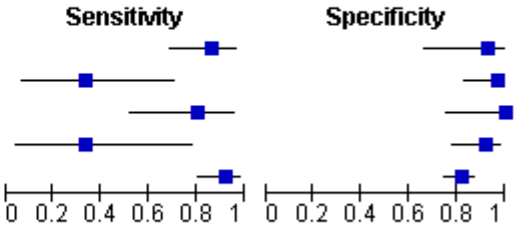


Figure 3.14 Diagnostic accuracy of CT, US and MRI for the detection of omental metastases
[Back]

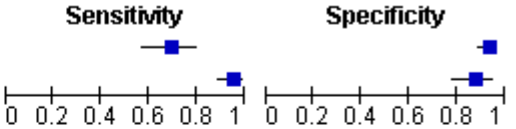
CT for detection of omental metastases

Study	TP	FP	FN	TN	Sensitivity	Specificity
Forstner 1995b	25	1	4	13	0.86 [0.68, 0.96]	0.93 [0.66, 1.00]
Kitajima 2008	3	1	6	30	0.33 [0.07, 0.70]	0.97 [0.83, 1.00]
Meyer 1995	12	0	3	13	0.80 [0.52, 0.96]	1.00 [0.75, 1.00]
Nelson 1993	2	3	4	33	0.33 [0.04, 0.78]	0.92 [0.78, 0.98]
Tempany 2000	46	30	4	132	0.92 [0.81, 0.98]	0.81 [0.75, 0.87]



US for detection of omental metastases

Study	TP	FP	FN	TN	Sensitivity	Specificity
Tempany 2000	47	13	21	181	0.69 [0.57, 0.80]	0.93 [0.89, 0.96]
Testa 2006	95	9	5	64	0.95 [0.89, 0.98]	0.88 [0.78, 0.94]



MRI for detection of omental metastases

Study	TP	FP	FN	TN	Sensitivity	Specificity
Forstner 1995b	23	3	7	17	0.77 [0.58, 0.90]	0.85 [0.62, 0.97]
Ricke 2003	24	3	10	20	0.71 [0.53, 0.85]	0.87 [0.66, 0.97]
Tempany 2000	39	27	2	107	0.95 [0.83, 0.99]	0.80 [0.72, 0.86]

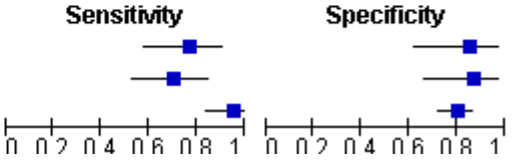


Figure 3.15 Diagnostic accuracy of CT, US and MRI for the detection of omental metastases, summary ROC curve [Back]

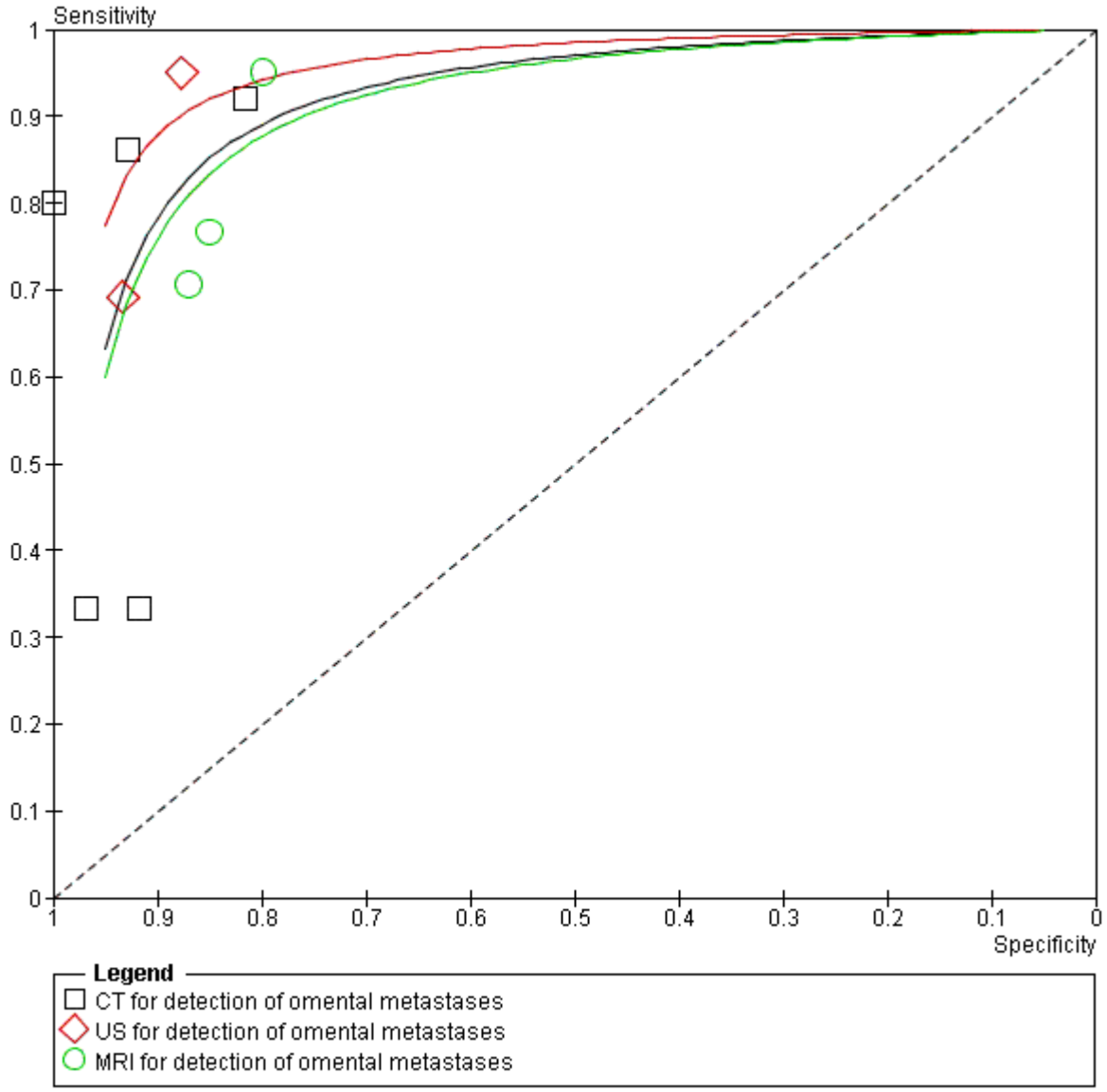
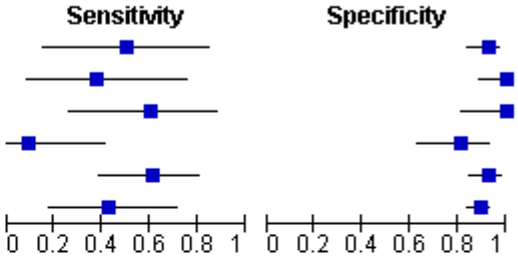


Figure 3.16 Diagnostic accuracy of CT, US and MRI for the detection of lymph node metastases [Back]

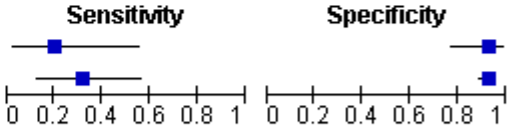
CT for detection of lymph node metastases

Study	TP	FP	FN	TN	Sensitivity	Specificity
Forstner 1995b	4	6	4	72	0.50 [0.16, 0.84]	0.92 [0.84, 0.97]
Kitajima 2008	3	0	5	32	0.38 [0.09, 0.76]	1.00 [0.89, 1.00]
Meyer 1995	6	0	4	18	0.60 [0.26, 0.88]	1.00 [0.81, 1.00]
Nelson 1993	1	6	10	25	0.09 [0.00, 0.41]	0.81 [0.63, 0.93]
Sugiyama 1995	14	5	9	67	0.61 [0.39, 0.80]	0.93 [0.85, 0.98]
Tempany 2000	6	21	8	170	0.43 [0.18, 0.71]	0.89 [0.84, 0.93]



US for detection of lymph node metastases

Study	TP	FP	FN	TN	Sensitivity	Specificity
Henrich 2007	2	2	8	27	0.20 [0.03, 0.56]	0.93 [0.77, 0.99]
Tempany 2000	6	17	13	219	0.32 [0.13, 0.57]	0.93 [0.89, 0.96]



MRI for detection of lymph node metastases

Study	TP	FP	FN	TN	Sensitivity	Specificity
Forstner 1995b	10	4	2	84	0.83 [0.52, 0.98]	0.95 [0.89, 0.99]
Ricke 2003	18	7	10	21	0.64 [0.44, 0.81]	0.75 [0.55, 0.89]
Tempany 2000	5	26	8	132	0.38 [0.14, 0.68]	0.84 [0.77, 0.89]

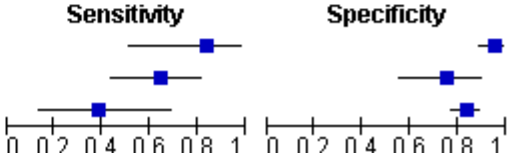


Figure 3.17 Diagnostic accuracy of CT, US and MRI for the detection of lymph node metastases, summary ROC curve [Back]

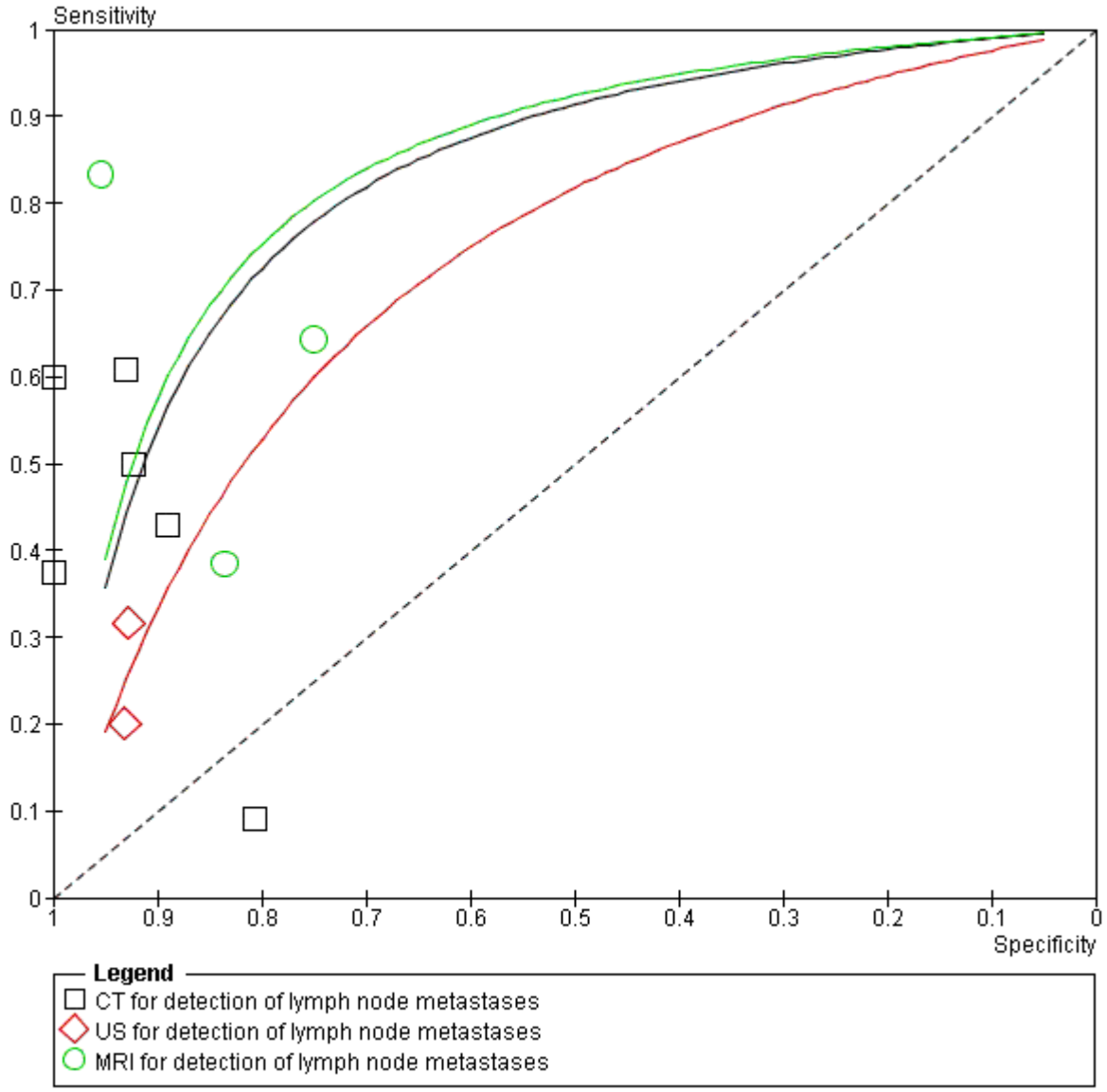
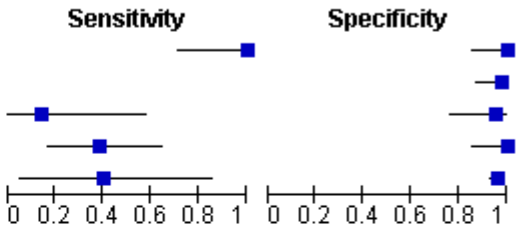


Figure 3.18 Diagnostic accuracy of CT, US and MRI for the detection of liver parenchymal metastases [Back]

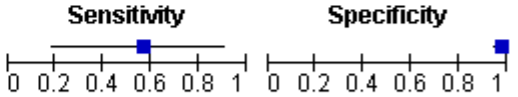
CT for detection of liver parenchymal metastases

Study	TP	FP	FN	TN	Sensitivity	Specificity
Forstner 1995b	11	0	0	24	1.00 [0.72, 1.00]	1.00 [0.86, 1.00]
Kitajima 2008	0	1	0	39	Not estimable	0.97 [0.87, 1.00]
Meyer 1995	1	1	6	20	0.14 [0.00, 0.58]	0.95 [0.76, 1.00]
Nelson 1993	7	0	11	24	0.39 [0.17, 0.64]	1.00 [0.86, 1.00]
Tempany 2000	2	8	3	199	0.40 [0.05, 0.85]	0.96 [0.93, 0.98]



US for detection of liver parenchymal metastases

Study	TP	FP	FN	TN	Sensitivity	Specificity
Tempany 2000	4	6	3	245	0.57 [0.18, 0.90]	0.98 [0.95, 0.99]



MRI for detection of liver parenchymal metastases

Study	TP	FP	FN	TN	Sensitivity	Specificity
Forstner 1995b	9	1	1	27	0.90 [0.55, 1.00]	0.96 [0.82, 1.00]
Tempany 2000	2	7	3	153	0.40 [0.05, 0.85]	0.96 [0.91, 0.98]

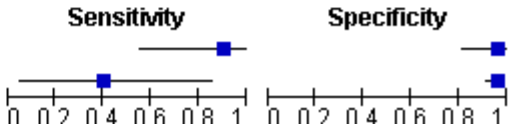


Figure 3.19 Diagnostic accuracy of CT, US and MRI for the detection of liver parenchymal metastases, summary ROC curve [Back]

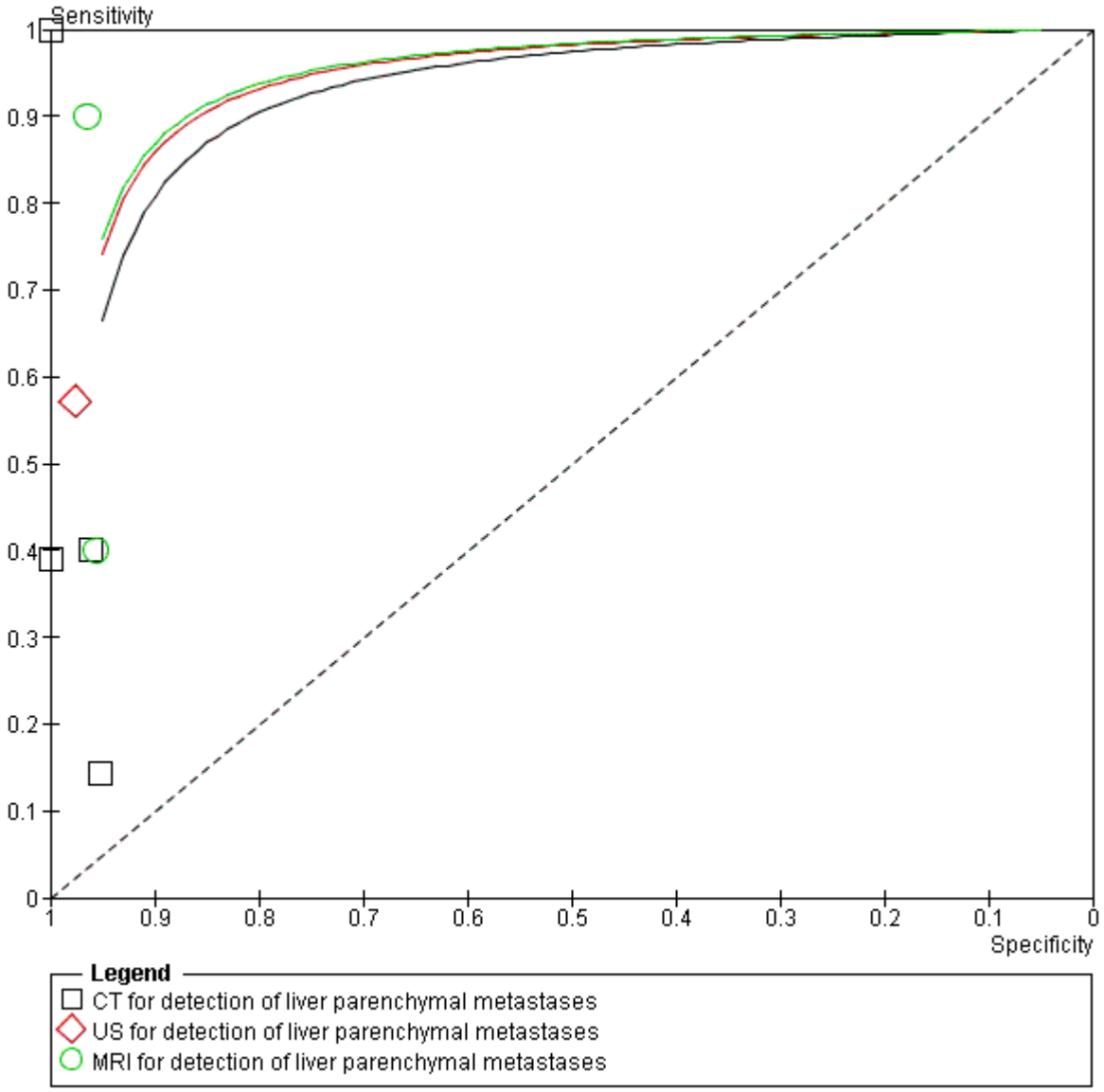
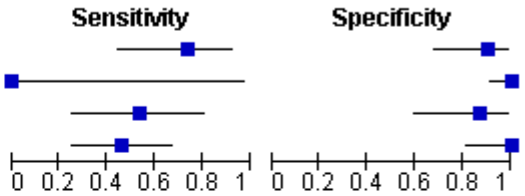


Figure 3.20 Diagnostic accuracy of CT, US and MRI for the detection of diaphragm involvement [Back]

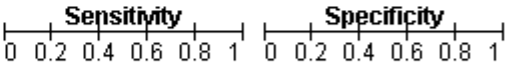
CT for detection of diaphragm involvement

Study	TP	FP	FN	TN	Sensitivity	Specificity
Forstner 1995b	11	2	4	18	0.73 [0.45, 0.92]	0.90 [0.68, 0.99]
Kitajima 2008	0	0	1	39	0.00 [0.00, 0.97]	1.00 [0.91, 1.00]
Meyer 1995	7	2	6	13	0.54 [0.25, 0.81]	0.87 [0.60, 0.98]
Nelson 1993	11	0	13	18	0.46 [0.26, 0.67]	1.00 [0.81, 1.00]



US for detection of diaphragm involvement

Study	TP	FP	FN	TN	Sensitivity	Specificity



MRI for detection of diaphragm involvement

Study	TP	FP	FN	TN	Sensitivity	Specificity
Forstner 1995b	12	2	4	19	0.75 [0.48, 0.93]	0.90 [0.70, 0.99]
Ricke 2003	11	5	3	37	0.79 [0.49, 0.95]	0.88 [0.74, 0.96]

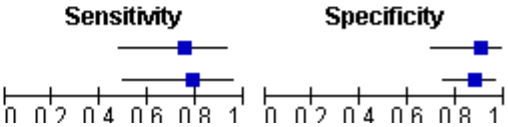


Figure 3.21 Diagnostic accuracy of CT, US and MRI for the detection of diaphragm involvement, summary ROC curve [Back]

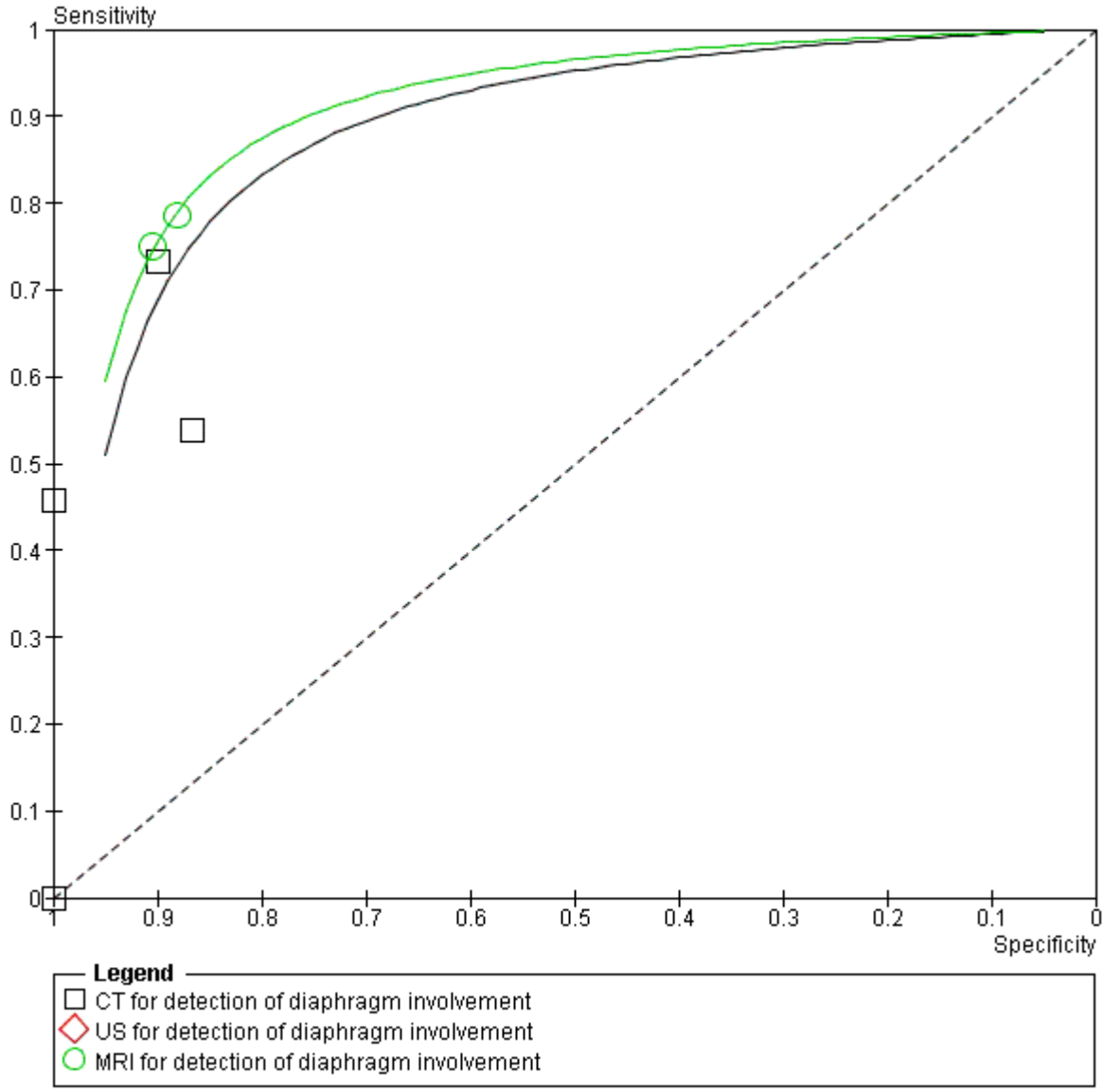


Figure 3.22 Diagnostic accuracy of CT, US and MRI for the detection of pelvic organ involvement [Back]

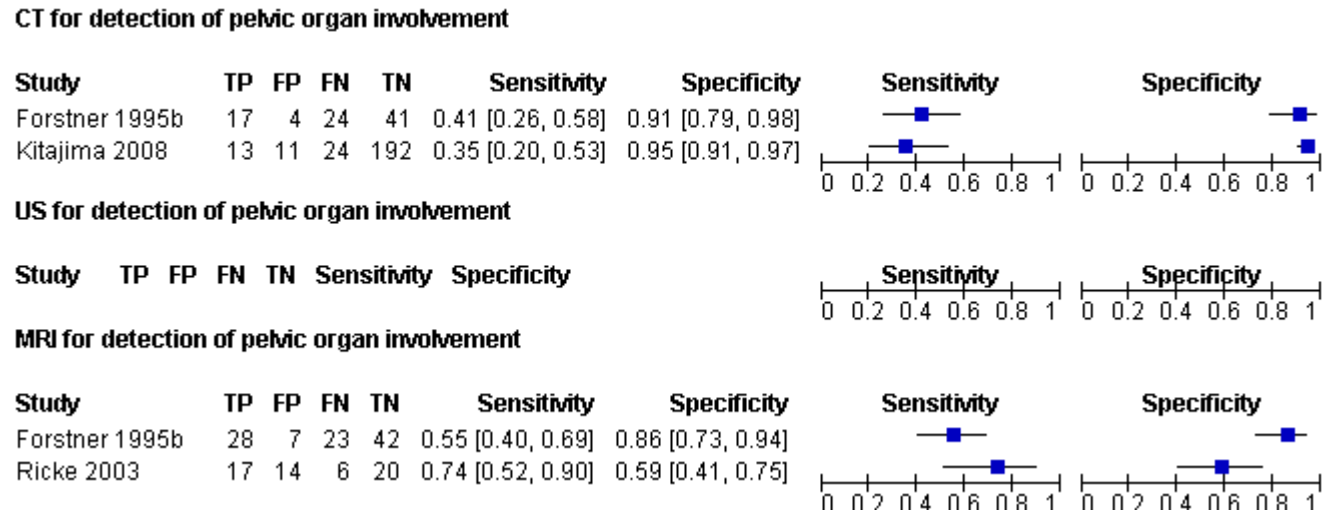


Figure 3.23 Diagnostic accuracy of CT, US and MRI for the detection of pelvic organ involvement, summary ROC curve [Back]

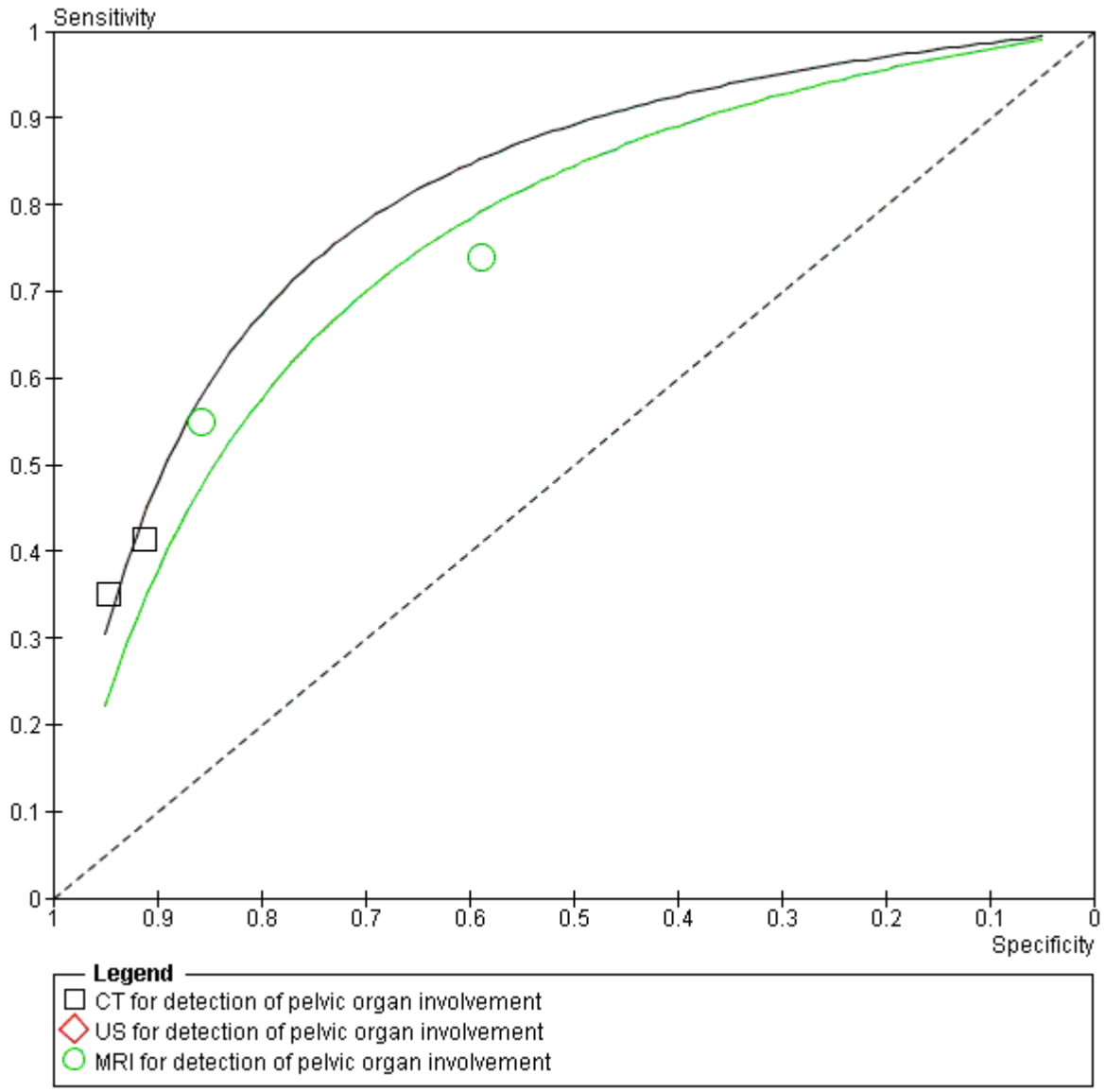
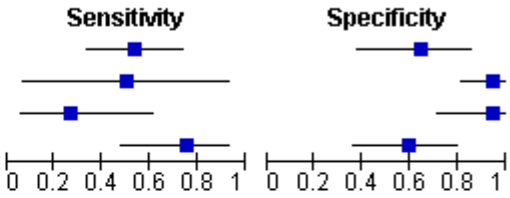


Figure 3.24 Diagnostic accuracy of CT, US and MRI for the detection of small bowel, large bowel or mesentery involvement [Back]

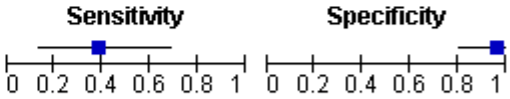
CT for detection of bowel involvement (small, large and mesentery)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Forstner 1995b	14	6	12	11	0.54 [0.33, 0.73]	0.65 [0.38, 0.86]
Kitajima 2008	2	2	2	34	0.50 [0.07, 0.93]	0.94 [0.81, 0.99]
Meyer 1995	3	1	8	16	0.27 [0.06, 0.61]	0.94 [0.71, 1.00]
Nelson 1993	12	9	4	13	0.75 [0.48, 0.93]	0.59 [0.36, 0.79]



US for detection of bowel involvement (small, large and mesentery)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Henrich 2007	5	1	8	25	0.38 [0.14, 0.68]	0.96 [0.80, 1.00]



MRI for detection of bowel involvement (small, large and mesentery)

Study	TP	FP	FN	TN	Sensitivity	Specificity
Forstner 1995b	31	3	5	11	0.86 [0.71, 0.95]	0.79 [0.49, 0.95]
Ricke 2003	32	6	8	11	0.80 [0.64, 0.91]	0.65 [0.38, 0.86]

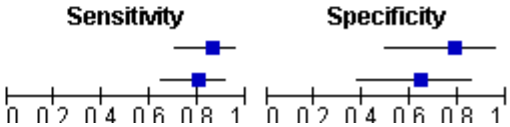
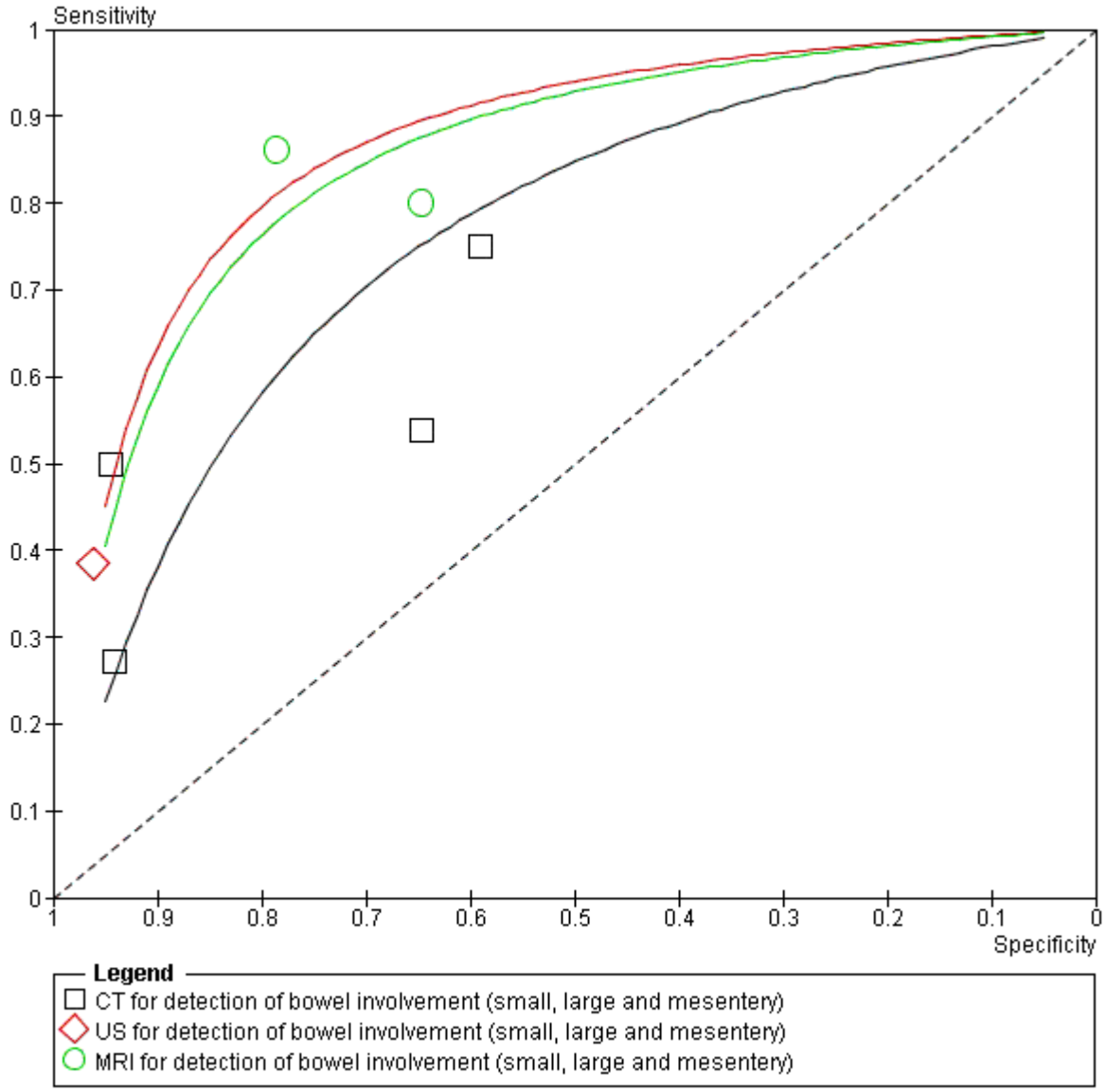


Figure 3.25 Diagnostic accuracy of CT, US and MRI for the detection of small bowel, large bowel or mesentery involvement, summary ROC curve [Back]



Evidence tables:

Author(s): Axtell *et al.,* 2007
Settings: Women with stage III/IV epithelial ovarian cancer who had primary cytoreduction and preoperative CT.
Participants: 65 women. 51/65 had optimal cytoreduction
Study Design: Retrospective case series, single institution
Target Condition: Prediction of optimal cytoreduction (residual disease 1cm or less in maximum diameter). Reference standard was
Tests: CT, using 14 CT criteria for sub optimal cytoreduction Five prediction models were tested: Bristow, Dowdy, Nelson, Meyer and Qayyum. Bristow model: sensitivity 93%, specificity 55%, accuracy 74% Dowdy model: sensitivity 7%, specificity 88%, accuracy 48% Nelson model: sensitivity 79%, specificity 45%, accuracy 62% Meyer model: sensitivity 57%, specificity 45%, accuracy 51% Qayyum model: sensitivity 50%, specificity 65%, accuracy 58%
Follow up: Not reported

Author(s): Booth *et al.,* 2008
Settings: Women with ovarian pathology who also had 3T MRI, and surgery of some kind.

Participants: 172 women: 98 with ovarian malignancy (57 primary malignancy, 20 borderline malignancy, 7 ovarian metastases) and 74 with benign disease.
Study Design: Retrospective case series
Target Condition: Detection of ovarian malignancy, staging of ovarian malignancy. Reference standard tests were surgical stage recorded in patient records and histopathological stage.
Tests: Index test was MRI (Signa HDX 3T MR scanner) MRI staging and histopathological staging were compared by assigning a score to each stage and then calculating weighted kappa (K of 0 indicates complete disagreement and K=1 indicates perfect agreement). For histopathological staging versus MR staging K was 0.866
Follow up: Not reported

Author(s): Bristow *et al.,* 2000
Settings: Women with FIGO stage III or IV epithelial ovarian cancer treated with primary cytoreductive surgery who had a preoperative CT scan.
Participants: 41 women. FIGO stage III (32/41) , FIGO stage IV (9/41) . Optimal cytoreduction 20/41 patients.
Study Design: Retrospective case series, single institution
Target Condition: Optimal cytoreductive surgery, defined as remaining tumour deposits of 1 cm or less maximal diameter. Reference standard was surgical findings recorded in medical records.
Tests: CT: Siemens Somatom Plus-4 scanner, with oral/intravenous contrast

CT Predictive Index score for sub optimal surgery was derived by summing points for 14 individual features on CT. Authors found predictive index of 4 points or more had the highest accuracy.
Notes: Sensitivity and specificity data were extracted for the Predictive Index score of 4 or more, although the sensitivity and specificities of individual CT features were also reported.

Author(s): Byrom *et al.,* 2002
Settings: Women who had laparotomy for pelvic mass, and a conclusive preoperative CT scan. Women with obvious benign disease or obvious stage III disease did not have CT scans.
Participants: 77 women. 26 had benign disease, 26 resectable malignant disease and 25 residual malignant disease after resection.
Study Design: Retrospective case series, single institution
Target Condition: Identification of resectable disease, identification of malignancy. Reference standard was surgical findings reported in medical records.
Tests: CT (Picker PQ 5000 or Toshiba Xpress GX), with oral and IV contrast. The authors developed a scoring index for the prediction of optimal cytoreduction, the index consisted of mesenteric disease, omental cake and CA-125
Follow up: Not reported

Author(s): Conte *et al.,* 1994
Settings: Women treated with surgery for ovarian cancer

Participants: 50 women, 37/50 had omental metastases.
Study Design: Case series
Target Condition: Detection of omental metastases. Reference standard was surgical and pathologic findings.
Tests: Ultrasound, (high resolution abdominal scanner: RT 3600, G.E.) Test results: True positives 23, true negatives 13, false negatives 14, false positives 0. The authors excluded 7 patients with micronodular metastases from the analysis, because they were below the resolution of the US. For this review, however, they are classified as false negatives.
Follow up: Not reported

Author(s): Dowdy *et al.,* 2004
Settings: Women treated with primary cytoreductive surgery for ovarian cancer between 1996 and 2001, with preoperative CT scan available.
Participants: 87 women. FIGO stage III 67/87, FIGO stage IV 20/87. 62/87 had optimal cytoreduction; the remaining 25 had sub optimal cytoreduction.
Study Design: Retrospective multi centre case series
Target Condition: Prediction of optimal cytoreduction, optimal cytoreduction was defined as remaining tumour deposits of 1 cm or less in diameter. The reference standard was reports of surgical findings in medical records.

Tests:

CT - technical details varied between centres but all had oral/intravenous contrast.

Criteria used to classify patients as at risk of sub optimal cytoreduction: diffuse peritoneal thickening (defined as > 4mm) and ascites on most sections (ascites present on at least two thirds of CT sections).

Follow up:

Not reported

Author(s): Ferrandina *et al.,* 2009

Settings:

Women with suspected advanced ovarian cancer and ECOG PS of less than 2. Women with large volume extra-abdominal disease were excluded.

Participants:

195 women. 86/195 had optimal cytoreduction

Study Design:

Prospective case series, single institution.

Target Condition:

Prediction of sub optimal cytoreduction (residual tumour of 1 cm maximum diameter or less).

Reference standard not reported, but was presumably the findings of laparotomy / surgical staging

Tests:

CT (Hi Speed Nx/i Pro, G.E.)

CT prediction index for sub optimal cytoreduction, incorporating age CA-125 level and ECOG performance status

ROC curves for 2 models presented. Authors do not suggest the appropriate cut-off score for their model, but TP, FP, FN and FP can only be calculated using model 2 and prediction index score of more than 5.

Follow up:

Not reported

Author(s): Forstner *et al.,* 1995b
Settings: Women with suspected ovarian cancer who were candidates for surgical staging
Participants: 82 women. 43 had CT and 50 MRI. Cytoreduction was optimal in 65 and sub optimal in 17 patients.
Study Design: Prospective observational study
Target Condition: Staging of ovarian cancer; reference standard was histopathology (resected surgical specimens as well as biopsies and lymph node sampling).
Tests: MRI: 1.5T (Signa G.E.), CT: typically using oral, IV and rectal contrast
Follow up: Not reported
Notes: Correlation between MRI stage, CT stage and histopathologic stage is reported

Author(s): Gemer *et al.,* 2009
Settings: Women with FIGO stage III or IV invasive epithelial cancer treated with primary cytoreductive surgery, who had a preoperative CT scan.
Participants: 123 women. FIGO stage III 108/123, FIGO stage IV 15/123. 90/123 had optimal cytoreduction; the remaining 33 had sub optimal cytoreduction.
Study Design: Retrospective multi centre case series
Target Condition:

Prediction of sub optimal cytoreduction (remaining tumour deposits 1 cm or less in maximal diameter). 4 criteria were tested for validity: Nelson, Bristow, Dowdy and Qayyum. The reference standard was the surgical findings reported in the patient's medical records.
Tests: CT, reported using the Nelson, Bristow, Dowdy and Qayyum criteria for prediction of sub optimal cytoreduction. Nelson criteria: sensitivity 64%, specificity 64%, accuracy 64% Bristow criteria (score of 4 or more) : sensitivity 70%, specificity 64%, accuracy 66% Dowdy criteria: sensitivity 33%, specificity 86%, accuracy 73% Qayyum criteria: sensitivity 67%, specificity 57%, accuracy 60%
Follow up: Not reported
Notes: The Dowdy criteria is used in the summary figures of sensitivity and specificity, it was identified as the most accurate

Author(s): Geomini *et al.,* 2009
Settings: Women with adnexal mass before surgery.
Participants: 109 studies were included in the review: reporting on 21750 adnexal masses: 15490 benign, 5826 malignant (27%) and 434 (2%) of borderline malignancy.
Study Design: Systematic review and meta-analysis. The included studies were observational, at least 56% were prospective, in 77% blinding of the pathologist was not mentioned and in 14% verification bias could not be excluded. Literature search included papers published up to 2008
Target Condition: The target condition was ovarian malignancy; the reference standard test was the histopathological diagnosis following surgery.
Tests: Index and comparator tests were diagnostic models predicting malignancy in ovarian masses.

Models had to contain at least two parameters. 83 models were reported in the included studies: incorporating ultrasound parameters, age, menopausal status and CA 125 level. Some models relied on ultrasound parameters only (Sassone, Alcazar, Lerner, Ferrazzi, DePriest) others included additional parameters such as age, CA-125 level, and menopausal status (RMI I to IV, Tailor) The model with the optimal combination of sensitivity and specificity was the RMI I: sensitivity 78% (95% CI 71 to 85%), specificity 87% (95% CI 83 to 91%) to with a cut-off value of 200). See evidence summary for the estimated accuracy of models for prediction of malignancy on ultrasound parameters.
Follow up: Not applicable.

Author(s): Henrich *et al.,* 2007
Settings: Women with clinically suspected ovarian cancer, who received a preoperative TVS and had an exact description of intra-operative findings.
Participants: 39 women. FIGO stage I 23%, stage II 8%, stage III 64%, stage IV 5%.
Study Design: Prospective case series, single institution
Target Condition: Preoperative staging of ovarian cancer (identification of metastases and or tumour involvement in various anatomical structures). The reference standard was intra-operative findings and histopathology of surgical specimens.
Tests: Transvaginal ultrasound (using colour and power Doppler in addition to the conventional mode)
Follow up: Not reported

Author(s): Jung *et al.,* 2010
Settings:

Women with advanced ovarian cancer treated with surgery at the same institution (by the same surgeon) between 1999 and 2008.
Participants: 77 women, all were FIGO stage IIIC or IV. 30/77 had optimal cytoreduction and 47/77 suboptimal cytoreduction. Korea
Study Design: Retrospective case series
Target Condition: The target condition was optimal cytoreduction, defined as the largest remaining tumour nodule less than 1cm in diameter The reference standard was the postoperative record including the measurement of any remaining peritoneal implants.
Tests: The index test was preoperative multi detector CT. Radiologists determined the presence or absence of the following criteria on the axial plane of the CT scan: 1. Extra-peritoneal disease (except for isolated pleural effusion) 2. Involvement of the *porta hepatis* 3. Para-aortic lymph node metastasis above the level of the left renal vein 4. Sub-diaphragmatic peritoneal implant larger than 2cm 5. Diffuse sub-diaphragmatic peritoneal thickening 6. Upper abdominal ascites above the level of the left renal vein 7. Nodularity in the sub-diaphragmatic peritoneum 8. Implants in the gastro-transverse meso-colon-splenic space 9. Implants in the hepatorenal recess.
Notes: Identified in update search.

Author(s): Kebapci *et al.,* 2010
Settings: Women referred to a single gynaecological oncology clinic with the finding of a pelvic mass suspicious for ovarian cancer between 2003 and 2008. All patients had abdominal / pelvic CT

before surgery for cytoreduction and staging. All had histopathological diagnosis of ovarian cancer.
Participants: 48 women with ovarian cancer. Histological type was serous in 37/48, mucinous in 3/48, endometrioid in 5/48 and 3 other types. FIGO stage was I in 11/48, II in 2/48, III in 30/48 and IV in 4/48.
Study Design: Retrospective case series
Target Condition: Target condition was prediction of optimal cytoreduction (< 1cm maximal diameter of any residual tumour). The reference standard was explorative laparotomy and surgical staging within 2 weeks of CT scan.
Tests: The index test was preoperative CT scab. The imaging field covered the area between the dome of the diaphragm and the *pubis symphysis*. Oral and IV contrast agents were used in all cases. Detailed criteria for a CT scan predicting suboptimal cytoreduction were presented in the study. These included findings in any of 15 specific anatomical areas. The CT imaging criteria predicted 18 patients would have optimal cytoreduction, but 3 of these 18 had suboptimal cytoreduction. The CT imaging criteria predicted 30 patients would have suboptimal cytoreduction, but 3 of these 30 had optimal cytoreduction.
Notes: Identified in update search.

Author(s): Kinkel *et al.,* 2005
Settings: Studies of MRI, CT or colour Doppler US as a second test in women with suspected ovarian cancer, following an indeterminate grey-scale ultrasound. Published between 1980 and 2002.
Participants: 3 CT studies, 14 MRI studies and 8 US studies included
Study Design:

Systematic review and meta-analysis
Target Condition: Ovarian cancer. Reference standard was histopathologic findings.
Tests: Combined grey-scale and colour Doppler ultrasonography, MRI (separate analysis for contrast enhanced and un-enhanced) and CT.
Follow up: Not reported

Author(s): Kitajima *et al.,* 2008
Settings: Women with ovarian cancer, who received primary cytoreductive surgery
Participants: 40 women. FIGO stage I 18/40, stage II 7/40, stage III 14/
Study Design: Prospective study, single institution
Target Condition: Target condition was prediction of metastasis at 17 specific anatomical locations. Reference standard was histopathological evaluation of cytoreductive surgery or biopsy specimens from the 17 specific anatomical locations.
Tests: CT (PET/CT was also investigated, but the results are not included in this review)
Follow up: Not reported

Author(s): La Fianza *et al.,* 1992
Settings:

Women with primary or recurrent epithelial ovarian cancer
Participants: 58 women, FIGO stage I 26%, stage II 3%, III 55%, IV 16%. 24% of women had pelvic lymph node metastases, 39% of women had para-aortic lymph node metastases.
Study Design: Retrospective case series, single institution
Target Condition: Identification of pelvic or para-aortic lymph node metastases. Reference standard was the histopathologic results of lymphadenectomy. Systematic pelvic lymphadenectomy was performed in all patients. Systematic para-aortic lymphadenectomy was performed when imaging was negative, selective para-aortic lymphadenectomy was performed if imaging was positive.
Tests: Index tests were CT (Somatom 2, Siemens) and lymphography
Follow up: 12 months

Author(s): Liu *et al.,* 2007
Settings: Women with adnexal mass (not discovered during screening for ovarian cancer), who had ultrasound, CT or MRI before surgery.
Participants: 69 studies with 6364 patients. Ultrasound was evaluated in 65 studies with 126 data sets, of these 54 articles with 58 data sets (5524 patients) used morphologic information alone. Colour/power Doppler were used in 42 studies. Combined morphologic and colour/power Doppler were used in 7 studies. Literature search included papers published between 1990 and 2006. Menopausal status was mentioned in 34/69 studies. There were 2016/3125 (64.5%) premenopausal women in these 34 studies. At least 49% of studies were prospective, at least 53% of studies used blinded interpretation of test results but reporting of the study population was inadequate in 36% of the studies. Prevalence of malignant tumours was 24%.
Study Design: Systematic review and meta-analysis

Target Condition:

Target condition was identification of malignancy in adnexal mass, the reference standard was histopathology of the adnexal mass.

Tests:

Ultrasound

Any ultrasound: sensitivity 89% (95% CI 88 to 90%), specificity 84% (82% to 86%)

Morphologic assessment ultrasound: sensitivity 85% (95% CI 83 to 87%), specificity 83% (81% to 85%)

Colour Doppler flow imaging: sensitivity 75% (95% CI 72 to 77%), specificity 73% (71% to 75%)

Combined Doppler and morphologic US: sensitivity 87% (95% CI 85 to 90%), specificity 88% (85% to 91%)

Contrast enhanced US: sensitivity 90% (95% CI 87 to 93%), specificity 89% (87% to 91%)

MRI (11 articles with 13 data sets, N=not reported)

MRI sensitivity 89% (95% CI 88% to 92%), specificity 86% (95% CI 84% to 88%)

CT (4 articles with 4 data sets, N=not reported)

CT sensitivity 85% (95% CI 83% to 86%), specificity 86% (95% CI 72% to 92%)

Follow up:

not applicable

Notes:

The review does not report the setting of each study (primary, secondary or tertiary care), unclear what diagnostic tests women had already had before the ultrasound.

Author(s): Medeiros *et al.,* 2009

Settings:

Women with clinically suspected adnexal mass, evaluated using 5 MHz transvaginal probe ultrasonography with colour Doppler, who went on to have histopathological analysis of the adnexal mass.

Participants:

12 studies included (2398 women): 7 were prospective studies, all were non-blinded. Prevalence of malignant tumours was 20% and borderline tumours 3%. Literature search included studies published between 1990 and 2007.

Study Design:

Systematic review and meta-analysis.

Target Condition:

The target condition was the identification of malignancy in adnexal masses. The reference standard was histopathology in all cases.

Tests:

Transvaginal colour Doppler ultrasound (resistance index of 0.5 or less) for malignant/borderline tumours versus benign tumours.

Pooled sensitivity was 84% (95% CI 84% to 90%)

Pooled specificity was 89% (95% CI 84% to 90%)

Follow up:

Not applicable.

Notes:

Uncertain US results were excluded from the analysis (would inflate the estimates of diagnostic accuracy). The setting of each study is not reported (primary, secondary or tertiary care).

Author(s): Meyer *et al.,* 1995

Participants:

28 patients who received primary cytoreductive surgery for epithelial ovarian cancer. FIGO stages at diagnosis were I (8 patients), II (2 patients), stage III (13 patients) and stage IV (5 patients).

Study Design:

Retrospective single institution case series

Target Condition:

Target conditions were identification of metastatic disease and prediction of optimal cytoreductive surgery (all remaining tumour deposits reduced to less than 2 cm in diameter), reference standard was surgical findings.

Tests:

CT (Siemens Somatom or Picker 1200).

Five regions were analysed for evidence of metastatic disease: omentum, liver, small bowel mesentery, para-aortic nodes and diaphragm and lung base.

Follow up: Not reported

Author(s): Myers *et al.,* 2006
Settings: Four clinical settings: patients with suspected adnexal masses, patients with adnexal masses, patients with suspected benign adnexal masses and patients with suspected malignant adnexal masses.
Participants: 14 studies examined pelvic examination, 153 studies ultrasound, Almost all studies were case series, although 13 population based screening studies were also included.
Study Design: Systematic review
Target Condition: Target condition was detection of adnexal mass, discrimination of malignant from benign adnexal masses,
Tests: Bimanual pelvic examination, ultrasound morphology (Sassone.DePriest, Ferrazzi, Finkler or other scoring systems), ultrasound Doppler (resistance index, pulsatility index and maximum systolic velocity), combined morphology and Doppler, MRI, CT, FDG-PET, serum tumour markers (CA-125

Author(s): Nelson *et al.,* 1993
Settings: Women with epithelial ovarian cancer who had preoperative abdominopelvic CT and primary exploratory laparotomy.
Participants: 42 women. 81% had stage III or stage IV
Study Design: Retrospective case series, single institution

Target Condition:

Prediction of optimal cytoreduction (defined as remaining tumour deposits less than 2cm diameter). Diagnostic accuracy for metastases in mesentery, diaphragm, liver, omentum to spleen, *porta hepatis* and lymph nodes.

The reference standard was the findings of exploratory laparotomy recorded in patient records.

Tests:

CT, performed on a variety of machines, using oral and IV contrast.

Follow up:

Not reported

Author(s): Qayyum *et al.,* 2005

Settings:

Women treated with cytoreductive surgery for epithelial ovarian cancer at a single institution in a 9 year period.

Participants:

137 women. 26, 6, 94 and 11 patients were classified as FIGO stag I,II,III and IV respectively.

Study Design:

Retrospective single institution case series

Target Condition:

The target condition was optimal cytoreduction. The adequacy of cytoreduction was determined from operative reports. The criterion of adequate cytoreduction was the reduction of all tumour sites to less than 2cm in maximum diameter.

Tests:

Index tests were CT (N=91) , MRI (N=46) and CT+MRI (N=137)

Follow up:

Not reported

Author(s): Ricke *et al.,* 2003

Settings: Women with suspected primary or recurrent ovarian malignancy, who had MRI at a single institution between 1998 and 2001.
Participants: 57 women with suspected primary (18/57) or suspected recurrent ovarian cancer (39/57). 28/57 patients had lymph node involvement. 27/57 patients had diffuse carcinomatosis, 34/57 had upper abdomen metastases, 40/57 bowel involvement, 31/57 lower pelvis involvement, 30/57 abdominal wall involvement.
Study Design: Prospective consecutive case series
Target Condition: Detection of intra-abdominal malignancy, reference standard was laparotomy findings and histopathology (if available).
Tests: MRI: contrast enhanced, fat saturated T1 SE, 1.5T Magnetom SP 63 (Siemens) using body coil. Detailed results for 17 potential intra-abdominal tumour locations are reported, as well as 5 groups of tumour locations: upper abdomen, bowel, lower pelvis, abdominal wall, lymph nodes and diffuse peritoneal carcinomatosis.
Follow up: Post operative follow up not reported.

Author(s): Sokalska *et al.,* 2009
Settings: Women with one or more adnexal masses entered into the International Ovarian Tumor Analysis Study (IOTA) at any of nine participating centres.
Participants: 1066 women. 800/1066 had benign tumours and 266 malignant tumours. 144/1066 women had primary invasive malignant tumours.
Study Design: Prospective diagnostic accuracy study.

Target Condition:

The study presents diagnostic accuracy for nine classes of benign tumour and four classes of malignant tumour. The reference standard was the histology of the surgically removed adnexal tumour.

Tests:

Index test was transvaginal ultrasound (transabdominal sonography was done if large masses could not be visualized via the transvaginal route). On the basis of subjective grey-scale and colour Doppler findings the ultrasound examiner classified the mass as: certainly benign, probably benign, difficult to classify as benign or malignant (but examiners had to choose benign or malignant), probably malignant and certainly malignant.

Diagnostic accuracy (for primary invasive tumours)

Sensitivity 72% (95% C.I. 64 to 78%), specificity 94% (93% to 96%)

Notes:

Identified in update search.

Author(s): Sugiyama *et al.,* 1995

Settings:

Women with ovarian carcinoma (including tumours of low malignant potential.

Participants:

95 women with ovarian cancer. 72/95 patients were negative for lymph node metastases. FIGO stage I 55%, stage II 6%, stage III 35%, stage IV 4%.

Study Design:

Retrospective case series, single institution

Target Condition:

Identification of malignant lymph nodes.

The reference standard was postoperative histology.

Tests:

CT (TCT-60A, Toshiba). Lymph nodes 1.5 cm or larger on CT were classified malignant.

Author(s): Tempany *et al.,* 2000

Settings: Patients with suspected ovarian cancer on the basis of pelvic examination and/or imaging. All patients must have completed at least two of the three imaging examinations (CT, US or MRI) 4 weeks before full pelvic/abdominal surgery or surgical exploration.
Participants: 280 women. 118/280 had malignancy. Final stage was III or more in 73/118 (62%).
Study Design: Prospective multi centre observational study.
Target Condition: Target condition: reference standard was a combination of surgical and histopathological findings. Surgical protocol varied and imaging results were used to plan each procedure.
Tests: Ultrasound: grey scale - transvaginal and transabdominal probes. CT, of pelvis and abdomen MRI, of pelvis using pelvic multi coil array if possible, and abdomen using body coil.

Author(s): Testa *et al.,* 2006
Settings: Women treated with surgery for suspicious pelvic masses at a single institution between 2001 and 2004
Participants: 184 women. 145/180 patients had malignancy.
Study Design: Retrospective case series
Target Condition: Omental metastases, reference standard was histology
Tests: Index test was transabdominal ultrasonography

Follow up:

No follow up beyond surgery reported.

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3.4 Tissue diagnosis

"*For women with suspected advanced ovarian cancer, when is it appropriate not to have a tissue diagnosis before starting chemotherapy?*"

Short summary:

There were no studies comparing the outcomes of women with suspected versus confirmed advanced ovarian cancer treated with chemotherapy. Evidence from case series suggests a minority of women with presumed advanced ovarian cancer on the basis of clinical and imaging findings will not have ovarian cancer (Griffin *et al.,* 2009).

Cytomorphology combined with immunocytochemistry had a rate of definitive diagnosis of primary tumour site in malignant effusions ranging from 57% to 87%. In comparison histopathology plus immunohistochemistry had a diagnostic rate between 93% and 97%.

There were no data about complications of effusion cytology. Percutaneous core biopsy was associated with minor local bruising and discomfort. Minor complications were reported in less than two percent of laparoscopies from four series with 1284 patients (including cases with non-malignant aetiology). Major complications occurred at a rate of less than one percent.

Review Protocol:

Question

For women with suspected advanced ovarian cancer, when is it appropriate not to have a tissue diagnosis before starting chemotherapy?

Objectives

Study inclusion criteria

- **Studies:** Any study design
- **Participants:** Women with suspected advanced ovarian cancer.
- **Index tests:** Histopathology (laparoscopy or image guided biopsy) or cytology
- **Target conditions:** Diagnosis of ovarian cancer
- **Reference standards:** Histopathology

Search strategy

The following electronic databases were searched: Medline, PreMEDLINE, EMBASE, Cochrane Library, CINAHL, BNI, PsycINFO, AMED, Web of Science (SCI & SSCI) and Biomed Central.

Papers were also identified from a review of histology versus cytology in patients presenting with ascites, done for the NICE Cancer of Unknown Primary clinical guideline (2010).

Review strategy

The titles and abstracts of the studies identified in the literature search were screened for potentially relevant studies by one reviewer (NB).

Search results:

The literature searches identified 132 potentially relevant studies, of which 19 were eventually included.

Study quality:

The methodological quality is summarised in Figure 3.26. Few studies were in directly relevant populations. The methodological quality was generally low: most papers were case series and not designed as prospective diagnostic studies.

Evidence summary:

Biopsy before chemotherapy in presumed advanced ovarian cancer

The literature searches found no studies which compared pre-treatment biopsy versus no pre-treatment biopsy in women treated with chemotherapy for presumed advanced ovarian cancer. Indirect evidence came from studies reporting the final diagnosis in women presenting with clinical and imaging findings consistent with advanced ovarian cancer, who were not candidates for surgery (see Table 3.5).

The most applicable evidence came from three UK case series of image guided biopsy (Griffin *et al.,* 2009; Hewitt *et al.,* 2007 and Spencer *et al.,* 2001), including 208 women in total and one Canadian case series (Freedman *et al.,* 2010). The prevalence of epithelial ovarian cancer, or primary peritoneal carcinomatosis, ranged from 81% to 96% in these series. Between 2% and 17% of the women in these studies had a non ovarian malignancy. If tissue diagnosis was omitted before treatment these women would have received inappropriate ovarian cancer chemotherapy. The decision whether or not to biopsy before chemotherapy in this group requires a judgement about of the relative importance of the harms of biopsy and the harms of sub-optimal treatment for the minority of women without ovarian cancer.

Freedman *et al.* (2010) reported that when the initial diagnosis of epithelial ovarian cancer was based on clinical factors alone (including radiology, serum CA125 levels and clinical presentation) 13% of patients had an alternate final diagnosis.

Evidence could come from the ongoing CHORUS randomised trial of neoadjuvant chemotherapy versus upfront surgery. Patients randomised to the neoadjuvant chemotherapy arm, who have not had confirmation of cancer prior to randomisation, are required to have histological or cytological confirmation of their disease prior to starting chemotherapy. Both Griffin *et al.* (2009) and Hewitt *et al.* (2007) reported performing image guided biopsies on women entered into the neoadjuvant chemotherapy arm of this trial.

McCluggage *et al.* (2002) described morphological changes following neoadjuvant chemotherapy in tissue samples from 18 women with advanced epithelial ovarian cancer. They recommended that pre-chemotherapy biopsies were essential for accurate tumour typing and grading.

Diagnostic yield of image guided biopsy versus effusion cytology

Diagnostic yield (the proportion of biopsy procedures sufficient to make a diagnosis) is summarised in Table 3.6.

Image guided biopsy (histology plus immunohistochemistry)

Two studies originating from the same UK gynaecologic oncology centre (Hewitt *et al.*, 2007 and Spencer *et al.,* 2001) reported the use of image guided percutaneous core needle biopsy in women with peritoneal carcinomatosis of unknown origin. A definitive diagnosis was made on the basis of

histopathology and immunohistochemistry in 97% of cases in Spencer *et al.* (2001) and in 93% of cases in Hewitt *et al.* (2007).

Griffin *et al.* (2009) reported a diagnostic yield of 87% for image guided core needle biopsy in their series of women with a clinical diagnosis of ovarian cancer, recommended for neoadjuvant chemotherapy by gynaecological oncologists.

Technical failure or sample inadequacy meant that secondary intervention was required to obtain tissue for diagnosis in all of these series. The rate of repeat percutaneous or surgical biopsy ranged from 3% (Spencer *et al.,* 2001) in to 12% (Griffin *et al.,* 2009).

Effusion cytomorphology alone

Longatto-Filho *et al.* (1995) conducted a blinded study of serous effusions from 208 women with metastatic adenocarcinoma. They examined the ability of 11 cytomorphologic parameters to discriminate between breast, ovary, stomach and lung primary tumours. No combination of morphological parameters was specific enough to allow the diagnosis of the primary site of adenocarcinoma.

Spencer *et al.* (2001) reported a blinded cytological analysis of malignant ascites of unknown origin, in which a definitive diagnosis of ovarian cancer was made on the basis of cytology in 3/19 cases (two were confirmed by histopathological analysis, one was false positive).

Cytomorphology plus immunohistochemistry

All but one of the studies reporting the combined use of cytomorphology and immunocytochemistry included patients with any malignant serous effusion (peritoneal, pleural and sometimes pericardial effusions). Therefore these studies included a wider range of primary tumour sites which in turn is likely to inflate the estimates of diagnostic accuracy.

Mottolese *et al.* (1988) reported the use of immunocytochemistry in patients with pleural or peritoneal effusions and unknown primary tumour. Using a panel of 5 monoclonal antibodies a definitive diagnosis was made in 56/60 cases (87%), confirmed by clinical follow up in 53/60 cases. In a follow up to their earlier Mottolese *et al.* (1992) used a panel of ten monoclonal antibodies and reported a definitive diagnosis rate of 103/125 (82%).

Pomjanski *et al.* (2005) reported a correct diagnosis of primary tissue of origin in 86/101 (85%) of patients with effusions and cancer of unknown primary syndrome.

In Longatto-Filho *et al.* (1997), cytomorphology plus immunocytochemistry (panel of 2 monoclonal antibodies) led to a correct diagnosis of the primary tissue of origin adenocarcinoma in 119/208 (57%) women with metastatic serous effusions.

DiBonito *et al.* (1993) reported that the cytologic prediction of histotype was correct in 12/15 (80%) patients with pancreatic primary tumour, and in 25/36 (69%) patients with ovarian primary. For other tumour types cytology was less accurate, but no figures were provided.

None of the cytology papers explicitly reported the rate of surgical biopsy to obtain tissue for diagnosis. If tissue biopsies were required in cases when cytology and immunocytochemistry failed to give a definitive diagnosis the secondary biopsy rate would have ranged from 13 to 43 percent.

Harms of biopsy

Harms are summarised in Table 3.7. There was no data about complications due to fine needle aspiration or paracentesis of ascites for effusion cytology, as no cytology studies reported this outcome.

There was no direct evidence about the harms of diagnostic laparoscopy or laparotomy in women with suspected advanced ovarian cancer due to receive chemotherapy. Indirect evidence comes from studies reporting diagnostic laparoscopy in patients with ascites of unknown origin (Dedioui *et al.,* 2007, Chu *et al.,* 1994 and Yoon *et al.,* 2007). Minor complications were reported in less than two percent of laparoscopies from four series with 1284 patients (including cases with non-malignant aetiology). Major complications occurred at a rate of less than one percent, although one series (Chu *et al.*, 1994) observed intestinal perforation due to laparoscopy in six percent of patients with peritoneal tuberculosis.

Percutaneous core biopsy was associated with minor complications, such as local bruising and discomfort (Fisherova *et al.,* 2008, Griffin *et al.,* 2009, Hewitt *et al.,* 2007, Pombo *et al.,* 1997, Spencer *et al.,* 2001). Fischerova *et al.* (2008) reported one instance of bleeding which required laparotomy following core needle biopsy of an ovarian mass.

A recognised complication of needle biopsy and laparoscopy is tumour seeding in the needle tract or trocar site, but this outcome was poorly reported in the studies. Spencer *et al.* (2001) reported no clinically apparent needle tract metastases during follow up. Hewitt *et al.* (2007) reported that the rate of subcutaneous tumour deposits was unchanged since the introduction of image guided core biopsy in their institution, but no supporting figures were given.

Table 3.5 Final diagnosis in women with suspected advanced ovarian cancer [Back]

Study and country	N	Inclusion criteria	Epithelial ovarian cancer*	Non-ovarian malignancy	Benign, or low malignant potential	Meosthelioma	Tuberculosis	No final diagnosis
Faulkner 2005. UK	14	Provisional diagnosis of ovarian cancer, unsuitable for surgery, tumour amenable to transvaginal biopsy	50%	14% GI primary tumour, 7% breast cancer, 7% sarcoma	0%	0%	0%	14%
Freedman 2010. Canada	149	Women treated with neoadjuvant platinum based chemotherapy following an initial diagnosis of ovarian cancer	96%	1% uterine carcino-sarcoma 1% GI cancer	2%	0%	0%	0%
Griffin 2009. UK	60	Clinical diagnosis of ovarian cancer, recommended for neoadjuvant chemotherapy and IGB	95%	2% SCC (probable lung origin)	0%	2%	0%	2%
Hewitt 2006. UK	121	Peritoneal carcinomatosis, with presumed ovarian cancer and unsuitable for surgery or where clinical/radiological impression is not of ovarian primary	81% (Mullerian tumour)	5% GI cancer 4% poorly differentiated tumour 3% breast cancer 2%	2%	0%	0%	0%

				lymphoma 3% other				
Spencer 2001. UK	27	Peritoneal carcinomatosis, with presumed ovarian cancer and unsuitable for surgery (25/27) or where clinical/radiological impression was not of ovarian primary (2/27)	92%	4% colorectal cancer 4% lymphoma	0%	0%	0%	0%
Milingos 2007. Greece	9	Unexplained ascites following initial investigations and pre-operative diagnosis of malignancy	50%	0%	0%	0%	33%	17%

Abbreviations: IGB, image guided biopsy; SCC, squamous cell carcinoma.

Table 3.6 Diagnostic yield of image guided biopsy and effusion cytology [Back]

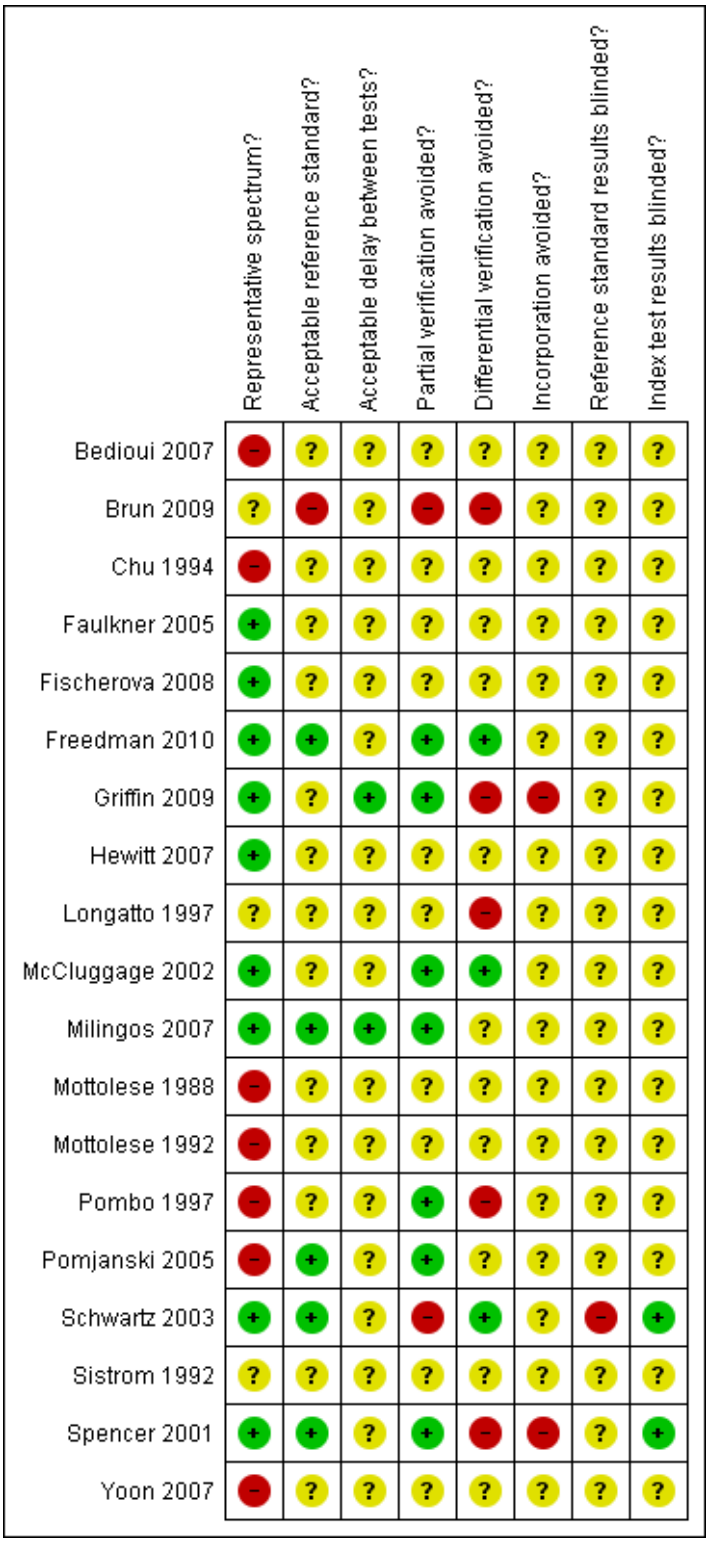
Study	N	Biopsy type	Diagnostic yield (primary tumour site)	Sample inadequacy	Rate of secondary intervention to obtain tissue for diagnosis
Griffin 2009	60	Percutaneous US or CT guided core needle biopsy	87%	13%	12% surgical biopsy
Hewitt 2007	149	Percutaneous US or CT guided core needle biopsy + immunohistochemistry (panel of at least 4 antibodies)	93%	7%	7% repeat percutaneous biopsy
Spencer 2001	35	Percutaneous US or CT guided core biopsy + immunohistochemistry (panel of at least 4 antibodies)	97%	3%	3% surgery
Pombo 1997	25	Percutaneous CT guided core biopsy (pathological analysis not reported)	Diagnosis was not more detailed than metastatic adenocarcinoma	4%	1/25 (4%) required a repeat biopsy procedure.
Fischerova 2008	90	Percutaneous US guided core biopsy (pathological analysis not reported)		7%	7% surgical biopsy 4% repeat percutaneous biopsy

Schwartz 2003	60	Effusion cytology (Pap staining)	89% (epithelial ovarian cancer versus not epithelial ovarian cancer)	2%	N.R.
Spencer 2001	19	Effusion cytology	2/19 (11%)	N.R.	N.R.
Longato-Filho 1995	208	Effusion cytology + immunocytochemistry (2 antibodies)	119/208 (57%)	N.R.	N.R.
Mottolese 1988	60	Effusion cytology + immunocytochemistry (6 antibodies)	52/60 (87%)	N.R.	N.R.
Mottolese 1992	125	Effusion cytology + immunocytochemistry (10 antibodies)	103/125 (82%)	N.R.	N.R.
Pomjanski 2005	101	Effusion cytology + immunocytochemistry (6 antibodies)	86/101 (85%)	Only specimens with sufficient tumour cells included in the study.	N.R.

Table 3.7 Harms of biopsy [Back]

	N	Biopsy type	Minor complications	Major complications	Tumour seeding to biopsy site	Mortality
Griffin 2009	60	Percutaneous US or CT guided core needle biopsy	0%	0%	0%	0%
Spencer 2001	35	Percutaneous US or CT guided core needle biopsy, plus IHC	0%	0%	Not reported	0%
Hewitt 2007	149	Percutaneous US or CT guided core needle	Minor local bruising and discomfort. 1/149 (<1%) rectus sheath haematoma.	0%	Authors note that the rate did not increase with IGB	0%
Pombo 1997	25	Percutaneous CT guided core needle	0% within 24 hours of biopsy.	0%	Not reported	0%
Fischerova 2008	86	Percutaneous US guided core needle	0%	1/86 bleeding from ovarian mass requiring laparotomy	Not reported	Not reported
Bedioui 2007	90	Laparoscopy	1/90 (1%) leakage of ascites	0%	Not reported	0%
Chu 1994	129	Laparoscopy	2/129 (2%) leakage of ascites 2/129 (2%) subcutaneous emphysema 1/129 (1%) wound infection	Intestinal perforation in 2/31 (6%) patients with tuberculous peritonitis	Not reported	0%
Yoon 1997	855	Laparoscopy	N.R.	6/855 (0.7%) biopsy site bleeding 2/855 (0.2%) liver laceration 1/855 (0.1%) spleen laceration 1/855 (0.1%) pneumothorax	Not reported	0%

Figure 3.26 Summary of methodological quality [Back]



Evidence tables:

Author(s): Bedioui *et al.,* 2007
Settings: Patients presenting with isolated ascites of unknown aetiology that had laparoscopy, over a 10 year period (1996 to 2006). Before laparoscopy patients received tests for tuberculosis including chest X-ray, and direct examination of sputum, urine, gastric products and ascites. Women received gynaecological examination with pelvic ultrasound. In patients with suspected carcinomatosis work-up included CT scan. All had aspiration of ascitic fluid for cytochemistry and bacteriology.
Participants: 90 patients. Tunisia
Study Design: Prospective case series
Target Condition: Diagnosis of peritoneal tuberculosis versus carcinomatosis. Reference standard was histology of the laparoscopic biopsies.
Tests: Index test was diagnostic laparoscopy including visual inspection and biopsies of peritoneum and liver where possible. The predictive values of atypical cells on cytology and of individual symptoms are also reported.
Follow Up: Not reported
Pathologic analysis: Not reported
Final diagnosis: Malignancy in 31/90 (34%)

Author(s): Brun *et al.,* 2009
Settings: Women with stage III or IV ovarian cancer, before primary therapy
Participants: 55 women, 81% had stage III disease and 19% stage IV
Study Design: Retrospective case series
Target Condition: Prediction of optimal debulking surgery. Reference standard was not reported
Tests: Diagnostic laparoscopy, including biopsies of ovaries or peritoneal metastases
Follow Up: Not reported
Pathologic analysis Frozen section analysis
Final diagnosis Ovarian cancer in all cases (stated in inclusion criteria)
Notes: Women were candidates for surgery; diagnostic laparoscopy was done as a triage for debulking surgery or neoadjuvant chemotherapy. Study does not attempt to estimate the predictive value of laparoscopy, but contains some data about harms.

Author(s): Chu *et al.,* 1994
Settings: Patients with ascites of unknown origin, following ultrasound and CT.
Participants:

129 Patients. Taiwan
Study Design: Retrospective case series.
Target Condition: Diagnosis of the origin of ascites. Visual diagnoses of *carcinomatosis peritonei* were confirmed by either histology or ascitic cytology. Tuberculous peritonitis was confirmed variously by histology, response to chemotherapy or focus of tuberculosis elsewhere. Patients with visual diagnosis of liver cirrhosis or normal looking peritoneum were not biopsied.
Tests: Laparoscopic visual and histological evaluation of ascites. Ascitic cytology.
Follow Up: Not reported
Pathologic analysis: Not reported
Final diagnosis: Malignancy in 67/129 (52%)

Author(s): Faulkner *et al.,* 2005
Settings: Women with clinically suspected ovarian cancer who were not candidates for surgery and who had palpable tumour immediately beneath the vaginal surface with the mass thought to be filling the Pouch of Douglas. CT or US consistent with ovarian cancer was also required.
Participants: 14 women. 10/14 had ascites.
Study Design: Retrospective case series.
Target Condition: Target condition was diagnosis of pelvic tumour. Reference standard was histopathology with further biopsies in some cases.

Tests:

Core needle biopsy (TruCut) - no image guidance: the needle tip was advanced in an axial plane beyond the examining finger.

Follow Up:

Not reported.

Pathologic analysis

Not reported, although results of immunohistochemistry are reported in some cases.

Final diagnosis

7/14 ovarian cancer, 2/14 GI primary tumour, 1/14 breast cancer, 1/14 sarcoma, 2/14 inadequate biopsy sample.

Author(s): Fischerova *et al.,* 2008

Settings:

Women referred for US guided transvaginal or transabdominal core needle biopsy for the following indications: primary inoperable pelvic tumour, poor performance status and recurrent disease requiring histological verification.

Participants:

90 women. Czech Republic.

Study Design:

Prospective case series.

Target Condition:

Diagnosis of tumour malignancy and histological type. No reference standard was reported, presumably histopathology of the biopsy specimen was considered the definitive diagnosis. Some patients had laparoscopy.

Tests:

US guided core needle biopsy: 46/86 (53.5%) transvaginal, and 40/86 (46.5%) transabdominal.

Follow Up:

Not reported.

Pathologic analysis:

Histopathology, H&E staining and unspecified IHC.
Final diagnosis: 54/86 primary ovarian carcinoma, 9/86 ovarian metastases, 23/86 extra-ovarian pathology.
Notes: 4/90 were unsuitable for core needle biopsy (due to tumour location) and were referred for laparotomy or laparoscopy.

Author(s): Freedman *et al.,* 2010
Settings: Women undergoing platinum based neoadjuvant chemotherapy for presumed advanced ovarian cancer, treated at a single institution between 1994 and 2007.
Participants: 149 women. Canada
Study design: Retrospective case series
Target Condition and reference standard: The target condition was epithelial ovarian cancer. The reference standard was histopathology following surgery.
Tests: The initial diagnosis was made on the basis of clinical factors alone in 15 patients. Initial diagnosis was made by cytology in 108 patients (paracentesis in 82 patients, thoracentesis in 9 and fine needle aspirate in 17). Initial diagnosis was made by histology in 26 patients (core needle biopsy in 21 and surgery in 5). The finial diagnosis was consistent with epithelial ovarian cancer in 143/149 women (96%). The remaining 6 final diagnoses were ovarian tumours of low malignant potential (4 cases), uterine carcinosarcoma (1 case) and tumour of gastrointestinal origin (1 case). The diagnostic accuracies of the three strategies (for epithelial ovarian cancer versus not EOC) were 98% cytology, 92% for histology and 87% for clinical. The diagnostic rate for specific epithelial ovarian cancer subtype was 77% for histology and 55% for cytology. When a specific EOC subtype was identified it was consistent with the final diagnosis in 86% of cases for cytology and 80% of cases for histology.
Pathologic analysis: Cytology: 108 patients (paracentesis in 82 patients, thoracentesis in 9 and fine needle aspirate in 17). Specimens were processed using the Thin-Prep systems plus a formalin fixed paraffin embedded cell block. Immunohistochemistry was used at the discretion of the clinical pathologist. Histology: 26 patients (core needle biopsy in 21 and surgery in 5; surgery included dilatation and curettage, sigmoid resection, diagnostic laparoscopy, umbilical mass resection and excisional lymph node dissection). Tissue specimens were formalin fixed, paraffin embedded and stained with haematoxylin and eosin. Immunohistochemistry was used at the discretion of the clinical

pathologist.

Author(s): Griffin *et al.,* 2009
Settings: Women with clinically suspected advanced ovarian cancer or peritoneal carcinomatosis who had US or CT guided percutaneous biopsy between 2002 and 2007 at a single institution. Only women recommended by gynaecological oncologists to receive neoadjuvant chemotherapy were included.
Participants: 60 women. 47 had omental disease, biopsied under US (N=30) or CT (N=17) guidance. 12 patients had a discrete pelvic mass, biopsied under US (N=5) or CT (N=7) guidance. One woman had a CT guided biopsy of an enlarged para-aortic node. UK
Study Design: Retrospective, consecutive case series
Target Condition: Target condition was identification of .Reference standard was histopathological analysis of the biopsy sample. 7/60 women had surgical biopsy due to percutaneous biopsy sample inadequacy.
Tests: US or CT guided percutaneous biopsy. The median number of biopsy per patient was 3 (range 2 to 5).
Follow Up: Median follow-up 30.6 months (range 2.2 to 72.3 months)
Pathologic analysis: Paraffin embedded, H&E staining. IHC panel including CK7, CK20, CA125, CA19-9 and CEA.
Final diagnosis: 58/60 (97%) ovarian malignancy (including primary peritoneal carcinomatosis), 1/60 (1.6%) metastatic squamous cell carcinoma and 1/60 (1.6%) primary peritoneal mesothelioma.

Author(s): Hewitt *et al.,* 2007
Settings:

Women with peritoneal carcinomatosis of unknown origin.
Participants: 149 women (32 had a previous history of malignancy). UK
Study Design: Case series, retrospective.
Target Condition: Identification of the primary site. Histopathology of the core sample was considered the definitive diagnosis.
Tests: Percutaneous core needle biopsy of peritoneum, guided by ultrasound or CT.
Follow Up: Not reported
Pathologic analysis: Biopsy material was embedded in paraffin, sectioned, and H&E stained. Immunohistochemical analysis was performed using monoclonal antibodies to CAE, CK 7, CK 20 and CA125. Additional monoclonal antibodies were used at the discretion of the pathologist.
Final diagnosis: In the 121 women who presented with peritoneal carcinomatosis and no previous malignancy the histological diagnosis was 81% Mullerian tumour, 5% gastrointestinal tumour, 4% poorly differentiated tumour (not otherwise specified, 3% breast primary tumour, 2% lymphoma, 1% pseudomyxoma, 1% hepatobiliary tumour, 1% renal cell tumour and 2% benign.
Notes: Not diagnostic accuracy study, since histopathology of the core sample was considered definitive

Author(s): Longatto *et al.,* 1997
Settings: Women with metastatic serous effusions and primary adenocarcinoma, selected from the hospital records of a single cancer hospital.
Participants:

208 women. Brazil
Study Design: Retrospective case series.
Target Condition: Histotype of the primary tumour (breast, ovary, lung or stomach). Reference standard was clinical, radiologic and histological evidence of primary tumour.
Tests: Cytomorphology (11 parameters considered) and immunocytochemistry (CK7 and CK20 reactivity).
Follow Up: Not reported
Pathologic analysis: The smeared sample was stained with Papanicolaou stain for morphological analysis. Immunocytochemistry (CK7 and CK20 reactivity).
Final diagnosis: All had malignancy.
Notes: Known cases were selected for inclusion, likely to bias results in favour of the index test.

Author(s): McCluggage *et al.,* 2002
Settings: Histological sections were examined from 18 cases of ovarian carcinoma that had been treated by preoperative chemotherapy. The morphology was compared with any pre-chemotherapy biopsies that had been performed.
Participants: 18 cases. In 9 cases both pre-chemotherapy and post chemotherapy samples were available. Chemotherapy was typically carboplatin plus taxane.
Study Design: Retrospective review of pathology samples.

Target Condition: Identification of morphological changes
Tests: Histopathology, from needle biopsies or small biopsies of tumour obtained at laparotomy The authors note pronounced stromal changes following chemotherapy including: fibrosis, inflammation, collections of foamy histiocytes, cholesterol cleft formation, haemosiderin deposition, fat necrosis, and dystrophic calcification, including the presence of many free psammoma bodies.
Pathologic analysis Histopathology, IHC not reported
Final diagnosis Not applicable (ovarian cancer in all cases)
Notes: Authors conclude that accurate tumour typing and grading is difficult following chemotherapy, making it important that pre-chemotherapy tissue biopsies are obtained

Author(s): Milingos *et al.,* 2007
Settings: Women with unexplained ascites, following complete history and physical/pelvic examination, blood and urine biochemistry, tumour markers and abdominal / pelvic US.
Participants: 73 women were referred with diffuse ascites, and 9 had no firm diagnosis following the initial work-up. 6/9 had a provisional diagnosis of peritoneal malignancy - only their results will be included in this appraisal.
Study Design: Retrospective cases series
Target Condition: Diagnosis of the cause of ascites. Reference standard was laparoscopy with intraoperative frozen section analysis and histopathology.
Tests: Index test was the pre-laparoscopy diagnostic work-up: however the laparoscopy results are only

reported for those with ascites of uncertain cause.
Follow Up: Not reported
Pathologic analysis Intraoperative frozen section analysis, then histopathology and immunohistochemistry
Final diagnosis In the 6 women with provisional diagnosis of malignancy, 3/6 (50%) had serous papillary ovarian cancer or primary peritoneal carcinomatosis, 1/6 Kruckenberg tumour of unknown primary, 2/6 (33%) had peritoneal miliary tuberculosis In the entire cohort of 73 women referred with diffuse ascites the pre-laparoscopic diagnosis was 58.9% gynaecologic malignancy, 12.3% GI malignancy, 6.8% liver cirrhosis, 4.1% congestive heart failure, 2.7% pancreatitis, 2.7% nephrotic syndrome and 12.3% unidentified cause.

Author(s): Mottolese *et al.,* 1988
Settings: Patients with malignant effusions of unknown origin. Patients with known malignancy and patients with benign effusions were also included, to develop the immunocytochemical protocol.
Participants: 60 patients with unknown primary cancer. 23 with proven benign effusions and 65 with known malignancy. Italy.
Study Design: Retrospective case series.
Target Condition: Primary tumour site (organ of origin). Reference standard was clinical follow up
Tests: Cytology plus immunocytochemistry (6 antibodies: B72.3, B6.2, MBRI, MOv19, OC-125, KS1/4).
Follow Up: Not reported
Pathologic analysis

The sample was centrifuged then the sediment was smeared and stained with Papanicolaou and Giemsa stains. Immunocytochemistry (6 antibodies: B72.3, B6.2, MBRI, MOv19, OC-125, KS1/4).
Final diagnosis 125/148 (85%)
Notes: Known cases and controls would tend to bias in favour of the index test

Author(s): Mottolese *et al.,* 1992
Settings: Patients with malignant effusions (pleural and/or peritoneal)
Participants: 135 patients with unknown primary tumour (44 men and 91 women). 179 patients with known primary tumour (not included in this appraisal). Italy
Study Design: Retrospective case series
Target Condition: Identification of the primary tumour. Reference standard is not reported
Tests: Cytology and immunocytochemistry (panel of 10 monoclonal antibodies)
Follow Up: Not reported
Pathologic analysis The sample was centrifuged then the sediment was smeared and Papanicolaou stained. Immunocytochemistry (panel of 10 monoclonal antibodies). Samples with a low proportion of tumour cells were also short-term cultured for 6 to 8 days.
Final diagnosis Malignancy in 125/135 (93%)
Notes:

Short term culture of the tumour cells improved the sensitivity of cytology + ICC

Author(s): Pombo *et al.,* 1997
Settings: Patients referred for CT guided biopsy of omental lesions and with no clinical or radiological evidence of primary tumour or infectious or inflammatory condition that could be responsible.
Participants: 25 patients with focal (N=2) or diffuse (N=23) omental pathology. Spain
Study Design: Retrospective case series.
Target Condition: Specific diagnosis of malignancy. Reference standard was either histopathology of the resected tumour, laparoscopic biopsy or endoscopic biopsy; or clinical follow up.
Tests: CT guided biopsy of omental lesions: core biopsy (N=16) and other biopsy (N=9).
Follow Up: Patients monitored for 24 hours for acute complications. Longer term follow up not reported
Pathologic analysis Histopathology, not specified in detail. Some non-core samples were obtained and were smeared on glass for analysis, presumably cytopathology.
Final diagnosis 13/25 peritoneal carcinomatosis secondary to ovarian cancer or unidentified primary, 2/25 appendix primary tumour, 1/25 stomach primary tumour, 1/25 hepatocellular carcinoma, 1/25 lymphoma, 5/25 tuberculosis and 1/25 actinomycosis.
Notes: Series included 7 men, but the results were not reported by gender.

Author(s): Pomjanski *et al.,* 2005

Settings: Patients with cytologically positive effusions, with sufficient tumour cells in effusion and non-small cell carcinoma morphology.
Participants: 180 patients. Effusions were: pleural (118/180, 66%), peritoneal (53/180, 29%) and pericardial (5%). Germany
Study Design: Retrospective case series
Target Condition: Identification of the primary tumour site (breast, ovary, lung, colon, stomach, pancreas or other). Reference standard was clinical follow up or histology.
Tests: Cytology plus immunocytochemistry with 6 tumour markers (CK 5/6, CK 7, CK 20, CA 125, TTF1, Cdx 2)
Follow Up: Not reported
Pathologic analysis The sample was centrifuged then the sediment was smeared and stained according to May-Grunewald Giemsa and Papanicolaou.
Final diagnosis All had malignancy
Notes: Only patients with sufficient tumour cells were included: bias in favour of cytology. Algorithm for use of tumour markers is presented.

Author(s): Schwartz *et al.,* 2003
Settings: Women treated with neoadjuvant chemotherapy for clinically apparent advanced ovarian cancer, who also had pre-treatment cytology slides available for review.

Participants: 72 women. Pre-treatment cytology slides were only available for 60. USA
Study Design: Retrospective case series
Target Condition: Target condition was identification of epithelial ovarian cancer. Reference standard diagnosis was surgical staging and histopathology.
Tests: Ascitic fluid was tapped (usually between 30 and 60 ml), the technique was not reported.
Follow Up: Not reported.
Pathologic analysis Cytopathology: an average of one slide with Pap staining was made from each ascitic fluid sample. No immunocytochemistry was used.
Final diagnosis For the 60 women with cytology available: 70% epithelial ovarian cancer, 7% other ovarian cancer, 2% no evidence of disease and 22% had no surgical confirmation of diagnosis.

Author(s): Sistrom *et al.,* 1992
Settings: Patients with omental abnormalities, who had FNAB at a single institution
Participants: 11 patients: 1 male (excluded from analysis). 3 women had a history of epithelial ovarian cancer, and one breast cancer.
Study Design: Retrospective case series.
Target Condition: Diagnosis of malignancy (adenocarcinoma, sarcoma, lymphoma or benign). Discharge diagnosis

was reported, but it is unclear what the reference standard was.
Tests: US guided fine needle aspiration biopsy. Ascitic fluid was sampled in 3 cases.
Follow Up: Not reported.
Pathologic analysis Cytology, techniques not reported.
Final diagnosis 8/10 (80%) ovarian cancer or peritoneal carcinomatosis with likely ovarian primary, 1/10 (10%) carcinomatosis of probable colon primary, 1/10 (10%) carcinomatosis of unknown primary.

Author(s): Spencer *et al.,* 2001
Settings: Women with peritoneal carcinomatosis (on the basis of clinical and imaging features) treated by a single gynaecological oncology team during a 2 year period.
Participants: 35 women. 8/35 had previous tumours known to metastasize to the peritoneal cavity. 25/35 had suspected ovarian cancer (on the basis of clinical and imaging features), 2/35 women had peritoneal carcinomatosis in the absence of pelvic mass or elevated CA125. there was. UK
Study Design: Prospective case series
Target Condition: Diagnosis of tumour type. Reference standard was multidisciplinary review of all clinical information, findings of any subsequent surgery and response to therapy.
Tests: Image guided core needle biopsy. Immunohistochemistry, cytology in selected cases.
Follow Up: Not reported

Pathologic analysis Histological analysis, H&E staining. Immunohistochemistry using antibodies to: CEA, CK-7, CK-20 and CA125. Additional breast cancer specific antibodies were used in women with a history of breast cancer. Ascites was drained in 19/35 women and analysed cytologically.
Final diagnosis In the entire group: 29/35 (83%) ovarian or primary peritoneal carcinoma, 2/35 (6%) metastatic colorectal cancer, 2/35 (6%) metastatic breast cancer, 1/35 (3%) lymphoma, 1 not reported. In women with no previous primary tumour: 25/27 (92%) ovarian or primary peritoneal carcinoma, 1/27 (4%) metastatic colorectal cancer, 1/27 (4%) lymphoma

Author(s): Yoon *et al.,* 2007
Settings: Patients referred for a diagnostic laparoscopy in a single gastroenterology unit. Only results for patients with ascites of unknown origin are included in this appraisal.
Participants: 855 patients in total, 141 diagnostic laparoscopy procedures were done for ascites of unknown origin. Korea
Study Design: Retrospective case series.
Target Condition: Diagnosis of metastatic carcinoma, peritoneal tuberculosis, no disease, or mesothelioma. Reference standard was
Tests: Laparoscopy with biopsy
Follow Up: Not reported
Pathologic analysis Not reported
Final diagnosis Malignancy 46/141 (32%)

Notes:

In patients with ascites of unknown origin and peritoneal disease, the diagnostic yield was 87.2% (123/141). In 24 (19.5%) of the 123 patients, the diagnosis changed or the less probable diagnosis was confirmed after laparoscopic examination.

References:

Bedioui H, Ksantini R, Nouira K, Mekni A, Daghfous A, Chebbi F, *et al.(2007)* Role of laparoscopic surgery in the etiologic diagnosis of exsudative ascites: a prospective study of 90 cases. *Gastroenterol Clin Biol* **31(12):** 1146-9

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Griffin N, Grant LA, Freeman SJ, Jimenez-Linan M, Berman LH, Earl H, Ahmed A, Crawford R, Brenton J and Sala E (2009) Image-guided biopsy in patients with suspected ovarian carcinoma: a safe and effective technique? *Eur.Radiol.* **19:** 230-235.

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Pombo F, Rodriguez E, Martin R and Lago M (1997) CT-guided core-needle biopsy in omental pathology *Acta Radiol.* **38:** 978-981.

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Spencer JA, Swift SE, Wilkinson N, Boon AP, Lane G and Perren TJ (2001) Peritoneal carcinomatosis: Image-guided peritoneal core biopsy for tumor type and patient care *Radiology* **221:** 173-177.

Yoon YJ, Ahn SH, Park JY, Chon CY, Kim do Y, Park YN, *et al.* (2007) What is the role of diagnostic laparoscopy in a gastroenterology unit*? J Gastroenterol* **42(11):** 881-6

"*What is the best method of tissue diagnosis before chemotherapy, samples from image guided biopsy or laparoscopic biopsy?*"

Short summary:

The literature search found no studies directly comparing image-guided with laparoscopic biopsy. Evidence from case series indicates a definitive diagnostic rate between 87% and 97% for image-guided biopsy, but our searches found no studies reporting the diagnostic yield of laparoscopic biopsy.

Percutaneous core biopsy was associated with minor local bruising and discomfort. Minor complications were reported in less than two percent of laparoscopies from four series with 1,284 patients (including cases with non-malignant aetiology). Major complications occurred at a rate of less than one percent.

Review Protocol:

Question

What is the best method of tissue diagnosis before chemotherapy, samples from image-guided biopsy or laparoscopic biopsy?

Study inclusion criteria

- **Studies:** Any study design
- **Participants:** Women with suspected advanced ovarian cancer.
- **Index tests:** Image guided biopsy or laparoscopic biopsy
- **Target conditions:** Rate of definitive diagnosis of ovarian cancer, adverse events, morbidity and patient acceptability
- **Reference standards:** Histopathology

Search strategy

The following electronic databases were searched: Medline, PreMEDLINE, EMBASE, Cochrane Library, CINAHL, BNI, PsycINFO, AMED, Web of Science (SCI & SSCI) and Biomed Central.

Papers were also identified from a review of histology versus cytology in patients presenting with ascites, done for the NICE Cancer of Unknown Primary clinical guideline (2010).

Review strategy

The titles and abstracts of the studies identified in the literature search were screened for potentially relevant studies by one reviewer (NB).

Search results:

The literature searches identified 132 potentially relevant studies, of which 12 were eventually included.

Study quality:

The methodological quality is summarised in Figure 3.27. Most papers were case series and not designed as prospective diagnostic studies: in only one of the studies (Spencer *et al.*, 2001) were the pathologists who analysed the biopsy specimens blind to the clinical and imaging findings. The study

populations in the laparoscopic biopsy case series included women with unexplained ascites of any aetiology: not just those with suspected advanced ovarian cancer.

Evidence summary:

Diagnostic yield

Diagnostic yield (the proportion of biopsy procedures sufficient to make a definitive diagnosis) is summarised in Table 3.8.The literature searches found no evidence about the diagnostic yield of laparoscopic biopsy in this population. Two studies originating from the same UK gynaecologic oncology centre (Hewitt *et al.*, 2007 and Spencer *et al.*, 2001) reported the use of image guided percutaneous core needle biopsy in women with peritoneal carcinomatosis of unknown origin. A definitive diagnosis was made on the basis of histopathology and immunohistochemistry in 97% of cases in Spencer *et al.* (2001) and in 93% of cases in Hewitt *et al.* (2007).

Griffin *et al.* (2009) reported a diagnostic yield of 87% for image guided core needle biopsy in their series of women with a clinical diagnosis of ovarian cancer, recommended for neoadjuvant chemotherapy by gynaecological oncologists.

Technical failure or sample inadequacy meant that secondary intervention was required to obtain tissue for diagnosis in all of these series. The rate of repeat percutaneous or surgical biopsy ranged from 3% (Spencer *et al.*, 2001) in to 12% (Griffin *et al.*, 2009).

Harms of biopsy

Harms are summarised in Table 3.9.

There was no direct evidence about the harms of diagnostic laparoscopy or laparotomy in women with suspected advanced ovarian cancer due to receive chemotherapy. Indirect evidence comes from studies reporting diagnostic laparoscopy in patients with ascites of unknown origin (Bedioui *et al.* 2007, Chu *et al.*, 1994 and Yoon *et al.*, 2007). Minor complications were reported in less than two percent of laparoscopies from four series with 1284 patients (including cases with non-malignant aetiology). Major complications occurred at a rate of less than one percent, although one series (Chu *et al.*, 1994) observed intestinal perforation due to laparoscopy in six percent of patients with peritoneal tuberculosis.

Percutaneous core biopsy was associated with minor complications, such as local bruising and discomfort (Fisherova *et al.* 2008, Griffin *et al.* 2009, Hewitt *et al.* 2007, Pombo *et al.* 1997, Spencer *et al.* 2001). Fischerova *et al.* (2008) reported one instance of bleeding which required laparotomy following core needle biopsy of an ovarian mass.

A recognised complication of needle biopsy and laparoscopy is tumour seeding in the needle tract or trocar site, but this outcome was poorly reported in the studies. Spencer *et al.* (2001) reported no clinically apparent needle tract metastases during follow up. Hewitt *et al.* (2007) reported that the rate of subcutaneous tumour deposits was unchanged since the introduction of image guided core biopsy in their institution, but no supporting figures were given.

Table 3.8 Diagnostic yield of image guided biopsy [Back]

Study	N	Biopsy type	Diagnostic yield (primary tumour site)	Sample inadequacy	Rate of secondary intervention to obtain tissue for diagnosis
Griffin 2009	60	Percutaneous US or CT guided core needle biopsy	87%	13%	12% surgical biopsy
Hewitt	149	Percutaneous US or CT	93%	7%	7% repeat

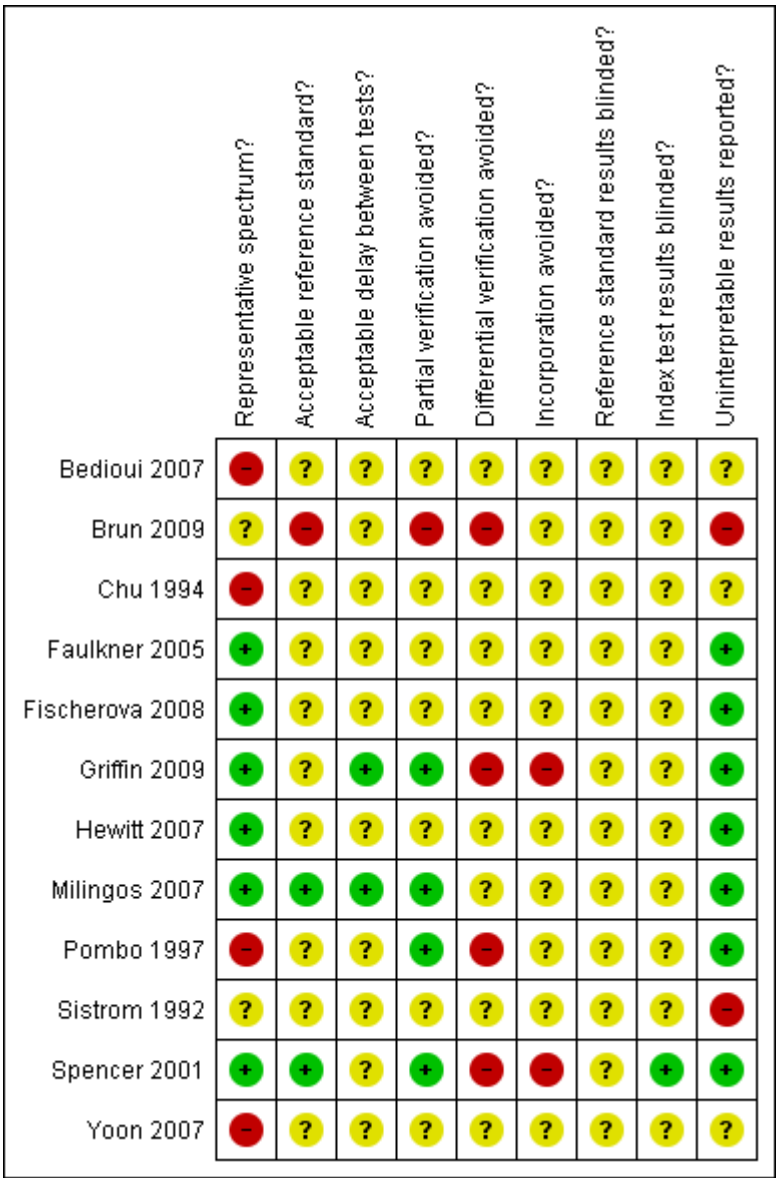
2007		guided core needle biopsy + immunohistochemistry (panel of at least 4 antibodies)			percutaneous biopsy
Spencer 2001	35	Percutaneous US or CT guided core biopsy + immunohistochemistry (panel of at least 4 antibodies)	97%	3%	3% surgery
Pombo 1997	25	Percutaneous CT guided core biopsy (pathological analysis not reported)	Diagnosis was not more detailed than metastatic adenocarcinoma	4%	1/25 (4%) required a repeat biopsy procedure.
Fischerova 2008	90	Percutaneous US guided core biopsy (pathological analysis not reported)		7%	7% surgical biopsy 4% repeat percutaneous biopsy

Table 3.9 Harms of biopsy [Back]

Study	N	Biopsy type	Minor complications	Major complications	Tumour seeding to biopsy site	Mortality
Griffin 2009	60	Percutaneous US or CT guided core needle biopsy	0%	0%	0%	0%
Spencer 2001	35	Percutaneous US or CT guided core needle biopsy, plus IHC	0%	0%	Not reported	0%
Hewitt 2007	149	Percutaneous US or CT guided core needle	Minor local bruising and discomfort. 1/149 (<1%) rectus sheath haematoma.	0%	Authors note that the rate did not increase with IGB	0%
Pombo 1997	25	Percutaneous CT guided core needle	0% within 24 hours of biopsy.	0%	Not reported	0%
Fischerova 2008	86	Percutaneous US guided core needle	0%	1/86 bleeding from ovarian mass requiring laparotomy	Not reported	Not reported
Bedioui 2007	90	Laparoscopy	1/90 (1%) leakage of ascites	0%	Not reported	0%
Chu 1994	129	Laparoscopy	2/129 (2%) leakage of ascites 2/129 (2%) subcutaneous emphysema	Intestinal perforation in 2/31 (6%) patients with tuberculous peritonitis	Not reported	0%

			1/129 (1%) wound infection			
Yoon 1997	855	Laparoscopy	N.R.	6/855 (0.7%) biopsy site bleeding 2/855 (0.2%) liver laceration 1/855 (0.1%) spleen laceration 1/855 (0.1%) pneumothorax	Not reported	0%

Figure 3.27 Summary of methodological quality [Back]



Evidence tables:

Author(s): Bedioui *et al.,* 2007
Settings: Patients presenting with isolated ascites of unknown aetiology who had laparoscopy, over a 10 year period (1996 to 2006). Before laparoscopy patients received tests for tuberculosis including chest X-ray, and direct examination of sputum, urine, gastric products and ascites. Women received gynaecological examination with pelvic ultrasound. In patients with suspected carcinomatosis work-up included CT scan. All had aspiration of ascitic fluid for cytochemistry and bacteriology.
Participants: 90 patients. Tunisia
Study Design: Prospective case series
Target Condition: Diagnosis of peritoneal tuberculosis versus carcinomatosis. Reference standard was histology of the laparoscopic biopsies.
Tests: Index test was diagnostic laparoscopy including visual inspection and biopsies of peritoneum and liver where possible. The predictive values of atypical cells on cytology and of individual symptoms are also reported.
Follow Up: Not reported
Pathologic analysis: Not reported
Final diagnosis: Malignancy in 31/90 (34%)

Author(s): Brun *et al.,* 2009
Settings: Women with stage III or IV ovarian cancer, before primary therapy

Participants: 55 women, 81% had stage III disease and 19% stage IV
Study Design: Retrospective case series
Target Condition: Prediction of optimal debulking surgery. Reference standard was not reported
Tests: Diagnostic laparoscopy, including biopsies of ovaries or peritoneal metastases
Follow Up: Not reported
Pathologic analysis Frozen section analysis
Final diagnosis Ovarian cancer in all cases (stated in inclusion criteria)
Notes: Women were candidates for surgery; diagnostic laparoscopy was done as a triage for debulking surgery or neoadjuvant chemotherapy. Study does not attempt to estimate the predictive value of laparoscopy, but contains some data about harms.

Author(s): Chu *et al.,* 1994
Settings: Patients with ascites of unknown origin, following ultrasound and CT.
Participants: 129 Patients. Taiwan
Study Design: Retrospective case series.

Target Condition: Diagnosis of the origin of ascites. Visual diagnoses of carcinomatosis peritonei were confirmed by either histology or ascitic cytology. Tuberculous peritonitis was confirmed variously by histology, response to chemotherapy or focus of tuberculosis elsewhere. Patients with visual diagnosis of liver cirrhosis or normal looking peritoneum were not biopsied.
Tests: Laparoscopic visual and histological evaluation of ascites. Ascitic cytology.
Follow Up: Not reported
Pathologic analysis Not reported
Final diagnosis Malignancy in 67/129 (52%)

Author(s): Faulkner *et al.,* 2005
Settings: Women with clinically suspected ovarian cancer who were not candidates for surgery and who had palpable tumour immediately beneath the vaginal surface with the mass thought to be filling the Pouch of Douglas. CT or US consistent with ovarian cancer was also required.
Participants: 14 women. 10/14 had ascites.
Study Design: Retrospective case series.
Target Condition: Target condition was diagnosis of pelvic tumour. Reference standard was histopathology with further biopsies in some cases.
Tests: Core needle biopsy (TruCut) - no image guidance: the needle tip was advanced in an axial plane beyond the examining finger.

Follow Up: Not reported.
Pathologic analysis Not reported, although results of immunohistochemistry are reported in some cases.
Final diagnosis 7/14 ovarian cancer, 2/14 GI primary tumour, 1/14 breast cancer, 1/14 sarcoma, 2/14 inadequate biopsy sample.

Author(s): Fischerova *et al.,* 2008
Settings: Women referred for US guided transvaginal or transabdominal core needle biopsy for the following indications: primary inoperable pelvic tumour, poor performance status and recurrent disease requiring histological verification.
Participants: 90 women. Czech Republic.
Study Design: Prospective case series.
Target Condition: Diagnosis of tumour malignancy and histological type. No reference standard was reported, presumably histopathology of the biopsy specimen was considered the definitive diagnosis. Some patients had laparoscopy.
Tests: US guided core needle biopsy: 46/86 (53.5%) transvaginal, and 40/86 (46.5%) transabdominal.
Follow Up: Not reported.
Pathologic analysis: Histopathology, H&E staining and unspecified IHC.
Final diagnosis:

54/86 primary ovarian carcinoma, 9/86 ovarian metastases, 23/86 extra-ovarian pathology.
Notes: 4/90 were unsuitable for core needle biopsy (due to tumour location) and were referred for laparotomy or laparoscopy.

Author(s): Griffin *et al.,* 2009
Settings: Women with clinically suspected advanced ovarian cancer or peritoneal carcinomatosis who had US or CT guided percutaneous biopsy between 2002 and 2007 at a single institution. Only women recommended by gynaecological oncologists to receive neoadjuvant chemotherapy were included.
Participants: 60 women. 47 had omental disease, biopsied under US (N=30) or CT (N=17) guidance. 12 patients had a discrete pelvic mass, biopsied under US (N=5) or CT (N=7) guidance. One woman had a CT guided biopsy of an enlarged para-aortic node. UK
Study Design: Retrospective, consecutive case series
Target Condition: Target condition was identification of .Reference standard was histopathological analysis of the biopsy sample. 7/60 women had surgical biopsy due to percutaneous biopsy sample inadequacy.
Tests: US or CT guided percutaneous biopsy. The median number of biopsy per patient was 3 (range 2 to 5).
Follow Up: Median follow-up 30.6 months (range 2.2 to 72.3 months)
Pathologic analysis: Paraffin embedded, H&E staining. IHC panel including CK7, CK20, CA125, CA19-9 and CEA.
Final diagnosis: 58/60 (97%) ovarian malignancy (including primary peritoneal carcinomatosis), 1/60 (1.6%) metastatic squamous cell carcinoma and 1/60 (1.6%) primary peritoneal mesothelioma.

Author(s): Hewitt *et al.,* 2007
Settings: Women with peritoneal carcinomatosis of unknown origin.
Participants: 149 women (32 had a previous history of malignancy). UK
Study Design: Case series, retrospective.
Target Condition: Identification of the primary site. Histopathology of the core sample was considered the definitive diagnosis.
Tests: Percutaneous core needle biopsy of peritoneum, guided by ultrasound or CT.
Follow Up: Not reported
Pathologic analysis: Biopsy material was embedded in paraffin, sectioned, and H&E stained. Immunohistochemical analysis was performed using monoclonal antibodies to CAE, CK 7, CK 20 and CA125. Additional monoclonal antibodies were used at the discretion of the pathologist.
Final diagnosis: In the 121 women who presented with peritoneal carcinomatosis and no previous malignancy the histological diagnosis was 81% Mullerian tumour, 5% gastrointestinal tumour, 4% poorly differentiated tumour (not otherwise specified, 3% breast primary tumour, 2% lymphoma, 1% pseudomyxoma, 1% hepatobiliary tumour, 1% renal cell tumour and 2% benign.
Notes: Not diagnostic accuracy study, since histopathology of the core sample was considered definitive

Author(s): Milingos *et al.,* 2007
Settings: Women with unexplained ascites, following complete history and physical/pelvic examination,

blood and urine biochemistry, tumour markers and abdominal / pelvic US.
Participants: 73 women were referred with diffuse ascites, and 9 had no firm diagnosis following the initial work-up. 6/9 had a provisional diagnosis of peritoneal malignancy - only their results will be included in this appraisal.
Study Design: Retrospective cases series
Target Condition: Diagnosis of the cause of ascites. Reference standard was laparoscopy with intraoperative frozen section analysis and histopathology.
Tests: Index test was the pre-laparoscopy diagnostic work-up: however the laparoscopy results are only reported for those with ascites of uncertain cause.
Follow Up: Not reported
Pathologic analysis Intraoperative frozen section analysis, then histopathology and immunohistochemistry
Final diagnosis In the 6 women with provisional diagnosis of malignancy, 3/6 (50%) had serous papillary ovarian cancer or primary peritoneal carcinomatosis, 1/6 Kruckenberg tumour of unknown primary, 2/6 (33%) had peritoneal miliary tuberculosis In the entire cohort of 73 women referred with diffuse ascites the pre-laparoscopic diagnosis was 58.9% gynaecologic malignancy, 12.3% GI malignancy, 6.8% liver cirrhosis, 4.1% congestive heart failure, 2.7% pancreatitis, 2.7% nephrotic syndrome and 12.3% unidentified cause.

Author(s): Pombo *et al.,* 1997
Settings: Patients referred for CT guided biopsy of omental lesions and with no clinical or radiological evidence of primary tumour or infectious or inflammatory condition that could be responsible.
Participants: 25 patients with focal (N=2) or diffuse (N=23) omental pathology. Spain

Study Design: Retrospective case series.
Target Condition: Specific diagnosis of malignancy. Reference standard was either histopathology of the resected tumour, laparoscopic biopsy or endoscopic biopsy; or clinical follow up.
Tests: CT guided biopsy of omental lesions: core biopsy (N=16) and other biopsy (N=9).
Follow Up: Patients monitored for 24 hours for acute complications. Longer term follow up not reported
Pathologic analysis Histopathology, not specified in detail. Some non-core samples were obtained and were smeared on glass for analysis, presumably cytopathology.
Final diagnosis 13/25 peritoneal carcinomatosis secondary to ovarian cancer or unidentified primary, 2/25 appendix primary tumour, 1/25 stomach primary tumour, 1/25 hepatocellular carcinoma, 1/25 lymphoma, 5/25 tuberculosis and 1/25 actinomycosis.
Notes: Series included 7 men, but the results were not reported by gender.

Author(s): Sistrom *et al.,* 1992
Settings: Patients with omental abnormalities, who had FNAB at a single institution
Participants: 11 patients: 1 male (excluded from analysis). 3 women had a history of epithelial ovarian cancer, and one breast cancer.
Study Design: Retrospective case series.
Target Condition: Diagnosis of malignancy (adenocarcinoma, sarcoma, lymphoma or benign). Discharge diagnosis

was reported, but it is unclear what the reference standard was.
Tests: US guided fine needle aspiration biopsy. Ascitic fluid was sampled in 3 cases.
Follow Up: Not reported.
Pathologic analysis Cytology, techniques not reported.
Final diagnosis 8/10 (80%) ovarian cancer or peritoneal carcinomatosis with likely ovarian primary, 1/10 (10%) carcinomatosis of probable colon primary, 1/10 (10%) carcinomatosis of unknown primary.

Author(s): Spencer *et al.,* 2001
Settings: Women with peritoneal carcinomatosis (on the basis of clinical and imaging features) treated by a single gynaecological oncology team during a 2 year period.
Participants: 35 women. 8/35 had previous tumours known to metastasize to the peritoneal cavity. 25/35 had suspected ovarian cancer (on the basis of clinical and imaging features), 2/35 women had peritoneal carcinomatosis in the absence of pelvic mass or elevated CA125. there was. UK
Study Design: Prospective case series
Target Condition: Diagnosis of tumour type. Reference standard was multidisciplinary review of all clinical information, findings of any subsequent surgery and response to therapy.
Tests: Image guided core needle biopsy. Immunohistochemistry, cytology in selected cases.
Follow Up: Not reported

Pathologic analysis Histological analysis, H&E staining. Immunohistochemistry using antibodies to: CEA, CK-7, CK-20 and CA125. Additional breast cancer specific antibodies were used in women with a history of breast cancer. Ascites was drained in 19/35 women and analysed cytologically.
Final diagnosis In the entire group: 29/35 (83%) ovarian or primary peritoneal carcinoma, 2/35 (6%) metastatic colorectal cancer, 2/35 (6%) metastatic breast cancer, 1/35 (3%) lymphoma, 1 not reported. In women with no previous primary tumour: 25/27 (92%) ovarian or primary peritoneal carcinoma, 1/27 (4%) metastatic colorectal cancer, 1/27 (4%) lymphoma

Author(s): Yoon *et al.,* 2007
Settings: Patients referred for a diagnostic laparoscopy in a single gastroenterology unit. Only results for patients with ascites of unknown origin are included in this appraisal.
Participants: 855 patients in total, 141 diagnostic laparoscopy procedures were done for ascites of unknown origin. Korea
Study Design: Retrospective case series.
Target Condition: Diagnosis of metastatic carcinoma, peritoneal tuberculosis, no disease, or mesothelioma. Reference standard was
Tests: Laparoscopy with biopsy
Follow Up: Not reported
Pathologic analysis Not reported
Final diagnosis Malignancy 46/141 (32%)

Notes:

In patients with ascites of unknown origin and peritoneal disease, the diagnostic yield was 87.2% (123/141). In 24 (19.5%) of the 123 patients, the diagnosis changed or the less probable diagnosis was confirmed after laparoscopic examination.

References:

Bedioui H, Ksantini R, Nouira K, Mekni A, Daghfous A, Chebbi F, *et al.(2007)* Role of laparoscopic surgery in the etiologic diagnosis of exsudative ascites: a prospective study of 90 cases. *Gastroenterol Clin Biol* **31(12):** 1146-9

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Chu CM, Lin SM, Peng SM, Wu CS, Liaw YF.(1994) The role of laparoscopy in the evaluation of ascites of unknown origin. *Gastrointestinal Endoscopy* **40(3):** 285-9

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Spencer JA, Swift SE, Wilkinson N, Boon AP, Lane G and Perren TJ (2001) Peritoneal carcinomatosis: Image-guided peritoneal core biopsy for tumor type and patient care *Radiology* **221:** 173-177.

Yoon YJ, Ahn SH, Park JY, Chon CY, Kim do Y, Park YN, *et al.* (2007) What is the role of diagnostic laparoscopy in a gastroenterology unit*? J Gastroenterol* **42(11):** 881-6

Chapter 4: Management of suspected early stage ovarian cancer

4.1 Staging - the role of systematic retroperitoneal lymphadenectomy

"For women with ovarian cancer whose disease appears confined to the ovaries, what is the effectiveness of systematic retroperitoneal lymphadenectomy in surgical management?"

Short summary:

The evidence for this topic was generally of low quality, comprising two retrospective observational studies, one non-randomised comparative study and a small randomised controlled trial (RCT). Across all studies, the majority of women had stage I ovarian cancer. Only the RCT reported the incidence of post-surgical morbidity and none of the papers reported on patient quality of life. The results of survival outcomes were inconsistent between studies.

Maggioni *et al.* (2006) presented results from a small, underpowered study that was unable to demonstrate a difference in short or long term survival between patients having surgery alone or surgery with systematic lymphadenectomy (SL). But the more extensive operation was associated with increased morbidity. Conversely, Yokoyama *et al.* (1999) found a significant difference in the rates of 5 and 10 year survival for women with stage I/II disease who had received SL compared with those who had not (100% vs. 71.4% (P<0.05) and 83.9% vs. 61.1% (P<0.05) respectively). These results may have been confounded by the addition of different chemotherapy regimens to the study arms.

The retrospective studies also reported conflicting results for survival. The largest of them (Chan *et al.,* 2007; N=6,686) found a significant improvement in the rate of 5 year disease-specific survival for women who underwent SL as part of staging compared with women who did not (92.6% ± 0.6 vs. 87% ± 0.6 P<0.001). However, during the study period participants had unrecorded treatments including surgery and/or chemotherapy which could have confounded these results. The smaller study (Yang *et al.,* 2007) found no significant differences in survival after 1, 3, 5 or 10 years between women that had undergone SL after primary surgery and those who had not. Again, some participants had subsequently received chemotherapy which could have confounded the results.

Updated evidence

Kim *et al.,* (2010) conducted a thorough systematic review and meta-analysis of RCTs and observational studies to determine the possible benefit of systematic retroperitoneal lymphadenectomy to women with all stages of ovarian cancer. A sub-set of patients had stage I-II disease and these data showed a survival advantage with SL (HR: 0.80 (95% C.I: 0.70-0.92) (P=0.001) with no between studies heterogeneity. However, the included studies were not of high evidential quality consisting of Chan *et al.,* 2007; Maggioni *et al.,* 2006 and a small retrospective observational study (Suzuki *et al.,* 2008).

Review Protocol

Objectives

To determine whether removal of the retroperitoneal lymph nodes during standard surgical treatment for suspected ovarian cancer would confer any added benefit to adjuvant therapy.

Study inclusion criteria

- **Population:** Women with early ovarian cancer believed to be confined to the ovaries
- **Interventions:** Retroperitoneal lymphadenectomy, ovariectomy, oophorectomy, standard pelvic clearance
- **Comparators:** Compared with each other
- **Outcome:** Overall and disease-free survival, morbidity and quality of life

Search strategy

The following electronic databases were searched: Medline, PreMedline, EMBASE, Cochrane Library, CINAHL, BNI, PsychInfo, AMED, Web of Science (SCI & SSCI) and Biomed Central. A general exclusion filter was applied (to eliminate non-reviewable material, for example notes, comments etc). No date filter was applied.

Review strategy

The titles and abstracts of the studies identified in the literature search were screened for potential relevance by one reviewer (KF).

One reviewer (KF) recorded survival and toxicity data but none of the included studies reported quality of life outcomes.

Study quality was assessed using modified GRADE methodology (see Table 4.1).

Search results:

The literature search identified 250 potentially relevant studies. After reading study titles and abstracts 6 papers were ordered of which 4 papers were eventually included.

Evidence summary:

The evidence for this topic is generally of poor quality, comprising two retrospective observational studies (Chan *et al.,* 2007 and Yang *et al.,* 2007) one non-randomised comparative study (Yokoyama *et al.,* 1999) and a small, underpowered randomised controlled trial (RCT) (Maggioni *et al.,* 2006). Across all studies, women had been treated in the United States of America, Italy, China and Japan and the majority had stage I ovarian cancer. Only the RCT reported the incidence of post-surgical morbidity and none of the papers reported on patient quality of life. The results of survival outcomes were inconsistent between studies.

Maggioni *et al.* (2006) recruited 268 women with histologically confirmed stage I or II ovarian cancer and randomised them to receive lymphadenectomy after primary surgery (removal of at least 15 aortic nodes and 20 pelvic nodes) or random nodal sampling. Some patients (56% of the intervention group and 66% of the control group) received adjuvant chemotherapy at the discretion of their physician. The primary outcome of this study was to examine the distribution of nodal malignancy but the trial was underpowered to detect a difference in study arms in terms of survival, although the data were reported as a secondary outcome.

After surgery and staging it was shown that 72% of patients had stage I and the remainder stage II ovarian cancer. Systematic lymphadenectomy reduced the risk of disease progression (HR 0.72 (95% C.I: 0.46-1.14)) and death (HR 0.85 (95% C.I: 0.49-1.47)) compared with controls but the differences were not statistically significant. The rates of 5-year progression-free survival and overall survival were also higher for women who had received systematic lymphadenectomy when compared with controls (78.3% vs. 73.4% and 84% vs. 81.6% respectively) but again these differences were not statistically significant. Median event rates were not reached after a median follow-up of 87.8 months. The authors reported a higher incidence of blood loss (median 600ml vs. 300ml P<0.001), requirement for blood transfusions (35.5% vs. 21.8%) and longer operating times (240min vs. 150min P<0.001) in women from the intervention arm. They concluded that these adverse effects might be considered acceptable in light of the fact that systemic retroperitoneal lymphadenectomy provided the means to improve staging and subsequent treatment. However, this study offers little evidence to answer this question since statistical underpowering does not allow conclusions to be drawn from apparently non-significant results.

Chan *et al.,* 2007 reported data retrieved from the United States National Cancer Institute Surveillance, Epidemiology and End Results (SEER) database. 6,686 women with stage I ovarian cancer had been diagnosed over a fourteen year period up to 2001 and had received primary surgery with or without lymphadenectomy, as part of the staging procedure (median number of nodes = 9). The primary outcome of this study was 5-year disease-specific survival. None of the nodes removed were found to be malignant. As a group, women who had undergone lymphadenectomy showed a significantly increased rate of 5-year survival compared with controls (92.6% vs. 87% P<0.001). A similar, statistical outcome was found for several sub-groups of patients such that the authors suggested that, in particular, women with stage I non-clear cell cancer undergoing lymphadenectomy had a significant improvement in survival. A retrospective study is, by design, limited in answering an interventional question since confounding factors cannot be controlled for. Hence it would be difficult to ascertain the absolute contribution of lymphadenectomy to survival given that women may well have had various other interventions such as further surgery and/or chemotherapy. In addition, many other patient details were not taken into consideration such as the specialty of the treating surgeon, co-morbidities etc.

Yang *et al.,* 2007 reported a small (N=287) retrospective, observational study conducted in China using data from patient records of one university hospital. Over a ten year period up to 2006, women with all stages of ovarian cancer received primary surgery either with or without systematic lymphadenectomy. Many women also received adjuvant chemotherapy. Survival outcomes were combined for women with stage I/II or stage III/IV disease. The authors found no significant differences in 1-, 3-, 5- or 10-year survival between study groups, either in women with stage I or stage II ovarian cancer. It was not possible to separate findings further by stage. As with the larger retrospective study, such confounders as co-morbidity and adjuvant therapy were not taken into account.

Yokoyama *et al.,* 1999 reported a small (N=155) non-randomised comparative study that had recruited two groups of women with any stage of ovarian cancer who were treated with surgery at different points between 1980 and 1995. One group received primary surgery with pelvic and aortic lymphadenectomy followed by three cycles of adjuvant chemotherapy (cisplatin, doxorubicin and cyclophosphamide; PAC) and then seven cycles of intermittent chemotherapy with PAC. The second group received primary surgery and between two and five cycles of adjuvant chemotherapy with PAC. The outcomes of interest were the rates of 5- and 10-year survival. The estimated 5-year survival for the intervention group compared with the controls was 100% vs. 71.4% (P<0.05) and the 10-year survival for the intervention group compared with the controls was 83.9% vs. 61.1% (P<0.05). It was not possible to separate findings further by stage.

Taken together, these studies offered very little evidence of quality to suggest that the addition of systematic retroperitoneal lymphadenectomy to primary therapy was of value in extending the survival of women with early stage ovarian cancer.

Evidence tables:

Author(s): Chan *et al.* (2007)

Design: Retrospective observational study
Country: United States of America

Inclusion criteria: Women with stage I ovarian cancer.

Exclusion criteria: Women with borderline tumours.

Population: N=6,686 women. Median age: 54 years. More women in the intervention group were <50 years (47%) than in the control group (39.8%) (P<0.001).

Intervention(s) and comparator(s):

Intervention (N=2,862): Lymphadenectomy as part of a staging procedure (median number of nodes = 9). In this group, only 6 women did not have surgery compared with 242 in the comparator group (P<0.001). Women in this group had either an epithelial tumour (N=2,136) clear cell tumour (N=305) or other types not in the scope of this guideline (N=328)*.

Comparator (N=3,824): No lymphadenectomy. Women in this group had either an epithelial tumour (N=2,900) clear cell tumour (N=398) or other types not in the scope of this guideline (N=619)*.

*Sex cord stromal tumour, germ cell tumour or sarcoma.

Outcomes: 5 year disease-specific survival using Kaplan Meier analyses and Cox's proportional hazards models. Data were censored if a woman died from any cause not related to ovarian cancer.

Results:

All resected lymph nodes were negative for metastatic disease.

- **Outcome: 5 year disease-specific survival (%). All participants:**
  - Lymphadenectomy (N=2,862): 92.6% ± 0.6
    No lymphadenectomy (N=3,824): 87% ± 0.6 (P<0.001)
- **Outcome: 5 year disease-specific survival (%). Sub-groups of study participants that significantly benefited from lymphadenectomy:**
  - Lymphadenectomy (women >50 yrs N=1,562): 92.0% ± 0.9
    No lymphadenectomy (women >50 yrs N=2,360): 82.3% ± 0.9 (P<0.001).
    Age <50 yrs: no significant difference between intervention and comparator (NSD). NB. Far fewer women >50 years underwent lymphadenectomy (39.8% vs. 60.2%. P<0.001).
  - Lymphadenectomy (non clear cell epithelial tumour N=2,136): 93.3% ± 0.7
    No lymphadenectomy (non clear cell epithelial tumour N=2,900): 85.9% ± 0.9 (P<0.001).
    Other tumour types: NSD. NB. Only 42.7% of women with non-clear cell cancer had a lymphadenectomy vs. 56.6% of women with clear cell cancer (P<0.001).

- Lymphadenectomy (surgery excluding hysterectomy N=603): 96.5% ± 0.9
  No lymphadenectomy (surgery excluding hysterectomy N=1,240): 92.0% ± 0.9 (P<0.001).

- Lymphadenectomy (surgery including hysterectomy N=2,253): 91.5% ± 0.5
  No lymphadenectomy (surgery including hysterectomy N=2,342): 88.3% ± 0.7 (P=0.01).

- Lymphadenectomy (no surgery N=6): 100.0% ± 0.0
  No lymphadenectomy (no surgery N=242): 32.9% ± 4.2 (P=0.02). NB. Patient number too low for this to be a meaningful comparison.

- Lymphadenectomy (stage IC disease N=845): 88.1% ± 1.4
  No lymphadenectomy (stage IC disease N=995): 72.8% ± 1.6 (P<0.001).
  Other disease stages: NSD.

- Lymphadenectomy (grade 3 disease N=631): 88.8% ± 1.6
  No lymphadenectomy (grade 3 disease N=633): 74.4% ± 2.0 (P<0.001).
  Other disease grades: NSD. NB. More women (49.9%) with grade 3 disease underwent lymphadenectomy than other grade tumours (P<0.001).

- Lymphadenectomy (no radiation therapy N=2,758): 92.9% ± 0.6
  No lymphadenectomy (no radiation therapy N= 3,722): 87.1% ± 0.6 (P<0.001).
  Radiation therapy: NSD.

- Lymphadenectomy (Caucasian N=2,166): 92.9% ± 0.7
  No lymphadenectomy (Caucasian N=2,906): 86.1% ± 0.7 (P<0.001).
  Other ethnic groups: NSD.

- **Outcome: 5 year disease-specific survival (%). Number of nodes resected during lymphadenectomy and the effect on sub-groups with significant benefit:**

  - (nodes=0) (all participants): 87.0% ± 0.6
    (nodes<10) (all participants): 91.9% ± 0.8
    (nodes>10) (all participants l): 93.8% ± 0.8 (P<0.001)

  - (nodes=0) (women >50 yrs): 82.3% ± 0.9
    (nodes<10) (women >50 yrs): 91.0% ± 1.2
    (nodes>10) (women >50 yrs): 93.5% ± 1.1 (P<0.001)

  - (nodes=0) (non clear cell epithelial tumour): 85.6% ± 0.7
    (nodes<10) (non clear cell epithelial tumour): 93.3% ± 0.9
    (nodes>10) (non clear cell epithelial tumour): 93.5% ± 1.0 (P<0.001)

  - (nodes=0) (stage IC disease): 72.8% ± 1.6
    (nodes<10) (stage IC disease): 86.7% ± 1.9
    (nodes>10) (stage IC disease): 90.1% ± 1.8 (P<0.001)

  - (nodes=0) (stage IB disease): 84.3% ± 2.9
    (nodes<10) (stage IB disease): 97.4% ± 1.8
    (nodes>10) (stage IB disease): 96.4% ± 2.5 (P=0.04)

  - (nodes=0) (grade 3 disease): 74.4% ± 2.0
    (nodes<10) (grade 3 disease): 87.5% ± 2.3
    (nodes>10) (grade 3 disease): 90.5% ± 2.1 (P<0.001)

- (nodes=0) (no radiation therapy): 87.1% ± 0.6
  (nodes<10) (no radiation therapy): 92.1% ± 0.8
  (nodes>10) (no radiation therapy): 94.2% ± 0.8 (P<0.001)

- (nodes=0) (Caucasian): 86.1% ± 0.7
  (nodes<10) (Caucasian): 91.9% ± 1.0
  (nodes>10) (Caucasian): 94.2% ± 0.9 (P<0.001)

- (nodes=0) (no hysterectomy): 92.0% ± 0.9
  (nodes<10) (no hysterectomy): 96.8% ± 1.1
  (nodes>10) (no hysterectomy): 96.1% ± 1.5 (P=0.004)

- (nodes=0) (hysterectomy): 88.3% ± 0.7
  (nodes<10) (hysterectomy): 90.4% ± 1.0
  (nodes>10) (hysterectomy): 93.2% ± 0.9 (P=0.004)

- **Multivariate sub-group analysis:**

Stage of disease (IA/IB vs. IC/'not known') grade of disease (1 vs. 2 and 1 vs. 3) age at diagnosis (continuous variable) extent of lymphadenectomy (0 nodes vs. <10 nodes vs. >10 nodes) and surgery (surgery vs. no surgery) were all significant independent prognostic variables for improved disease-specific survival (all P<0.001).

Follow-up: N/A

Notes:

This retrospective observational study presented the findings from analyses of survival using data extracted from the United States National Cancer Institute Surveillance, Epidemiology and End Results (SEER) database. Patients had been diagnosed between 1st January 1988 and 31st December 2001.

Factors to consider from these data:

1. The observed survival benefit may have been due to adequate staging and therefore more appropriate treatment, or may have been due to the removal of hitherto undetected micrometastases or nodes that may have developed chemoresistance.
2. The authors were unable to gather information on subsequent therapy e.g. further surgery or adjuvant chemotherapy. It would be difficult, therefore, to ascribe enhanced survival to the intervention alone. However, women with grade 3 disease, who may be more likely to have received chemotherapy, still demonstrated a progressive improvement in survival as the number of nodes resected was increased.
3. The authors were unable to identify the subspecialty of the treating physician in each case which, had it been a surgical oncologist, may have resulted in more aggressive therapy and hence an improved chance of survival.
4. In favour of the findings of this study is the high patient number in all but one of the sub-group analyses that showed statistical significance. The limitation of the study is that it is retrospective with all the attendant restrictions on data collection as described in the authors' discussion.
5. According to the GRADE process, an observational study may be improved from an initial classification as 'low' quality evidence by three factors: demonstrating a large magnitude of effect, where plausible confounders would reduce the demonstrated effect or showing a dose-response gradient. A straightforward comparison between all participants (N=6,686) that either had or did not have retroperitoneal lymphadenectomy was highly significant (P<0.001) however, the confounders would probably tend to weigh against the

intervention. The way in which the increasing number of nodes removed appeared to enhance survival in many sub-groups might be seen as the equivalent of a dose response. Thus, the evidence might be classified as between 'low' and 'moderate'.

6. The authors concluded that their data showed that women with stage I non-clear cell ovarian cancer that underwent lymphadenectomy had a significant improvement in (disease specific) survival.

Author(s): Maggioni *et al.* (2006)

Design: Randomised controlled trial (therapy)
Country: Italy

Inclusion criteria: Women with histologically proven epithelial ovarian cancer apparently confined to the pelvis (stages I and II) and optimally debulked (residual tumour ≤1 cm). Age <75 years. Karnofsky performance status ≥80. No previous chemotherapy or radiotherapy. Informed, written consent was obtained.

Exclusion criteria: Women with other primary tumours, wrong initial FIGO stage or histological sub-type other than an epithelial cancer were excluded after randomisation (N=28 from control arm and N=14 from intervention arm). Authors point out that they did not believe this to be a detection bias due to the different surgery received by women in the two study arms.

Population: N=268 women. Median age 51-52 years.

Intervention(s) and comparator(s):

Intervention (N=138): Lymphadenectomy following primary surgery. This was considered 'satisfactory' when at least 15 aortic nodes and 20 pelvic nodes were removed.

Comparator (N=130): Primary surgery: total abdominal hysterectomy, bilateral salpingo-oophorectomy, total omentectomy, appendectomy, random peritoneal biopsy, peritoneal washing and removal of all macroscopically detected intra-pelvic tumour. Random removal of pelvic and aortic nodes (nodal sampling) at the end of primary surgery.

After surgery and staging, patients with stages IIB/C, IIIA or IIIC were scheduled to receive platinum-based chemotherapy, regardless of randomisation. Patients with stage I or IIA disease may have received adjuvant chemotherapy at the discretion of their physician but this was not common practice at the time of the study.

Outcomes: Determining the progression-free survival, overall survival and surgical morbidity were secondary outcomes of this trial. The primary outcome was to compare the proportion of patients with retroperitoneal nodal involvement between treatment groups.

Overall survival was defined as the period between randomisation and death from any cause. Progression-free survival was defined as the period between randomisation and disease progression or death from any cause.

Results:

About 72% of women were post-operatively staged as stage I and the remainder as stage II. The majority (96%) had no residual tumour. There was no significant difference in the number of women receiving adjuvant chemotherapy between study arms (66% of controls vs. 56% of the intervention group). There was a statistically significant difference in the number of women with negative nodes who were given adjuvant chemotherapy (66% in the control group vs. 51% in the interventional group, P=0.03).

- **Outcome: Progression-free survival**

At a median follow-up of ~88 months, 69 patients experienced tumour recurrence, more of whom (30%) were in the control arm compared with those women who had received systematic lymphadenectomy (22%).

- HR for progression-free survival: 0.72 (95% C.I: 0.46-1.14) (P=0.16)
- Median progression-free survival was not reached by either study arm.
- 5 year progression-free survival: 73.4% (control) vs. 78.3% (intervention) (diff: 4.9%, 95% C.I: -5.9-12.5) (not significantly different).

- **Outcome: Overall survival**

At a median follow-up of ~88 months, 52 patients had died, 6 of them without evidence of disease recurrence.

- HR for overall survival: 0.85 (95% C.I: 0.49-1.47) (P=0.56)
- Median overall survival was not reached by either study arm.
- 5 year overall survival: 81.6% (control) vs. 84.0% (intervention) (diff: 2.4%, 95% C.I: -8.3-8.9) (not significantly different).

Even after applying adjustments for between-groups differences in histological grade or post-surgical chemotherapy, the control and intervention arms remained statistically not significantly different from one another with respect to progression-free and overall survival.

- **Outcome: Peri- and post-surgical complications**

There were no surgery related deaths in either study arm. Overnight hospital stays were on average 1 day longer for women in the systematic lymphadenectomy arm. These patients also had longer median operating times (240 min vs. 150 min, P<0.001), experienced higher median blood loss (600 ml vs. 300 ml, P<0.001) and required more blood transfusions (35.5% vs. 21.8%). However, there were no significant differences between study arms with respect to post-surgical or late complications.

Follow-up: Baseline data were collected soon after surgery. Chemotherapy and follow-up data were collected after 6 months and then annually. Median follow-up per patient was 87.8 months.

Notes:

This paper described the results from a small controlled trial of women with early ovarian cancer randomised to receive primary surgery with or without retroperitoneal lymphadenectomy. Study participants were recruited at seven Italian centres between January 1991 and May 2003. The authors stated that there were no important between group differences but did not present comparative statistics.

Study participants were randomised by a block method stratified by treatment centre and assigned by telephone in six sites. The seventh site assigned patients using a sealed envelope technique and a random number generator. Patients were randomised intra-operatively after primary surgery. All data analyses were performed using intention-to-treat principles. The trial was powered to detect group differences for the primary outcome but not for survival outcomes. This means that to detect even a slight survival advantage (authors quoted 6%) the study was probably inadequately powered, thus any positive outcome may have been missed using such a small data set. Survival outcomes were computed using Kaplan Meier analyses and Cox's proportional hazards models. Chemotherapy was adjusted for as a time dependent co-variable for any patient that had received at least once cycle of treatment.

Factors to consider with these data:

1. The main concern with this study is that, due to low patient numbers, there is inadequate power to detect a significant difference between study arms for either progression-free or overall survival. This means that finding 'no significant difference' does not mean that such a difference might not exist but that the study is not big enough to detect one anyway. It would be unsafe, therefore, to conclude that such a difference does not exist.
2. A randomised controlled trial might be downgraded from that of 'high quality' by certain factors including inadequate allocation concealment, randomisation methodology or blinding, failure to use an intention-to-treat analysis, inequality of groups at baseline and not accounting for any loss to follow-up etc. Blinding may have been impractical but otherwise this study does not have obvious methodological shortcomings, excepting as noted above.
3. The authors state that their data show that although the systematic lymphadenectomy involved more theatre time, greater patient blood loss, higher transfusion rates and a longer hospital stay, other morbidity was the same as the less radical surgery and may be acceptable in light of being able to upstage and treat more cancers appropriately.
4. Considering that fewer women in the lymphadenectomy arm received adjuvant chemotherapy, this may suggest that the observed survival benefits, although of no statistical significance are, if anything, underestimated.
5. The authors of this study were primarily concerned with comparing the proportion of patients with retroperitoneal nodal involvement, not with survival. As secondary outcomes, this study does not offer high quality evidence on survival.

Author(s): Yang *et al.* (2007)
Design: Retrospective observational study **Country:** Peoples Republic of China
Inclusion criteria: Women with primary epithelial ovarian cancer.
Exclusion criteria: None stated.
Population: N=287 women. Mean age ~49 years. Women had cancer of all stages: I (N=51) II (N=33) III (N=185) and IV (N=18).
Intervention(s) and comparator(s): Intervention (N=168): Systematic lymphadenectomy (SL) following primary surgery. Post-operative chemotherapy. Of these 168 patients, 59 had no residual disease, 74 women had

residua ≤2 cm and the remainder had residua >2 cm.

Comparator (N=119): Primary surgery: hysterectomy, bilateral salpingo-oophorectomy, total omentectomy and appendectomy. Post-operative chemotherapy. Of these 119 patients, 38 had no residual disease, 54 women had residua ≤2 cm and the remainder had residua >2 cm.

Adjuvant chemotherapy regimens included: platinum/cyclophosphamide with or without adriamycin i.v. and i.p. Patients with ascites were given cisplatin or carboplatin i.p.

Outcomes:

Overall survival (3, 5 and 10 years) defined as the period between the date of surgery and death or 30th December 2006, whichever date fell the earliest. Data are only presented here for patients with stage I or stage II disease.

Results:

In total there were 55 women in the intervention group with positive lymph nodes, but none of these patients had stages I or II disease.

- **Outcome:** 1 year survival stage I (%): 97.5 without SL vs. 99.4 with SL
- **Outcome:** 3 year survival stage I (%): 91.9 without SL vs. 92.3 with SL
- **Outcome:** 5 year survival stage I (%): 82.7 without SL vs. 83.5 with SL
- **Outcome:** 10 year survival stage I (%): 81.0 without SL vs. 82.1 with SL

- **Outcome:** 1 year survival stage II (%): 86.3 without SL vs. 87.2 with SL
- **Outcome:** 3 year survival stage II (%): 74.6 without SL vs. 76.5 with SL
- **Outcome:** 5 year survival stage II (%): 65.4 without SL vs. 68.9 with SL
- **Outcome:** 10 year survival stage II (%): 50.6 without SL vs. 54.3 with SL

None of these comparisons were statistically significant. At the start of this study, only 84 women had ovarian cancer at stages I or II (control group = 18 stage I and 11 stage II; intervention group = 33 stage I and 22 stage II). The relative numbers alive at each measurable time point is likely to have been very low, although these numbers were not reported by the authors. Low patient numbers would have increased data variability, reducing the likelihood of statistical significance.

Overall, there was no significant difference in survival between study groups with stage I or stage II epithelial ovarian cancer either having or not having systematic lymphadenectomy.

Follow-up: Follow-up data were collected 'periodically' for median period per patient of 35.4 months. Twenty-five women were lost to follow-up (no further details given).

Notes:

This retrospective observational study presented the findings from analyses of survival using data extracted from the records of the West China Second University Hospital in the Chengdu Province. Patients were treated between January 1995 and December 2006. There were no statistically significant differences between the study groups at baseline.

A low number, retrospective observational study offers very limited, low quality evidence on a survival outcome. This study did not have sufficient numbers of participants with stage I ovarian cancer to demonstrate statistical, or clinical, significant differences between study arms.

Author(s): Yokoyama *et al.* (1999)
Design: Non-randomised comparative study **Country:** Japan
Inclusion criteria: None stated
Exclusion criteria: None stated
Population: N=155 women. Mean age group A = 50.7 years (range: 20-74) and group B = 51.9 years (range: 38-75)
Intervention(s) and comparator(s): Group A (N=80 treated 1988-1995): Total hysterectomy, bilateral salpingo-oophorectomy, omentectomy, appendectomy and pelvic and aortic lymphadenectomy. Adjuvant chemotherapy, comprising: cisplatin at 60 mg per m^2, doxorubicin at 40 mg per m^2 and cyclophosphamide at 300 mg per m^2 (PAC) for three cycles every three weeks (induction) and then seven cycles every three months (intermittent). Patients were staged according to the FIGO system. For women experiencing complete surgical remission, a second-look operation was performed after 1 year. For those in which surgery had been incomplete, second-look operation (SLO) was performed after clinical remission was obtained following induction chemotherapy. Five women did not receive SLO. Patients were staged on the results of intraperitoneal findings. Group B (N=75 treated 1980-1987): Total hysterectomy and bilateral salpingo-oophorectomy. Adjuvant chemotherapy, comprising: (PAC) for two to five cycles every three weeks (2 cycles N=5; 3 cycles N=27; 4 cycles N=26 or 5 cycles N=17). Second-look surgery was performed after clinical remission was obtained following chemotherapy.
Outcomes: Overall survival at 5 and 10 years (not defined).
Results: Optimal surgery (residual lesion ≤ 2 cm) was performed for 76/80 women in the intervention group and 69/75 women in the comparator group. Survival data were presented as stage I and II combined and stages III and IV combined (the latter is omitted from this table). Group A (N=80): stage I = 33 and stage II = 9 Group B (N=75): stage I = 20 and stage II = 11 ● **Outcome:** Estimated 5 year survival for stages I and II (%): 100 Group A vs. 71.4 Group B. (P<0.05) ● **Outcome:** Estimated 10 year survival for stages I and II (%): 83.9 Group A vs. 61.1 Group B.

(P<0.05)
Follow-up: Short term follow-up comprised monthly physical and gynaecological examinations. Long term follow-up was not described.
Notes: This paper presented the results from a non-randomised comparative study of women treated by surgery and chemotherapy for all stages of ovarian cancer. Unfortunately, the data for women with stages I and II were combined as were those for the more advanced stages. The Kaplan Meier curve in the text illustrated that of the forty-two women in group A, two women died within the ten years, nineteen were censored before five years and eleven thereafter suggesting enrolment of patients one by one over the seven year recruitment period. The curve for group B patients showed that over ten years, seven women died, two were censored after five years and the remainder in two clumps at nine and ten years, suggesting that some women were recruited in batches or were stratified. This potential problem was dealt with by the use of the generalised Wilcoxon test to analyse the differences between Kaplan Meier curves. The resulting data indicated a statistically significant survival advantage for group A vs. group B patients with stage I and II ovarian cancer. Despite the positive findings in this study, the patient number was low and there were also possible confounders, for example the difference in surgery between groups (group A had omentectomy and appendectomy in addition to other resection) and chemotherapy (group B did not receive the extended intermittent PAC). Hence it would be difficult to separate the relative contribution of lymphadenectomy alone.

Author(s): Kim *et al.* (2010)
Design: Systematic review and meta analysis of RCTs and observational studies **Country:** Korea
Inclusion criteria: Studies had to be of women with epithelial ovarian cancer (EOC) of all stages and have made a comparison between systematic lymphadenectomy (SL) and unsystematic lymphadenectomy (USL) where 'lymphadenectomy was defined as removal of para-aortic and pelvic lymph nodes (LN).
Exclusion criteria: Non-EOC e.g. germ cell tumours, fallopian tube cancer and peritoneal carcinomatosis; non-comparative studies; non-English papers.
Population: N~7,158 (with stage I/II)
Interventions and comparators: Systematic lymphadenectomy: described by studies as >11, ≥20 or 'any' resected LN Non-systematic lymphadenectomy: described by studies as ≤10, 'random removal' or 'exploration or sampling' of LN.

Outcomes: Overall survival

Results:

Most studies in the main meta-analysis are not relevant to this question as they deal with all stages of disease; however there is a sub-group analysis of early stage disease (I-II) which is reported here. This analysis combined data from three publications (Chan *et al.,* 2007; Maggioni *et al.,* 2006; Suzuki *et al.,* 2008).

Overall survival (SL versus USL):

- **All three studies:**

HR: 0.80 (95% C.I: 0.70-0.92) (P=0.001). No between studies heterogeneity.

- **Excluding the SEER study (Chan *et al.,* 2007):**

HR: 0.85 (95% C.I: 0.62-1.16) (P=0.30). Low between studies heterogeneity (I^2=9%)

- **Excluding the RCT (Maggioni *et al.,* 2006):**

HR: 0.81 (95% C.I: 0.70-0.93) (P=0.004). Low between studies heterogeneity (I^2=18%).

Follow-up: N/R

Notes:

This paper describes the results of a systematic review and meta analysis of data from randomised controlled trials and observational studies. The authors derived hazard ratios by the method of Tierney *et al.,* (2007) to incorporate time to event data from included studies. The methodology was thorough and reported study selection, search terms and statistics in a similar manner to a Cochrane review.

The authors analysed the same data in three ways, excluding and including one or more of the three studies. It was apparent that inclusion of the largest observational study (Chan *et al.,* 2007) gave significant advantage to SL because it carried the most weight. However, when this study was appraised (see evidence table) it was noted that, according to the GRADE process, an observational study may be improved from an initial classification as 'low' quality evidence by three factors: demonstrating a large magnitude of effect, where plausible confounders would reduce the demonstrated effect or showing a dose-response gradient. A straightforward comparison between all participants (N=6,686) that either had or did not have retroperitoneal lymphadenectomy was highly significant (P<0.001) even though the confounders would probably tend to weigh against the intervention. In addition, the way in which the increasing number of nodes removed appeared to enhance survival in many sub-groups might be seen as the equivalent of a dose response. Thus, the evidence might be classified as between 'low' and 'moderate'.

Of the two other included studies, Maggioni *et al.,* (2006) was a low patient number RCT which was underpowered to have detected a survival benefit had one existed (see evidence table) and Suzuki *et al.,* (2008) was a low patient number (N=204) retrospective study of patients who had been treated for clear cell carcinoma over a twenty year period.

The review authors concluded that the evidence might suggest a slight benefit of SL for women with early stage disease but this could only be properly addressed by prospective randomised

studies.

References:

Chan JK., Munro EG., Cheung MK., Husain A., Teng NN., Berek JS and Osann K (2007) Association of lymphadenectomy and survival in stage I ovarian cancer patients. *Obstetrics & Gynecology* **109:** 12-19.

Kim HS, Ju W, Jee BC, Kim YB, Park NH, Song YS *et al.* (2010) Systematic lymphadenectomy for survival in epithelial ovarian cancer a meta-analysis. *Int J Gynecol Cancer* **20(4):**520-528.

Maggioni A., Benedetti PP., Dell'Anna T., Landoni F., Lissoni A., Pellegrino A., Rossi RS., Chiari S., Campagnutta E., Greggi S., Angioli R., Manci N., Calcagno M., Scambia G., Fossati R., Floriani I., Torri V., Grassi R and Mangioni C (2006) Randomised study of systematic lymphadenectomy in patients with epithelial ovarian cancer macroscopically confined to the pelvis. *Br J Cancer* **95:** 699-704

Suzuki S, Kajiyama H, Shibata K, Ino K, Nawa A, Sakakibara K, Matsuzawa K, Takeda A, Kinoshita Y, Kawai M, Nagasaka T and Kikkawa F (2008). Is there any association between retroperitoneal lymphadenectomy and survival benefit in ovarian clear cell carcinoma patients? *Ann.Oncol.* **19:** 1284-1287.

Yang X., Hou M., Yang K., Wang H., Peng., Cao Z and Mingrong X. (2007) Prognosis in epithelial ovarian cancer: clinical analysis of 287 pelvic and para-aortic lymphadenectomy. *Chinese-German Journal of Clinical Oncology* **6 (5):** 492-496.

Yokoyama Y., Sakamoto T., Sato S and Saito Y (1999). Evaluation of cytoreductive surgery with pelvic and para-aortic lymphadenectomy and intermittent cisplatin-based combination chemotherapy for improvement of long-term survival in ovarian cancer. *Eur J Gynaecol Oncol* **20:** 361-366.

Table 4.1 GRADE profile: : For women with ovarian cancer whose disease appears confined to the ovaries, what is the effectiveness of systematic retroperitoneal lymphadenectomy in surgical management? [Back]

Quality							Summary of findings				
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Ppts withSL**	**Ppts with no SL**	**% survived SL**	**% survived no SL**	**Quality**
5 year disease-specific survival. All study participants (P<0.001) Chan *et al.* (2007).											
1	retrospective observational study	N/A	N/A	N/A	N/A	nil	2,862	3,824	92.6 ± 0.6	87 ± 0.6	⊕○○○ VERY LOW
5 year disease-specific survival. Age >50 years (P<0.001) Chan *et al.* (2007).											
1	retrospective observational study	N/A	N/A	N/A	N/A	nil	1,562	2,360	92 ± 0.9	82.3 ± 0.9	⊕○○○ VERY LOW
5 year disease-specific survival. Non-clear cell epithelial carcinoma (P<0.001) Chan *et al.* (2007).											
1	retrospective observational study	N/A	N/A	N/A	N/A	nil	2,136	2,900	93.3 ± 0.7	85.9 ± 0.9	⊕○○○ VERY LOW
5 year disease-specific survival. No hysterectomy (P<0.001) Chan *et al.* (2007).											
1	retrospective observational study	N/A	N/A	N/A	N/A	nil	603	1,240	96.5 ± 0.9	92.0 ± 0.9	⊕○○○ VERY LOW
5 year disease-specific survival. Hysterectomy (P=0.01) Chan *et al.* (2007).											
1	retrospective observational study	N/A	N/A	N/A	N/A	nil	2,253	2,342	91.5 ± 0.5	88.3 ± 0.7	⊕○○○ VERY LOW

Quality							Summary of findings				
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Ppts withSL**	**Ppts with no SL**	**% survived SL**	**% survived no SL**	**Quality**
5 year disease-specific survival. No surgery (P=0.02) Chan *et al.* (2007).											
1	retrospective observational study	N/A	N/A	N/A	N/A	nil	6	242	100 ± 0.0	32.9 ± 4.2	⊕○○○ VERY LOW
5 year disease-specific survival. Stage I disease (P<0.001) Chan *et al.* (2007).											
1	retrospective observational study	N/A	N/A	N/A	N/A	nil	845	995	88.1 ± 1.4	72.8 ± 1.6	⊕○○○ VERY LOW
5 year disease-specific survival. Grade 3 disease (P<0.001) Chan *et al.* (2007).											
1	retrospective observational study	N/A	N/A	N/A	N/A	nil	631	633	88.8 ± 1.6	74.4 ± 2.0	⊕○○○ VERY LOW
5 year disease-specific survival. No radiation therapy (P<0.001) Chan *et al.* (2006).											
1	retrospective observational study	N/A	N/A	N/A	N/A	nil	2,758	3,722	92.9 ± 0.6	87.1 ± 0.6	⊕○○○ VERY LOW
5 year disease-specific survival. Caucasian race (P<0.001) Chan *et al.* (2007).											
1	retrospective observational study	N/A	N/A	N/A	N/A	nil	2,166	2,906	92.9 ± 0.7	86.1 ± 0.7	⊕○○○ VERY LOW
1 year survival stage I (% only) Yang *et al.* (2007)											

Quality							Summary of findings				
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Ppts withSL**	**Ppts with no SL**	**% survived SL**	**% survived no SL**	**Quality**
1	retrospective observational study	N/A	N/A	N/A	N/A	nil	33	18	99.4	97.5	⊕○○○ VERY LOW
3 year survival stage I (% only) Yang *et al.* (2007)											
1	retrospective observational study	N/A	N/A	N/A	N/A	nil	33	18	92.3	91.9	⊕○○○ VERY LOW
5 year survival stage I (% only) Yang *et al.* (2007)											
1	retrospective observational study	N/A	N/A	N/A	N/A	nil	33	18	83.5	82.7	⊕○○○ VERY LOW
10 year survival stage I (% only) Yang *et al.* (2007)											
1	retrospective observational study	N/A	N/A	N/A	N/A	nil	33	18	82.1	81.0	⊕○○○ VERY LOW
1 year survival stage II (% only) Yang *et al.* (2007)											
1	retrospective observational study	N/A	N/A	N/A	N/A	nil	22	11	87.2	86.3	⊕○○○ VERY LOW
3 year survival stage II (% only) Yang *et al.* (2007)											
1	retrospective observational study	N/A	N/A	N/A	N/A	nil	22	11	76.5	74.6	⊕○○○ VERY LOW
5 year survival stage II (% only) Yang *et al.* (2007)											

Quality							Summary of findings				
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**Ppts withSL**	**Ppts with no SL**	**% survived SL**	**% survived no SL**	**Quality**
1	retrospective observational study	N/A	N/A	N/A	N/A	nil	22	11	68.9	65.4	⊕○○○ VERY LOW
10 year survival stage II (% only) Yang *et al.* (2007)											
1	retrospective observational study	N/A	N/A	N/A	N/A	nil	22	11	54.3	50.6	⊕○○○ VERY LOW
Estimated 5 year survival for stages I and II (% only) Yokoyama *et al.* (1999)											
1	non-randomised comparative study	N/A	N/A	N/A	N/A	nil	80	75	100	71.4	⊕○○○ VERY LOW
Estimated 10 year survival for stages I and II (% only) Yokoyama *et al.* (1999)											
1	non-randomised comparative study	N/A	N/A	N/A	N/A	nil	80	75	83.9	61.1	⊕○○○ VERY LOW

Quality							Summary of findings				
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**SL**	**No SL**	**Relative effect**	**Absolute effect**	**Quality**
Risk of death. All participants (P>0.05) Maggioni *et al.* (2006)											

Quality							Summary of findings				
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other**	**SL**	**No SL**	**Relative effect**	**Absolute effect**	**Quality**
1	randomised controlled trial	no serious limitations	N/A	N/A	underpowered study	N/A	138	130	HR=0.85 (0.49-1.47)	-	⊕⊕◯◯ LOW
Risk of progression All participants (P>0.05) Maggioni *et al.* (2006)											
1	randomised controlled trial	no serious limitations	N/A	N/A	underpowered study	N/A	138	130	HR=0.72 (0.46-1.14)	-	⊕⊕◯◯ LOW
5 year overall survival Maggioni *et al.* (2006)											
1	randomised controlled trial	no serious limitations	N/A	N/A	underpowered study	N/A	84%	81.6%	MD=2.4 (-8.3-8.9)		⊕⊕◯◯ LOW
5 year progression-free survival Maggioni *et al.* (2006)											
1	randomised controlled trial	no serious limitations	N/A	N/A	underpowered study	N/A	78.3%	73.4%	MD=4.9 (-5.9-12.5)	-	⊕⊕◯◯ LOW
Overall survival. Kim *et al.*, (2010)[1]											
3	randomised trial and observational studies	serious limitations[1]	no serious inconsistency	no serious indirectness	no serious imprecision	N/A	-	-	HR=0.80 (0.70-0.92)	-	⊕⊕⊕◯ MODERATE

Footnotes:

[1] This study combined one small RCT and two observational studies which showed no between studies heterogeneity (0%) and gave a significant result. Nonetheless, the included studies were themselves between 'low' and 'moderate' quality.

4.2 Adjuvant systemic chemotherapy in stage I disease: patient selection

"For women with stage I ovarian cancer, what is the most effective first line chemotherapy"?

Short summary:

The evidence for this topic was sparse consisting of one high quality Cochrane review and a lower quality randomised controlled trial (RCT). Across these studies, women had undergone primary surgery and had stage I or II ovarian cancer.

Winter-Roach *et al*. (2009) conducted a review which investigated whether adjuvant therapy with mainly platinum-containing regimes was associated with a survival advantage compared to withholding chemotherapy until disease progression, and whether certain sub-groups of patients gained more or less from this approach. After an average follow-up of nearly ten years it was found that women receiving adjuvant therapy had a considerable advantage in overall survival (HR=0.71 (95% C.I: 0.53 to 0.93) P=0.015) and progression-free survival (HR=0.67 (95% C.I: 0.53-0.84) P=0.00046). In particular, those women who had been adequately staged gained no survival advantage from immediate adjuvant chemotherapy (HR=1.22 (95% C.I: 0.63-2.37) P=0.56) whereas women who had been adequately staged did (HR=0.63 (95% C.I: 0.46 to 0.85) P=0.0031).

Bell *et al*. (2006) compared six vs. three cycles of adjuvant carboplatin and paclitaxel in women with early stage ovarian cancer (N=457). Across all patients and after an average follow-up of 6.8 years, there were no statistically significant differences in the risk of death (HR=1.02 (95% C.I: 0.66-1.57) P=0.94) or the rate of disease recurrence (HR=0.76 (95% C.I: 0.51-1.13) P=0.18). The higher number of treatment cycles was associated with significantly increased morbidity.

The systematic review (Winter-Roach *et al.,* 2009) included evidence from the Adjuvant Chemotherapy in Ovarian neoplasm (ACTION) trial which has now been updated by Trimbos *et al*. (2010). The results showed that, even with observation, optimally surgically staged patients had a significantly better prognosis compared with patients who had been non-optimally staged: cancer-specific survival (risk of death: HR 3.28 (95% C.I: 1.47-7.33) P=0.002); recurrence-free survival (risk of death: HR 1.91 (95% C.I: 1.17-3.11) P=0.009). In non-optimally staged patients only, adjuvant chemotherapy provided significantly improved cancer-specific survival (risk of death: HR 0.58 (95% C.I: 0.35-0.95) P=0.029) and recurrence-free survival (risk of death: HR 0.60 (95% C.I: 0.41-0.87) P=0.007) when compared with observation. The authors concluded, therefore, that the benefit of adjuvant chemotherapy appeared to be limited to patients with non-optimal staging who, perhaps, had a greater risk of unidentified residual disease.

The results of Bell *et al.,* 2006 were re-analysed in a more recent report (Chan *et al.,* 2010) after a median follow-up of 91 months. The authors grouped data by tumour type (i.e. serous or non-serous) and showed that only women with serous cancer derived a significant benefit from six cycles compared with three cycles of adjuvant carboplatin and paclitaxel chemotherapy (HR=0.33 (95% C.I: 0.14-0.77) P=0.007). Although interesting, the original study was underpowered for sub-group analyses which, in any event, have been performed *post hoc*.

Review Protocol:

Objectives

To determine the clinical benefits and toxicity of first-line adjuvant chemotherapy for women with stage I ovarian cancer.

Study inclusion criteria

- **Population:** Women with stage I ovarian cancer
- **Interventions:** Carboplatin, carboplatin and taxol (paclitaxel)
- **Comparators:** Compared with another or with no chemotherapy
- **Outcome:** Overall and disease-free survival, morbidity and quality of life

Search strategy

The following electronic databases were searched: Medline, PreMedline, EMBASE, Cochrane Library, CINAHL, BNI, PsychInfo, AMED, Web of Science (SCI & SSCI) and Biomed Central. A general exclusion filter was applied (to eliminate non-reviewable material, for example notes, comments etc). Systematic reviews (2002 onwards), RCT's and observational studies filters were applied to the basic search parameters.

Review strategy

The titles and abstracts of the studies identified in the literature search were screened for potential relevance by one reviewer (AM).

Two reviewers (AM and KF) recorded survival outcomes. Adverse events were not fully reported and quality of life was not addressed.

Study quality was assessed using modified GRADE methodology (see Table 4.2).

Search results:

The literature search identified 87 potentially relevant studies. After reading study titles and abstracts 7 papers were ordered of which 2 papers were eventually included.

Evidence summary:

The evidence for this topic is sparse consisting of one high quality Cochrane review (Winter-Roach *et al*., 2009) and a lower quality randomised controlled trial (RCT) (Bell *et al*., 2006). Across these studies, women had undergone surgery and had been staged histologically as stage I or II ovarian cancer.

The systematic review investigated whether or not adjuvant therapy, with mainly platinum-containing regimes, was associated with a survival advantage when compared with withholding chemotherapy until disease progression and whether certain sub-groups of patients gained more or less from this approach. After an average follow-up period of nearly ten years it was found that women receiving adjuvant therapy had a considerable advantage in overall survival (HR 0.71 (95% C.I: 0.53 to 0.93) P=0.015) and progression-free survival (HR 0.67 (95% C.I: 0.53 to 0.84) P=0.00046). Most striking were the sub-group analyses which demonstrated that thorough staging could identify those patients who might most benefit from adjuvant therapy. Hence women who had been adequately staged had no survival advantage in having chemotherapy directly after surgery rather than waiting until disease progression: HR 1.22 (95% C.I: 0.63 to 2.37) P= 0.56. Conversely, women who had been inadequately staged did have a survival advantage with adjuvant chemotherapy compared with women treated on progression only (HR 0.63 (95% C.I: 0.46 to 0.85) P=0.0031). It is noteworthy, therefore, that of all the patients in this review, 752 were deemed to have been inadequately staged whereas only 234 had their cancer

well staged. The authors, having referred to other studies in addition to their own, concluded that women with adequately staged, low risk ovarian cancer whilst being exposed to the risk of adverse side effects from adjuvant chemotherapy might not benefit in terms of survival or progression-free survival. On the other hand, women with adequately staged, medium to high risk cancer may well receive such survival benefits against the possible side effects of adjuvant chemotherapy could be balanced.

The RCT compared six cycles vs. three cycles of adjuvant carboplatin and paclitaxel in women with early stage ovarian cancer. Across all patients and after an average follow-up of 6.8 years, there were no statistically significant differences in the risk of death (HR 1.02 (95% C.I: 0.66 to 1.57) P=0.94) or in the rate of disease recurrence (HR 0.76 (95% C.I: 0.51 to 1.13) P=0.18). Six cycles of treatment were associated with significantly higher levels of granulocytopenia, neurotoxicity and anaemia and fewer patients completed the treatment protocol. Again, the authors observed that a high number (29%) of women were inadequately staged after surgery, despite this being a condition of enrolment to the study. The estimated hazard ratio for disease recurrence after six cycles vs. three cycles was higher amongst women who had been thoroughly staged (HR 0.796) compared with women who had not (HR 0.660) but this difference was not significant. Similarly, after adjusting for histological grade, the relative hazard for disease recurrence after six cycles vs. three cycles was higher for FIGO stage I (HR 0.769) than FIGO stage II (HR 0.751) but this difference was not significant. The authors concluded that an additional three cycles of adjuvant carboplatin and paclitaxel did not equate to an equivalent reduction in cancer recurrence rates but was associated with higher levels of toxicity and that three cycles of this regime would provide a reasonable post-operative strategy for women with high risk early ovarian cancer.

Evidence tables:

Author(s): Winter-Roach (2009)
Design: (Cochrane) Systematic Review with meta-analyses **Country:** N/A
Included population: Women with stage I and II epithelial ovarian cancer, staged at laparotomy **Included studies:** Randomised controlled trials (RCTs)
Excluded studies: Studies which compared chemotherapy with radiotherapy. Studies which did not demonstrate adequate randomisation, allocation, blinding or an imbalance of prognosis between study arms.
Population: N= 1,277
Interventions and comparators in 5 included studies: [1] Adjuvant platinum-based chemotherapy vs. treatment on progression (no details given) [2] Adjuvant cisplatin at 75mg per m^2 or carboplatin at 350mg per m^2 vs. treatment on progression [3] Adjuvant carboplatin: 6 (1 x 28 day) cycles of at AUC=7 vs. treatment on progression: [4] Adjuvant melphalan (an alkylating agent) v no further treatment [5] Adjuvant cisplatin: 6 (1 x 28 day) cycles at 50mg per m^2 vs. no further treatment
Outcomes: To determine whether, for women with early stage ovarian cancer, adjuvant chemotherapy leads to a survival advantage when compared with post-surgical observation and whether certain sub-groups of women have more or less to gain from these approaches. Primary outcomes: Overall survival (OS) Secondary outcome: Disease-specific survival (DSS), progression-free survival (PFS), death from ovarian cancer and adverse events.
Results: • **OS 5 years (reported in 3 trials)** See GRADE profile (table i) • **OS 5 years (above data sub-grouped by staging)** See GRADE profile (table i) • **OS 10 years (reported in 1 trial, sub-grouped by risk)** See GRADE profile (table i) • **PFS 5 years (reported in 4 trials)** See GRADE profile (table i) • **PFS 5 years (above data sub-grouped by staging)** See GRADE profile (table i) • **PFS 10 years (reported in 1 trial, sub-grouped by risk)** See GRADE profile (table i) • **DSS (reported in 1 trial)** See GRADE profile (table i) • **Death from ovarian cancer (reported in 3 trials)** See GRADE profile (table i) • **Grade 3 or 4 adverse effects (not reported – see general discussion)**
Follow-up: Across all the studies, the mean follow-up was between forty six and one hundred and ten months.

Notes:

This good quality paper reviewed adjuvant chemotherapy in women with early stage ovarian cancer who had undergone cytoreductive surgery. Two authors searched the Cochrane Gynaecological Cancer Specialised Registers, Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, TRIP and CancerLit databases up to 2008 for relevant studies. Details of the MEDLINE search strategy and MESH headings were presented. Hand searches of the clinical literature were conducted where appropriate and authors contacted where possible.

Papers were selected, reviewed and data were extracted by two independent researchers and disagreements were resolved by discussion with a third author. Each trial was assessed for bias with respect to methods of randomisation, allocation, blinding (of the outcome assessors), loss to follow-up, intention-to-treat analyses and prognostic balance between treatment arms. Overall quality was then judged on these parameters and five studies were found to be of uniformly high quality and were included in this review. All used intention-to-treat analyses. One study (Young *et al.* 1990) was excluded from all meta analyses due to internal data inconsistency and the use of melphalan rather than platinum therapy.

Meta analyses were performed. Pooled time-to-event data were presented as hazard ratio (HR) and dichotomous data as relative risk ratios (RR). Random effects models were applied to all meta analyses. Sub group analyses of data by type of chemotherapy was planned but could not be performed since most trials used the same treatment regimes. All trials were reported to have demonstrated adequate randomisation, allocation and blinding and hence sensitivity analyses were not required. Adverse events were not reported in two of the five trials and in the remaining three studies were only reported in the chemotherapy, but not control, arms.

Meta analysis of data from three of the five trials (N=1,008) indicated that women that had received adjuvant platinum-containing chemotherapy had a better OS (lower risk of death) than those who did not (HR=0.71, 95% C.I: 0.53-0.93; P=0.015) (Numbers needed to treat=17, 95% C.I: 9-100). Similarly, meta analysis of data from four trials (N=1,170) indicated that receiving adjuvant platinum chemotherapy was associated with a better PFS (lower risk of progression) when compared with having no treatment (HR=0.67, 95% C.I: 0.53-0.84; P=0.00046) (Numbers needed to treat=12, 95% C.I: 7-33).

The authors were of the opinion, despite having only small numbers for sub-group analyses, that optimal surgical staging would identify those women who would have little or nothing to gain from adjuvant therapy. Among optimally staged women there was no difference in OS between those who did or did not receive adjuvant chemotherapy (HR=1.22, 95% C.I: 0.63-2.37; P=0.56) but sub-optimally staged women did have such an advantage (HR=0.63, 95% C.I: 0.46-0.85; P=0.0031). Similarly, PFS was superior in sub-optimally staged women who had received adjuvant therapy (HR=0.64, 95% C.I: 0.50-0.82; P=0.00041) but not in those women who had been optimally staged (HR=0.67, 95% C.I: 0.36-1.22; P=0.19). The authors concluded that it would appear safe to withhold adjuvant therapy from women who had been optimally staged and who had well differentiated tumours.

Included studies

Trimbos JB., Vergote I., Bolis G., Vermorken JB., Mangioni C., Madronal C. *et al*. (2003) EORTC-ACTION collaborators. European Organisation for Research and Treatment of Cancer - Adjuvant chemotherapy in ovarian neoplasm. Impact of adjuvant chemotherapy and surgical staging in early-stage ovarian carcinoma. *J Natl Cancer I* **95**(2):113-25.

Bolis G, Colombo N, Pecorelli S, Torri V, Marsoni S, Bonazzi C, *et al*. (1995) Adjuvant treatment for early epithelial ovarian cancer: results of two randomised clinical trials comparing cisplatin to no further treatment or chromic phosphate (32P). G.I.C.O.G.: Gruppo Interregionale Collaborativo

in Ginecologia Oncologica. *Ann Oncol* **6**(9):887-93.

Colombo N, Guthrie D, Chiari S, Parmar M, Qian W, Swart AM, *et al*. (2003) International Collaborative Ovarian Neoplasm trial 1: a randomized trial of adjuvant chemotherapy in women with early-stage ovarian cancer. *J Natl Cancer I* 2003 **95**(2): 125-32.

Swart AC on behalf of ICON collaborators (2007) Long-term follow-up of women enrolled in a randomized trial of adjuvant chemotherapy for early stage ovarian cancer (ICON1). *J Clin Oncol* 2007 **25**(18S):5509.

Trope C, Kaern J, Hogberg T, Abeler V, Hagen B, Kristensen G, *et al*. (2000) Randomized study on adjuvant chemotherapy in stage I high risk ovarian cancer with evaluation of DNA-ploidy as prognostic instrument. *Ann Oncol* **11**(3):281-8.

Young RC, Walton LA, Ellenberg SS, Homesley HD, Wilbanks GD, Decker DG, *et al*. (1990) Adjuvant therapy in stage I and stage II epithelial ovarian cancer. Results of two prospective randomized trials. *New Engl J Med* **322**(15):1021-7.

Citation: Bell, J., M. F. Brady, R. C. Young, J. Lage, J. L. Walker, K. Y. Look, G. S. Rose, N. M. Spirtos, And Gynaecologic Oncology Group. 2006. Randomized phase III trial of three versus six cycles of adjuvant carboplatin and paclitaxel in early stage epithelial ovarian carcinoma: a Gynaecologic Oncology Group study. Gynaecologic Oncology 102: 432-439.

Design: RCT (moderate quality)
Country: USA

Aim: To compare recurrence rates following randomization to either a standard regimen of 3 cycles of carboplatin plus paclitaxel or 6 cycles of the same agents.

Short Summary or findings: This study demonstrated that the addition of 3 cycles of carboplatin plus paclitaxel to the standard 3 cycles does not significantly reduce the cancer recurrence rates for patients with high risk, early stage ovarian cancer. Conversely, the additional cycles of chemotherapy did significantly increase toxicity, but, fewer patients completed the 6-cycle regimen. Whereas 95% of patients (pooling both treatment groups) completed 3 cycles, only 83% completed 6 cycles of therapy, primarily due to increased toxicity (4%) or patient decline (14%). From this study's findings it is reasonable to conclude that this group of patients with early stage ovarian cancer appears to have a fairly similar risk of recurrence regardless of the type of adjuvant therapy received.

Inclusion criteria

- All eligible patients had a histological diagnosis of epithelial ovarian cancer including serous, mucinous, endometrioid, mixed, undifferentiated, Brenner, clear cell, and transitional types.
- After a staging operation, patients were to have completely resected stage IA grade 3 (or clear cell), stage IB grade 3 (or clear cell), stage IC, or stage II disease.
- Other eligibility criteria included: no prior treatment except surgery, adequate bone marrow, renal, and hepatic function, and a GOG performance status less than 4.
- All patients were to be entered onto the trial within 6 weeks following staging laparotomy.

Exclusion criteria

Borderline or low malignant potential tumours were ineligible.

Population

- 457 patients were enrolled, 427 (93%) were considered eligible following centralized pathologic and medical review.

- 293 (69%) were surgical stage I and 134 (31%) were stage II

- 213 participants were assigned to the 3-cycle regimen
- 214 to the 6-cycle regimen

- Patients who received fewer than 3 cycles = 4% in the 3-cycle regimen and 5% in the 6-cycle regimen.

Attrition rate: The proportion of patients completing the 3- cycle regimen was 96% compared to 83% for the 6-cycle

Interventions

- Patients were to receive either 3 or 6 cycles of chemotherapy consisting of paclitaxel (P) 175 mg/m2 by 3 h infusion and carboplatin (C) dosed at AUC 7.5 by infusion over 30 min.
- Treatment cycles were scheduled every 21 days.
- Standard preparative regimen for paclitaxel included dexamethasone, diphenhydramine, and cimetidine.

Randomisation/ Allocation concealment/ Blinding:

- All patients were registered and randomly allocated at the Gynaecologic Oncology Group (GOG) Statistical and Data Centre.
- The randomized treatment was revealed after patient registration.
- This report includes an accounting of all patients registered onto the study (intention to treat analysis)

Comment: while these details have been provided in brief, they are lacking in required detail about how randomisation and allocation concealment were achieved.

Outcomes

- Recurrence was defined as any clinical or radiographic evidence of new tumour.
- Time at risk of recurrence was assessed from the date the patient was registered onto the study to the date of recurrence or to the date of last contact if no recurrence was observed.
- The recurrence rates for the study regimens were compared using a proportional hazards model adjusted for FIGO (International Federation of Gynaecology and Obstetrics) stage and histological grade.
- Overall Survival
- Toxicity: evaluated according to standard GOG toxicity criteria

Power calculation:

The study design provided an 85% chance of identifying a treatment regimen as active if it reduced the recurrence rate 50% when the type I error was set to 0.05 for a one-tail test. This treatment effect is comparable to increasing the expected percentage of patients who are recurrence-free at 4 years from 80.6% to 89.8%.

Results

Treatment compliance

- 96% of patients completed the 3- cycle regimen
- 83% of patients completed the 6-cycle regimen
- 4% of patients in the 3-cycle regimen patients received fewer than 3
- 5% of patients in the 6-cycle regimen patients received fewer than 3

Toxicity data:

- Grade 3 and 4 neurotoxicity occurred:

2% of patients in the 3-cycle arm and
11% in the 6-cycle regimen ($p<0.01$).

- Grade 4 granulocytopenia was reported in:

52% of the 3-cycle and

66% of the 6-cycle arms, (p<0.01).

- Grade 2 or higher anaemia occurred in:

32% of the 3-cycle and
48% of the 6-cycle arms, (p<0.01).

- Treatment may have contributed to the death of two patients (One patient experienced a fatal cardiac arrest during her second cycle of treatment; another died from acute respiratory distress after her second cycle of chemotherapy)

Recurrence

- Reported recurrences = 101
- 2 women (one in each treatment arm), anticancer salvage therapy was initiated even though a rising CA125 level was the only indication for recurrent disease.
- Date of event: 48 months and 53 months, respectively (and was used to indicate recurrence for these two patients in this report.)

- Among the patients in the 3-cycle arm:

Estimated cumulative incidence of cancer recurring within 5 years was 25.4% compared to 20.1% in the 6-cycle arm.

- Adjusting for initial FIGO stage and tumour grade, the recurrence rate = 24% lower for patients treated with 6 cycles of chemotherapy (relative hazard=0.761, 95% CI=0.512–1.13, P=0.18).

- Adjusting for histological grade, the estimated treatment:
- Hazard ratio(HR) = 0.769 among patients with stage I disease and
- HR = 0.751 among those with stage II disease.

- The cumulative incidence of recurrence within 5 years:

18% for those women diagnosed with FIGO stage I
33% for those women diagnosed with FIGO stage II disease.

Staging Outcomes

- 29% of pts had surgical procedures that were considered inadequately documented or less thorough than specified by the protocol.
- 58 pts had an incomplete or inadequately documented surgical staging procedure in the 3-cycle arm and 68 in the 6-cycle arm; not statistically significantly diff.

- Among the 126 patients without a complete staging procedure,

88 (70%) had stage I disease and
38 (30%) had stage II disease.

- Cumulative incidence of recurrence within 5 years (without a complete staging procedure):

20% stage I disease
40% stage II disease

- Of the 427 patients deemed pathologically and medically eligible:

293 (69%) were surgical stage I
134 (31%) were stage II.

- Cumulative incidence of recurring within 5 years:

22% for those who did have a documented complete staging procedure
26% for those who did not. (difference is not statistically significant)

- In patients for whom complete surgical staging was documented; Cumulative incidence of

recurrence within 5 years:
23% for the 3- cycle
20% 6-cycle regimens
I.e. among women who were completely staged, the probability of remaining disease-free for at least 5 years is 77% and the estimated benefit of 3 additional cycles of therapy is to reduce the cumulative incidence of recurrence by 3%.

- The treatment hazard ratios (adjusted for FIGO stage and histological grade):

0.796 for those who did have a documented complete staging procedure or the former group
0.660 for those who did not i.e. the estimated benefit of 6 cycles was slightly less among those having complete staging surgery, although there is no significant evidence of heterogeneity in the treatment effect.

- Among the 301 patients considered to have had complete staging surgery:

205 (68%) had stage I disease
96 (32%) had stage II disease.

- Cumulative incidence of recurrence within 5 years (for those with complete staging surgery):

for FIGO stage I disease = 18%
for FIGO stage II disease = 31%

Survival

- The estimated probability of surviving 5 years:

84% for those women diagnosed with FIGO stage I and
73% for those women diagnosed with FIGO stage II disease.

- The estimated probability of surviving 5 years =

81% on the 3- cycle regimen and
83% on the 6-cycle regimen.

- The overall death rate is very similar for the two treatment groups (HR= 1.02; 95% CI=0.662–1.57, P=0.94).

Follow-up
Median duration of follow-up for the 344 patients who were alive at last contact = 6.8 years (1st and 3rd quartile are 5 and 8 years, respectively).

General comments
Outcome assessors were not blinded, which could have influenced the findings reported. Neither the investigators nor participants (but this would be very difficult to achieve unless a placebo was given to all participants.)

Author(s): Chan *et al.* (2010)

Design: Sub-group analysis of a Randomised Controlled Trial
Country: United States of America

Aim of study: To explore if there are sub-groups of patients with early stage high risk ovarian cancer that may benefit from more (6 cf. 3) cycles of chemotherapy based on demographic and clinic-pathological features.

Inclusion criteria (taken from Bell *et al.* (2006):

- Histological diagnosis of epithelial ovarian cancer including serous, mucinous, endometrioid, mixed, undifferentiated, Brenner, clear cell, and transitional types.

- Completely resected stage IA or 1B grade 3, stage IC, or stage II disease (any grade) and stage I or II clear cell early ovarian cancer.
- No prior treatment except surgery, adequate bone marrow, renal, and hepatic function, and a GOG performance status less than 4.
- Patients to be entered onto the trial within 6 weeks following staging laparotomy.

Exclusion criteria:

Borderline or low malignant potential tumours were ineligible.

Population:

- 457 patients were enrolled; 427 (93%) were considered eligible following centralized pathologic and medical review. 293 women (69%) were surgical stage I and 134 (31%) were stage II. Median age: 55 years.

- Group A: (N=213)
- Group B: (N=214)

Interventions and comparators (taken from Bell *et al.* (2006):

- Group A: 3 cycles of chemotherapy consisting of paclitaxel (P) 175 mg/m2 by 3 h infusion and carboplatin (C) dosed at AUC 7.5 by infusion over 30 min.
- Group B: 6 cycles of chemotherapy as above

Treatment cycles were scheduled every 21 days. The standard preparative regimen for paclitaxel included dexamethasone, diphenhydramine, and cimetidine.

- 4% of patients in Group A received <3 cycles and 5% of patients in Group B received <6 cycles.

Attrition rate: 96% of patients in Group A completed treatment compared with 83% in Group B.

Outcomes (taken from Bell *et al.* (2006):

- Recurrence was defined as any clinical or radiographic evidence of new tumour.
- Time at risk of recurrence was assessed from the date the patient was registered onto the study to the date of recurrence or to the date of last contact if no recurrence was observed.
- The recurrence rates for the study regimens were compared using a proportional hazards model adjusted for FIGO (International Federation of Gynaecology and Obstetrics) stage and histological grade.
- Overall Survival
- Toxicity: evaluated according to standard GOG toxicity criteria

<u>Power calculation:</u>
The study design provided an 85% chance of identifying a treatment regimen as active if it reduced the recurrence rate 50% when the type I error was set to 0.05 for a one-tail test. This treatment effect is comparable to increasing the expected percentage of patients who are recurrence-free at 4 years from 80.6% to 89.8%.

Results:

<u>Recurrence</u>

It was noted that the relative risk of recurrence between patients on three vs. six cycles of chemotherapy was similar for endometrioid, clear cell, mucinous and other sub-types, it was decided to sub-divide the data into 'serous' vs. 'non-serous'. Data were then stratified by demographic and clinic-pathological prognostic factors.

Recurrence between six cycles vs. three cycles:

Age, performance status, stage of disease, grade of disease, presence or absence of ascites, rupture or status of cytology were all non-significant (p>0.05).

Serous cancer: HR: 0.33 95% C.I: 0.14-0.77) (P=0.007)
Non-serous cancer: HR: 0.94 (95% C.I: 0.60-1.49) (P=0.806)
These ratios are statistically significantly different from one another (P=0.04).

When the sub-set of patients with serous tumours were evaluated, once more age, performance status, stage of disease, grade of disease, presence or absence of ascites, rupture or status of cytology were still all non-significant (p>0.05). This led the authors to conclude that the observed effect must, therefore, have been due to the increased number of chemotherapy cycles.

Five year recurrence-free survival in serous cancer patients was 82.7% with six cycles vs. 60.4% with three cycles (P=0.007) but a similar improvement was not observed in patients with non-serous cancer after five years: six cycles (78.7%) vs. three cycles (78.6%) (P=0.19).

Survival

Five year survival of serous cancer patients was 85.6% with six cycles vs. 73.2% with three cycles (P=0.19).

Follow-up: Median follow-up: 91 months

At this time point, 102 women had experienced disease recurrence and 94 had died.

Notes:

This paper describes a sub-group analysis of data reported previously in Bell *et al.* (2006). In that earlier report the authors had shown that the addition of 3 cycles of carboplatin plus paclitaxel to the standard 3 cycles did not significantly reduce the cancer recurrence rates for patients with high risk, early stage ovarian cancer. Conversely, the additional cycles of chemotherapy did significantly increase toxicity, but fewer patients completed the 6-cycle regimen. Whereas 95% of patients (pooling both treatment groups) completed 3 cycles, only 83% completed 6 cycles of therapy, primarily due to increased toxicity (4%) or patient decline (14%).

In this report, the authors have performed a sub-group analysis with data from the original trial, which had negative findings, and have shown a positive result in that women with serous tumours appear to derive a recurrence benefit from an additional three cycles of chemotherapy. This analysis was not planned in the original trial and the study was underpowered to have performed such sub-group calculations. Although of considerable clinical interest, the results should be interpreted with great caution and should be seen more as a guide to future planned prospective research than of proven clinical significance at this stage.

Author(s): Trimbos *et al.* (2010)

Design: Long term analysis from a randomised controlled trial

Country: The Netherlands

Aim of study: Long term follow-up analysis of the ACTION trial

Inclusion criteria: Women with epithelial ovarian cancer of stages IA-IIB, grade 2-3 and all stages IC and IIA and women with clear cell cancer stages I-IIA.

Exclusion criteria: None stated

Population: 488 women were enrolled:

Interventions and comparators:

Adjuvant cisplatin at 75mg per m^2 or carboplatin at 350mg per m^2 (N=224)

Treatment on progression (N=224).

Outcomes:

Cancer-specific survival (measured from the date of randomisation to the date of death from ovarian cancer).

Recurrence-free survival (measured from the date of randomisation to the first documented date of recurrence or death from any cause, whichever came first).

Results:

10 year cancer-specific survival

All patients (N=448)

Chemotherapy arm: 82% (range: 75-87%)
Observation arm: 76% (range: 69-82%)
Risk of death: HR 0.73 (95% C.I: 0.48-1.13) (P=0.16)

Optimally staged patients only

Chemotherapy arm: 85% (range: 73-92%)
Observation arm: 89% (range: 79-95%)
Risk of death: HR 1.58 (95% C.I: 0.61-4.08) (P=0.34)

Non-optimally staged patients only

Chemotherapy arm: 80% (range: 71-86%)
Observation arm: 69% (range: 60-77%)
Risk of death: HR 0.58 (95% C.I: 0.35-0.95) (P=0.029) in favour of chemotherapy.

10 year recurrence-free survival

All patients (N=448)

Chemotherapy arm: 70% (range: 62-76%)
Observation arm: 62% (range: 54-66%)
Risk of death: HR 0.64 (95% C.I: 0.46-0.89) (P=0.007) in favour of chemotherapy.

Optimally staged patients only

Chemotherapy arm: 78% (range: 66-86%)
Observation arm: 72% (range: 59-81%)
Risk of death: HR 0.73 (95% C.I: 0.38-1.42) (P=0.351)

Non-optimally staged patients only

Chemotherapy arm: 65% (range: 56-73%)
Observation arm: 56% (range: 47-64%)
Risk of death: HR 0.60 (95% C.I: 0.41-0.87) (P=0.007) in favour of chemotherapy.

Cancer-specific survival in patients with grade 3 disease

Chemotherapy arm: 75% (range: 62-84%)
Observation arm: 66% (range: 51-74%)
Risk of death: HR 0.62 (95% C.I: 0.34-1.12) (P=0.108)

Cancer-specific survival between optimally and non-optimally staged patients

Chemotherapy in optimally versus non-optimally patients

Chemotherapy arm optimally staged: 85% (range: 73-92%)
Chemotherapy arm non-optimally staged: 80% (range: 71-86%)
Risk of death: HR 1.27 (95% C.I: 0.62-2.58) (P=0.52)

Observation in optimally versus non-optimally staged patients

Observation arm optimally staged: 89% (range: 79-95%)
Observation arm non-optimally staged: 69% (range: 60-77%)
Risk of death: HR 3.28 (95% C.I: 1.47-7.33) (P=0.002)

Recurrence-free survival between optimally and non-optimally staged patients

Chemotherapy in optimally versus non-optimally patients

Chemotherapy arm optimally staged: 78% (range: 66-86%)
Chemotherapy arm non-optimally staged: 65% (range: 56-73%)
Risk of death: HR 1.64 (95% C.I: 0.91-2.93) (P=0.09) in favour of optimal staging.

Observation in optimally versus non-optimally staged patients

Observation arm optimally staged: 72% (range: 59-81%)
Observation arm non-optimally staged: 56% (range: 47-64%)
Risk of death: HR 1.91 (95% C.I: 1.17-3.11) (P=0.009) in favour of optimal staging.

Follow-up: Median follow-up was 10.1 years.

Notes:

This paper describes the long term results from the Adjuvant Chemotherapy in Ovarian Neoplasm (ACTION) trial first reported by Trimbos *et al.,* (2003). The original multi-centre trial was conducted between November 1st 1990 and January 23rd 2000.

The authors, whilst acknowledging some shortcomings in the original trial design with respect to the numbers recruited and the fact that the stratification into disease stages was retrospective, feel that these long term results largely support the original findings. The completeness of surgical staging in early ovarian cancer is an independent prognostic factor for recurrence-free and overall survival, even when adjuvant chemotherapy is given. The authors concluded that the benefit of adjuvant chemotherapy appeared to be limited to patients with non-optimal staging who might have had a greater risk of unidentified residual disease.

References:

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Chan JK, Tian C, Fleming GF, Monk BJ, Herzog TJ, Kapp DS *et al.*. (2010). The potential benefit of 6 vs. 3 cycles of chemotherapy in subsets of women with early-stage high-risk epithelial ovarian cancer: an exploratory analysis of a Gynecologic Oncology Group study. *Gynecol Oncol* **116(3):** 301-306.

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Winter-Roach BA., Kitchener HC and Dickinson HO (2009). Adjuvant (post-surgery) chemotherapy for early stage epithelial ovarian cancer. *Cochrane DB Sys Rev* 2009, Issue 3. Art. No: CD004706. DOI: 10.1002/14651858.CD004706.pub3.

Table 4.2 GRADE profile: For women with stage I ovarian cancer, what is the most effective first line chemotherapy [Back]

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	Chemo-therapy	Obser-vation	Relative (95% CI)	Absolute	
OS 5 years. Follow-up 46-110 months. Winter-Roach *et al* (2009)											
3	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	N/A	506	502	HR 0.71 (0.53 to 0.93) P=0.015	-	⊕⊕⊕⊕ HIGH
OS 5 years (sub-grouped by staging - all data). Follow-up 46-110 months. Winter-Roach *et al* (2009)											
3	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	N/A	506	500	HR 0.72 (0.53 to 0.97) P=0.033	-	⊕⊕⊕⊕ HIGH
OS 5 years (sub-grouped by staging - optimal staging). Follow-up 46-110 months. Winter-Roach *et al* (2009)											
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious imprecision[1]	N/A	117	117	HR 1.22 (0.63 to 2.37) P= 0.56	-	⊕⊕⊕ MODERATE
OS 5 years (sub-grouped by staging - sub-optimal staging. Follow-up 46-110 months. Winter-Roach *et al* (2009)											
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	N/A	389	383	HR 0.63 (0.46 to 0.85) P=0.0031	-	⊕⊕⊕⊕ HIGH

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	Chemo-therapy	Obser-vation	Relative (95% CI)	Absolute	
OS 10 years (sub-grouped by risk - all). Follow-up 46-110 months. Winter-Roach *et al* (2009)											
1	randomised trials	no serious limitations	N/A	no serious indirectness	N/A	N/A	-	-	totals not selected	-	N/A
OS 10 years (sub-grouped by risk - low/medium risk). Follow-up 46-110 months. Winter-Roach *et al* (2009)											
1	randomised trials	no serious limitations	N/A	no serious indirectness	N/A	N/A	-	-	not estimable	-	N/A
OS 10 years (sub-grouped by risk - high risk). Follow-up 46-110 months. Winter-Roach *et al* (2009)											
1	randomised trials	no serious limitations	N/A	no serious indirectness	N/A	N/A	-	-	not estimable	-	N/A
PFS 5 years. Follow-up 46-110 months. Winter-Roach *et al* (2009)											
4	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	N/A	587	583	HR 0.67 (0.53 to 0.84) P=0.00046	-	⊕⊕⊕⊕ HIGH
PFS 5 years (data sub-grouped by staging - all). Follow-up 46-110 months. Winter-Roach *et al* (2009)											
4	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	N/A	587	581	HR 0.64 (0.52 to 0.78) P=0.000012	-	⊕⊕⊕⊕ HIGH
PFS 5 years (data sub-grouped by staging - optimal staging). Follow-up 46-110 months. Winter-Roach *et al* (2009)											
2	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	serious imprecision[2]	N/A	117	117	HR 0.67 (0.36 to	-	⊕⊕⊕

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	Chemo-therapy	Obser-vation	Relative (95% CI)	Absolute	
									1.22) P=0.19		MODERATE
PFS 5 years (data sub-grouped by staging - sub-optimal staging). Follow-up 46-110 months. Winter-Roach *et al* (2009)											
3	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	N/A	470	464	HR 0.64 (0.50 to 0.82) P=0.00041	-	⊕⊕⊕⊕ HIGH
PFS 10 years (sub-grouped by risk). Follow-up 46-110 months. Winter-Roach *et al* (2009)											
1	randomised trial	no serious limitations	N/A	no serious indirectness	N/A	N/A	-	-	totals not selected	-	N/A
PFS 10 years (sub-grouped by risk - low/medium risk). Follow-up 46-110 months. Winter-Roach *et al* (2009)											
1	randomised trial	no serious limitations	N/A	no serious indirectness	N/A	N/A	-	-	not estimable	-	N/A
PFS 10 years (sub-grouped by risk - high risk). Follow-up 46-110 months. Winter-Roach *et al* (2009)											
1	randomised trial	no serious limitations	N/A	no serious indirectness	N/A	N/A	-	-	not estimable	-	N/A
DSS. Follow-up 46-110 months. Winter-Roach *et al* (2009)											
1	randomised trial	no serious limitations	N/A	no serious indirectness	serious imprecision[3]	N/A	81	81	HR 0.94 (0.37 to 2.37) P=0.90	-	⊕⊕⊕ MODERATE

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	Chemo-therapy	Obser-vation	Relative (95% CI)	Absolute	
Death from ovarian cancer. Follow-up 46-110 months. Winter-Roach *et al* (2009)											
3	randomised trials	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	N/A	41/346	54/347	RR 0.76 (0.52 to 1.11) P=0.16	-	⊕⊕⊕⊕ HIGH
10 year cancer-specific survival, all patients. Follow-up 10.1 years. Trimbos *et al* (2010)											
1	randomised trial	no serious limitations	N/A	no serious indirectness	N/A	N/A	82% (75-87%)	76% (69-82%)	HR 0.73 (0.48 to 1.13) P=0.16	-	⊕⊕⊕⊕ HIGH
10 year cancer-specific survival, optimally staged patients. Follow-up 10.1 years. Trimbos *et al* (2010)											
1	randomised trial	no serious limitations	N/A	no serious indirectness	N/A	N/A	85% (73-92%)	89% (79-95%)	HR 1.58 (0.61 to 4.08) P=0.34	-	⊕⊕⊕⊕ HIGH
10 year cancer-specific survival, non-optimally staged patients. Follow-up 10.1 years. Trimbos *et al* (2010)											
1	randomised trial	no serious limitations	N/A	no serious indirectness	N/A	N/A	80% (71-86%)	69% (60-77%)	HR 0.58 (0.35 to 0.95) P=0.029	-	⊕⊕⊕⊕ HIGH
10 year recurrence-free survival, all patients. Follow-up 10.1 years. Trimbos *et al* (2010)											

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	Chemo-therapy	Obser-vation	Relative (95% CI)	Absolute	
1	randomised trial	no serious limitations	N/A	no serious indirectness	N/A	N/A	70% (62-76%)	62% (54-66%)	HR 0.64 (0.46 to 0.89) P=0.007	-	⊕⊕⊕⊕ HIGH
10 year recurrence-free survival, optimally staged patients. Follow-up 10.1 years. Trimbos *et al* (2010)											
1	randomised trial	no serious limitations	N/A	no serious indirectness	N/A	N/A	78% (66-86%)	72% (59-81%)	HR 0.73 (0.38-1.42) P=0.351	-	⊕⊕⊕⊕ HIGH
10 year recurrence-free survival, non-optimally staged patients. Follow-up 10.1 years. Trimbos *et al* (2010)											
1	randomised trial	no serious limitations	N/A	no serious indirectness	N/A	N/A	65% (56-73%)	56% (47-64%)	HR 0.60 (0.41 to 0.87) P=0.007	-	⊕⊕⊕⊕ HIGH
10 year cancer-specific survival, patients with grade 3 disease. Follow-up 10.1 years. Trimbos *et al* (2010)											
1	randomised trial	no serious limitations	N/A	no serious indirectness	N/A	N/A	75% (62-84%)	66% (51-74%)	HR 0.62 (0.34-1.12) P=0.108	-	⊕⊕⊕⊕ HIGH

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	3 cycles	6 cycles	Relative (95% CI)	Absolute	
Overall death rate 5 years. 6 cycles vs. 3 cycles. Follow-up 6.8 years. Bell *et al* (2006)											

1	randomised trial	serious limitation[4]	N/A	no serious indirectness	serious imprecision[5]	N/A	213	214		HR 1.02 (0.66 to 1.57) P=0.94	⊕⊕ LOW
Rate of recurrence 5 years. 6 cycles vs. 3 cycles. Follow-up 6.8 years. Bell *et al* (2006)											
1	randomised trial	serious limitation[4]	N/A	no serious indirectness	serious imprecision[6]	N/A	213	214		HR 0.76 (0.51 to 1.13) P=0.18	⊕⊕ LOW
Rate of recurrence. 6 cycles vs. 3 cycles. Follow-up 91 months. Serous tumours. Chan *et al.* (2010)											
1	randomised trial	serious limitation[4]	N/A	no serious indirectness	serious imprecision[6]	N/A	60.4%	82.7%		HR 0.33 (0.14 to 0.77) P=0.007	⊕⊕ LOW
Rate of recurrence. 6 cycles vs. 3 cycles. Follow-up 91 months. Non-serous tumours. Chan *et al.* (2010)											
1	randomised trial	serious limitation[4]	N/A	no serious indirectness	serious imprecision[6]	N/A	78.6%	78.7%		HR 0.94 (0.60 to 1.49) P=0.806	⊕⊕ LOW

Footnotes

[1] The 95% confidence interval spans the line of no effect and exceeds the limits of both <0.75 x the effect size (0.92) and >1.25 x the effect size (1.53). The result suggests no significant difference between comparators.
[2] The 95% confidence interval spans the line of no effect and exceeds the limits of both <0.75 x the effect size (0.50) and >1.25 x the effect size (0.84). The result suggests no significant difference between comparators.
[3] The 95% confidence interval spans the line of no effect and exceeds the limits of both <0.75 x the effect size (0.71) and >1.25 x the effect size (1.20). This may due to low sample number. The result suggests no significant difference between comparators.
[4] There were few details of the randomisation allocation or assessment blinding methodology given.
[5] The 95% confidence interval spans the line of no effect and exceeds the limits of both <0.75 x the effect size (0.76) and >1.25 x the effect size (1.28). The result suggests no significant difference between comparators.
[6] The 95% confidence interval spans the line of no effect and exceeds the limits of both <0.75 x the effect size (0.57) and >1.25 x the effect size (0.95). The result suggests no significant difference between comparators.

Chapter 5: Management of advanced stage (II-IV) ovarian cancer

5.1 The value of primary surgery

"What is the effectiveness of surgery in the primary management of women with ovarian cancer who will receive chemotherapy?"

Short summary:

The evidence for this topic was limited and consisted of two Cochrane systematic reviews and two small randomised controlled trials (RCT) which dealt with different aspects of surgery. The total number of women across studies was 1,206 and all but stage I disease was represented. None of the studies addressed patient quality of life.

Morrison *et al.* (2007) conducted a Cochrane review of chemotherapy vs. surgery for the initial treatment of advanced ovarian cancer. Despite an extensive search of the literature, the authors identified only one small RCT which had randomised 85 women to receive either one cycle of chemotherapy followed by embolisation of the ovarian artery, debulking surgery and adjuvant chemotherapy or debulking surgery and adjuvant chemotherapy only. There was no statistically significant difference in median overall survival (26 months (95% C.I: 19.2-32.8 months) vs. 25 months (95% C.I: 22.8-27.2 months) (P>0.05)) between treatments. The chemo-embolisation arm did experience less surgery related morbidity but no other adverse events were reported.

Tangitjamol *et al.* (2009) reviewed three RCTs in which women with ovarian cancer who had undergone sub-optimal primary surgery were randomised to chemotherapy with interval debulking surgery (IDS) or chemotherapy without IDS. There was significant between studies heterogeneity and so the authors performed sub-group analyses. They concluded that if women had received their primary surgery from a general surgeon, as opposed to a gynaecological oncologist, or had received less extensive surgery, then IDS showed a marginal survival benefit (RR=0.68 (95% C.I: 0.53-0.87) P=0.003). There was no statistically significant difference between study arms in terms of either adverse events or quality of life.

Nicoletto *et al.* (1997) randomised 102 women with ovarian cancer, who had an apparently complete clinical response to primary surgery and adjuvant chemotherapy, to either second-look surgery (SSL) or a watch and wait policy. After a mean follow-up of 70 months the authors could demonstrate no significant difference in overall survival (HR=0.68 (95% C.I: 0.28-1.64) P=0.39) even though patients with a positive SSL were subsequently treated with non cross-reactive chemotherapy. (Luesley *et al.* (1988) recruited women with ovarian cancer who had received primary surgery (but were left with residual disease) and adjuvant cisplatin, randomising them to receive either SSL followed by chemotherapy with chlorambucil or pelvic irradiation. A third group received chemotherapy only. With an average follow-up of 46 months, there was no significant difference in median overall survival between the two surgical groups (21 months (95%: 11-31 months) vs. 15 months (95% C.I: 11-19 months) (P=0.75)) or between the surgery plus chemotherapy group vs. the chemotherapy only group (21 months (95%: 11-31 months) vs. 17 months (95% C.I: 13-21 months) (P=0.75)).

Review Protocol

Objectives

To assess the role of surgery in the treatment of women with ovarian cancer and to determine the optimal timing of surgery within the treatment pathway.

Study inclusion criteria

- **Population:** Women with ovarian cancer
- **Interventions:** Surgery before, during or after chemotherapy
- **Comparators:** Compared with each other or with no surgery
- **Outcome:** Overall and disease-free survival, morbidity and quality of life

Search strategy

The following electronic databases were searched: Medline, PreMedline, EMBASE, Cochrane Library, CINAHL, BNI, PsychInfo, AMED, Web of Science (SCI & SSCI) and Biomed Central. A general exclusion filter was applied (to eliminate non-reviewable material, for example notes, comments etc). No date filter was applied.

Review strategy

The titles and abstracts of the studies identified in the literature search were screened for potential relevance by one reviewer (AM).

One reviewer (KF) extracted data

Study quality was assessed using modified GRADE methodology (see Table 5.1).

Search results:

The literature search identified 288 potentially relevant studies. After reading study titles and abstracts 12 papers were ordered of which 4 papers were eventually included.

Evidence summary:

The evidence on this topic was quite limited and consisted of two Cochrane systematic reviews and two small randomised controlled trials (RCT). The total number of women across studies was 1,206 and all but stage I disease was represented.

One review (Morrison *et al.* 2007) found only one relevant RCT randomising women with advanced ovarian cancer to receive chemotherapy either before (neoadjuvant) or after (adjuvant) debulking surgery. Women in the neoadjuvant arm received one cycle of chemotherapy before and seven cycles after surgery whereas women in the adjuvant arm received eight cycles of chemotherapy after surgery. There was no statistically significant difference in overall survival between intervention (26 months (95% C.I: 19.2-32.8 months) and control arms (25 months (95% C.I: 22.8-27.2 months) (P>0.05). The median disease-free survival was 18.2 months in the intervention arm and 14.2 months in the control arm (no statistical comparison made). There were no quality of life statistics or adverse events reported, other than post-operative blood loss which was significantly lower in those women from the interventional group. The included study (Liu *et al.* 2004) did not give adequate methods of randomisation and allocation was not concealed. Blinding of treatment assessors was not mentioned and withdrawal from treatment

was also unclear. As a single paper, this may well have been considered as being of only low quality.

The second review (Tangitjamol *et al.* 2009) included three RCTs in which women with ovarian cancer who had undergone sub-optimal primary surgery were randomised to chemotherapy with interval debulking surgery (IDS) vs. chemotherapy without IDS. Unfortunately, due to differences in methodological criteria, there was significant between studies heterogeneity that precluded the detection of any significant difference between study arms for either overall survival or progression-free survival. The authors explored these findings by performing sub-group analyses and concluded that if women had received their primary surgery from a general surgeon then IDS showed a marginal survival benefit (RR=0.68, 95% C.I: 0.53-0.87; P=0.003). But, for those women who had primary surgery performed by a gynaecological oncologist no survival advantage was seen with IDS (RR=0.99, 95% C.I: 0.79-1.24; P=0.93). This observation might be explained in that the more thorough the initial surgery, the less improvement could possibly be made by IDS but if initial surgery was sub-optimal then further surgery might prove worthwhile. One advantage of IDS was reported in a single study suggesting that giving the patient a break between successive chemotherapy cycles (i.e. during IDS) there was a consequent reduction of neurological problems. There was, however, no statistically significant difference between study arms in terms of either adverse events or quality of life.

The RCT (Nicoletto *et al.* 1997) randomised women with ovarian cancer who had an apparently complete clinical response to primary surgery and adjuvant chemotherapy to either second look surgery or a watch and wait policy. After a mean follow-up of seventy months, the authors could demonstrate no significant difference in overall survival (HR=0.68 (95% C.I: 0.28-1.64) although this may have been due to the underpowering of the study. The trial was of low quality, with no details of randomisation or allocation to study arms.

The second RCT (Luesley *et al.,* 1988) recruited women with ovarian cancer who had undergone primary surgery (but with disease residua) and adjuvant cisplatin, randomising them to receive either second look surgery followed by more chemotherapy, with chlorambucil, or pelvic irradiation. A third group received chemotherapy only. With an average follow-up of forty-six months, there was no significant difference in median OS between the two surgical groups (21 months (95%:11-31 months) vs. 15 months (95% C.I:11-19 months) X^2=0.11 P=0.75) or between the surgery plus chemotherapy group vs. the chemotherapy only group (21 months (95%:11-31 months) vs. 17 months (95% C.I: 13-21 months) X^2=0.11 P=0.75). This relatively small study was probably underpowered to have detected a difference between treatments, had one existed. The trial was also of limited quality, with no details of randomisation or allocation to study arms.

Evidence tables:

Author(s): Morrison *et al* (2007)
Design: (Cochrane) Systematic Review **Country:** UK
Inclusion criteria: **Population:** Women with advanced ovarian cancer (FIGO stages IIIc and IV). **Studies:** Randomised controlled trials (RCT) in which women were randomised to chemotherapy before or after debulking surgery.
Exclusion criteria: None stated
Population: N=85. Mean age intervention arm: 53.3 years. Mean age control arm: 54.2 years.
Intervention(s) and comparator(s) in included studies: • Intervention (N=42): 1 dose of neoadjuvant platinum-based chemotherapy given directly into the ovarian artery followed by embolisation. Then, de-bulking surgery followed by 7 cycles of platinum-based chemotherapy. • Control (N=43): Debulking surgery then 8 cycles of platinum-based chemotherapy.
Outcomes: • Primary outcome: Overall survival • Secondary outcome: Disease-free interval
Results: There was no statistically significant difference between overall survival in intervention (26 months (95% C.I: 19.2-32.8 months) and control arms (25 months (95% C.I: 22.8-27.2 months) (P>0.05). The median disease-free survival was 18.2 months in the intervention arm and 14.2 months in the control arm (no statistical comparison made). There were no quality of life statistics or adverse events reported, other than post-operative blood loss which was significantly lower in those women from the interventional group.
Follow-up: The median follow-up period was 32 months (range: 8-98 months). All patients were accounted for.
Notes: This moderate quality paper reviewed one RCT comparing chemotherapy before or after surgery for women with advanced ovarian cancer. Two authors searched The Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, MEDLINE, EMBASE,

CANCERLIT, PDQ and MetaRegister up to September 2006. Details of the search strategy were presented. Hand searching of gynaecological journals was also conducted and journal authors contacted for elaboration where required. Papers were selected, reviewed and data were extracted by two independent researchers and disagreements were resolved by discussion. Each trial was assessed for bias with respect to methods of randomisation, allocation, blinding (of the outcome assessors) loss to follow-up and intention-to-treat analyses. Only one RCT was selected as being suitable to provided evidence on this topic and hence a data meta analysis could not be performed. Median overall survival was determined by Kaplan-Meier analysis but a hazard ratio was not calculated.

The selected RCT (Liu *et al.* 2004) did not give adequate methods of randomisation and allocation was not concealed. Blinding of treatment assessors was not mentioned. Withdrawal from treatment was also unclear. As a single paper, this may well have been considered as being of only low quality. Although the intentional population was women with stage IIIc and IV ovarian cancer, the eventual breakdown of staging was as follows:

Stage II: Intervention (73.8%) vs. control (76.4%)
Stage IV: Intervention (26.2%) vs. controls (23.3%)
Grade 3: Intervention (57.1%) vs. control (51.2%)
Serous cystadenocarcinoma: Intervention (90.5%) vs. control (83.7%)

The authors acknowledge the poor quality and quantity of evidence and could not satisfactorily conclude whether or not there was a survival advantage with neoadjuvant chemotherapy. The addition of embolisation to the intervention arm may well have confounded the observations on the efficacy of neoadjuvant chemotherapy. The authors also noted that Liu *et al* did not perform a power calculation and hence their study may well be underpowered to have detected any statistically meaningful differences between treatments.

Whilst this review is of moderate quality, the evidence within it is poor and inconclusive.

Included study:

Liu EL and Mi RR. (2004) Neoadjuvant intraarterial chemotherapy and embolization in treatment of advanced ovarian epithelial carcinoma. *Chinese Medical Journal (Engl)* **117**(10):1547–51.

Author(s): Tangjitgamol *et al* (2009)

Design: (Cochrane) Systematic Review
Country: Thailand

Population: N=853

Inclusion criteria:

Population: Women with resectable ovarian cancer (FIGO stages II to IV).

Studies: Randomised controlled trials (RCT) in which women who had undergone primary surgery, but had residual disease, were randomised to chemotherapy with interval debulking surgery (IDS) vs. chemotherapy without IDS.

Exclusion criteria: None stated

Intervention(s) and comparator(s):

[1] Intervention (N=37): Primary surgery (with residual disease > 2cm) followed by 1-4 three-week cycles of iv cisplatin at 75 mg per m^2 plus cyclophosphamide at 750 mg per m^2 or cisplatin at 75 mg per m^2 plus doxorubicin at 50 mg per m^2 plus bleomycin at 50 mg per m^2. IDS followed by an escalated dose of cyclophosphamide at 0.5-2.5 g per m^2 up to 5 cycles. Control (N=42): Chemotherapy as above, given consecutively without further surgery.

[2] Intervention (N=226): Primary surgery (with residual disease > 1cm) followed by 3 three-week cycles of iv paclitaxel at 135 mg per m^2 plus cisplatin at 75 mg per m^2. IDS then 3 cycles of chemotherapy as above. Control N=222): Chemotherapy as above, given consecutively without further surgery.

[3] Intervention (N=140): Primary surgery (with residual disease > 1cm) followed by 3 three-week cycles of iv cyclophosphamide at 750 mg per m^2 plus iv cisplatin at 75 mg per m^2. IDS then 3 more cycles. Control: Control (N=138): Chemotherapy as above, given consecutively without further surgery.

Outcomes:

- Primary outcome: Overall survival
- Secondary outcomes: Progression-free survival, adverse events, QOL

Results:

The data for overall survival showed significant between studies heterogeneity (I^2=58%) hence the authors explored the reason for this by performing sub-group analysis. By dividing the studies on the basis of surgical expertise they concluded that for women who had their primary surgery performed by a general surgeon, IDS showed a marginal survival benefit (RR=0.68, 95% C.I: 0.53-0.87; P=0.003). For those women who had primary surgery performed by a gynaecological oncologist no survival advantage was seen with IDS (RR=0.99, 95% C.I: 0.79-1.24; P=0.93).

Meta analysis of data for progression-free survival also demonstrated significantly high between studies heterogeneity (I^2=75%) and no sub-group analysis could be performed. From these results it would be impossible to determine whether or not there was an advantage to IDS for this outcome.

Only data for one adverse event (toxic reaction to chemotherapy) could be combined across studies. The results showed no significant between studies heterogeneity and no significant difference in incidence of toxicity between study arms (RR=1.23, 95% C.I: 0.42-3.56, P=0.71). One study (Rose *et al*., 2004) reported that they had noted a significantly higher rate of neurological problems in women who had received chemotherapy only (P=0.01). Similarly, only that study team reported QOL outcomes and found apart from women in the continuous chemotherapy (cisplatin and paclitaxel) arm experiencing more persistent peripheral numbness and tingling (P=0.012), QOL was otherwise similar between study groups.

Follow-up:

The median follow-up period was between 42 and 48 months across all three studies.

Notes:

This moderate quality paper reviewed three RCTs investigating the role of interval debulking surgery in women with advanced ovarian cancer. Two authors searched The Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, MEDLINE, EMBASE and reference lists of the included studies up to June 2008. Details of the search strategy were presented. Hand searching of gynaecological journals was also conducted and journal authors contacted for elaboration where required. Papers were selected, reviewed and data were extracted by two independent researchers and disagreements were resolved by discussion. Each trial was assessed for bias with respect to methods of randomisation, allocation, blinding (of the outcome assessors) and loss to follow-up. All trials were reported to have demonstrated adequate randomisation and allocation but blinding (of treatment assessors) was not detailed. Sensitivity analyses were not required. All trials reported intention to treat analyses.

The term 'interval debulking' varied across studies, defined as residual tumour of < 2cm or < 1cm. Similarly, overall survival was calculated from different time points i.e. from the day of induction chemotherapy, day of randomisation or after three cycles of chemotherapy and the definitions of disease recurrence and disease progression also varied between studies. Consideration should be given to whether this variability may adversely have affected the pooling of data.

Meta analyses were performed for survival outcomes but were not feasible for most adverse events or QOL since data were insufficient. In the only study that analysed data on QOL, significantly fewer women in the IDS arm completed the second questionnaire compared with women in the chemotherapy arm and it is possible that the reason for this was a QOL issue in itself. Pooled time-to-event data were presented as log relative risk ratios (RR) and dichotomous data as relative risk (RR). It was stated that a fixed effects model was applied to the meta analyses and the authors stated that it was their intention, on finding between studies heterogeneity, to attempt an explanation

The results from the survival analyses were confounded by heterogeneity between studies which precluded sound conclusions from the review authors. They suggested that the meta analyses were underpowered to detect a small effect, had one existed, in terms of survival advantage for IDS. As detailed above, some of the heterogeneity is likely to have been as a result of the observed differences in terminology and assessment timepoints. However, the authors also highlight the differences in surgical expertise between studies and suggest that women who had primary surgery performed by a general surgeon or gynaecologist had a better outcome in terms of survival. Intuitively, it might be supposed that the more thorough the initial surgery, the less improvement could be made by IDS but if the initial surgery was sub-optimal then further surgical intervention (IDS) would appear to be more worthwhile.

The authors concluded that although the evidence was sparse, women who had optimal primary surgery may not receive such a benefit from IDS but women for whom primary surgery was sub-optimal, or contraindicated, IDS may give a survival benefit in addition to chemotherapy.

Whilst this review is of moderate quality, the evidence within it is inconclusive.

Included studies:

Redman CW, Warwick J, Luesley DM, Varma R, Lawton FG, Blackledge GR. (1994) Intervention debulking surgery in advanced epithelial ovarian cancer. *Br J Obstet Gynae.* **101**:142–6.

Rose PG, Nerenstone S, Brady M, Clarke Pearson D, Olt G, Rubin SC, *et al*. (2002)A phase III randomised study of interval secondary cytoreduction in patients with advanced stage ovarian carcinoma with suboptimal residual disease: a Gynecologic Oncology Group study. *Proc Am Soc Clin Oncol.* **Vol. 21** (Pt 1):201a.

van der Burg ME, Coens C, van Lent M, Kobierska A, Colombo N, Favalli G, *et al*. (2004) After ten years follow-up interval debulking surgery remains a significant prognostic factor for survival and progression free survival for advanced ovarian cancer: the EORTC Gynaecological Cancer Group study. *Int J Gynecol Cancer* **Vol. 1**4 (Suppl 1):3.

Author(s): Luesley *et al*. (1988)

Design: RCT
Country: UK

Population: N=166

Inclusion criteria:

Population: Women with FIGO stages IIb residual, III and IV biopsy confirmed epithelial ovarian cancer. Creatinine clearance rate had to be adequate to in order to allow treatment with cisplatin.

Exclusion criteria: None stated

Intervention(s) and comparator(s):

[1] Group A (N=53): Cisplatin at 100mg per m2 x 5 cycles then second-look laparotomy followed by cyclical oral chlorambucil at 0.2 mg per kg x 12 courses.

[2] Group B (N=56): Cisplatin at 100mg per m2 x 5 cycles then second-look laparotomy followed by total abdominal and pelvic irradiation (only for women whose residual disease <2cm).

[3] Group C (N=57): Cisplatin at 100mg per m2 x 5 cycles then oral chlorambucil 0.2 mg per kg x 12 courses.

Outcomes:

- Primary outcome: Overall survival
- Secondary outcomes: Response to cisplatin: complete response (CR), partial response (PR), stable disease (SD) or disease progression (PD). Adverse events.

Results:

Response to chemotherapy:
Of the total number of women with clinically evaluable disease before receiving cisplatin (N=94/166), the response rate was 44/94 (47%). The response per group was:

Group A:
CR = 4/27 (15%) PR = 5/27 (19%) SD = 6/27 (22%) and PD = 12/27 (44%)

Group B:
CR = 6/36 (17%) PR = 15/36 (42%) SD = 8/36 (22%) and PD = 7/36 (19%)

Group C:

CR = 8/31 (26%) PR = 6/31 (19%) SD = 3/31 (10%) and PD = 14/31 (45%)

There was no significant difference between groups in cisplatin response.

Findings after second-look laparotomy:

Group A: 32/53 (60%):

CR (microscopic or no disease) = 16/32 (50%)
Bulky disease remaining = 6/36 (17%)
Optimal resection = 10/36 (28%)

Group B: 38/56 (68%):

CR (microscopic or no disease) = 9/38 (24%)
Bulky disease remaining = 10/38 (26%)
Optimal resection = 19/38 (50%)

Median overall survival:

Group A: 21 months (95% C.I: 11-31 months)
Group B: 15 months (95% C.I: 11-19 months)
Group C: 17 months (95% C.I: 13-21 months)

* Authors stated that there was no significant difference in median OS between groups A and B (chi2 = 0.11 P=0.75) when the data were adjusted for residual disease and stage variables although the differences were highly significantly different unless women with inoperable disease were excluded from the calculations. The confidence interval for the true difference suggests highly variable data since it spanned from -10 to +18 months. The authors also stated that there was no significant difference in median OS between groups A and C (chi2 = 0.11 P=0.75).** From the actuarial survival curve stratified by residual disease at second-look surgery, the median OS for women with a complete pathological remission was ~23 months compared with a median OS of ~13 months for women with inoperable disease.

** note that these figures are the same as for the comparison between groups A and B. This may be an error.

Adverse events:

Various adverse events were reported but no data were given on their severity or incidence among the women who received second-look surgery. The events listed were cerebrovascular event (N=1 fatal) small bowel ileus, urinary tract infection, respiratory tract infection and anaemia.

Follow-up: Median follow-up was 46 months (range: 21-64 months). Patients were assessed monthly for the first year and then every two months in the second year and were examined clinically and by imaging (CT, ultrasound). Women were withdrawn from the study if they showed disease progression.

In group A, 21/53 (40%) women did not have second-look surgery due to PD (N=10) toxicity (N=1) refusal (N=5) or because of the treating physician's decision (N=5). In group B, 18/56 (32%) women also did not undergo further surgery due to PD (N=10) toxicity (N=2) refusal (N=2) or because of the treating physician's decision (N=4). In group C, 11/57 (19%) women did not have chlorambucil due to PD (N=10) or protocol violation (N=1).

Notes: This is a small RCT assessing the benefits of second-look laparotomy. Women were recruited by the West Midlands Ovarian Cancer Group between October 1981 and June 1985. Whilst the women had undergone primary surgery to remove as much as possible of the tumour, all had some residual macroscopic disease. Surgery was followed, three weeks later, by five cycles of cisplatin. Two out of three groups were then given a second laparotomy six weeks after chemotherapy and the third group, women with residual disease <2 cm, received chemotherapy only.

Second-look laparotomy included (if not already done) peritoneal fluid sampling, total hysterectomy, bilateral salpingoophorectomy, total omentectomy and, if there was no sign of macroscopic disease, multiple peritoneal biopsies and para-aortic lymph node biopsy. Any apparently diseased looking tissue was removed.

The study authors gave no details of any randomisation or allocation methodology. Blinding was probably not feasible given the nature of the treatment and survival was the primary outcome of interest. With different post-surgical treatments i.e. chemotherapy versus radiotherapy, with variable clinical responses to cisplatin, stratification for disease residua and stage plus relatively small patient numbers, it may not have been possible to accurately assess the effects of second-look surgery in this trial. However, the authors conclude that their data demonstrated that there was no difference in survival amongst patients who received second-look surgery compared with patients who did not. On the other hand, this study was probably statistically underpowered to have demonstrated a difference anyway, had one existed.

Author(s): Nicoletto *et al.* (1997)

Design: RCT
Country: Italy

Inclusion criteria: Women with histologically confirmed ovarian cancer of any grade having had a complete response following primary surgery and first line chemotherapy with either doxorubicin and cyclophosphamide or cisplatin and cyclophosphamide.

Exclusion criteria: Women with surgical stages Ia, Ib or IIa at presentation

Population: N=102

Interventions and comparators:

Intervention (N=54): Surgical second look (SSL) including biopsy of sites of apparent disease, sites of previous disease (even if normal in appearance) sites of a suspicious appearance and elective sites where seeding is generally held to be common i.e. pelvic peritoneum, colonic gutters, falciform ligament of the liver, inferior aspects of the diaphragm and retroperitoneal nodes). Women with a positive finding received second line chemotherapy of fluorouracil at 500 mg per m^2 and cisplatin at 100 mg per m^2. Control (N=48): Watch and wait policy.

Outcomes: Overall survival (measured from date of surgery) in an intention to treat analysis.

Results: There were no significant differences in baseline characteristics between study arms, including age, stage, grade, histology and residual tumour after surgery. Of forty-six women who received SSL, thirty-five subsequently had negative findings and eleven had positive findings.

Intervention vs. control: HR=0.68 (95% C.I: 0.28-1.64) (P=0.39). There was no significant difference between study arms in terms of overall survival. Sub-group analysis of survival showed that compared with earlier stages, women with stage III disease had a statistically significantly higher risk of death: HR=3.08 (95% C.I: 1.12-8.43) (P=0.02). No other factors e.g. age or tumour grade proved of significance in similar sub-group analyses.
Follow-up: Eight of the forty-eight patients assigned to surgery refused treatment. Follow-up was 70 months.
Notes: This small RCT was conducted from multiple centres in Italy. There were no technical details of randomisation or allocation and hence the risk of bias cannot be excluded with certainty. The study also had only 70% power to detect a significant difference and hence may have benefitted from a higher patient number. The authors could not demonstrate any significant benefit of surgical second effort. Additionally, since many women who had positive findings then received second line chemotherapy, the results suggest that this was also ineffective at prolonging survival when compared with a watch and wait policy. It was apparent that women with later stage disease had a higher risk of death with laparotomy compared with laparoscopy (i.e. intervention vs. control) than women with early stage disease. This paper, therefore, offered no evidence to support second surgery in women who demonstrated a complete clinical response to surgery and adjuvant chemotherapy.

References:

Luesley D, Blackledge G, Kelly K, Wade-Evans T, Fielding J, Lawton F, Hilton C, Rollason T, Jordan J, Latief T, Chan KK. (1988) Failure of second-look laparotomy to influence survival in epithelial ovarian cancer. *Lancet* **332 (8611):** 599-603

Morrison J, Swanton A, Collins S, Kehoe S. (2007) Chemotherapy versus surgery for initial treatment in advanced ovarian epithelial cancer. *Cochrane Database of Systematic Reviews* 2007, Issue 4. Art. No.: CD005343. DOI: 10.1002/14651858.CD005343.pub2.

Nicoletto MO, Tumolo S, Talamini R, Salvagno L, Franceschi S, Visona E, Marin G, Angelini F, Brigato G, Scarabelli C, Carbone A, Cecchetto A, Prosperi A, Rosabian A, Giusto M, Cima GP, Morassut S, Nascimben O, Vinante O, Fiorentino MV. (1997) Surgical second look in ovarian cancer: a randomized study in patients with laparoscopic complete remission--a Northeastern Oncology Cooperative Group-Ovarian Cancer Cooperative Group Study. *J Clin Oncol.* **15(3):** 994-9.

Tangjitgamol S, Manusirivithaya S, Laopaiboon M, Lumbiganon P. Interval debulking surgery for advanced epithelial ovarian cancer. *Cochrane Database of Systematic Reviews* 2009, Issue 2. Art. No.: CD006014. DOI: 10.1002/14651858.CD006014.pub4.

Table 5.1 GRADE profile: What is the effectiveness of surgery in the primary management of women with ovarian cancer who will receive chemotherapy? [Back]

Quality assessment							Summary of findings				
							Time in months		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	Chemo-therapy before surgery	Chemo-therapy after surgery	Relative (95% CI)	Absolute	Quality
Mean OS (P>0.05). Follow-up 32 months (range: 8-98 months) Liu *et al.*, 2004 (in Morrison *et al.* 2007)											
1	RCT	serious limitations[1]	N/A	no serious indirectness	serious imprecision[2]	N/A	33.7 (95% C.I: 24.7-42.6)	32.4 (95% C.I: 24.9-39.8)	-	-	⊕⊕ LOW
Median OS (P>0.05). Follow-up 32 months (range: 8-98 months) Liu *et al.*, 2004 (in Morrison *et al.* 2007)											
1	RCT	serious limitations[1]	N/A	no serious indirectness	serious imprecision[2]	N/A	26 (95% C.I: 19.2-32.8)	25 (95% C.I: 22.8-27.2)	-	-	⊕⊕ LOW
Median DFI (P>0.05). Follow-up 32 months (range: 8-98 months) Liu *et al*., 2004 (in Morrison *et al.* 2007)											
1	RCT	serious limitations[1]	N/A	no serious indirectness	serious imprecision[2]	N/A	18.2 (no 95%CI)	14.2 (no 95%CI)	-	-	⊕⊕ LOW
Overall survival (χ^2= 6.48; P>0.05). Follow-up 32 months (range: 8-98 months) Liu *et al.*, 2004 (in Morrison *et al.* 2007)											
1	RCT	serious limitations[1]	N/A	no serious indirectness	serious imprecision[2]	N/A	-	-	-	-	⊕⊕ LOW

Footnotes:

[1] This was a non-English language study that had not apparently been translated by the Cochrane reviewers. Although the original study authors stated that they had randomised patients, there were no details of randomisation or allocation and blinding of outcome assessors was not mentioned. ITT analysis was used but treatment withdrawals were no discussed.

[2] The Kaplan Meier plot and tables accompanying the text of Liu *et* al (2004) were not accessible and may have included more data with regard to survival however this was a low patient number trial. Patients: women with stage III (actually II) or IV EOC; Intervention: neoadjuvant intra-arterial chemo (1 cycle), ovarian artery embolisation then primary surgery followed by adjuvant i.v. chemo (7 cycles) (N=42); Control: primary surgery followed by adjuvant i.v. chemo (8 cycles) (N=43).

Quality assessment							Summary of findings				
							Patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	Interval debulking surgery	No interval debulking surgery	Relative (95% CI)	Absolute	Quality
Risk of death (P=0.04) (if surgery was performed by general surgeons). Follow-up 42-48 months. Tangjitgamol *et al.*, 2009											
2	RCT	no serious limitations[1]	no serious inconsistency[2]	no serious indirectness	no serious imprecision	N/A	177	180	RR=0.68 (0.53-0.87)	-	⊕⊕⊕⊕ HIGH
Risk of death (P=0.9) (if surgery was less extensive or performed by gynaecological surgeons). Follow-up 42-48 months. Tangjitgamol *et al.*, 2009											
1	RCT	no serious limitations[1]	N/A	no serious indirectness	no serious imprecision	N/A	216	208	RR=0.99 (0.79-1.24)	-	⊕⊕⊕⊕ HIGH
Toxic reactions to chemotherapy (P=0.7). Follow-up 42-48 months. Tangjitgamol *et al.*, 2009											
2	RCT	no serious limitations[1]	no serious inconsistency	no serious indirectness	serious imprecision[3]	N/A	7/177	6/180	RR=1.23 (0.42-3.56)	1 fewer per 100	⊕⊕⊕ MODERATE

[1] The three included studies in this systematic review were described by the authors as having given sufficient details of randomisation and allocation but blinding of treatment assessors was not described. All studies used ITT analysis.

[2] The original pooled data for survival from the three included studies showed significant heterogeneity (I^2=58%) and the authors addressed this by stratifying data by surgical speciality, as shown in the table.

[3] The confidence interval around the estimate of effect spans '1' (the line of no effect) and the limits for 'appreciable harm' and 'appreciable benefit'.

Quality assessment							Summary of findings				
							Patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	2nd look surgery	Watchful waiting	Relative (95% CI)	Absolute	
Overall survival (χ^2=0.74; P=0.39). Follow-up ~70 months. Nicoletto *et al.,* 1997											
1	RCT	serious limitations[1]	N/A	no serious indirectness	serious imprecision[2]	N/A	54	48	HR=0.68 (0.28-1.64)	-	⊕⊕ LOW

[1] This study did not demonstrate adequate details of randomisation, allocation or blinding of treatment assessors. The study used ITT analyses.
[2] The confidence interval is wide and crosses the line of no effect as well as exceeding limits for 'appreciable harm' and 'appreciable benefit'. This is probably due to the low patient number

Quality assessment							Summary of findings			
							Patients			Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	[A] 2nd look surgery then chemo-therapy	[B] 2nd look surgery then radio-therapy	[C] Chemo-therapy	
Median survival (A vs. B: χ^2=0.11; P=0.75; A vs. C: χ^2=0.11; P=0.75). Follow-up 46 months (range: 21-64 months). Luesley *et al.,* 1988										
1	RCT	very serious limitations[1]	N/A	no serious indirectness	very serious imprecision[2]	N/A	21 months (95% C.I: 11-31 months) N=42/53	15 months (95% C.I: 11-19 months) N=49/56	17 months (95% C.I: 13-21 months) N=44/57	⊕ VERY LOW

[1] This study did not demonstrate adequate details of randomisation, allocation, blinding of treatment assessors or ITT analysis.
[2] The comparison of Group A vs. Group C may be unsafe since, on the Kaplan Meier plot shown, the lines representing each population cross several times. The statistics (chi square and P value) from Groups A vs. B and A vs. C are identical which may be accurate or not. The study is probably underpowered to detect a significant difference between study arms.

5.2 Intra-peritoneal chemotherapy

"For women with ovarian cancer, is intra-peritoneal chemotherapy effective in primary management?"

Short summary:

The evidence for this topic comprises two high quality systematic reviews (Jaaback and Johnson, 2006 and Elit *et al.,* 2007) and one randomised controlled trial (RCT) (Wenzel *et al.*, 2007). Between them, these studies reported on all the outcomes of interest. The two systematic reviews included meta-analyses of data from the same RCTs but both reviews were appraised because the authors reported different survival outcomes. The majority of trial data derived from the United States of America and all the studies compared the use of standard intravenous chemotherapy with chemotherapy regimens incorporating a component of intraperitoneal drug delivery for the first line adjuvant treatment of primary ovarian cancer.

High quality evidence from pooled data from up to eight trials suggested that chemotherapy given directly into the peritoneal cavity as part of adjuvant treatment, may significantly reduce the risk of death (HR: 0.80, 95% C.I: 0.71-0.90; P=0.0003) and disease recurrence (HR: 0.79, 95% C.I: 0.69-0.90; P=0.0004) an effect also seen after five years of follow-up (RR of death: 0.88, 95% C.I: 0.81-0.95; P=0.002; RR of disease progression: 0.91, 95% C.I: 0.85; P=0.02). However, incidences of pain, fever, fatigue, hearing loss, infection and gastrointestinal and metabolic effects occurred up to eight times more frequently in women receiving intraperitoneal chemotherapy. The one exception to this observation was the incidence of cardiovascular effects which were not significantly different between study arms. The evidence about haematological, pulmonary, renal and neurological adverse effects was too poor in quality to allow conclusions to be drawn about the relative contribution of the drug delivery route. Health-related quality of life was measured in one trial and found to be significantly worse for women receiving intraperitoneal chemotherapy in the early days of treatment and shortly (3 to 6 weeks) after all study treatment, but a difference between study arms was not apparent after one year of follow-up.

Review Protocol:

Objectives

To determine the clinical benefits and toxicity of intraperitoneal chemotherapy given as part of the first line management of ovarian cancer.

Study inclusion criteria

- **Population:** Women with ovarian cancer who require chemotherapy
- **Interventions:** Systemic chemotherapy, intraperitoneal chemotherapy
- **Comparators:** Compared with each other or in combination
- **Outcome:** Overall and disease-free survival, morbidity and quality of life

Search strategy

The following electronic databases were searched: Medline, PreMedline, EMBASE, Cochrane Library, CINAHL, BNI, PsychInfo, AMED, Web of Science (SCI & SSCI) and Biomed Central. A Cochrane Library systematic review ('Intraperitoneal chemotherapy for the initial management of primary epithelial ovarian cancer' - Jaaback *et al*., January 2006) was used as a basis for the search using the authors' published search strategy. Databases such as Medline and EMBASE

were last searched for evidence in March 2005 and so this update search was executed from 2004 onwards. The specialised databases were searched with no date limit as they had not been searched in original review. A general exclusion filter was applied (to eliminate non-reviewable material, for example notes, comments etc).

Review strategy

The titles and abstracts of the studies identified in the literature search were screened for potential relevance by one reviewer (KF).

One reviewer (KF) extracted data on the various treatment schedules from included studies and recorded survival, toxicity and quality of life outcomes.

Study quality was assessed using modified GRADE methodology (see Table 5.2).

Search results:

The literature search identified 255 potentially relevant studies. After reading study titles and abstracts 10 papers were ordered of which 3 papers were eventually included.

Evidence summary:

The evidence for this topic comprises two high quality systematic reviews (Jaaback and Johnson, 2006 and Elit *et al.,* 2007) plus a randomised controlled trial (RCT) (Wenzel *et al.*, 2007). Between them these studies reported on all the outcomes of interest. The systematic reviews included meta-analyses of data from the same RCTs but both reviews were appraised because the authors reported different outcomes. The majority of trial data derived from the United States of America and all the studies compared the use of standard intravenous chemotherapy with chemotherapy regimens incorporating intraperitoneal drug delivery for the treatment of primary ovarian cancer.

Consideration should be given to the particular drug regimes and doses employed in these trials since they may not accord with current treatment policy in the UK. Additionally, in some trials, higher drug doses were given to women randomised to the intraperitoneal-containing chemotherapy arm which may have contributed both to the increased incidence of adverse effects, short term decreased quality of life and perhaps even to the observed improvements in overall and disease-free survival. On the other hand, significant survival benefits were observed with intraperitoneal therapy even though a high proportion of women on this regime had failed to complete their treatment course, possibly because of catheter related complications.

Jaaback and Johnson (2006) presented a Cochrane review identifying eight key studies from which they extracted and combined data in several meta-analyses, reporting on time to death, time to disease recurrence and adverse effects. Elit *et al.* (2007) returned to seven of these same RCTs but, with more mature data, were able to construct meta-analyses on five year rates of survival and time to progression. Within both reviews, only one trial (GOG172) was identified that had systematically investigated patient quality of life associated with the two chemotherapy routes. These data were reported by Wenzel *et al.* (2007).

The results in this evidence review have been reported using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) system which is based on the assessment of evidence quality for each individual outcome (see Atkins *et al*. (2004)). The GRADE profile is shown in Table 5.2.

The majority of trials reported on survival outcomes and the quality of the evidence is generally moderate to high. The results showed that treatment with chemotherapy having an element of intraperitoneal delivery was associated with significantly reduced risks of death and disease recurrence (time to death: HR 0.80, 95% C.I: 0.71-0.90; P=0.0003 and time to recurrence: HR 0.79, 95% C.I: 0.69-0.90; P=0.0004). High quality evidence also showed that 5 year overall survival and progression-free survival were significantly improved for women who had received some component of chemotherapy via intraperitoneal delivery: RR of death: 0.88, 95% C.I: 0.81-0.95; P=0.002; RR of disease progression: 0.91, 95% C.I: 0.85; P=0.02.

There were significant differences between the eight trials in the use of specific chemotherapy drugs, treatment schedules and dosages which, although not adversely affecting the analyses of survival outcomes, were very problematic in the analyses of adverse effects. The between studies heterogeneity, sometimes coupled with low control event rates, meant that pooling these data was of little statistical or clinical value for judging the comparative risks of intraperitoneal therapy. This was particularly true for the incidence of anaemia, leucopoenia, thrombocytopenia, renal, pulmonary or neurological side effects.

High quality evidence was available for the assessment of treatment regimen on other adverse effect outcomes, demonstrating in each case that intraperitoneal chemotherapy was associated with higher reported incidences of: fever (RR 1.92, 95% C.I: 1.2-3.06; P=0.0063) fatigue RR 3.63, 95% C.I: 1.95-6.74; P=0.00046) infection (RR 2.78, 95% C.I: 1.6-4.82; P=0.00029) metabolic effects (RR 4.38, 95% C.I: 2.68-7.15; P<0.00000) pain (RR 8.13, 95% C.I: 4.11-16.1; P<0.00001) and hearing loss (RR 0.67, 95% C.I: 0.46-0.99; P=0.044). High quality evidence did show that there was no significant difference in the incidence of the reporting of cardiovascular effects between patients on the two chemotherapy regimens (RR 1.69, 95% C.I: 0.93-3.09; P=0.085).

One trial (Gynecologic Oncology Group 172) collected health-related quality of life (HRQOL) data, analyses of which were reported by Wenzel *et al.* (2007). This outcome was measured on the Functional Assessment of Cancer Therapy–Ovarian (FACT-O) scale which included a 27 item FACT-General (FACT-G) questionnaire plus 12 items targeted specifically at ovarian cancer patients (FACT-O subscale). FACT-G comprised sub-scales of well-being (physical, social, emotional and functional). Data were reported for 399 trial participants. This RCT provided high quality evidence which showed that patients recruited to the intraperitoneal-containing chemotherapy arm reported a significantly poorer HRQOL at baseline, after the 4th cycle of chemotherapy and between 3 and 6 weeks after treatment. However, after one year of follow-up, there was no significant difference in HRQOL between the surviving participants based on their original study arm allocation.

In summary, high quality evidence from up to eight trials suggested that chemotherapy administered directly to the peritoneal cavity as part of an adjuvant therapy regime, may offer significantly reduced risks of death and disease recurrence, an effect sustained to a slightly lesser extent after five years of follow-up. However, the adverse effects associated with this route of drug administration occurred, in all cases, more frequently than similar effects experienced by women given standard intravenous chemotherapy, although the difference was not always significant. For at least six adverse effects, the evidence was too poor in quality to allow conclusions to be drawn about the relative contribution of delivery route. Health-related quality of life was measured in one trial and found to be significantly worse for women receiving intraperitoneal chemotherapy in the early days of treatment and shortly afterwards, but this difference was not apparent a year after the start of chemotherapy.

Evidence tables:

Author(s): Jaaback and Johnson (2006)

Design: (Cochrane) Systematic Review with meta-analyses
Country: N/A

Included population: Women of any age with a new diagnosis of primary ovarian cancer (of any FIGO stage) requiring chemotherapy following cytoreductive surgery.

Included studies: Randomised controlled trials (RCT) comparing chemotherapy that included a component of intraperitoneal (i.p.) administration with standard intravenous (i.v.) chemotherapy.

Excluded studies: RCTs of treatment with radio-labelled monoclonal antibodies, matrix metalloproteinase inhibitors, immunomodulators, vascular growth factors, radio isotopes, biologic therapy, gene therapy or radio colloids. Trials in which the participants had recurrent disease.

Population: N=1,819 (no patient demographics reported)

Interventions and comparators in included studies[1]:

- Kirmani *et al*., 1994 (N=62) Stage: IIc-IV
  Intraperitoneal: Cisplatin 200 mg per m^2 i.p; etoposide 350 mg per m^2 i.p. q 4 wks x 6
  Intravenous: Cisplatin 100 mg per m^2 i.v; cyclophosphamide 600 mg per m^2 q 3 wks x 6

- Alberts *et al*., 1996 (SWOG 8501 per GOG 104 (N=546) Stage: III, <2 cm residual
  Intraperitoneal: Cisplatin 100 mg per m^2 i.p; cyclophosphamide 600 mg per m^2 i.v. q 3 wks x 6
  Intravenous: Cisplatin 100 mg per m^2 i.v; cyclophosphamide 600 mg per m^2 i.v. q 3 wks x 6

- Polyzos *et al*., 1999 (N=90) Stage: III
  Intraperitoneal: Carboplatin 350 mg per m^2 i.p; cyclophosphamide 600 mg per m^2 i.v. q 3 wks x 6
  Intravenous: Carboplatin 350 mg per m^2 i.v; cyclophosphamide 600 mg per m^2 i.v. q 3 wks x 6

- Gadducci *et al*., 2000 (N=113) Stage: I-IV, <2 cm residual
  Intraperitoneal: Cisplatin 50 mg per m^2 i.p; cyclophosphamide 600 mg per m^2 i.v; epidoxorubicin 60mg per m^2 i.v. q 4 wks x 6
  Intravenous: Cisplatin 50 mg per m^2 i.v; cyclophosphamide 600 mg per m^2 i.v; epidoxorubicin 60 mg per m^2 i.v. q 4 wks x 6

- Markman *et al.*, 2001 GOG 114 per SWOG 9227 (N=462) Stage: III, <1cm residual
  Intraperitoneal: Carboplatin (AUC9) i.v. q 28 days x 2; cisplatin 100 mg per m^2 i.p; paclitaxel 135 mg per m^2 (24 hr) i.v. q 3 wks x 6
  Intravenous: Cisplatin 75 mg per m^2; i.v. paclitaxel 135 mg per m^2 (24 hr) i.v. q 3 wks x 6

- Yen *et a*l., 2001 (N=118) Stage: III, <1cm residual
  Intraperitoneal: Cisplatin 100 mg per m^2; i.p. cyclophosphamide 500mg per m^2 i.v; epidoxorubicin or doxorubicin 50 mg per m^2 i.v. q 3 wks x 6
  Intravenous: Cisplatin 50 mg per m^2 i.v; cyclophosphamide 50mg per m^2 i.v; epidoxorubicin or doxorubicin 50 mg per m^2 i.v. q 3 wks x 6

- Armstrong *et al*., 2002. GOG 172 (N=415) Stage: III, <1cm residual
  Intraperitoneal: Paclitaxel 135 mg per m^2 (24 hr) i.v; cisplatin 100 mg per m^2 i.p; paclitaxel 60

mg per m^2 i.p. on day 8 q 3 wks x 6
Intravenous: Cisplatin 75 mg per m^2 i.v; paclitaxel 135 mg per m^2 (24 hr) i.v. q 3 wks x 6

- Zylberberg *et al*., 1986. (N=20) Stage: III
  Intraperitoneal: Cisplatin i.v; doxorubicin i.v; fluorouracil i.v; bleomycin i.v; vinorelbine i.v; ifosfamide i.v; cisplatin i.p; doxorubicin i.p; fluorouracil i.p; bleomycin i.p; vinorelbine i.p. q 4 wks x10
  Intravenous: Cisplatin i.v; doxorubicin i.v; fluorouracil i.v; bleomycin i.v; vinorelbine i.v; ifosfamide i.v. q 4 wks x10

[1]Abbreviations: SWOG - Southwest Oncology Group; GOG - Gynecologic Oncology Group; i.p. - intraperitoneal; i.v. - intravenous

Outcomes:

Primary outcomes: Time to death, time to relapse.
Secondary outcome: Adverse effects.

Results:

Time-to event outcomes (time to death or relapse) were reported as hazard ratios (HR) and dichotomous outcomes (adverse effects) as relative risk (RR). Where no significant heterogeneity existed between combined studies, data were analysed using a fixed effects model but where heterogeneity exceeded I^2 > 25%, data were analysed by a random effects model. All analyses compared intraperitoneal therapy with intravenous therapy hence HR <1 favour intraperitoneal therapy but RR (adverse effects) >1 favour intravenous therapy.

- **Time to death (reported in 7 trials (5 high quality))** See GRADE profile
- **Time to relapse (reported in 4 trials (3 high quality))** See GRADE profile
- **Grade 3 or 4 adverse effects (reported in up to 7 trials)** See GRADE profile

Follow-up:

Follow-up periods ranged between 46 and 74 months with the majority >60 months.

Notes:

This moderate quality paper reviewed eight RCTs of intraperitoneal vs. intravenous chemotherapy for women with newly diagnosed ovarian cancer who had undergone cytoreductive surgery. Only two of the trials were conducted in a single centre whereas the remainder involved from two to forty participating centres each. The majority of studies were from the USA. Two authors searched The Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, MEDLINE, EMBASE, TRIP, the Gynaecological Cancer Review Groups Specialised Registers and others for relevant studies. Details of the search strategy were presented. Hand searching of gynaecological journals was also conducted and journal authors contacted for elaboration where required. Papers were selected, reviewed and data were extracted by two independent researchers and disagreements were resolved by discussion. Each trial was assessed for bias with respect to methods of randomisation, allocation, blinding (of the outcome assessors) loss to follow-up and intention-to-treat analyses. Overall quality was then judged on these parameters and five studies were found to be of high quality whilst three were judged to be of low quality.

Most study participants had stage III disease but some (N=200) were eligible for inclusion if staged II-IV. Only three from eight RCTs compared the same drug regimes between arms such that any observed differences in outcomes in those studies could be fairly said to be due to the delivery route. The remainder of the studies used different regimes with respect to drug, dose or both thus frustrating a true comparison between arms. In addition, the drug combinations have changed over time and only two of the more recent studies have used platins with a taxane, albeit in different doses.

The review authors did not present a comprehensive summary of treatment withdrawals but presented data that were available from six of the included studies. Using these it is possible to show that the probability of trial participants receiving all the scheduled treatment cycles was significantly higher for patients assigned to intravenous therapy compared with those on intraperitoneal chemotherapy: OR 2.0 (95% C.I: 1.6-2.4) P<0.0001. Loss to follow-up was not reported and, as this is an important consideration in assessing study quality, all studies were downgraded for GRADE evaluation.

Meta-analyses were conducted, pooling data from two or more of the included trials to assess all outcomes with the exception of quality of life which was reported by only one study. With regard to many of the adverse effects outcomes, it was noted that the data may have been unsuitable for pooling due to the variable treatment regimes used by different studies. The resultant high between-studies heterogeneity resulted in wide confidence intervals around point estimates of effect size. In addition, many patients receiving intraperitoneal chemotherapy had been given relatively high drug doses and therefore might be expected to have experienced more serious side effects which may explain the large effect sizes for some outcomes. The combination of low event rates with large effect sizes but wide confidence intervals (that crossed both the line of 'no effect' and a point that could be considered as indicating 'appreciable harm' or 'appreciable benefit') render these results statistically and clinically of little value.

Included studies

Alberts DS, Liu PY, Hannigan EV, O'Toole R, Williams SD, Young JA, *et al.* (1996) Intraperitoneal cisplatin plus intravenous cyclophosphamide versus intravenous cisplatin plus intravenous cyclophosphamide for stage III ovarian cancer. *NEJM* **335(26):**1950-5.

Armstrong DK, Bundy BN, Baergen R, Lele SB, Copeland LJ, Walker, *et al.* (2002) Randomized phase III study of intravenous (IV) paclitaxel and cisplatin versus IV paclitaxel, intraperitoneal (IP) cisplatin and IP paclitaxel in optimal stage III epithelial ovarian cancer (OC): a Gynecologic Oncology Group trial (GOG 172). *Proc Am Soc Clin Oncol* **21:**201a.

Gadducci A, Carnino F, Chiara S, Brunetti I, Tanganelli L, Romanini A, *et al.* (2000) Intraperitoneal versus intravenous cisplatin in combination with intravenous cyclophosphamide and epidoxorubicin in optimally cytoreduced advanced epithelial ovarian cancer: a randomized trial of the Gruppo Oncologico Nord-Ovest. *Gynecol Oncol* **76(2):**157-62.

Kirmani S, Braly PS, McClay EF, Saltzstein SL, Plaxe SC, Kim S, *et al.* (1994) A comparison of intravenous versus intraperitoneal chemotherapy for the initial treatment of ovarian cancer. *Gynecol Oncol* **54(3):** 338-44.

Markman M, Bundy BN, Alberts DS, Fowler JM, Clark-Pearson DL, Carson LF, *et al.* (2001) Phase III trial of standard-dose intravenous cisplatin plus paclitaxel versus moderately high-dose carboplatin followed by intravenous paclitaxel and intraperitoneal cisplatin in small-volume stage III ovarian carcinoma: an intergroup study of the Gynecologic Oncology Group, Southwestern Oncology Group, and Eastern Cooperative Oncology Group. *J Clin Oncol* **19(4):**1001-7.

Polyzos A, Tsavaris N, Kosmas C, Giannikos L, Katsikas M, Kalahanis N, *et al.* (1999) A comparative study of intraperitoneal carboplatin versus intravenous carboplatin with intravenous cyclophosphamide in both arms as initial chemotherapy for stage III ovarian cancer. *Oncology* **56(4):** 291-6.

Yen MS, Juang CM, Lai CR, Chao GC, Ng HT, Yuan CC. (2001) Intraperitoneal cisplatin-based chemotherapy vs. intravenous cisplatin-based chemotherapy for stage III optimally cytoreduced epithelial ovarian cancer. International *J Gynecol Obstet* **72(1):** 55-60.

Zylberberg B, Ravina JH, Salat-Baroux J, Dormont D, Lipp B, Guillet JL. (1986) Polychimiotherapie des cancers de l'ovaire par voie mixte intraveineuse et intraperitoneale. Technique et resultats preliminaires. *J Gynecol Obstet Biol Reprod* **15(5):** 671-6.

Author(s): Elit *et al.* (2007)

Design: Systematic Review with meta-analyses
Country: Canada

Included population: Women of any age with stage III ovarian cancer.

Included studies: Randomised controlled trials (RCT) comparing first line intraperitoneal-containing chemotherapy with first line intravenous chemotherapy.

Excluded studies: RCTs of treatment involving immunomodulators, intraperitoneal radioactive phosphorus or hypothermia. Trials reported in non-English language or those from which data could not be extracted.

Population: N=1,806 (no patient demographics reported)

Intervention(s) and comparator(s):

See evidence table for Jaaback and Johnson (2006) for details of treatment regimes.

Outcomes:

Primary outcomes: Overall survival (5yrs), progression-free survival (5yrs).
Secondary outcomes: Toxicity, catheter-related complications, quality of life (QOL).

Results:

Dichotomous outcomes (survival, progression-free survival at 5 years) were reported as relative risk (RR). Data were analysed using a random effects model regardless of the presence or absence of between studies heterogeneity (I^2). All analyses compared intraperitoneal therapy with intravenous therapy where RR <1 favours intraperitoneal therapy and RR >1 favour intravenous therapy. Five trials reported intention-to-treat analyses either on eligible patients or on the whole study population.

- **Overall survival at 5 years (reported in 6 trials):** See GRADE profile

- **Progression-free survival at 5 years (reported in 3 trials):** See GRADE profile
- **Toxicity:** Reported in Jaaback and Johnson (2006).
- **Catheter-related complications:** The type of catheters used were described in six studies as: 'implantable' (N=1) Tenchkoff (N=2) Port-A-Cath (N=2) or 'temporary' (N=1). Across the six studies, 24% to 75% of patients did not complete the scheduled program of intraperitoneal-containing therapy. In one study (Armstrong *et al.*, 2006) 34% of the 119 patients discontinuing intraperitoneal chemotherapy did so primarily due to catheter-related complications and for a further 8% of women it was a contributory factor. Complications included abdominal pain, bleeding, infection, peritonitis, catheter blockage, leakage, movement, malfunction and/or access problems. This specific outcome was not reported in the remainder of the trials.
- **Quality of life (QOL) (reported in 1 trial):** Only one trial (GOG-172) monitored QOL. The outcomes were reported in detail by Wenzel *et al.* (2007).

Follow-up:

Follow-up periods ranged between 46 and 74 months with the majority >60 months. In six out of seven trials, completeness of follow-up was reported to exceed 80%.

Notes:

This moderate quality paper reviewed seven RCTs of intraperitoneal vs. intravenous chemotherapy for women with stage III ovarian cancer. There is a very high overlap of studies (N=6) between this review and that of Jaaback and Johnson (2006) but since the survival outcomes are reported in a different way, the evidence may be complementary.

Only one of the trials was conducted in a single centre whereas the remainder involved from two to forty participating centres each. The majority of studies were from the USA. An unknown number of reviewers searched The Cochrane Library, MEDLINE, EMBASE, Physician Data Query Database, the Canadian Medical Association Infobase, the National Guidelines Clearinghouse and others for relevant studies. Details of the search strategy were given very briefly.

Most study participants had stage III disease but some (N=175) were eligible for inclusion if staged II-IV. Only three from eight RCTs compared the same drug regimes between arms such that any observed differences in outcomes in those studies could be fairly said to be due to the delivery route. The remainder of the studies used different regimes with respect to drug, dose or both thus frustrating a true comparison between arms. In addition, the drug combinations have changed over time and only two of the more recent studies have used platins with a taxane, albeit in different doses.

Papers were selected, reviewed and data were extracted by an unknown number of researchers. A detailed analysis of study quality was given for the included papers but there was no formal grading of studies such as is performed for a Cochrane review. However, those papers selected for GRADE reporting were assessed for quality by Jaaback and Johnson (2006) and these criteria have been used with data from this study.

Included studies

Alberts DS, Liu PY, Hannigan EV, O'Toole R, Williams SD, Young JA, *et al.* (1996) Intraperitoneal cisplatin plus intravenous cyclophosphamide versus intravenous cisplatin plus intravenous cyclophosphamide for stage III ovarian cancer. *NEJM* **335(26):**1950-5.

Armstrong DK, Bundy BN, Wenzel L, Huang H, Baergen R, Lele S *et al.* (2006) Intraperitoneal cisplatin and paclitaxel in ovarian cancer *NEJM* **354(1):** 34-43.

Gadducci A, Carnino F, Chiara S, Brunetti I, Tanganelli L, Romanini A, *et al.* (2000) Intraperitoneal versus intravenous cisplatin in combination with intravenous cyclophosphamide and epidoxorubicin in optimally cytoreduced advanced epithelial ovarian cancer: a randomized trial of the Gruppo Oncologico Nord-Ovest. *Gynecol Oncol* **76(2):**157-62.

Kirmani S, Braly PS, McClay EF, Saltzstein SL, Plaxe SC, Kim S, *et al.* (1994) A comparison of intravenous versus intraperitoneal chemotherapy for the initial treatment of ovarian cancer. *Gynecol Oncol* **54(3):** 338-44.

Markman M, Bundy BN, Alberts DS, Fowler JM, Clark-Pearson DL, Carson LF, *et al.* (2001) Phase III trial of standard-dose intravenous cisplatin plus paclitaxel versus moderately high-dose carboplatin followed by intravenous paclitaxel and intraperitoneal cisplatin in small-volume stage III ovarian carcinoma: an intergroup study of the Gynecologic Oncology Group, Southwestern Oncology Group, and Eastern Cooperative Oncology Group. *J Clin Oncol* **19(4):**1001-7.

Polyzos A, Tsavaris N, Kosmas C, Giannikos L, Katsikas M, Kalahanis N, *et al.* (1999) A comparative study of intraperitoneal carboplatin versus intravenous carboplatin with intravenous cyclophosphamide in both arms as initial chemotherapy for stage III ovarian cancer. *Oncology* **56(4):** 291-6.

Yen MS, Juang CM, Lai CR, Chao GC, Ng HT, Yuan CC. (2001) Intraperitoneal cisplatin-based chemotherapy vs. intravenous cisplatin-based chemotherapy for stage III optimally cytoreduced epithelial ovarian cancer. International *J Gynecol Obstet* **72(1):** 55-60.

Author(s): Wenzel *et al.* (2007)
Design: Randomised controlled trial **Country:** United States of America
Inclusion criteria: Women with histologically confirmed stage III epithelial ovarian cancer or primary peritoneal cancer who, after surgical debulking, had no residual disease >1cm in diameter.
Exclusion criteria: None stated
Population: N=399.
Intervention(s) and comparator(s): Intraperitoneal-containing chemotherapy: Paclitaxel 135 mg per m^2 (24 hr) i.v.; Cisplatin 100 mg per m^2 i.p; Paclitaxel 60 mg per m^2 i.p. on day 8 q 3 weeks x 6. Intravenous chemotherapy: Cisplatin 75 mg per m^2 i.v., Paclitaxel 135 mg per m^2 (24 hr) i.v. q 3 weeks x 6.
Outcomes: Health related quality of life (HRQOL).

Quality of life assessments were completed by consenting patients at four time points: before randomisation, before chemotherapy cycle 4, between 3 to 6 weeks after all treatment and 12 months after all treatment. HRQOL was measured by means of the following scales: Functional Assessment of Cancer Therapy–Ovarian (FACT-O) which includes a 27 item FACT-General (FACT-G) questionnaire plus 12 items targeted specifically at ovarian cancer patients (FACT-O subscale). FACT-G includes sub-scales of well-being (physical, social, emotional and functional). Two further outcomes (pain and neurotoxicity) are not reproduced here since the data were included in the above mentioned meta-analyses.
Results: • **Health-related quality of life**: See GRADE profile.
Follow-up: N/A
Notes: This paper presents data collected during the GOG-172 trial which was reported by Armstrong *et al.* (2006) other outcomes of which were included in the systematic reviews and meta-analyses of Jaaback and Johnson (2006) and Elit *et al.* (2007). This study is concerned only with the results of health-related quality of life (HRQOL) measurements. The quality of the trial itself was considered to be high with respect to design and reporting (see Jaaback and Johnson, 2006). Compared with those on conventional, lower dose, intravenous chemotherapy, women receiving high drug doses of intraperitoneal chemotherapy reported worse QOL both at baseline before randomisation, before the 4th chemotherapy cycle and three to six weeks after completion of chemotherapy. However, one year post-treatment there were no differences in QOL measurements between study groups.

References:

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Elit L., Oliver TK., Covens A., Kwon J., Fung MF., Hirte HW and Oza AM. (2007) Intraperitoneal chemotherapy in the first-line treatment of women with stage III epithelial ovarian cancer: a systematic review with metaanalyses. *Cancer* **109(4)**: 692-702.

Jaaback K and Johnson N (2006). Intraperitoneal chemotherapy for the initial management of primary epithelial ovarian cancer. *Cochrane Database of Systematic Reviews* 2006 Issue 1. Art. No. CD005340.

Wenzel LB., Huang HQ., Armstrong DK., Walker JL and Cella D. (2007) Health-related quality of life during and after intraperitoneal versus intravenous chemotherapy for optimally debulked ovarian cancer: A Gynecologic Oncology Group Study. *J Clin Oncol* **25 (4)**: 437-443.

Table 5.2 GRADE profile: For women with ovarian cancer, is intra-peritoneal chemotherapy effective in primary management [Back]

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	IP chemo-therapy	IV chemo-therapy	Relative (95% CI)	Absolute	Quality
Time to death (follow-up 46 to 74 months[1]). Effect size <1 favours intraperitoneal chemotherapy. Jaaback and Johnson (2006).											
7	randomised trials	serious[2,3]	no serious inconsistency	no serious indirectness	no serious imprecision	N/A	895	924	HR 0.80 (0.71 to 0.9) P=0.000333		⊕⊕⊕○ MODERATE
Time to death (high quality studies only) (follow-up 46 to 74 months[1]). Effect size <1 favours intraperitoneal chemotherapy. Jaaback and Johnson (2006).											
5	randomised trials	no serious limitations[2,4]	no serious inconsistency	no serious indirectness	no serious imprecision	N/A	808	833	HR 0.79 (0.7 to 0.89) P=0.00021		⊕⊕⊕⊕ HIGH
Time to recurrence (follow-up 46 to 74 months[1]). Effect size <1 favours intraperitoneal chemotherapy. Jaaback and Johnson (2006).											
4	randomised trials	no serious limitations[2,5]	no serious inconsistency	no serious indirectness	no serious imprecision	N/A	519	526	HR 0.79 (0.69 to 0.9) P=0.00044		⊕⊕⊕⊕ HIGH
Time to recurrence (high quality studies only) (follow-up 46 to 74 months[1]). Effect size <1 favours intraperitoneal chemotherapy. Jaaback and Johnson (2006).											
3	randomised trials	no serious limitations[2,6]	no serious inconsistency	no serious indirectness	no serious imprecision	N/A	486	491	HR 0.78 (0.68 to 0.89) P=0.00025		⊕⊕⊕⊕ HIGH
Survival (risk of death) 5 years (follow-up 46 to 74 months[1]). Effect size <1 favours intraperitoneal chemotherapy. Elit *et al.* (2007).											

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	IP chemo-therapy	IV chemo-therapy	Relative (95% CI)	Absolute	Quality
6	randomised trials	no serious limitations[8]	no serious inconsistency	no serious indirectness	no serious imprecision	N/A	439/851 (51.6%)	531/886 (59.9%)	RR 0.88 (0.81 to 0.95) P=0.002	7 fewer per 100 (from 30 fewer to 114 fewer)	⊕⊕⊕⊕ HIGH
Progression-free survival (risk of progression) at 5 years (follow-up 46 to 74 months[1]). Effect size <1 favours intraperitoneal chemotherapy. Elit *et al.* (2007).											
3	randomised trials	no serious limitations[6]	no serious inconsistency	no serious indirectness	no serious imprecision	N/A	352/496 (71%)	384/494 (77.7%)	RR 0.91 (0.85 to 0.98) P=0.02	7 fewer per 100 (from 16 fewer to 117 fewer)	⊕⊕⊕⊕ HIGH
Adverse effects anaemia. Effect size <1 favours intraperitoneal chemotherapy. Jaaback and Johnson (2006).											
4	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	serious[20]	N/A	79/383 (20.6%)	91/429 (21.2%)	RR 0.97 (74 to 1.26) P=0.80	1 fewer per 100 (from 6 more to 1548 more)	⊕⊕◯◯ LOW
Adverse effects thrombocytopenia. Effect size <1 favours intraperitoneal chemotherapy. Jaaback and Johnson (2006).											
7	randomised trials	serious[3]	very serious[13,14]	no serious indirectness	serious[20]	N/A	169/867 (19.5%)	65/912 (1.1%)	RR 1.16 (0.33 to 4.06) P=0.81	1 more per 100 (from 5 fewer to 22 more)	⊕◯◯◯ VERY LOW
Adverse effects leukopenia. Effect size <1 favours intraperitoneal chemotherapy. Jaaback and Johnson (2006).											
7	randomised trials	serious[3]	very serious[13,15]	no serious indirectness	no serious imprecision[19]	N/A	477/867 (55%)	482/912 (52.9%)	RR 0.94 (0.75 to 1.19) P=0.63	3 fewer per 100 (from 13 fewer to 10 more)	⊕◯◯◯ VERY LOW
Adverse effects renal. Effect size <1 favours intraperitoneal chemotherapy. Jaaback and Johnson (2006).											
4	randomised trials	serious[5]	serious[13,16]	no serious indirectness	no serious imprecision[19]	N/A	22/518 (4.2%)	8/527 (1.5%)	RR 2.55 (0.8 to 8.1) P=0.11	2 more per 100 (from 0 fewer to 11 more)	⊕⊕◯◯ LOW

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	IP chemo-therapy	IV chemo-therapy	Relative (95% CI)	Absolute	Quality
Adverse effects pulmonary. Effect size <1 favours intraperitoneal chemotherapy. Jaaback and Johnson (2006).											
2	randomised trials	no serious limitations[9]	serious[13,17]	no serious indirectness	no serious imprecision[19]	N/A	10/455 (2.2%)	6/486 (1.2%)	RR 2.9 (0.49 to 17.36) P=0.24	2 more per 100 (from 1 fewer to 20 more)	⊕⊕⊕○ MODERATE
Adverse effects cardiovascular. Effect size <1 favours intraperitoneal chemotherapy. Jaaback and Johnson (2006).											
2	randomised trials	no serious limitations[9]	no serious inconsistency	no serious indirectness	no serious imprecision[19]	N/A	27/440 (6.1%)	16/437 (3.7%)	RR 1.69 (0.93 to 3.09) P=0.085	3 more per 100 (from 0 fewer to 8 more)	⊕⊕⊕⊕ HIGH
Adverse effects fever. Effect size <1 favours intraperitoneal chemotherapy. Jaaback and Johnson (2006).											
4	randomised trials	no serious limitations[10]	no serious inconsistency	no serious indirectness	no serious imprecision	N/A	47/736 (6.4%)	26/767 (3.4%)	RR 1.92 (1.2 to 3.06) P=0.0063	3 more per 100 (from 1 more to 7 more)	⊕⊕⊕⊕ HIGH
Adverse effects fatigue. Effect size <1 favours intraperitoneal chemotherapy. Jaaback and Johnson (2006).											
2	randomised trials	no serious limitations[9]	no serious inconsistency	no serious indirectness	no serious imprecision	N/A	43/440 (9.8%)	12/437 (2.7%)	RR 3.63 (1.95 to 6.74) P=0.00046	7 more per 100 (from 3 more to 16 more)	⊕⊕⊕⊕ HIGH
Adverse effects gastrointestinal. Effect size <1 favours intraperitoneal chemotherapy. Jaaback and Johnson (2006).											
4	randomised trials	serious[5]	serious[17]	no serious indirectness	no serious imprecision	N/A	202/518 (39%)	117/527 (22.2%)	RR 1.60 (1.13 to 2.25) P=0.0079	13 more per 100 (from 3 more to 28 more)	⊕⊕○○ LOW
Adverse effects infection. Effect size <1 favours intraperitoneal chemotherapy. Jaaback and Johnson (2006).											

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	IP chemo-therapy	IV chemo-therapy	Relative (95% CI)	Absolute	Quality
2	randomised trials	no serious limitations[9]	no serious inconsistency	no serious indirectness	no serious imprecision	N/A	44/440 (10%)	16/437 (3.7%)	RR 2.78 (1.6 to 4.82) P=0.00029	7 more per 100 (from 2 more to 14 more)	⊕⊕⊕⊕ HIGH
Adverse effects metabolic. Effect size <1 favours intraperitoneal chemotherapy. Jaaback and Johnson (2006).											
2	randomised trials	no serious limitations[9]	no serious inconsistency	no serious indirectness	no serious imprecision	N/A	78/440 (17.7%)	18/227 (7.9%)	RR 4.38 (2.68 to 7.15) P<0.00001	27 more per 100 (from 13 more to 49 more)	⊕⊕⊕⊕ HIGH
Adverse effects neurological. Effect size <1 favours intraperitoneal chemotherapy. Jaaback and Johnson (2006).											
5	randomised trials	no serious limitations[11]	serious[13,18]	no serious indirectness	serious[20]	N/A	108/768 (14.1%)	99/803 (12.3%)	RR 1.18 (0.66 to 2.05) P=0.58	2 more per 100 (from 4 fewer to 13 more)	⊕⊕◯◯ LOW
Adverse effects pain. Effect size <1 favours intraperitoneal chemotherapy. Jaaback and Johnson (2006).											
2	randomised trials	no serious limitations[9]	no serious inconsistency	no serious indirectness	no serious imprecision	N/A	68/455 (14.9%)	9/486 (1.9%)	RR 8.13 (4.11 to 16.1) P<0.00001	13 more per 100 (from 6 more to 28 more)	⊕⊕⊕⊕ HIGH
Adverse effects hearing loss. Effect size <1 favours intraperitoneal chemotherapy. Jaaback and Johnson (2006).											
3	randomised trials	no serious limitations[12]	no serious inconsistency	no serious indirectness	no serious imprecision	N/A	36/487 (7.4%)	59/522 (11.3%)	RR 0.67 (0.46 to 0.99) P=0.044	4 fewer per 100 (from 0 fewer to 6 fewer)	⊕⊕⊕⊕ HIGH
QOL at baseline (FACT-G) (FACT-O measured from 0 to 156 units. Higher values indicate better QOL). MD compares IV to IP chemotherapy. Wenzel *et al.* (2007).											
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	N/A	198	201	-	MD 3.6 higher (0.61 to 6.59 higher)[21]	⊕⊕⊕⊕ HIGH

Quality assessment							Summary of findings				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	IP chemo-therapy	IV chemo-therapy	Relative (95% CI)	Absolute	
										P=0.018	
QOL at baseline (FACT-O subscale) (FACT-O measured from 0 to 156 units. Higher values indicate better QOL). MD compares IV to IP chemotherapy. Wenzel *et al.* (2007).											
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	N/A	198	201	-	MD 1.8 higher (0.43 to 2.97 higher)[21] P=0.007	⊕⊕⊕⊕ HIGH
QOL before cycle 4 (FACT-G) (FACT-O measured from 0 to 156 units. Higher values indicate better QOL). MD compares IV to IP chemotherapy. Wenzel *et al.* (2007).											
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	N/A	148	172	-	MD 6.6 higher (4.95 to 11.45 higher) P<0.001	⊕⊕⊕⊕ HIGH
QOL before cycle 4 (FACT-O subscale) (FACT-O measured from 0 to 156 units. Higher values indicate better QOL). MD compares IV to IP chemotherapy. Wenzel *et al.* (2007).											
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	N/A	148	172	-	MD 2.9 higher (2.27 to 4.73 higher) P<0.001	⊕⊕⊕⊕ HIGH
QOL 3-6 weeks after treatment (FACT-G) (FACT-O measured from 0 to 156 units. Higher values indicate better QOL). MD compares IV to IP chemotherapy. Wenzel *et al.* (2007).											
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	N/A	159	171	-	MD 4.6 higher (2.89 to 9.51 higher) P=0.002	⊕⊕⊕⊕ HIGH

Quality assessment							Summary of findings				
							No of patients		Effect		
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	IP chemo-therapy	IV chemo-therapy	Relative (95% CI)	Absolute	Quality
QOL 3-6 weeks after treatment (FACT-O subscale) (FACT-O measured from 0 to 156 units. Higher values indicate better QOL). MD compares IV to IP chemotherapy. Wenzel *et al.* (2007).											
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	N/A	159	171	-	MD 1.3 higher (0.4 to 2.1 higher) P=0.041	⊕⊕⊕⊕ HIGH
QOL 1 year after treatment (FACT-G) (measured from 0 to 156 units. Higher values indicate better QOL). MD compares IV to IP chemotherapy. Wenzel *et al.* (2007).											
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	N/A	139	140	-	MD 0.3 higher (1.47 lower to 5.47 higher) P=0.85	⊕⊕⊕⊕ HIGH
QOL 1 year after treatment (FACT-O subscale) (measured from 0 to 156 units. Higher values indicate better QOL). MD compares IV to IP chemotherapy. Wenzel *et al.* (2007).											
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	N/A	139	140	-	MD 0.2 higher (1.15 lower to 1.55 higher) P=0.71	⊕⊕⊕⊕ HIGH

Footnotes:

[1] 7/8 trials reported duration of follow-up which in 3 trials was stated to be >60 months.
[2] The review authors reported and assessed the allocation method, concealment, assessor blinding and intention-to-treat for all studies. On this basis they judged 3 studies to be 'good', 2 studies as 'fair' and 3 studies as 'poor' in quality. Details of loss to follow-up are not reported for individual studies or overall.
[3] For this outcome, 3 papers have been graded 'good', 2 as 'fair' and 2 as 'poor'.
[4] For this outcome, 3 papers have been graded 'good' and 2 as 'fair'.
[5] For this outcome, 2 papers have been graded 'good', 1 as 'fair' and 1 as 'poor'.
[6] For this outcome, 2 papers have been graded 'good' and 1 as 'fair'.
[7] For this outcome, 1 paper has been graded 'good', 2 as 'fair' and 1 as 'poor'.

[8] For this outcome, 3 papers have been graded 'good', 2 as 'fair' and 1 as 'poor'.
[9] For this outcome, 2 papers have been graded 'good'.
[10] For this outcome, 3 papers have been graded 'good' and 1 as 'fair'.
[11] For this outcome, 3 papers have been graded 'good', 1 as 'fair' and 1 as 'poor'.
[12] For this outcome, 2 papers have been graded 'good' and 1 as 'poor'.
[13] High levels of between studies heterogeneity in adverse effects outcomes are explained adequately in the review discussion highlighting the fact that different drugs, doses and regimes were used across studies. Also, 2/8 of the studies used extremely high doses of chemotherapy in the intraperitoneal chemotherapy which increased the likelihood of adverse events. The authors conclude that for leukopenia, thrombocytopenia, renal, neurological and pulmonary outcomes, data pooling (although undertaken) could be considered inappropriate.
[14] Between studies heterogeneity was measured at 90%.
[15] Between studies heterogeneity was measured at 80%.
[16] Between studies heterogeneity was measured at 36%.
[17] Between studies heterogeneity was measured at 59%.
[18] Between studies heterogeneity was measured at 76%.
[19] The 95% confidence interval crosses the line of no effect plus the lower value of the interval is <0.75 and/or upper value >1.25. But the event rate is <5% so study quality is not downgraded.
[20] The 95% confidence interval crosses the line of no effect plus the lower value of the interval is <0.75 and/or upper value >1.25. But the event rate is >5% so study quality is downgraded
[21] Calculated as a raw difference for data before randomisation and adjusted mean difference for all time points thereafter. NB. FACT-O score = scores of FACT-O subscale & FACT-G combined.

Chapter 6: Support needs for women with ovarian cancer

6.1 Support regimens

"For women diagnosed with ovarian cancer, what support should be offered?"

Short summary:

The evidence suggests that most women with ovarian cancer need emotional support. 'Improving outcomes in gynaecological cancer (Department of Health, 1999), made a series of recommendations to improve supportive care in this group. However, there is evidence that emotional support needs still go unmet in a minority of patients.

Clinical nurse specialists play an important role in emotional support for women with ovarian cancer, but there is evidence from the Pathfinder study (Target Ovarian Cancer, 2009) that there is considerable variation in the workloads of nurse specialists and the resources available to them.

Review Protocol:

Question

For women newly diagnosed with ovarian cancer, what support should be offered?

Objectives

This question will hopefully reveal evidence about information needs (specifically related to psychosocial or psychosexual issues) for women with ovarian cancer. This question will focus on what patients describe, request or need and not what health professionals report that patients describe, request or need.

Study inclusion criteria

- **Studies:** Qualitative studies.
- **Participants:** For women newly diagnosed with ovarian cancer and their carers.
- **Interventions:** Information needs associated with psychosocial or psychosexual issues specific to women with ovarian cancer. At the time of their diagnosis.
- **Outcomes:** This question will hopefully reveal evidence about information needs (specifically related to psychosocial or psychosexual issues) for women with ovarian cancer. Where possible the content, format and context of information that women with ovarian cancer describe, request or need will be reported. This question will focus on what patients describe, request or need and NOT what health professionals report that patients describe, request or need.

Search strategy

The information specialist (EC) searched the following electronic databases: Medline, PreMEDLINE, EMBASE, Cochrane Library, CINAHL, BNI, PsycINFO, AMED Web of Science (SCI & SSCI) and Biomed Central

Review strategy

Two reviewers (KF and NB) assessed the list of studies for inclusion.

The risk of bias was assessed using the NICE checklist for qualitative studies.

Search results:

The literature search identified 85 potentially relevant papers. An additional study was suggested by the guideline development group. Ten studies were included as evidence.

Description of included studies:

Study designs

The Pathfinder Study (Target Ovarian Cancer, 2009) was a cross-sectional study of people living or working with ovarian cancer in the UK, commissioned and published by the Target Ovarian Cancer charity. Beesley *et al.* (2008) was a population based Australian cross-sectional study about supportive care needs

Three reviews articles were included: Gamel *et al.* (2000) was an expert literature review about the effects of gynaecological cancer on sexuality. The Sweeney (2006) paper included an expert literature review about information needs and the role of the clinical nurse specialist. The recommendations in 'Improving outcomes in gynaecological cancers' (Department of Health, 1999) guidance were based on a systematic review of the evidence.

The remaining papers were single institution studies. Browall *et al.* (2004) was a prospective study, Jefferies (2002), Power *et al.* (2008), Fitch and Steele (2010) and Sweeney (2006) were cross-sectional or retrospective studies.

Ovarian cancer studies

Six of the studies included only patients with ovarian cancer (Target Ovarian Cancer, 2009; Jefferies, 2002; Power *et al.*, 2008; Browall *et al.*, 2004; Sweeney, 2006 and Fitch and Steele, 2010), the remainder included women with any gynaecological cancer.

Recently diagnosed patients

The research question was about recently diagnosed ovarian cancer, but only one of the studies was restricted to women with recently diagnosed disease: Browall *et al.* (2004) was a prospective study that followed women for the year after their diagnosis. Sweeney (2006), Power *et al.* (2008), Jefferies (2002) and The Pathfinder Study (Target Ovarian Cancer, 2009) asked women to recall their needs in the time around their diagnosis. The Gamel *et al.* (1999) study and 'Improving outcomes in gynaecological cancers' (Department of Health, 1999) considered the period around diagnosis in their reviews of the evidence.

In the remaining cross-sectional studies (Beesley *et al.* 2008; Steele and Fitch, 2008 and Fitch and Steele, 2010) the participants were interviewed after diagnosis and were only asked about their current information or support needs.

Study quality:

The risk of bias is summarised in Figure 6.1. According to the NICE checklist the included studies were at low risk of bias.

Evidence summary:

Psychosocial support needs

The evidence suggests that most women with ovarian cancer report a need for emotional support. In the Pathfinder Study (Target Ovarian Cancer, 2009) 75% of the women diagnosed said they had needed emotional support since their diagnosis.

Evidence also shows that many women's support needs go unmet. A third of the women who needed emotional support in the Pathfinder study actually asked for help, another third were offered help and the remaining third were neither offered help nor asked for it. Thus 25% of those women had un-met support needs. In a Canadian study of patients with gynaecological cancer, 43% reported at least one moderate or high level unmet supportive care need (Beesley *et al.,* 2008).

Existing improving outcomes guidance

The Department of Health guidance on 'Improving outcomes in gynaecological cancers' (1999), recommends that psychosocial support should be available at every stage to help patients and their families cope with the effects of the disease and its treatment.

The guidance also recommends that all women who have treatment that is likely to affect sexual activity should be aware that advice is available on minimising adverse effects on their sexual experience and relationships.

The improving outcomes recommendations are incorporated as peer review measures in the National Cancer Peer Review Programme (National Cancer Peer Review Programme, 2008).

Clinical nurse specialists

The Department of Health guidance on 'Improving outcomes in gynaecological cancers' (1999), recommends that each patient should have access to a to a named oncology clinical nurse specialist with counselling expertise.

The evidence suggests that these clinical nurse specialists are an important source of emotional support for women with ovarian cancer in the UK. Clinical nurse specialists were the most common source of emotional support reported by patients in both Jefferies (2002) and the Pathfinder study (Target Ovarian Cancer, 1999). Patients in the Jefferies (2002) study found it was better to receive information from the clinical nurse specialist and consultant, rather than the consultant alone.

In some institutions the key worker role is being well covered by clinical nurse specialists. For example in a small UK study of 14 women with ovarian cancer (Sweeney, 2006), 85% reported they had received sufficient information about their illness and treatment options. All the women in this study had seen the clinical nurse specialist at their first appointment and had been given the nurse's contact details

However there is also evidence that the role of the clinical nurse specialist is not well covered in some places. In the Pathfinder study (Target Ovarian Cancer, 2009) only 55% of the women who responded were given contact details for a clinical nurse specialist at the time of diagnosis. Over a third of the women who responded (36%) were not given any contact details at all. Eventually most women (84%) had access to a clinical nurse specialist at some

point during their cancer journey. In the same study 25% of the 57 clinical nurse specialists interviewed felt that the key worker role was not well covered in their area. 63% of these nurses felt that the key worker role could be improved, for example by employing more specialist nurses or by creating more time for those already employed.

Prioritisation of information and support needs

Women reported a range of information and support needs, reflecting different values, preferences and circumstances. However certain types of information and support needs were more commonly reported than others. Women were most likely to report information and support needs connected with their treatment and its side effects and their disease and prognosis (Beesley *et al.,* 2008; Browall *et al.,* 2004; Steele and Fitch, 2008 and Fitch and Steele, 2010).

Psychosocial issues (including impact on family and social life) tended to rank just below treatment and disease issues in importance (Beesley *et al.,* 2008; Browall *et al.,* 2004; Steele and Fitch 2008).

While a proportion of women in the Browall *et al.,* (2004) study reported sexuality information needs; these were ranked below other needs in importance.

Power *et al.* (2008) reported that many patients expressed a desire not to find out all the information they could about their condition, and they purposefully avoided dealing with it whenever possible. They labelled this coping strategy *avoidance and blunting*.

Characteristics related to support needs

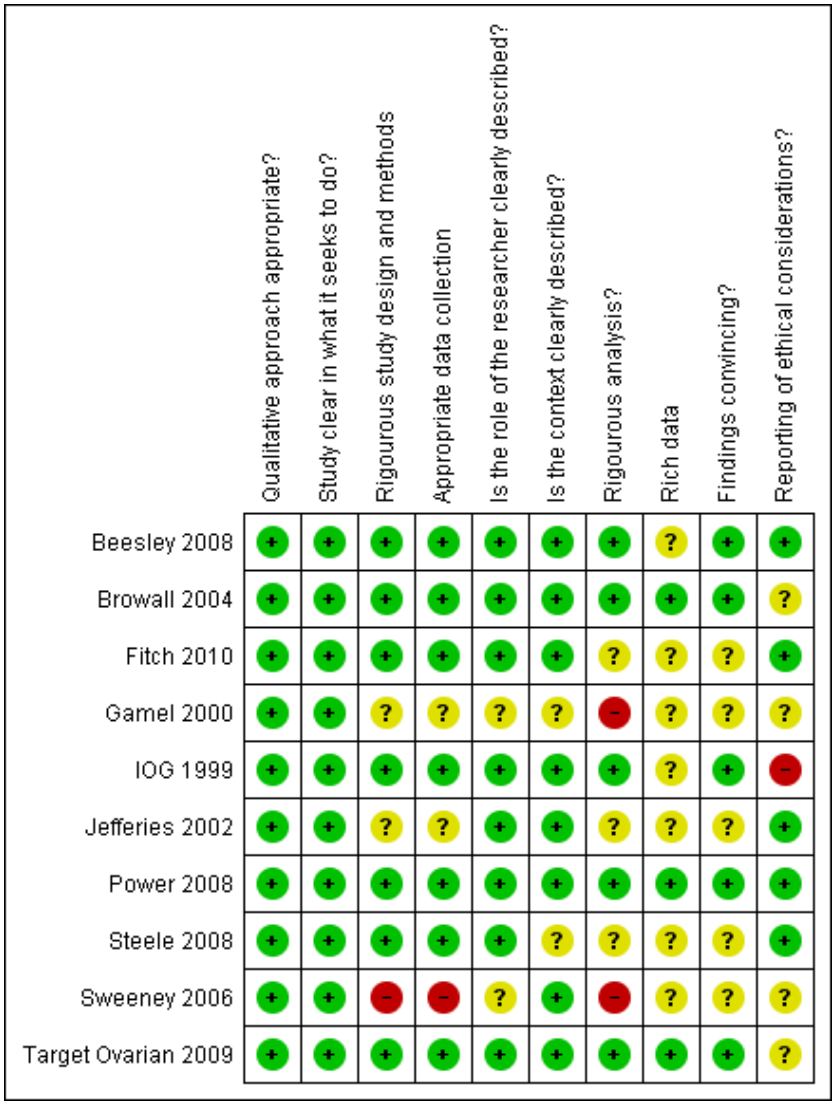
Beesley *et al.* (2008) examined whether certain patient and disease characteristics were associated with specific unmet supportive care needs.

Women with lymphoedema had significantly higher odds of unmet supportive care needs in all four of the domains (psychological, physical, sexuality and healthcare system/information).

Women with partners had higher odds of unmet needs within the sexuality and physical/daily living domains.

Relative to homemakers, women who were unable to work due to illness were more likely to have unmet needs in all domains.

Figure 6.1 Methodological quality summary [Back]



Evidence tables:

Author(s): Beesley *et al.,* 2008

Methods:

Observational study of women with gynaecological cancer in Queensland, Australia. Women were identified from a population based cancer registry which included an estimated 85% of eligible patients.

Participants:

802 women treated for gynaecological cancer: 197 with cervical cancer, 243 with uterine cancer, 234 with ovarian cancer and 128 with other cancers.

Interventions:

Women were mailed a questionnaire about their supportive care needs. The Supportive Care Needs Survey Short Form (SCNS-SF34) was used to assess needs in multiple domains.

Outcomes:

Unmet supportive care needs

43% of the participants reported having at least one moderate or high level unmet supportive care need. The five highest ranked moderate or high unmet need items were:

Needing help with fear of cancer spreading (17%, N=123)

Concerns about the worries of those close to them (15%, N=109)

Uncertainty about the future (14%, N=101)

Lack of energy / tiredness (14%, N=102)

Not being able to do things they used to (14%, N=102)

To compare the importance of the various domains of unmet needs the authors calculated standardised Likert summated scores for each domain. Using this method, unmet psychological needs were the most common, followed by health system/information needs, physical /daily living needs, and finally unmet sexuality needs and patient care/support needs.

Unmet psychological needs

Several factors were associated with an increased likelihood of having unmet psychological supportive care needs:

Unable to work due to illness versus full-time homemaker OR 7.07 (95% C.I. 2.13 to 23.44)

Lymphoedema, OR 5.58 (95% C.I. 2.26 to 13.81)

Chemotherapy treatment, OR 2.35 (95% C.I. 1.08 to 5.12)

Disease not in remission, OR 2.09 (95% C.I. 1.09 to 4.03)

Uterine versus cervical cancer OR 2.63 (1.14 to 6.08)

Unmet sexuality needs

Several factors were associated with an increased likelihood of having unmet sexuality supportive care needs:

Unable to work due to illness versus full-time homemaker OR 5.45 (95% C.I. 1.52 to 19.56)

Living with a partner versus separated/divorced, OR 4.76 (95% C.I. 1.59 to 14.29)

Lymphoedema, OR 3.49 (95% C.I. 1.31 to 9.30)

Disease not in remission, OR 2.57 (95% C.I. 1.17 to 5.58)

Unmet healthcare system and information needs

Several factors were associated with an increased likelihood of having unmet psychological supportive care needs:

Unable to work due to illness versus full-time homemaker OR 7.07 (95% C.I. 2.13 to 23.44)

Lymphoedema, OR 5.58 (95% C.I. 2.26 to 13.81)

Chemotherapy treatment, OR 2.35 (95% C.I. 1.08 to 5.12)

Disease not in remission, OR 2.09 (95% C.I. 1.09 to 4.03)

Open bowel resection OR 7.55 (1.64

Uterine versus cervical cancer OR 2.54 (1.03 to 6.24)

Notes:

Quantitative / qualitative study.

Author(s): Browall *et al.,* 2004

Methods:

Longitudinal study of women with recently diagnosed ovarian cancer who had undergone primary surgery and had no previous cancer diagnosis. Patients were identified via a single oncology department over a period of one year.

Participants:

64 women (Sweden).

Interventions:

Each patient's information needs were evaluated three times though structured interviews. Patients ranked their information needs in the following domains: chances of cure, spread of disease, treatment options, side effects, self care, family risk, social life, impact on family and sexuality.

Outcomes:

Rank of information needs at the time of diagnosis (from most to least important)

chances of cure, spread of disease, treatment options, side effects, self care, family risk, social life, impact on family, sexuality

Rank of information needs immediately after completing treatment

chances of cure, spread of disease, treatment options, side effects, family risk, social life, self care, impact on family, sexuality

Rank of information needs six months after completing treatment

chances of cure, spread of disease, treatment options, side effects, family risk, social life, self care, impact on family, sexuality

Demographic factors related to information needs

Younger patients (<60 years old) consistently attached higher importance to issues about sexuality than older patients did (P=0.005)

Author(s): Gamel *et al.,* 2000

Methods:

Expert literature review done to inform a nursing intervention to provide support and information about the effects of illness on sexuality.

Participants:

Women with gynaecological cancer. The authors searched CINAHL, MedLine and PsychLit databases up to the year 1998. (Although studies published after this date are included).

Interventions:

The review considered the effect of gynaecological cancer on four areas of sexuality:

sexual response and behaviours

body image and appearance

intimacy - including expressing feelings and emotions

fertility and hormone function.

The review also considered the question - "What information support and information concerning sexuality matters do women with gynaecological cancer want?"

Outcomes:

Sexuality information needs

The review listed nine studies reporting psychosocial problems and information or support after treatment for gynaecological cancer. These reports confirmed the need for sexuality information amongst women with different types of gynaecological cancer and in different cultures. But the review could not go into further detail, due to inadequate data collection and reporting in the primary studies.

Two other studies (Lamb and Shelton, 1994; Zegwaard *et al.*, 2000) offered detailed descriptions of specific topics to discuss and when to discuss them.

Timing and type of information needs.

Zegwaard *et al.* (2000) reported that information was needed at three times in the patient pathway: diagnosis and treatment, recovery and first intercourse, followed by the period of rebuilding sexual life

Author(s): Fitch and Steele, 2010

Methods:

Observational, cross sectional study. All women with ovarian cancer attending a Canadian cancer centre's gynaecological clinic over a four month period were invited to participate.

Participants:

50 women with ovarian cancer. 28/50 were within 1 year of diagnosis, 8/50 were 1 to 2 years from diagnosis and 14/50 were more than two years from diagnosis.

Interventions:

Participants were asked to complete a questionnaire about their supportive care needs (the Supportive Care Needs Survey), and a form for demographic information.

Outcomes:

The supportive needs questionnaire was divided into seven sections. Only informational needs will be reported in detail:

Information needs

The group reported experiencing information needs on the following issues

- the things you can do to help yourself get well: (30% reported this)
- test results as soon as possible: 28%

- tests for which you would like explanations: 26%
- cancer that is under control or diminishing: 20%
- benefits and side effects of treatment:: 16%
- support groups in your area: 12%
- sexual relationships: 10%
- important aspects of care: 10%
- aspects of managing illness and side effects: 10%

Some women wanted help with information needs on the following issues

- the things you can do to help yourself get well: (36% wanted help)
- test results as soon as possible: 24%
- tests for which you would like explanations: 26%
- cancer that is under control or diminishing: 22%
- benefits and side effects of treatment:: 18%
- support groups in your area: 18%
- sexual relationships: 10%
- important aspects of care: 22%
- aspects of managing illness and side effects: 24%

Emotional needs

At least 25% of women were currently experiencing emotional needs for six items: feelings of sadness (N=25), worry that the results of your treatment are beyond your control (N=24), feeling down or depressed (N=23), anxiety about having any treatment (N=22) and feeling bored or useless (N=17).

Psychological needs

Fears about cancer returning (N=39) and fears about cancer spreading were the two top needs overall and were two of six psychological items experienced by at least 25% of the women. The other four were: learning to feel in control of your situation (N=20), fears about pain (N=20), fears about physical disability or deterioration (N=19) and accepting changes in your physical appearance (N=17).

Physical needs

More than 25% of patients expressed physical needs for six items: lack of energy (N=28), not being able to do things you used to (N=26), abdominal discomfort (N=22), change in bowel pattern (N=19), not being able to work around the house (N=15) and change in appetite (N=14).

Spiritual needs

Six items were current issues for at least a quarter of patients: uncertainty about the future (N=28), feelings about death and dying (N=20), confusion about why this has happened to you (N=19), keeping a positive outlook (N=15), finding meaning in this experience (N=15) and making the most of your time (N=14).

Social needs

There were five items in the social category that were experienced by more than 25% of the women as current issues: concerns about the worries of those close to you (N=29). concerns about fulfilling your role as a partner (N=14), concerns about the ability of those close to you to cope with caring for you (N=19), concerns about your care giving role (N=13) and changes in people's attitudes and behaviours to you (N=13)

Practical needs

At least 25% of patients expressed current needs in two items: changes in usual routine and lifestyle (N=25) and waiting a long time for clinic appointments (N=15).

Most frequently experienced items across all supportive care domains:

Fear about cancer returning (reported by 72%), fear about cancer spreading (70%), concerns about the worries of those close to you (68%), uncertainty about the future (66%), lack of energy (66%), not being able to do the things you used to (52%), feelings of sadness (50%), changes in usual routine and lifestyle (50%).

Notes:

Identified in update search. Response rate was only 49% of eligible women.

Author(s): IOG, 1999

Methods:

Evidence based guidance for commissioning services for women with gynaecological cancers.

Participants:

The guidance covers UK services for women with ovarian, endometrial, cervical, vaginal or vulval cancer.

Interventions:

The guidance includes recommendations about psychosocial support and psychosexual counselling

Outcomes:

Psychosocial support recommendations

Psychosocial support should be available at every stage to help patients and their families to cope with the effects of the disease and its treatment.

From the time of diagnosis, each patient should have access to a named nurse who has been

trained in counselling patients, who has specialist knowledge of cancer, and who can offer continuity of care.

Clinical staff, particularly specialist nurses, should have training to enhance their ability to recognise the psychological needs of patients and to deal with them appropriately.

Patients should be encouraged to bring a partner, relative or close friend to provide support at diagnostic clinics and appointments at which distressing news may be communicated.

Adequate provision should be made to ensure that women have privacy and are able to maintain their dignity. Health service staff must be sensitive to potential embarrassment and to the needs of women from cultures with strong taboos about female sexuality and nudity.

Psychosocial support is also important for carers looking after women with advanced cancer at home. The primary and palliative care teams have particularly important roles in ensuring that the needs of both patients and carers are identified and met.

The above recommendations were supported by evidence from non-randomised controlled trials or observational studies, and a randomised trial showing that techniques such as relaxation training and education/information accompanied by counselling can reduce side-effects of therapy and alleviate psychological and functional disturbances

Psychosexual counselling recommendations
All women who have treatment that is likely to affect sexual activity (in particular, radiotherapy or surgery to the cervix, vagina or vulva) should be aware that advice is available on minimising adverse effects on their sexual experience and relationships.

Specialist interventions should be available for women and their partners to help them to understand and cope with the effects of treatment on sexual relationships.

The above recommendations were supported by evidence from non-randomised controlled trials or observational studies.

Author(s): Jefferies, 2002

Methods:

Women with ovarian cancer surgically treated at the same district general hospital.

Participants:

24 women (UK). The length of time since diagnosis ranged from 3 months to 7 years (average of 2 years).

Interventions:

The aim of the study was to measure the impact of the appointment of a gynaecology oncology specialist nurse on the emotional support received by ovarian cancer patients. The author developed her own questionnaire specifically for the study, which was tested and refined using a pilot study. The questionnaire was mailed to patients

Outcomes:

Information received

96% of patients had received verbal information and 66% had received written information.

Of the patients who received booklets, 31% said these did not answer all their questions.

Respondents found it better to receive information from both the gynaecologic oncology specialist nurse and the consultant, rather than the consultant alone.

Emotional support

Patients were asked who provided their emotional support. The answers included family, friends, nursing and medical staff. Healthcare professionals were mentioned about as frequently as family members as the sources of greatest help.

Around half the patients (54%) attended a support group. Patients reported both positive and negative aspects of the support group

Notes:

Few questions in the survey were open-ended - many were simple yes/no answers.

Author(s): Power *et al.,* 2008

Methods:

Qualitative study of women with epithelial ovarian cancer identified through a single gynaecologic oncology clinic at a Canadian cancer centre. English speaking patients only.

Participants:

30 women. 12 women had early stage ovarian cancer and 18 had advanced disease. 15 women were in treatment at the time of the interview and 15 were in the post treatment phase. No participants were in the immediate post-diagnosis phase.

Interventions:

Semi structured interview: most interviews lasted 30 to 45 minutes. All interviews were audio-taped and transcribed verbatim. The interviews were analysed using a grounded theory approach to identify the important themes. More women were interviewed until no new themes were identified.

Outcomes:

Core themes (only those relating to information needs are included here):

Absence of relevant information immediately after diagnosis. Some women experienced a gap in information and support immediately after diagnosis and before their initial consultation with an oncologist. The majority of women found that information was not readily available, with no centralised source of information on support and services. The participants needed to do extensive research on their own at a time when they were experiencing anxiety.

"He left the room and my husband and I were sort of left to deal with all that sort of information. And there wasn't any follow-up from there, that initial stage. That's when I think something would have been useful, right at that point. When the doctor gives you the diagnosis and you have to move on to the next stage.

"It seems like you have to figure all this on your own. It's like...it's like little secrets - the more you dig the more you find, but you have to do the digging. Like, I feel sorry for somebody who hasn't got the mentality and education to dig up this information."

Initially available information very frightening. Statistics about ovarian cancer, particularly the high mortality rates were frightening to the patients. Many women initially looked for information on the Internet after diagnosis. Unfortunately they often reported their Internet experience as quite terrifying and often stopped searching for information until they knew more about their own disease characteristics.

"I'd started looking up on, you know, on the Internet, and then what I'm doing is scaring myself"

"I went on the Internet for things, but then I found out things that I didn't want to know, so I stopped doing that".

Avoidance of information, as a coping strategy. Many of the women expressed a desire not to find out all the information they could about their condition as a coping strategy, and sometimes they actively avoided dealing with it.

"I don't want to know too much. I told the doctors right off the hop, I said, 'Don't tell me anything I don't need to know. I don't think it's necessary. I know enough on my own about the disease that that's enough to worry me.'"

"I have been absolutely non interested in hearing about ovarian cancer stuff, because I know how negative it is. So I have not paid any attention to it, and given the uniqueness of my case, I don't particularly want to know anyway."

"I don't need to know every detail right now and, you know, I've chosen to initially...I think maybe it's part of the denial process in many ways; that you know you've got something really serious and you don't really want to know how serious it is in some ways. You know, the fact you know it's serious is enough for the moment, you know."

Notes:

The authors concluded that support is needed immediately after diagnosis - and this should include both information and emotional support and be readily available for newly diagnosed patients.

The authors also discuss support throughout the treatment phase - with options including trained counsellors and long-term survivors of ovarian cancer. Given the long distances involved in Canada they suggest that face-to-face support is probably not practical, suggesting a telephone counselling service is more likely to succeed.

Author(s): Steele *et al.,* 2008

Methods:

Observational qualitative study of women with gynaecologic cancer attending an outpatient clinic

at Canadian cancer centre over a 4 month period.
Participants: 103 women (Canada). 209 women were approached to participate: 30 declined, 62 did not return the survey and 14 did not complete the survey properly - so results were available for 103 women. 50/103 had ovarian cancer, 21/103 cervical cancer, 19/103 vulval cancer, 6/103 uterine cancer, 2/103 endometrial cancer and 4/103 other cancer. 71% were interviewed more than a year after diagnosis.
Interventions: The study aimed to identify the supportive care needs of women with gynaecologic cancer and whether they wanted help in meeting these needs. The questionnaire was based on that of Bonevski *et al.* (Cancer: 2002; **94:**131-140), and designed to measure the supportive care needs of patients with cancer. The authors also added questions about desire for help with any supportive care needs.
Outcomes: **Supportive care needs and help desired** 69/103 (67%) women expressed fears about cancer returning, and 30/69 (44%) wanted help with this 66/103 (64%) women expressed fears about cancer spreading, and 33/66 (50%) wanted help with this 54/103 (52%) women expressed uncertainty about the future, and 23/54 (43%) wanted help with this 52/103 (50%) women were concerned about the worries of those close to them, and 22/52 (42%) wanted help with this 49/103 (48%) women had a lack of energy, and 22/49 (45%) wanted help with this 45/103 (44%) women had a feeling of sadness, and 26/45 (58%) wanted help with this 44/103 (48%) women reported feeling depressed, and 26/44 (58%) wanted help with this 44/103 (48%) women reported anxiety, and 27/44 (61%) wanted help with this 41/103 (39%) women reported worry about lack of control over outcome, and 18/41 (44%) wanted help with this 40/103 (39%) women reported not being able to do the things they used to, and 14/40 (35%) wanted help with this 23/103 (22%) women reported a need to be informed about the things you can do to help yourself get well, and all wanted help with this.

Author(s): Sweeney, 2006

Methods:

Expert literature review of the information needs of women with ovarian cancer, particularly the role of clinical nurse specialists in delivering information. Unclear how studies were selected for inclusion. Also includes results from a questionnaire study

Participants:

18 patients (UK) identified through a gynaecological oncology service.

Interventions:

Women were mailed a questionnaire about their experience

Outcomes:

Information needs of women with ovarian cancer

The author identified several themes in the included studies and guidelines: the importance of relaying information, assessing patients' information needs, what happens when needs go unmet.

The author notes that the 1999 Department of Health IOG recommends women with gynaecological malignancy should be provided with sufficient and relevant information - and notes the importance of the clinical nurse specialist in providing information and support.

Results of the questionnaire

12/14 (85%) of the women felt they had received sufficient information about their illness and treatment options. All women had seen the clinical nurse specialist at their initial visit, and had been given the nurse's contact information.

Author(s): Target Ovarian, 2009

Methods:

Survey study of ovarian cancer patients, gynaecological cancer clinical nurse specialists, ovarian cancer researchers and clinicians

Participants:

UK women diagnosed with ovarian cancer (N=132). Women were found though national advertising, professional referrals and through contacts of already recruited women.
A representative sample of UK women (N=1,000)

A representative sample of UK General Practitioners (GPs) (N=401)
UK gynaecological cancer clinical nurse specialists (CNS) (N=57). Nurses were found though found though the National Forum of Gynaecological Oncology nurses, national advertising, professional referrals, though the Target Ovarian Cancer website and through contacts of already recruited nurses.

Interventions:

Survey / interview (telephone or online)

Outcomes:

The study recorded the experiences of those living or working with ovarian cancer. The study also measured awareness of the symptoms of ovarian cancer in the general population and in GPs. The working environment of clinical nurse specialists was also examined.

Information needs at the time of diagnosis

Over half the women with ovarian cancer (55%) were not given (or could not remember being given) clear written or printed information about ovarian cancer at the time of their diagnosis. Most (72%) said that doctors of nurses gave them all the information they needed to answer any questions they had about ovarian cancer.

55% of women were given contact details for a clinical nurse specialist at the time of diagnosis. Over a third of women (36%) were not given any contact details at all. Despite this most women (84%) had access to a clinical nurse specialist at some point during their cancer journey.

Emotional support needs

Three quarters of the women surveyed felt they had needed some form of emotional support since their diagnosis. Of these women a third actively sought out support, a third were offered emotional support and the final third were neither offered nor sought support (even though they felt they needed it).

Sources of emotional support

Women reported the following sources of emotional support: clinical nurse specialist (44%), support group (30%), GP (23%), counsellor / psychotherapist (11%), telephone help line (6%), psychologist (4%), Macmillan nurse (4%), Ovacome (2%), Lauriston nurses (1%) and Angels of Hope (1%).

Those who gave the most emotional support

Women reported the source which gave the *most* emotional support as: clinical nurse specialist (26%), support group (9%), GP (9%), counsellor / psychotherapist (3%), telephone help line (1%), psychologist (1%), Macmillan nurse (1%), Ovacome (1%).

Clinical nurse specialist as a key worker

The key worker role for ovarian cancer patients was said to be well covered in their area by half of nurses (47%), and not covered well by one in four (25%).

A quarter of the nurses surveyed (25%) reported there was nothing that could help them fulfil the key worker role; but most (63% N=36) said there was something that could be done to help them as key workers. Of those 36 nurses, 28% mentioned more specialist nurses and 22% mentioned more time (to do a variety of job related tasks). One in five (19%) suggested suitable cover would help them fulfil their key worker role.

Notes:

The Pathfinder Study was commissioned and published by the Target Ovarian Cancer charity. Although not published in a peer reviewed journal, it was overseen by a multidisciplinary panel of

experts. The report's authors acknowledge the possibility of selection bias due to the recruitment methods.

References:

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Appendix 1 – Search strategies

NATIONAL COLLABORATING CENTRE FOR CANCER

Ovarian Cancer Clinical Guideline

Chapter 2 – Detection in Primary Care **Literature search summary**

Topic 1: What are the symptoms and signs of ovarian cancer?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2004 -	3409	64	06/07/09
Premedline	July 05, 2010	596	7	06/07/09
Embase	2004 -	1569	22	08/07/09
Cochrane Library	Issue 2, 2009	15	0	08/07/09
Cinahl	2004 -	143	6	08/07/09
BNI	2004 -	27	12	06/07/09
Psychinfo	2004 -	18	3	08/07/09
Web of Science (SCI & SSCI)	2004 -	529	31	08/07/09
Biomed Central	2004 -	502	0	08/07/09

Total References retrieved (after de-duplication): 110

Medline search strategy *(This search strategy is adapted to each database)*

1. exp Ovarian Neoplasms/di [Diagnosis]
2. (ovar$ adj5 (neoplasm$ or cancer$ or carcinom$ or tumo?r$)).tw.
3. exp Adnexal Diseases/di [Diagnosis]
4. (epithel$ ovar$ adj5 (neoplasm$ or cancer$ or carcinom$ or tumo?r$)).tw.
5. (early ovar$ adj5 (neoplasm$ or cancer$ or carcinom$ or tumo?r$)).tw.
6. (suspect$ ovar$ adj5 (neoplasm$ or cancer$ or carcinom$ or tumo?r$)).tw.
7. or/1-6
8. exp "Signs and Symptoms"/
9. exp Early Diagnosis/ or exp Diagnosis/
10. exp "Early Detection of Cancer"/
11. early warning$ sign$.tw.
12. (abdom$ adj5 (pressure$ or pain$ or swelling$ or hard)).tw.
13. (bowel irregularit$ or bloat$ or fullness$ or satiet$ or gastro$).tw.
14. (fatigue$ or weight loss$ or weight gain$ or constipat$ or diarrhoea$ or gas$ or nausea$ or indigestion$).tw.
15. ((loss adj appetite$) or (lack adj energ$)).tw.
16. (pelvic discomfort$ or chest pain$ or respirator$ difficult$ or lower back pain$).tw.
17. (abnormal vaginal bleeding$ or discharge$).tw.
18. (urin$ adj3 (frequenc$ or urgenc$)).tw.
19. or/8-18
20. 7 and 19

2. Health Economics Literature search details

This topic was identified as low priority in terms of health economics. The health economics scoping search identified any general health economics papers on ovarian cancer.

3. Any further comments

The search was undertaken from 2004 onwards as a systematic review was identified [through the Key Messages for

Ovarian Cancer for Health Professionals (February 2009) document] which was felt to be worthy of basing the search upon - **Bankhead et al** Symptoms associated with diagnosis of ovarian cancer: a systematic review *BJOG* (2005) 112: 857-865. The systematic review last searched the literature in April 2004 and so this search was executed to update that time period. Systematic reviews (2002 onwards), RCT's and Observational Studies filters applied to basic search for the clinical review.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search with a date limit of 2009 onwards. (NB: AMED was searched without date limit as not searched initially).

Database name	No of references found	No of references retrieved	Finish date of search
Medline	777	11	08/07/2010
Premedline (July 08, 2010)	296	5	08/07/2010
Embase	374	6	08/07/2010
Cochrane Library (Issue 3, 2010)	2	0	08/07/2010
Cinahl	43	5	08/07/2010
BNI	3	3	08/07/2010
Psychinfo	11	2	08/07/2010
AMED	20	0	08/07/2010
Web of Science (SCI & SSCI)	116	10	08/07/2010

Total References retrieved (after de-duplication): 30

Search alerts on Medline, Embase and Web of Science until 1st August – no additional references identified

Topic 2: What is the relationship between the duration of pre-diagnostic symptoms of ovarian cancer and survival?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1950 -	1608	55	04/03/2010
Premedline	Mar 03, 2010	2	2	04/03/2010
Embase	1980 -	516	42	04/03/2010
Cochrane Library	Issue 1, 2010	139	2	04/03/2010
Cinahl	1982 -	36	3	09/03/2010
BNI	1985 -	2	2	04/03/2010
Psychinfo	1806 -	9	3	04/03/2010
Amed	1985 -	2	0	04/03/2010
Web of Science (SCI & SSCI)	1970 -	453	38	09/03/2010
Biomed Central	As per database	3	0	04/03/2010

Total References retrieved (after de-duplication): 86

Medline search strategy *(This search strategy is adapted to each database)*

1 exp Ovarian Neoplasms/
2 exp Adnexal Diseases/
3 ((ovar* or fallopian or peritoneal*) adj5 (cancer* or carcinoma* or malignan* or neoplas* or tumour* or tumor* or adenocarcin* or adeno-carcin* or sarcoma* or choriocarcinoma* or chorioncarcinoma* or dysgerminoma* or seminoma* or teratoma* or teratocarcinoma* or terato-carcinoma* or cystadenocarcin* or fibrosarcoma* or fibro-sarcoma* or rhabdomyosarcoma* or rhabdo-myosarcoma* or rhabdosarcoma* or rhabdo-sarcoma* or leiomyosarcoma* or leio-myosarcoma* or carcinosarcoma* or carcino-sarcoma* or granulosa*)).tw.
4 ((borderline or border line) adj4 ovar*).tw.
5 or/1-4

6 exp "Signs and Symptoms"/
7 exp Early Diagnosis/ or exp Diagnosis/
8 exp "Early Detection of Cancer"/
9 symptom$.m_titl.
10 or/6-9
11 5 and 10
12 Ovarian Neoplasms/di [Diagnosis]
13 11 or 12
14 Time Factors/
15 (symptom$ adj5 predict$).tw.
16 (symptom$ adj5 (duration or frequency or severity)).tw.
17 (diagnos$ adj5 delay$).tw.
18 or/14-17
19 13 and 18

2. Health Economics Literature search details

This topic was identified as low priority in terms of health economics. The health economics scoping search identified any general health economics papers on ovarian cancer.

3. Any further comments

General exclusions filter only was used on the clinical evidence search.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search with a date limit of 2009 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline	127	4	15/07/2010
Premedline (July 15, 2010)	6	1	16/07/2010
Embase	73	4	15/07/2010
Cochrane Library (Issue 3, 2010)	17	0	15/07/2010
Cinahl	6	0	15/07/2010
BNI	2	1	15/07/2010
Psychinfo	0	0	15/07/2010
AMED	0	0	15/07/2010
Web of Science (SCI & SSCI)	88	4	15/07/2010

Total References retrieved (after de-duplication): 9

Search alerts on Medline, Embase and Web of Science until 1st August – no additional references identified

Topic 3: For women with suspected ovarian cancer, what are the most effective first tests in primary care?

1. Literature search details

3a Ultrasound

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1950 -	1389	115	03/08/09
Premedline	June 15, 2009	28	3	03/08/09
Embase	1980 -	1314	148	04/08/09
Cochrane Library	Issue 2, 2009	28	4	03/08/09
Cinahl	1982 -	77	15	10/08/09
BNI	1985 -	0	0	03/08/09
Psychinfo	1806 -	0	0	03/08/09

Amed	1985 -	0	0	03/08/09
Web of Science (SCI & SSCI)	1970 -	746	83	04/08/09
BIOSIS	All	369	35	05/08/09

Total References retrieved (after de-duplication): 234

3b Pelvic examination

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1950 -	498	27	05/08/09
Premedline	June 15, 2009	5	0	05/08/09
Embase	1980 -	544	34	05/08/09
Cochrane Library	Issue 2, 2009	15	1	05/08/09
Cinahl	1982 -	62	1	10/08/09
BNI	1985 -	0	0	05/08/09
Psychinfo	1806 -	0	0	05/08/09
Amed	1985 -	0	0	05/08/09
Web of Science (SCI & SSCI)	1970 -	273	8	10/08/09
BIOSIS	All	200	7	10/08/09

Total References retrieved (after de-duplication): 27

3c Tumour markers (CA 125)

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1950 -	521	84	04/08/09
Premedline	June 15, 2009	19	1	04/08/09
Embase	1980 -	585	91	11/08/09
Cochrane Library	Issue 2, 2009	18	2	04/08/09
Cinahl	1982 -	20	4	11/08/09
BNI	1985 -	0	0	10/08/09
Psychinfo	1806 -	0	0	10/08/09
Amed	1985 -	0	0	10/08/09
Web of Science (SCI & SSCI)	1970 -	525	54	11/08/09
BIOSIS	All	291	58	11/08/09

Total References retrieved (after de-duplication): 130

Medline search strategy *(This search strategy is adapted to each database)*

3a Ultrasound

1. exp Ovarian Neoplasms/
2. exp Adnexal Diseases/
3. exp Genital Neoplasms, Female/
4. exp Fallopian Tube Neoplasms/
5. exp Peritoneal Neoplasms/
6. exp Pelvic Neoplasms/
7. ((ovar$ or fallopian or peritoneal$) adj5 (cancer$ or carcinoma$ or malignan$ or neoplas$ or tumour$ or tumor$ or adenocarcin$ or adeno-carcin$ or sarcoma$ or choriocarcinoma$ or chorioncarcinoma$ or dysgerminoma$ or seminoma$ or teratoma$ or teratocarcinoma$ or terato-carcinoma$ or cystadenocarcin$ or fibrosarcoma$ or fibro-sarcoma$ or rhabdomyosarcoma$ or rhabdo-myosarcoma$ or rhabdosarcoma$ or rhabdo-sarcoma$ or leiomyosarcoma$ or leio-myosarcoma$ or carcinosarcoma$ or carcino-sarcoma$ or

granulosa$)).tw.
8. ((borderline or border line) adj4 ovar$).tw.
9. or/1-8
10. (suspect$ or suspicious or uncertain).tw.
11. ((pelvic or abdominal or adnexal) adj mass$).tw.
12. 11 or 10
13. 9 and 12
14. exp ultrasonography/
15. ultraso$.tw.
16. (transvagina$ adj2 sonogra$).tw.
17. 16 or 15 or 14
18. 13 and 17

3b Pelvic Examination
1. exp Ovarian Neoplasms/
2. exp Adnexal Diseases/
3. exp Genital Neoplasms, Female/
4. exp Fallopian Tube Neoplasms/
5. exp Peritoneal Neoplasms/
6. exp Pelvic Neoplasms/
7. ((ovar$ or fallopian or peritoneal$) adj5 (cancer$ or carcinoma$ or malignan$ or neoplas$ or tumour$ or tumor$ or adenocarcin$ or adeno-carcin$ or sarcoma$ or choriocarcinoma$ or chorioncarcinoma$ or dysgerminoma$ or seminoma$ or teratoma$ or teratocarcinoma$ or terato-carcinoma$ or cystadenocarcin$ or fibrosarcoma$ or fibro-sarcoma$ or rhabdomyosarcoma$ or rhabdo-myosarcoma$ or rhabdosarcoma$ or rhabdo-sarcoma$ or leiomyosarcoma$ or leio-myosarcoma$ or carcinosarcoma$ or carcino-sarcoma$ or granulosa$)).tw.
8. ((borderline or border line) adj4 ovar$).tw.
9. or/1-8
10. (suspect$ or suspicious or uncertain).tw.
11. ((pelvic or abdominal or adnexal) adj mass$).tw.
12. 11 or 10
13. 9 and 12
14. exp Physical Examination/
15. ((pelvic or physical or clinical or gyn*ecolog$ or bimanual) adj (assessment$ or exam$)).tw.
16. 14or 15
17. 13 and 16

3c Tumour Markers – CA125
1. exp Ovarian Neoplasms/
2. exp Adnexal Diseases/
3. exp Genital Neoplasms, Female/
4. exp Fallopian Tube Neoplasms/
5. exp Peritoneal Neoplasms/
6. exp Pelvic Neoplasms/
7. ((ovar$ or fallopian or peritoneal$) adj5 (cancer$ or carcinoma$ or malignan$ or neoplas$ or tumour$ or tumor$ or adenocarcin$ or adeno-carcin$ or sarcoma$ or choriocarcinoma$ or chorioncarcinoma$ or dysgerminoma$ or seminoma$ or teratoma$ or teratocarcinoma$ or terato-carcinoma$ or cystadenocarcin$ or fibrosarcoma$ or fibro-sarcoma$ or rhabdomyosarcoma$ or rhabdo-myosarcoma$ or rhabdosarcoma$ or rhabdo-sarcoma$ or leiomyosarcoma$ or leio-myosarcoma$ or carcinosarcoma$ or carcino-sarcoma$ or granulosa$)).tw.
8. ((borderline or border line) adj4 ovar$).tw.
9. or/1-8
10. (suspect$ or suspicious or uncertain).tw.
11. ((pelvic or abdominal or adnexal) adj mass$).tw.
12. 11 or 10
13. 9 and 12
14. CA-125 Antigen/
15. (CA125 or CA 125 or CA-125).tw.
16. cancer antigen 125.tw.

17. 16 or 15 or 14
18. 13 and 17

2. Health Economics Literature search details

This topic was identified as high priority in terms of health economics. The health economics search undertaken during scoping process used as a basis. Further searches for data input into the model were discussed and undertaken where appropriate.

3. Any further comments

General exclusions filter only was used on the clinical evidence search. Primary care setting was not used as the initial searches did not retrieve any relevant papers, so the searches were broadened to include all settings. CA125 was the only tumour marker required by the GDG to be searched.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search with a date limit of 2009 onwards. (NB: the search was executed as one update search rather than 3 separate parts).

Database name	No of references found	No of references retrieved	Finish date of search
Medline	82	7	15/07/2010
Premedline (July 15, 2010)	27	1	16/07/2010
Embase	134	11	15/07/2010
Cochrane Library (Issue 3, 2010)	25	0	15/07/2010
Cinahl	49	0	15/07/2010
BNI	0	0	15/07/2010
Psychinfo	1	0	15/07/2010
AMED	0	0	15/07/2010
Web of Science (SCI & SSCI)	168	19	15/07/2010

Total References retrieved (after de-duplication): 22

Search alerts on Medline, Embase and Web of Science until 1st August – no additional references identified

NATIONAL COLLABORATING CENTRE FOR CANCER

Ovarian Cancer Clinical Guideline

Chapter 3 – Establishing the Diagnosis in Secondary Care — Literature search summary

Topic 5: For women with suspected ovarian cancer, what serum tumour marker tests should be routinely carried out to aid in diagnosis?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1950 -	1522	133	04/12/09
Premedline	Nov 30, 2009	54	7	01/12/09
Embase	1980 -	1538	98	07/12/09
Cochrane Library	Issue 4, 2009	377	5	07/12/09
Cinahl	1982 -	7	2	07/12/09
BNI	1985 -	0	0	01/12/09
Psychinfo	1806 -	0	0	01/12/09
Amed	1985 -	0	0	01/12/09
Web of Science (SCI & SSCI)	1970 -	1165	120	08/12/09
Biomed Central	As per database	27	0	07/12/09

Total References retrieved (after de-duplication): 216

Medline search strategy *(This search strategy is adapted to each database)*

1 exp Ovarian Neoplasms/
2 exp Adnexal Diseases/
3 exp Genital Neoplasms, Female/
4 exp Fallopian Tube Neoplasms/
5 exp Peritoneal Neoplasms/
6 exp Pelvic Neoplasms/
7 ((ovar* or fallopian or peritoneal*) adj5 (cancer* or carcinoma* or malignan* or neoplas* or tumour* or tumor* or adenocarcin* or adeno-carcin* or sarcoma* or choriocarcinoma* or chorioncarcinoma* or dysgerminoma* or seminoma* or teratoma* or teratocarcinoma* or terato-carcinoma* or cystadenocarcin* or fibrosarcoma* or fibro-sarcoma* or rhabdomyosarcoma* or rhabdo-myosarcoma* or rhabdosarcoma* or rhabdo-sarcoma* or leiomyosarcoma* or leio-myosarcoma* or carcinosarcoma* or carcino-sarcoma* or granulosa*)).tw.
8 ((borderline or border line) adj4 ovar*).tw.
9 or/1-8
10 *CA-19-9 Antigen/
11 *Carcinoembryonic Antigen/
12 (AFP or "alpha fetoprotein$").tw.
13 (HCG or "chorionic gonadotropin").tw.
14 (CEA or "carcinoembryonic antigen$").tw.
15 (CA19-9 or CA-19* or CA19* or CA 19* or "CA 199").tw.
16 (CA72-4 or CA-72* or CA72* or CA 72* or "CA 724").tw.
17 (HE4 or HE-4 or HE 4 or CDX2 or CDX-2 or CDX 2).tw.
18 or/10-17
19 Ascites/
20 ascit$.tw.
21 19 or 20
22 ovar$.tw.
23 21 and 22
24 9 and 18

25 18 and 23
26 24 or 25

2. Health Economics Literature search details

This topic was identified as low priority in terms of health economics. The health economics scoping search identified any general health economics papers on ovarian cancer.

3. Any further comments

Systematic reviews (2002 onwards), RCT's, Observational Studies, Diagnostic Studies and Prognosis filters applied to basic search for the clinical review. The PICO was focused to include only the following tumour markers: CEA, CDX2, CA 72-4, CA 19-9, AFP, beta-hCG and HE4. (NB: CA125 is covered in Topic 3).

4. Update Search

For the update search, the same search criteria/filters were applied as initial search with a date limit of 2009 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline	158	7	15/07/2010
Premedline (July 15, 2010)	3	2	16/07/2010
Embase	151	7	15/07/2010
Cochrane Library (Issue 3, 2010)	69	0	15/07/2010
Cinahl	3	1	15/07/2010
BNI	0	0	15/07/2010
Psychinfo	2	0	15/07/2010
AMED	0	0	15/07/2010
Web of Science (SCI & SSCI)	147	9	15/07/2010

Total References retrieved (after de-duplication): 13

Search alerts on Medline, Embase and Web of Science until 1st August – no additional references identified

Topic 4: For women with suspected ovarian cancer, which malignancy index is the most effective?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1950 -	1377	84	12/06/09
Premedline	June 15, 2009	12	4	15/06/09
Embase	1980 -	876	76	12/06/09
Cochrane Library	Issue 2, 2009	477	2	12/06/09
Cinahl	1982 -	15	3	12/06/09
BNI	1985 -	0	0	12/06/09
Psychinfo	1806 -	1	0	12/06/09
Amed	1985 -	0	0	12/06/09
Web of Science (SCI & SSCI)	1970 -	1326	62	12/06/09
Biomed Central	As per database	12	0	12/06/09

Total References retrieved (after de-duplication): 136

Medline search strategy *(This search strategy is adapted to each database)*

1 exp Ovarian Neoplasms/
2 exp Adnexal Diseases/
3 exp Genital Neoplasms, Female/

4 exp Fallopian Tube Neoplasms/
5 exp Peritoneal Neoplasms/
6 exp Pelvic Neoplasms/
7 ((ovar* or fallopian or peritoneal*) adj5 (cancer* or carcinoma* or malignan* or neoplas* or tumour* or tumor* or adenocarcin* or adeno-carcin* or sarcoma* or choriocarcinoma* or chorioncarcinoma* or dysgerminoma* or seminoma* or teratoma* or teratocarcinoma* or terato-carcinoma* or cystadenocarcin* or fibrosarcoma* or fibro-sarcoma* or rhabdomyosarcoma* or rhabdo-myosarcoma* or rhabdosarcoma* or rhabdo-sarcoma* or leiomyosarcoma* or leio-myosarcoma* or carcinosarcoma* or carcino-sarcoma* or granulosa*)).tw.
8 ((borderline or border line) adj4 ovar*).tw.
9 or/1-8
10 Diagnosis, Differential/
11 CA-125 Antigen/
12 exp Ultrasonography, Doppler, Color/
13 Menopause/
14 Premenopause/
15 Postmenopause/
16 Tumor Markers, Biological/
17 or/11-16
18 10 and 9 and 17
19 exp discriminant analysis/ or exp regression analysis/
20 19 and 9 and 17
21 18 or 20
22 risk assessment ind$.mp.
23 (risk adj2 malignancy ind$).mp.
24 (RAI or RMI or LRM).mp.
25 malignancy ind$.mp.
26 logistic regression model$.mp.
27 or/22-26
28 27 and 9
29 28 or 21

2. Health Economics Literature search details

This topic was identified as low priority in terms of health economics. The health economics scoping search identified any general health economics papers on ovarian cancer.

3. Any further comments

General exclusions filter only was used on the clinical evidence search.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search with a date limit of 2009 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline	158	7	15/07/2010
Premedline (July 15, 2010)	7	1	16/07/2010
Embase	151	9	15/07/2010
Cochrane Library (Issue 3, 2010)	158	0	15/07/2010
Cinahl	3	1	15/07/2010
BNI	0	0	15/07/2010
Psychinfo	2	0	15/07/2010
AMED	0	0	15/07/2010
Web of Science (SCI & SSCI)	214	9	15/07/2010

Total References retrieved (after de-duplication): 14

Search alerts on Medline, Embase and Web of Science until 1st August – no additional references identified

Topic 6: For women with suspected ovarian cancer, what is the most appropriate imaging to be done to determine future management?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1950 -	2058	333	30/10/09
Premedline	Oct 14, 2009	32	10	30/10/09
Embase	1980 -	2071	228	30/10/09
Cochrane Library	Issue 4, 2009	671	24	30/10/09
Cinahl	1982 -	190	8	30/10/09
BNI	1985 -	0	0	30/10/09
Psychinfo	1806 -	20	0	30/10/09
Amed	1985 -	0	0	30/10/09
Web of Science (SCI & SSCI)	1970 -	1788	316	30/10/09
Biomed Central	As per database	24	1	30/10/09

Total References retrieved (after de-duplication): 625

Medline search strategy *(This search strategy is adapted to each database)*

1 exp Ovarian Neoplasms/
2 exp Adnexal Diseases/
3 (ovar* adj5 (cancer* or carcinoma* or malignan* or neoplas* or tumour* or tumor* or adenocarcin* or adeno-carcin* or sarcoma* or choriocarcinoma* or chorioncarcinoma* or dysgerminoma* or seminoma* or teratoma* or teratocarcinoma* or terato-carcinoma* or cystadenocarcin* or fibrosarcoma* or fibro-sarcoma* or rhabdomyosarcoma* or rhabdo-myosarcoma* or rhabdosarcoma* or rhabdo-sarcoma* or leiomyosarcoma* or leio-myosarcoma* or carcinosarcoma* or carcino-sarcoma* or granulosa*)).mp.
4 or/1-3
5 exp Radiography/
6 (radiograph$ or xray or x-ray).mp.
7 exp Ultrasonography/
8 (ultrasound$ or ultrasonograph$ or sonogra$ or ultrasonic or echogra$ or echotomogra$).mp.
9 exp Radionuclide Imaging/
10 (radionuclide adj1 (scan$ or imaging)).tw.
11 scintigraph$.mp.
12 exp Magnetic Resonance Imaging/
13 magnet$ resonance.mp.
14 (MRI or MRI$1 or NMR$1).tw.
15 (MR adj (imag$ or scan$)).tw.
16 (magnet$ adj (imag$ or scan$)).tw.
17 (magneti?ation adj3 imaging).tw.
18 exp Tomography/
19 exp Tomography, X-Ray Computed/
20 PET$1.tw.
21 PET-CT.tw.
22 (comput$ adj1 tomogra$).tw.
23 ((diffusion or planar or echoplanar or functional or nuclear or radionuclide or radioisotope or conventional) adj2 (scan$ or imag$ or tomogra$)).tw.
24 (FDG-PET or FES-PET or 18F-FDG-PET or FLT-PET).mp.
25 ((CT or CAT) adj (scan$ or imaging or examination)).tw.
26 (PET adj (scan$ or imag$ or examination)).tw.
27 positron emission tomograph$.mp.
28 or/5-27

2. Health Economics Literature search details

This topic was identified as low priority in terms of health economics. The health economics scoping search identified any general health economics papers on ovarian cancer.

3. Any further comments

Systematic reviews (2002 onwards), RCT's and Observational Studies filters applied to basic search for the clinical review.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search with a date limit of 2009 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline	151	14	15/07/2010
Premedline (July 15, 2010)	11	2	16/07/2010
Embase	165	7	15/07/2010
Cochrane Library (Issue 3, 2010)	93	0	15/07/2010
Cinahl	30	1	15/07/2010
BNI	0	0	15/07/2010
Psychinfo	6	0	15/07/2010
AMED	0	0	15/07/2010
Web of Science (SCI & SSCI)	234	18	15/07/2010

Total References retrieved (after de-duplication): 29

Search alerts on Medline, Embase and Web of Science until 1st August – no additional references identified

Topic 7 & 8: For women with suspected ovarian cancer, when is it appropriate not to have a tissue diagnosis before starting chemotherapy? What is the best method of tissue diagnosis before chemotherapy, samples from image-guided biopsy or laparoscopic biopsy?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1950 -	1738	99	19/01/2010
Premedline	Jan 19, 2009	56	0	19/01/2010
Embase	1980 -	1622	49	19/01/2010
Cochrane Library	Issue 1, 2009	134	0	20/01/2010
Cinahl	1982 -	132	6	19/01/2010
BNI	1985 -	0	0	19/01/2010
Psychinfo	1806 -	1	0	19/01/2010
Amed	1985 -	1	0	19/01/2010
Web of Science (SCI & SSCI)	1970 -	1197	59	19/01/2010
Biomed Central	As per database	89	2	19/01/2010

Total References retrieved (after de-duplication): 172

Medline search strategy *(This search strategy is adapted to each database)*

1 ((ovar*) adj5 (cancer* or carcinoma* or malignan* or neoplas* or tumour* or tumor* or adenocarcin* or adeno-carcin* or sarcoma* or choriocarcinoma* or chorioncarcinoma* or dysgerminoma* or seminoma* or teratoma* or teratocarcinoma* or terato-carcinoma* or cystadenocarcin* or fibrosarcoma* or fibro-sarcoma* or rhabdomyosarcoma* or rhabdo-myosarcoma* or rhabdosarcoma* or rhabdo-sarcoma* or leiomyosarcoma* or leio-myosarcoma* or carcinosarcoma* or carcino-sarcoma* or granulosa*)).tw.
2 Biopsy/ or exp Biopsy, Needle

3 biops$.tw.
4 2 or 3
5 Cell Biology/
6 Cytodiagnosis/
7 Cytological Techniques/
8 (cytology$ or aspiration or cytospin$).tw.
9 (tissue adj3 diagnos$).tw.
10 or/5-9
11 1 and 4
12 1 and 10
13 11 or 12

2. Health Economics Literature search details

This topic was identified as low priority in terms of health economics. The health economics scoping search identified any general health economics papers on ovarian cancer.

3. Any further comments

General exclusions filter only was used on the clinical evidence search. Initially the search was executed with the aim of answering topic 8 which called for comparative papers – none were found. So the search for Topic 7 was used to also pick-up studies analysing the single effectiveness of the biopsy methods indicated.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search with a date limit of 2009 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline	104	6	15/07/2010
Premedline (July 15, 2010)	32	1	16/07/2010
Embase	121	9	15/07/2010
Cochrane Library (Issue 3, 2010)	36	0	15/07/2010
Cinahl	29	1	15/07/2010
BNI	0	0	15/07/2010
Psychinfo	1	0	15/07/2010
AMED	0	0	15/07/2010
Web of Science (SCI & SSCI)	300	9	15/07/2010

Total References retrieved (after de-duplication): 15

Search alerts on Medline, Embase and Web of Science until 1st August – no additional references identified

NATIONAL COLLABORATING CENTRE FOR CANCER

Ovarian Cancer Clinical Guideline

Chapter 4 – Management of Suspected Early Stage Ovarian Cancer — Literature search summary

Topic 10: For women with ovarian cancer whose disease appears confined to the ovaries, what is the effectiveness of systematic retroperitoneal lymphadenectomy in surgical management?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1950 -	598	151	19/06/09
Premedline	June 18, 2009	16	4	19/06/09
Embase	1980 -	634	155	19/06/09
Cochrane Library	Issue 2, 2009	54	17	19/06/09
Cinahl	1982 -	9	3	19/06/09
BNI	1985 -	0	0	19/06/09
Psychinfo	1806 -	0	0	19/06/09
Amed	1985 -	0	0	19/06/09
Web of Science (SCI & SSCI)	1970 -	470	128	19/06/09
Biomed Central	As per database	22	0	19/06/09

Total References retrieved (after de-duplication): 250

Medline search strategy *(This search strategy is adapted to each database)*

1 Lymph Node Excision/
2 lymphadenectom$.mp.
3 (lymph node adj3 (excis$ or dissect$)).mp.
4 or/1-3
5 exp Ovarian Neoplasms/
6 exp Adnexal Diseases/
7 (ovar* adj5 (cancer* or carcinoma* or malignan* or neoplas* or tumour* or tumor*)).tw.
8 or/5-7
9 8 and 4

2. Health Economics Literature search details

This topic was identified as low priority in terms of health economics. The health economics scoping search identified any general health economics papers on ovarian cancer.

3. Any further comments

General exclusions filter only was used on the clinical evidence search.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search with a date limit of 2009 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline	51	5	15/07/2010
Premedline (July 15, 2010)	7	0	16/07/2010
Embase	105	7	15/07/2010
Cochrane Library (Issue 3, 2010)	9	0	15/07/2010

Cinahl	2	1	15/07/2010
BNI	0	0	15/07/2010
Psychinfo	0	0	15/07/2010
AMED	0	0	15/07/2010
Web of Science (SCI & SSCI)	83	7	15/07/2010

Total References retrieved (after de-duplication): 10
Search alerts on Medline, Embase and Web of Science until 1st August – no additional references identified

Topic 13: For women with stage I ovarian cancer, what is the most effective first line chemotherapy?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1950 -	1595	39	07/05/2009
Premedline	May 7, 2009	7	0	07/05/2009
Embase	1980 -	2106	42	07/05/2009
Cochrane Library	Issue 2, 2009	721	50	07/05/2009
Cinahl	1982 -	57	4	07/05/2009
BNI	1985 -	5 (no filters)	0	07/05/2009
Psychinfo	1806 -	1 (no filters)	0	07/05/2009
Amed	1985 -	4 (no filters)	0	07/05/2009
Web of Science (SCI & SSCI)	1970 -	1564	32	07/05/2009
Biomed Central	As per database	10	1	07/05/2009

Total References retrieved (after de-duplication): 87

Medline search strategy *(This search strategy is adapted to each database)*

1 exp Ovarian Neoplasms/
2 exp Adnexal Diseases/
3 exp Genital Neoplasms, Female/
4 exp Fallopian Tube Neoplasms/
5 exp Peritoneal Neoplasms/
6 exp Pelvic Neoplasms/
7 ((ovar* or fallopian or peritoneal*) adj5 (cancer* or carcinoma* or malignan* or neoplas* or tumour* or tumor* or adenocarcin* or adeno-carcin* or sarcoma* or choriocarcinoma* or chorioncarcinoma* or dysgerminoma* or seminoma* or teratoma* or teratocarcinoma* or terato-carcinoma* or cystadenocarcin* or fibrosarcoma* or fibro-sarcoma* or rhabdomyosarcoma* or rhabdo-myosarcoma* or rhabdosarcoma* or rhabdo-sarcoma* or leiomyosarcoma* or leio-myosarcoma* or carcinosarcoma* or carcino-sarcoma* or granulosa*)).tw.
8 ((borderline or border line) adj4 ovar*).tw.
9 or/1-8
10 exp Carboplatin/
11 (carboplatin* or paraplatin* or CBDCA).mp.
12 exp Paclitaxel/
13 (taxol or abraxane or paclitaxel).mp.
14 or/10-13
15 9 and 14

2. Health Economics Literature search details

This topic was identified as low priority in terms of health economics. The health economics scoping search identified any general health economics papers on ovarian cancer.

3. Any further comments

Systematic reviews (2002 onwards), RCT's and Observational Studies filters applied to basic search for the clinical review.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search with a date limit of 2008 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline	261	3	15/07/2010
Premedline (July 15, 2010)	9	1	16/07/2010
Embase	257	3	15/07/2010
Cochrane Library (Issue 3, 2010)	87	0	15/07/2010
Cinahl	13	0	15/07/2010
BNI	0	0	15/07/2010
Psychinfo	2	0	15/07/2010
AMED	1	0	15/07/2010
Web of Science (SCI & SSCI)	386	2	15/07/2010

Total References retrieved (after de-duplication): 6

Search alerts on Medline, Embase and Web of Science until 1st August – no additional references identified

NATIONAL COLLABORATING CENTRE FOR CANCER

Ovarian Cancer Clinical Guideline

Chapter 5 – Management of Advanced Stage (II-IV) Ovarian Cancer — Literature search summary

Topic 9: What is the effectiveness of surgery in the primary management of women with ovarian cancer who will receive chemotherapy?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2006 -	493	102	23/09/09
Premedline	Sept 22, 2009	33	10	23/09/09
Embase	2006 -	455	83	23/09/09
Cochrane Library	Issue 3, 2009	829	110	23/09/09
Cinahl	1982 -	58	9	23/09/09
BNI	1985 -	0	0	23/09/09
Psychinfo	1806 -	7	1	23/09/09
Amed	1985 -	1	1	23/09/09
Web of Science (SCI & SSCI)	2006 -	927	133	02/10/09
Biomed Central	As per database	78	4	23/09/09

Total References retrieved (after de-duplication): 288

Medline search strategy *(This search strategy is adapted to each database)*

1 exp Ovarian Neoplasms/
2 (ovar* adj5 (cancer* or carcinoma* or malignan* or neoplas* or tumour* or tumor* or adenocarcin* or adeno-carcin* or sarcoma* or choriocarcinoma* or chorioncarcinoma* or dysgerminoma* or seminoma* or teratoma* or teratocarcinoma* or terato-carcinoma* or cystadenocarcin* or fibrosarcoma* or fibro-sarcoma* or rhabdomyosarcoma* or rhabdo-myosarcoma* or rhabdosarcoma* or rhabdo-sarcoma* or leiomyosarcoma* or leio-myosarcoma* or carcinosarcoma* or carcino-sarcoma* or granulosa*)).tw.
3 1 or 2
4 exp Surgical Procedures, Operative/
5 surg*.tw.
6 4 or 5
7 (interval or debulk* or cytoreduct* or secondary or IDS or second-look or ultra-radical).tw.
8 6 and 3 and 7
9 ((neoadjuvant or neo-adjuvant or adjuvant or induction or combination or primary or cytoreduct*) adj2 chemotherap*).tw.
10 3 and 9
11 8 or 10

2. Health Economics Literature search details

This topic was identified as low priority in terms of health economics. The health economics scoping search identified any general health economics papers on ovarian cancer.

3. Any further comments

There were two Cochrane Reviews which were identified prior to the search being undertaken:

- Tangjitgamol S, Manusirivithaya S, Laopaiboon M, Lumbiganon P. **Interval debulking surgery for advanced epithelial ovarian cancer.** *Cochrane Database of Systematic Reviews* 2009, Issue 2.
- Morrison J, Swanton A, Collins S, Kehoe S. **Chemotherapy versus surgery for initial treatment in advanced**

ovarian epithelial cancer. *Cochrane Database of Systematic Reviews* 2007, Issue 4.
Between them, these became the basis of the clinical evidence search. The Morrison review was last searched in September 2006 and the Tangjitamol was last searched in July 2007, so the key databases were searched from 2006 onwards. Subject specific databases were searched without limit. Systematic reviews (2002 onwards), RCT's and Observational Studies filters applied to basic search for the clinical review.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search with a date limit of 2009 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline	230	21	15/07/2010
Premedline (July 15, 2010)	24	5	16/07/2010
Embase	240	27	15/07/2010
Cochrane Library (Issue 3, 2010)	101	0	15/07/2010
Cinahl	11	4	15/07/2010
BNI	0	0	15/07/2010
Psychinfo	1	0	15/07/2010
AMED	0	0	15/07/2010
Web of Science (SCI & SSCI)	460	40	15/07/2010

Total References retrieved (after de-duplication): 62

Search alerts on Medline, Embase and Web of Science until 1st August – no additional references identified

Topic 11: For women with ovarian cancer, is intra-peritoneal chemotherapy effective in primary management?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	2004 -	375	134	08/05/09
Premedline	May 07, 2009	50	22	08/05/09
Embase	2004 -	391	135	08/05/09
Cochrane Library	Issue 2, 2009	55	31	08/05/09
Cinahl	2004 -	37	17	08/05/09
BNI	1985 -	3	0	08/05/09
Psychinfo	1806 -	1	0	08/05/09
Amed	1985 -	0	0	08/05/09
Web of Science (SCI & SSCI)	2004 -	748	170	08/05/09
Biomed Central	2004 -	8	4	08/05/09

Total References retrieved (after de-duplication): 255

Medline search strategy *(This search strategy is adapted to each database)*

1. intraperitoneal
2. regional
3. parenteral
4. parenteral infusion
5. Infusions-Parenteral.DE.
6. Injections-Intraperitoneal.DE.
7. 1 OR 2 OR 3 OR 4 OR 5 OR 6
8. chemotherap$
9. Drug-Therapy.DE.

10. Chemotherapy-Adjuvant.DE.
11. Drug-Therapy-Combination.DE.
12. cisplatin
13. carboplatin
14. cyclophosphamide
15. etoposide
16. paclitaxel
17. doxorubicin
18. 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17
19. 7 AND 18
20. ovar$
21. 19 AND 20

2. Health Economics Literature search details

This topic was identified as low priority in terms of health economics. The health economics scoping search identified any general health economics papers on ovarian cancer.

3. Any further comments

For this topic we used the following Cochrane Library systematic review as a basis and updated the evidence since that review by using their published search strategy:

- Jaaback K, Johnson N. **Intraperitoneal chemotherapy for the initial management of primary epithelial ovarian cancer.** *Cochrane Database of Systematic Reviews* 2006, Issue 1.

A general update search had been undertaken on CENTRAL only in 2007. However, other databases such as Medline and Embase were last searched for evidence in March 2005, so this update search was executed from 2004 onwards. The specialised databases were searched with no date limit as they had not been searched in original review. General exclusions filter only was used on the clinical evidence search.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search with a date limit of 2008 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline	177	19	15/07/2010
Premedline (July 15, 2010)	14	1	16/07/2010
Embase	272	24	15/07/2010
Cochrane Library (Issue 3, 2010)	20	0	15/07/2010
Cinahl	5	0	15/07/2010
BNI	0	0	15/07/2010
Psychinfo	3	0	15/07/2010
AMED	0	0	15/07/2010
Web of Science (SCI & SSCI)	429	26	15/07/2010

Total References retrieved (after de-duplication): 33

Search alerts on Medline, Embase and Web of Science until 1st August – no additional references identified

NATIONAL COLLABORATING CENTRE FOR CANCER

Ovarian Cancer Clinical Guideline

Chapter 6 – Support Needs for Women with Newly Diagnosed Ovarian Cancer — Literature search summary

Topic 12: For women newly diagnosed with ovarian cancer, what support should be offered?

1. Literature search details

Database name	Dates Covered	No of references found	No of references retrieved	Finish date of search
Medline	1950 -	839	33	22/02/2010
Premedline	Feb 22, 2010	15	1	23/02/2010
Embase	1980 -	1058	28	24/02/2010
Cochrane Library	Issue 1, 2010	174	2	24/02/2010
Cinahl	1982 -	38	10	02/03/2010
BNI	1985 -	13	6	24/02/2010
Psychinfo	1806 -	62	8	24/02/2010
Amed	1985 -	7	0	24/02/2010
Web of Science (SCI & SSCI)	1970 -	1689	45	02/03/2010
Biomed Central	As per database	30	0	01/03/2010

Total References retrieved (after de-duplication): 84

Medline search strategy *(This search strategy is adapted to each database)*

1 exp Ovarian Neoplasms/
2 exp Adnexal Diseases/
3 ((ovar* or fallopian or peritoneal*) adj5 (cancer* or carcinoma* or malignan* or neoplas* or tumour* or tumor* or adenocarcin* or adeno-carcin* or sarcoma* or choriocarcinoma* or chorioncarcinoma* or dysgerminoma* or seminoma* or teratoma* or teratocarcinoma* or terato-carcinoma* or cystadenocarcin* or fibrosarcoma* or fibro-sarcoma* or rhabdomyosarcoma* or rhabdo-myosarcoma* or rhabdosarcoma* or rhabdo-sarcoma* or leiomyosarcoma* or leio-myosarcoma* or carcinosarcoma* or carcino-sarcoma* or granulosa*)).tw.
4 or/1-3
5 Choice Behavior/
6 Decision Making/
7 Decision Support Techniques/
8 ((patient$ or consumer$) adj3 (decision$ or choice or preference or participation)).tw.
9 ((personal or interpersonal or individual) adj3 (decision$ or choice or preference$ or participat$)).tw.
10 (wom#n adj3 (decision$ or choice or preference or participation)).tw.
11 (decision$ adj3 (aid$ or support$)).tw.
12 exp Patient Participation/
13 Pamphlets/
14 exp Audiovisual Aids/
15 (video$ or dvd$).tw.
16 exp Internet/
17 exp Self-Help Groups/
18 (support$ adj2 (group$ or meet$)).tw.
19 exp Patient Education as Topic/mt [Methods]
20 ((inform$ or support$) adj2 (tool$ or method$ or group$)).tw.
21 or/5-20
22 4 and 21
23 or/5-11
24 or/12-20
25 4 and 23 and 24

26 22 or 25
27 (information adj3 need$).tw.
28 information material$.tw.
29 (patient$ adj3 information).tw.
30 (information adj3 web$1).tw.
31 (information adj3 print$).tw.
32 (information adj3 electronic$).tw.
33 or/27-32
34 4 and 33
35 26 or 34

2. Health Economics Literature search details

This topic was identified as low priority in terms of health economics. The health economics scoping search identified any general health economics papers on ovarian cancer.

3. Any further comments

General exclusions filter only was used on the clinical evidence search.

4. Update Search

For the update search, the same search criteria/filters were applied as initial search with a date limit of 2009 onwards.

Database name	No of references found	No of references retrieved	Finish date of search
Medline	99	2	15/07/2010
Premedline (July 15, 2010)	12	1	16/07/2010
Embase	151	2	15/07/2010
Cochrane Library (Issue 3, 2010)	55	0	15/07/2010
Cinahl	13	1	15/07/2010
BNI	2	0	15/07/2010
Psychinfo	11	1	15/07/2010
AMED	1	0	15/07/2010
Web of Science (SCI & SSCI)	255	6	15/07/2010

Total References retrieved (after de-duplication): 7

Search alerts on Medline, Embase and Web of Science until 1st August – no additional references identified

Appendix 2 – Economic plan

This document identifies the priorities for economic analysis and the proposed methods for addressing these questions as described in section 8.1.3.1 of the Guidelines Manual (2009).

Guideline
Title of guideline: The recognition and initial management of ovarian cancer

Process for agreement
The economic plan was prepared by the guideline economist in consultation with the rest of the NCC technical team and GDG. It was discussed and agreed on by the following people[a]:

For the NCC and GDG:

NCC economist:	Eugenia Priedane
NCC representative(s)[b]:	John Graham, Karen Francis, Angela Bennett
GDG representative(s)[c]:	Sean Duffy, Charles Redman

For NICE:

CCP lead[d]:	Fergus Macbeth
Commissioning manager:	Nicole Elliott
Economic lead[e]:	Francis Ruiz, Stefanie Kinsley
Costing lead:	Edgar Masanga

Proposals for any substantive changes will be circulated by email to this group. If revisions are agreed, they will be listed as addenda to this document (section 5 below).

[a] This may be done by face-to-face meeting, teleconference, or email as convenient.

[b] May be the project manager, a systematic reviewer or research fellow and/or the centre director or manager, as appropriate for the NCC and guideline.

[c] May be GDG chair, clinical lead and/or other members as appropriate.

[d] CCP Director or Associate Director who is taking the lead for the guideline.

[e] One of the CCP health economic Technical Advisors.

Proposed economic plan
Complete one row for each clinical question in the guideline:

Clinical question	Economic question	Requires analysis?	Comment and explanation
Diagnosis			
1. What are the signs and symptoms of ovarian cancer?	N/A	Not relevant	This topic does not lend itself to economic evaluation (no comparative analysis of cost and outcomes)
2. What is the relationship between the duration of pre-diagnostic symptoms of ovarian cancer and survival?	N/A	Not relevant	This topic addresses an epidemiological issue and is unlikely to lend itself to economic evaluation
3. For women with suspected ovarian cancer, what is the most effective first diagnostic test in primary care? • Ultrasound • Pelvic examination • Tumour markers	What is the most cost-effective first test for women with suspected ovarian cancer in the primary care setting?	High	***Background*** Accurate diagnostic information at this stage will enable a timely referral and plays a key role in the subsequent choice of treatment. Initial investigation can indicate a possible ovarian mass without distal spread (i.e. stage 1-2); in this case chemotherapy or surgery would be the primary course of treatment. If initial investigation indicates an ovarian mass with evidence of distal spread (i.e. suspected advanced ovarian cancer stage 3-4) but complete surgical extirpation is a possibility, then surgery would be the primary treatment option. Conversely, if initial investigation reveals advanced ovarian cancer that cannot completely be removed (i.e. ascites, pleural effusions, widespread peritoneal involvement etc) then treatment would involve surgery and chemotherapy.

(CA-125)			The aim of this question is to identify the most cost-effective first test for women with suspected ovarian cancer in primary care. This topic encompasses all patients presenting with suspected ovarian cancer in primary care setting. In terms of health outcomes, patients who are suitable for more radical treatment will have most to gain from effective initial tests leading to timely referral. There are also differences in health outcomes from diagnostic procedures that are conducted in secondary care (for example imaging, biopsy), as well as potential health benefits to patients if they avoid unnecessary diagnostic procedures. There are relatively small differences in the costs associated with these tests. However, the cumulative cost of subsequent tests varies and there is a large variation in the costs of the different management options post referral. Considering the overall importance of this topic, characterized by a large patient subgroup and potentially significant difference in cumulative cost of diagnostic pathway this topic is highlighted as high priority.
4. For women with suspected ovarian cancer, which malignancy index is the most effective?	N/A	Not relevant	The aim of this question is to identify an index that is most appropriate for consistent use in communication and/or classification. It is unlikely that the different malignancy indices have an direct impact on patient outcomes. Therefore, this topic does not lend itself to economic evaluation.
5. For women with suspected ovarian cancer, what serum tumour marker test should be routinely carried out to determine future management?	In women with suspected ovarian cancer, what is the most cost-effective serum marker test?	Medium	The population for this topic is smaller to that in topic 3; however the underlying prevalence of ovarian cancer is higher in this group of patients. Presently, CA 125 is the current gold standard tumour marker in the evaluation of pelvic masses (Rasool 2003). Therefore, the main aim of this topic is to identify if there are any other clinically and cost-effective serological tests. The results of these tests determine the future management of the patient. There are potentially significant cost differences between the competing alternatives i.e.

• CA125 • CA19.9 • CEA • Germ cell tumour markers • HE4 • CDX2			the combination of markers currently used (CA125, CA19. etc and newer markers HE4 and CDX2). No independent economic analysis is planned since there are higher priority topics within the guideline. However, given the potentially high financial implications for the NHS this topic will be suggested for cost-impact analysis by the NICE costing unit once recommendations have been developed.
6. For women with suspected ovarian cancer, what is the most appropriate imaging to be done to determine future management? • CT • MRI • Chest X-ray • US	In women with suspected ovarian cancer, what is the most cost-effective imaging technique to determine future management?	Medium	As in topic 5, the population for this topic is relatively small, with a similarly high underlying prevalence of the disease. The aim of this topic is to identify the most appropriate imaging technique to determine future management and hopefully increase consistency in clinical practice. There is relatively small difference in cost between the competing alternatives. Therefore on balance, this topic is considered a medium priority for economic analysis.

7. For women with suspected advanced ovarian cancer, when is it appropriate not to have a tissue diagnosis before starting chemotherapy?	In women with suspected ovarian cancer, what is the cost-effectiveness of biopsy versus cytology before starting chemotherapy?	Low	The preliminary literature search did not reveal any relevant economic studies. Further discussion with the GDG revealed that at the present time there is a lack of good quality prospective clinical studies. It would not be feasible to conduct an economic evaluation due to paucity of clinical evidence. As such this topic is considered a low economic priority.
8. What is the best method of tissue diagnosis before chemotherapy, samples from image guided biopsy or laparoscopic biopsy?	What is the cost-effectiveness of image guided biopsy versus laproscopic biopsy in tissue diagnosis in women with advanced ovarian cancer prior to undergoing chemotherapy?	Low	This topic potentially encompasses 30-50% of patients suspected with advanced ovarian cancer. The treatment of advanced stage ovarian cancer is usually surgery followed by chemotherapy (Spencer 2001). However, in cases where debulking surgery is initially considered to be suboptimal or where it is precluded by the patient's condition, surgery may be undertaken after primary chemotherapy (Griffin 2009). In this circumstance, a definitive histological diagnosis of advanced ovarian cancer is usually made on histological analysis of tissue biopsy. Image-guided biopsy is associated with lower morbidity and as it is an outpatient procedure it is likely to be the cheaper of the two alternatives (Spencer 2005). Laparoscopic biopsy is the more invasive of the two techniques. It is significantly more resource intensive with costs including pre-operative preparation, general anaesthetic, recovery etc (Panici 2005). Given the potential health benefits and significant cost implications associated with this topic, it is highlighted as a high priority for economic analysis. **Post 3rd GDG:** An evidence search by the NCC-C technical team found no studies to inform this topic. As a result the priority level for topic 8 was revisited at the 3rd GDG.

			It was agreed that the absence clinical evidence would hinder development of a robust economic analysis. It was highlighted that results of economic evaluation based on poor quality data would carry high level of uncertainly and it would not be useful in informing clinical recommendation. Due to lack of evidence it was agreed that it would not be feasible to conduct an economic analysis.
Treatment – Surgery			
9. What is the effectiveness of surgery in the primary management of women with ovarian cancer who will receive chemotherapy? (I) • Surgery before chemotherapy (primary) • Surgery during chemotherapy (interval debulking, delayed debulking)	In women with ovarian cancer who will receive chemotherapy, what is the cost-effectiveness of the surgery?	Low	Currently primary surgery is considered in women with ovarian cancer, which encompass about 80% of all cases. There is a great deal of uncertainty surrounding the overall health benefits for this group of patients due to a lack of good quality (randomized) clinical evidence that would be necessary to inform an economic analysis. A trial comparing surgery before and during chemotherapy for ovarian, fallopian tube or primary peritoneal cancer (CHORUS phase 3) is currently underway; however it is not due to conclude until June 2010. There is a relatively small difference in cost between the alternatives. This topic is considered a low priority for economic analysis due to relatively small differences in cost between the interventions of interest and a lack of RCT data.

• Surgery after chemotherapy (second look) (ii) • Ultra-radical surgery • Optimal debulking surgery			
10. For women with ovarian cancer whose disease appears confined to the ovaries, what is the effectiveness of systematic retroperitoneal lymphadenectomy in surgical management? Retroperitoneal lymphadenectomy V Ovariectomy	What is the cost-effectiveness of systematic retroperitoneal lymphadenectomy in surgical management for women with ovarian cancer whose disease appears confined to the ovaries?	Low	The population of interest for this topic is patients with disease confined to the ovaries, encompassing about a quarter of patients diagnosed with ovarian cancer. Retrospective studies have suggested significant survival advantages following lymphadenectomy. However, this technique carries additional risks inherent to the surgery, such as longer operating time, postoperative complications and greater blood loss (Panici 2005). So the overall benefit to patients is unclear. The cost difference between these two procedures is mainly due to a longer postoperative recovery from lymphadenectomy, This topic is not considered a high priority because good quality RCT is not available. Given that an economic analysis would be unlikely to shed light on the uncertain health benefits associated with these interventions, the added value of such an analysis is lower than for other topics.
Treatment – Chemotherapy			

11. For women with ovarian cancer, is intra-peritoneal chemotherapy effective in primary management? • Systemic chemotherapy • Intra-peritoneal chemotherapy	What is the cost-effectiveness of intra-peritoneal chemotherapy in primary management of women with ovarian cancer?	Medium	This topic potentially encompasses about 20% of patients with stage III or IV disease. In this group of patients the amount and the extent of residual disease following surgery and subsequent chemotherapy play an important role in overall survival. Intraperitoneal chemotherapy has been advocated as a way of improving survival in patients with ovarian cancer. A Cochrane meta-analysis of eight RCTs reported that women receiving intraperitoneal chemotherapy are less likely to die and have a prolonged disease free interval. However, this treatment modality is complex and associated with higher rates of grade III and IV adverse event, particularly hematologic and gastrointestinal toxicity. Because intraperitoneal chemotherapy administrated in the ambulatory setting (i.e. in-patient infusion via catheter), there are substantial cost differences between intraperitoneal chemotherapy and the conventional systemic treatment modality. A broad search on NHS EED identified one (non-UK) cost-effectiveness study (Bristow 2007) reported incremental cost-effectiveness ratio of over $60K per QALY (Havrilesky 2008). No UK based analysis was found. This topic is considered to be medium priority due to relatively small patient group.

13. For women with ovarian cancer, what is the most effective primary chemotherapy? This topic is for subgroup of patients with **Stage I OC** Carboplatin (single agent) and Cabrotaxole combination	In women with stage I ovarian cancer, what is the most cost-effectiveness primary chemotherapy?	Low	The patient group considered for this question is very small contributing to low impact of an economic evaluation. As such yield this topic is not considered an economic priority.
Information for Patient and Carers			
12. For women newly diagnosed with ovarian cancer, what support should be offered?	N/A	Not relevant	This topic does not lend itself to economic evaluation (no comparative analysis of cost and outcomes)

For each question where economic analysis is proposed:

Question number(s) [f]	*Outline proposed method of analysis* [g]
TOPIC 3	**Background** Accurate diagnostic information at this stage of the investigation will enable timely referrals and plays a major role in the subsequent choice of treatment. If initial investigation indicates a possible ovarian mass without distal spread (i.e. Stage 1-2), surgery would be the primary course of treatment. If initial investigation indicates an ovarian mass with evidence of distal spread (i.e. suspected advanced ovarian cancer Stage 3-4) but complete surgical extirpation is a possibility then surgery would the primary treatment option. Conversely, if initial investigation reveals advanced ovarian cancer that cannot completely be removed (i.e. ascites, pleural effusions, widespread peritoneal involvement etc) treatment would involve surgery and chemotherapy. **Aim of analysis** To assess the cost effectiveness of the first diagnostic test in women with suspected ovarian cancer in the primary care setting. **Patient population** This topic encompasses all patients presenting in a primary care setting with suspected ovarian cancer. **Interventions** Pelvic examination Ultrasound Serum Marker CA125 test Ultrasound plus CA125 Pelvic Examination plus Ultrasound Pelvic Examination plus CA125 **Outcomes of the diagnostic tests** The aim of the test is to determine whether or not a patient would be referred urgently to

[f] Two or more questions may be addressed by a single analysis if appropriate.

[g] Give a brief description of the type of analysis that is proposed, as far as is known at this stage. Consider the type of economic evaluation (CEA, CUA, CCA,…); how outcomes will be measured (QALYs, LYS,…); the type of modelling (decision tree, Markov, simulation…); proposed comparators and population subgroups to be considered; potential sources of information and assumptions; and whether analysis could be based on an existing model. Follow methods advised in the Guidelines Manual whenever possible. Note that this is not expected to be a full project protocol, and that the methods of analysis may change.

	secondary care within 2-weelk wait criteria for further investigation. The outcomes of the tests are as follows: For Pelvic Examination and Ultrasound Normal Abnormal - patients with an abnormal test result are being referred for further tests as part of the 2-week urgent referral pathway (into secondary care) - watchful waiting CA125 <35 IU/l >35 IU/l - patients with an abnormal test result are being referred for further tests as part of the 2-week urgent referral pathway (into secondary care) - watchful waiting **Post-Referral test (in secondary care)** Once a patient is referred, any subsequent test will be dependent on what the initial set of tests had been, i.e. if the initial test was pelvic examination and CA125, the secondary test would be ultrasound. Given the complexity of the clinical pathway, the composition of the post-referral test and subsequent treatment options will be identified by the GDG subgroup, which in turn will be reflected in the structure of the decision tree. N.B. It would be very difficult to account for many permutations of the patient pathway; therefore, we may need to agree on a set assumption which will allow some level of simplification yet will enable our model to retain clinical relevance. **Treatment** - Surgery - Chemotherapy **Methods** A cost-utility analysis will be performed using quality adjusted life years (QALYs) as the measure of health outcome. However, there may be some data limitations. A decision tree approach will be taken to model the clinical pathway. The GDG then need to agree whether to assume average payoffs (the associated cost and QALYs) for each of the treatment options or to use a Markov process to more accurately represent the patient pathway after referral is determined. The latter is more likely, given that the time horizon of the analysis (lifetime) is likely to be longer than 1-2 years. **Clinical evidence** The clinical data used to populate the model will be mainly derived from the systematic reviews conducted to identify the clinical evidence for this topic. In addition, data related to other topics are likely to be required to populate this model. For example topics 9 and 13). To populate the model we will require: - Prevalence of disease (pre-test probabilities) - Characteristics of each test (TPR, FNR, TNR, FPR) - Characteristics of each possible subsequent test (assuming that the test results

probabilities are conditionally independent, given disease status)

- Estimate of QALY loss from the diagnostic tests (loss of utility associated with any adverse events of the tests)
- Proportion of patients receiving curative surgery
- Probability of death from surgery
- Proportion of patients receiving surgery+chemotherapy
- Proportion of patients receiving supportive care (or palliative chemotherapy)
- Average QALYs associated with surgery
- Average QALYs associated with surgery+chemotherapy
- Average QALYs associated with supportive care (or palliative chemotherapy)

Costs

- Costs associated with each of the tests
- Costs associated with each subsequent test
- Costs associated with treatment of adverse events (if any)
- Costs associated with treatments – surgery, chemotherapy, BSC.

NHS reference costs are unlikely to provide accurate unit costs for some diagnostic procedures, since they are likely to fall into the same category. In this case, in order to estimate incremental costs of the procedures we will require input from the guideline development group. Moreover, when estimating costs of a diagnostic test, we need to take into account costs (and disutility) of any adverse events associated with that test.

An NHS perspective will be adopted; i.e. the health benefits and costs to be considered in the analysis will only be those relevant to the NHS. Relevant costs include those borne by Personal Social Services (PSS) as well as those that fall on the NHS itself. Unit costs for items other than the tests themselves will be derived from publically available national sources whenever possible (e.g. NHS Reference Costs).

An incremental cost-effectiveness analysis will be conducted after ranking the alternative strategies from the most to the least cost-effective and excluding any dominated strategies. The results of the incremental analysis will be reported as the incremental cost per additional unit of benefit obtained with the most effective and most expensive strategy when compared to the next most effective and most expensive one.

If the data allow, probability distributions will be assigned to all stochastic parameters within the model so that a probabilistic sensitivity analysis can be carried out to assess the overall uncertainty of the model and the robustness of the results. In addition, one-way and multi-way deterministic sensitivity analyses will be conducted to identify those variables to which the results of the model are most sensitive.

Feasibility issues:

It is not clear at this point whether the available literature is sufficient to populate this model for all the comparators previously mentioned. Limited availability of evidence may lead to an additional set of assumptions or relevant feasibility problems developing and populating the model.

Key references

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Havrilesky, L. J., Alvarez Secord A., Darcy K.M., Armstrong D.K., Kulasingam S. (2008). "Cost effectiveness of intraperitoneal compared with intravenous chemotherapy for women with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group study." Journal Of Clinical Oncology 26(25): 4144-50.

Panici, P. B., Maggioni A., Hacker N., Landoni F., Ackermann S., Campagnutta E., Tamussino K., Winter R., Pellegrino A., Greggi S., Angioli R., Manci N., Scambia G., Dell'Anna T., Fossati R., Floriani I., Rossi R.S., Grassi R., Favalli G., Raspagliesi F., Giannarelli D. (2005). "Systematic Aortic and Pelvic Lymphadenectomy Versus Resection of Bulky Nodes Only in Optimally Debulked Advanced Ovarian Cancer: A Randomized Clinical Trial." Journal of the National Cancer Institute 97(8): 560-66.

Rasool, R., shah, Z.A., Salahuddin, M., Bashir, M. (2003). "CA-125 Tumour Marker for Ovarian Malgnancies " JK-Practitioner 10(3): 224-25.

Spencer, J. A. (2005). " A multidisciplinary approach to ovarian cancer at diagnosis." The British Journal Of Radiology 78(Spec No2): S94-102.

Spencer, J. A., Swift S.E., Wilkinson N., Boon A.P., Lane G., Perren T.J. (2001). "Peritoneal carcinomatosis: image-guided peritoneal core biopsy for tumor type and patient care." Radiology 221(1): 173-77.

Addenda to economic plan

The following substantive revisions to the plans set out in section 3 above have been agreed.

Date	*Question number(s)*	*Agreed change to number or type of analyses*

Appendix 3 – Health economics

A cost-utility analysis of diagnostic investigations in primary care for women with symptoms of ovarian cancer

1 Introduction

Around 6,700 new cases of ovarian cancer are diagnosed each year in the UK (CancerResearch UK, 2007) with an overall five-year survival of about 80% in women diagnosed with early disease (stage I-II) and 25% in women with advanced disease (stage III-IV) (Hamilton *et al*., 2009). For women presenting with symptoms in primary care, accurate diagnostic information at this stage enables timely referral which subsequently plays a vital role in the choice of treatment and achievable survival.

This clinical question was highlighted as a priority for economic analysis because of the large number of patients with symptoms suggestive of ovarian cancer. In addition, there are significant differences in costs and health outcomes associated with the different diagnostic pathways, as well as the considerable economic burden of treating ovarian cancer.

2 Objective

To assess the cost-effectiveness of diagnostic strategies in primary care for women presenting with symptoms suggestive of ovarian cancer.

3 Methods

Economic evaluations of a diagnostic investigation require evidence on a number of issues, including disease prevalence and test accuracy. Furthermore, the accurate estimation of cost-effectiveness of one diagnostic strategy over another requires the consideration of downstream treatment effects, health-related preferences (utilities), healthcare resource use and unit costs. Therefore, the evaluation was undertaken by synthesizing evidence from a number of different sources using decision analytic techniques.

3.1 Study population

The population considered within the analysis consisted of women presenting in primary care with symptoms consistent with suspected ovarian cancer.

3.2 Perspective

This analysis was carried out from the perspective of the UKs National Health Service (NHS), in line with NICEs methodological recommendations. Health outcomes were expressed in terms of quality-adjusted life-years (QALYs).

3.3 Interventions

Given the large number of different diagnostic tests and potential combinations, a decision was made at the outset to limit the number of interventions to those that were listed by the Guideline Development Group (GDG) in the PICO tables for this clinical question. In all, seven core strategies were evaluated. To capture downstream consequences following the

initial referral, the members of the GDG were asked to identify clinical pathways that were reflective of current UK clinical practice (Table A1.1).

Table A1.1 Summary of diagnostic strategies

Strategy	Primary care diagnostic investigation(s)	Secondary care diagnostic investigation(s) (following referral)
1	Pelvic examination • Ultrasound*	Serum CA125 and ultrasound CT scan
2	Serum CA125	Ultrasound CT scan
3	Pelvic examination and serum CA125	Ultrasound CT scan
4	Ultrasound	Serum CA125 CT scan
5	Pelvic examination and ultrasound	Serum CA125 CT scan
6	Serum CA 125 and ultrasound	CT scan
7	Pelvic examination, serum CA125 and ultrasound	CT scan

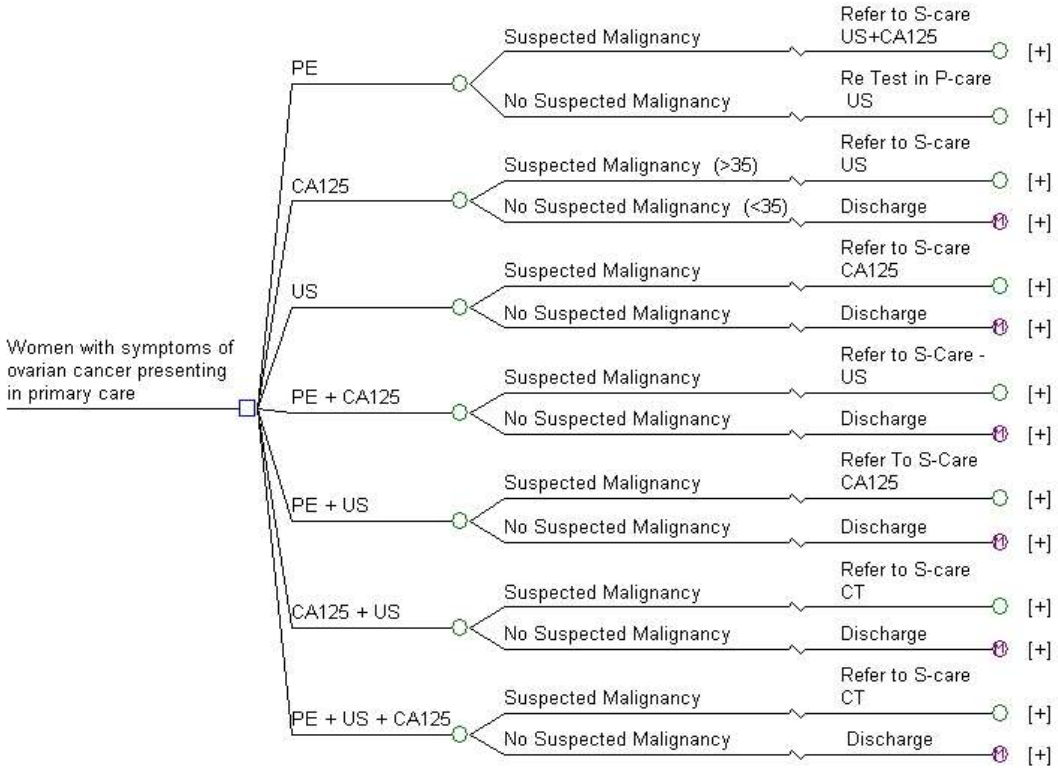
* Only done where pelvic examination did not detect a suspicious mass.

3.4 Structure of the model

A decision tree (Figure A1.1) was constructed outlining the seven strategies of interest: three of the strategies included a single first test and the remaining four strategies were combination tests. The model was constructed using TreeAge Pro (2009) software. A Markov process was embedded in the decision tree to model recurrence of the disease and survival based on the results of the diagnostic tests and the subsequent management of women presenting with symptom(s) of ovarian cancer.

A hypothetical cohort of women presenting with symptom(s) of ovarian cancer in the primary care setting was considered for the analysis. In the base case, it was considered that the starting age of the patient population in the model was 40 years of age, while further analyses considered a starting age of 50 years.

Figure A1.1 Diagnostic strategies in primary care



3.4.1 Decision tree for accuracy of staging procedures and related complications

The square node at the beginning of the decision tree shows graphically the seven diagnostic strategies (see Table A1.1) that have been defined as relevant to the decision problem (Figure A1.1).

Independent of which diagnostic strategy is undertaken; patients may or may not have a suspicious mass. This way of structuring the model allows information about the prevalence of a suspicious mass and accuracy of the diagnostic procedures as reported in the systematic reviews of the clinical evidence related to diagnostic investigation in primary care (in terms of their sensitivity and specificity values (Hunink and Glasziou, 2001)) to be used.

Patients in whom the results of primary care investigation did not identify a suspicious mass were assumed to be discharged, with the exception of those undergoing pelvic examination as their primary care test. Patients in whom malignancy has been suspected are referred to secondary care for further investigation. Patients who have undergone pelvic examination (strategy 1) as part of their initial investigation in primary care are referred to secondary care if the test outcome identifies a suspicious mass. Patients in whom pelvic examination did not identify an abnormality undergo ultrasound in primary care. The result of the ultrasound is used to decide whether to refer the patient to secondary care.

The pathway of diagnostic investigations in secondary care depends in part on the type of diagnostic test performed in primary care. The diagnostic pathway for each strategy following referral was outlined by the GDG. In order to maintain consistency within the guideline, imaging procedures reflect the current guideline recommendations.

Pelvic examination
Patients following strategy 1 (see Table A1.1) as part of their investigation pathway and where the initial test (pelvic examination) identified a suspicious mass, are referred to secondary care and undergo combination serum CA125 plus ultrasound as the next diagnostic tests. At this stage, patients in whom a suspicious mass was not detected following investigation in secondary care (i.e. combination of serum CA125 plus ultrasound), undergo a repeat of the same test within a month and are either referred for a computerised tomography (CT) scan (to confirmed ovarian cancer) or are discharged. Patients in whom a suspicious mass was detected undergo further investigation (in secondary care) with a CT scan, which may confirm the presence and extent of suspected ovarian malignancy.

Serum CA125; pelvic examination plus serum CA125; ultrasound; pelvic examination plus ultrasound
In the case of strategies 2, 3, 4 and 5 (see Table 1), those referred to secondary care with a suspicious mass either undergo ultrasound (strategies 2 and 3) or serum CA125 (strategies 4 and 5). If the result of the ultrasound further identifies a suspicious mass, the patient undergoes a CT scan to confirm the presence of ovarian malignancy. Similarly, patients in whom a suspicious mass was not detected following ultrasound or serum CA125 undergo a repeat of the same test within a month and are either referred to undergo a CT scan (to confirmed ovarian cancer) or are discharged.

Serum CA 125 plus ultrasound; pelvic examination plus CA125 plus ultrasound
Lastly, patients following strategies 6 and 7 (see Table A1.1)) where a suspicious mass was detected, are referred to secondary care and undergo a CT scan to assess the extent of the ovarian cancer or an alternate diagnosis.

To capture the downstream consequences of each diagnostic strategy, a clinical pathway was outlined encompassing treatment options following confirmation of ovarian malignancy. As such, it was agreed that following a CT scan, a proportion of patients with confirmed ovarian malignancy, will undergo either a surgical procedure, pathological investigation (biopsy) or will receive supportive care (where the patient is not fit for further treatment/investigation). For the purpose of this model it was agreed that following surgical and pathological procedures patients would be classified as either having disease confined to the ovaries (FIGO stage Ia – Ic) or disease which is not confined to the ovaries (FIGO stages II-IV). Furthermore, patients in whom the CT scan did not confirm ovarian malignancy, undergo further investigation to differentiate the nature of the suspicious mass. It was agreed that for the purposes of this model two subgroups of patients withouth confirmed ovarian malignancy would be considered: patients with a benign gynaecological problem (for example a simple cyst) and patients with colorectal malignancy. Treatment options were defined for each subgroup of patients. A summary of the key structural assumptions are listed in Box A1.1.

Box A1.1 Key Structural Assumptions

In primary care

- With the exception of those undergoing pelvic examination, patients in whom no malignancy was suspected from initial tests are discharged with no further follow up
- Patients who undergo pelvic examination in primary care and have no suspicious malignancy are re-tested using ultrasound

In secondary care

- Patients in whom further investigation showed no suspicion of malignancy are re-tested within a month
- Computerised tomography scan is able to differentiate between ovarian and non-ovarian masses
- Histopathological tests are assumed to be 100% accurate

3.4.2 Markov process to model prognosis of patients in the long term

A Markov process was embedded in the decision tree to reflect the prognosis of patients according to the management received following the test results. In a Markov process a patients' possible prognosis is divided into a series of discrete health states. Costs and benefits are assigned to each health state and transition probabilities are defined to model the movement of an individual between these health states over a particular time frame (cycle length). The costs and benefits of comparative treatments are then estimated on the basis of the length of time individuals spend in each health state.

The aim of introducing a Markov process at the end of the decision tree was to reflect the pattern of recurrences and survival of patients in a simplified way, depending on whether the diagnostic investigation had been accurate in identifying a suspected mass and, consequently, whether patients were appropriately managed according to their true condition.

Three heath states were considered for patients in whom malignancy is confined to the ovaries and who have completed treatment: remission, recurrence and death (all causes). For patients with advanced disease only two health states were considered: remaining in the advanced (recurrence) disease state or death. On each given cycle, patients with confined disease could remain in the disease-free state (remission), have a recurrence and progress to advanced disease or die. Patients with advanced disease could either remain in the advanced stage or die.

Patients in whom colorectal malignancy was identified could either remain in that disease stage (Dukes stage A-D), progress or die. Two health states were considered for patients who have undergone treatment for a benign gynaecological problem, who require no further treatment or were discharged following a negative test outcome: patients could either remain alive or die. A one-year cycle length was used in all instances.

The different probabilities of moving from one health state to another depend on the associated risk of recurrence, disease progression and death. Death can result from ovarian cancer (if the patient had progressed), colorectal malignancy, or from all other causes.

3.5 Clinical evidence

Economic modelling is a useful tool to synthesise data derived from multiple sources, given the fact that all the relevant costs and benefits of an intervention are rarely accurately captured by one single study. Although randomised controlled trials are usually the most reliable sources of evidence, they are not always available. Data is often used from non-randomised studies or from expert opinion in which case transparency and consistency is

essential. Conducting a sensitivity analysis examines the robustness of the results obtained and the variables most likely to influence the results.

3.6 Data inputs

3.6.1 Prevalence and test accuracy

The clinical evidence required to populate the model was obtained from the systematic reviews conducted within the ovarian cancer guideline. The prevalence of the disease in primary care was assumed to be a linear summation of the prevalence of ovarian and colorectal malignancies and benign gynaecological problems. The estimates of prevalence of ovarian and colorectal malignancies are obtained from published literature (CancerResearch UK, 2007; Hamilton *et al*., 2009). GDG consensus was used to estimate the prevalence of benign gynaecological problems. The accuracy of the diagnostic procedures, in terms of the corresponding sensitivity and specificity values, was obtained from the systematic reviews of the clinical evidence conducted for this guideline (see clinical evidence in sections 2.2 and 2.3). The accuracy of combination strategies were calculated assuming conditional independence. A summary of the estimates of disease prevalence and test accuracy used to populate the model are reported in Table A1.2.

Table A1.2 Disease prevalence and test accuracy

Parameter description	Parameter estimate		Data source
Disease			
	Disease prevalence		**Data source**
Ovarian cancer	0.23%		Hamilton *et al*., 2009
Benign gynaecological problem	25% Range (20% - 30%)		GDG consensus
Colorectal cancer	0.06%		CancerResearchUK, 2007
Test accuracy			
	Sensitivity	**Specificity**	**Data source**
Pelvic examination	0.45	0.90	Myers *et al*., 2006
Serum CA125	0.78	0.78	Myers *et al*., 2006
Ultrasound	0.85	0.83	Liu *et al*., 2007
Combination tests			
Pelvic examination + CA125	0.88	0.70	Derived from single test estimates assuming test independence (see section 2.2 of the Evidence Review)
Pelvic examination + ultrasound	0.92	0.75	
CA125 + ultrasound	0.97	0.65	
Pelvic examination + CA125 + ultrasound	0.98	0.58	
Secondary care test			
CT scan	0.85	0.86	Liu *et al*., 2007

3.6.2 Proportion estimates

The proportion of patients in each treatment arm, as defined by the model structure, was not consistently reported in the published literature. Therefore, proportions were estimated by the GDG. The estimates of the proportions are shown in Table A1.3.

Table A1.3 Estimates of proportions

Parameter description	Estimate (%)
Patients in whom *no cancer of the ovaries* was detected following secondary care test†:	
Proportion of patients who are diagnosed with a benign gynaecological problem (for example a simple cyst)	85
Proportion of patient who are diagnosed with 'other' cancer (colorectal)	15
Patients in whom *cancer of the ovaries* was detected following secondary care test[8]†:	
Proportion of patients undergoing percutaneous biopsy (or any other histopathological investigation)	35
Proportion of patients undergoing surgery	60
Proportion of patients who are not fit to undergo any further investigation and receive supportive care	5
Patients who have *undergone surgery*†:	
Proportion of patients in whom disease is **confined to the ovaries** (stage I)[9]	40
Proportion of patients in whom disease is **not confined to the ovaries** (stage II-IV)	60
Patients with disease *confined to the ovaries*‡ :	
Proportion of patients undergoing chemotherapy (carboplatin)	50
Proportion of patients who do not require further treatment (following surgery) and receive follow-up care	50
Patients with disease *not confined to the ovaries*†:	
Proportion of patients undergoing chemotherapy (paclitaxel/carboplatin)	85
Proportion of patients undergoing chemotherapy (paclitaxel/carboplatin) and further surgery	10
Proportion of patients who are not fit for further treatment (following staging surgery) and are receiving supportive care	5

Source: † GDG Consensus; ‡ Warwick *et al*. 2009

3.6.3 Treatment

Surgery

Historically, the mainstay of treatment for ovarian cancer was surgical excision. It has been estimated that the majority of patients with early and about half with advanced stage disease will require some form of surgery (Bell et al., 1998; Kosary 1994). For the purpose of this model, the GDG agreed that the majority of patients, in both groups, will undergo laparotomy with intent to perform total abdominal hysterectomy (TAH)/bilateral salpingo-oophorectomy (BSO)/omentectomy/peritoneal washings. In patients where no malignancy was suspected (for example, a simple cyst) it was agreed to assume the same procedures would be carried out. Mortality and morbidity rates associated with these surgical procedures were obtained from the published literature (Chien et al., 2005; Gerestein et al., 2009; Loft et al., 1991; Venesmaa and Ylikorkala 1992) or through GDG consensus and are shown Table A1.4.

[8] Estimation is based on an assumption that of all patients in whom cancer of the ovaries is detected: 75% will have advanced stage disease and 25% will have early stage disease (Kosary 1994; Bell *et al*., 1998). Of those with advanced stage disease 50% will undergo surgery and 50% biopsy.

[9] stage I includes stages Ia- Ic.

Table A1.4 Mortality and morbidity associated with laparotomy

	Confined to the ovaries (stages 1a-1c)	Not confined to the ovaries (stages II-IV)	Benign gynecological problem
Mortality	1%†	3%††	0.16%‡
Morbidity	5%*	10-15%*	**5%****

Source: † Venesmaa *et al.*, (1992); †† Gerestein *et al*., (2009) (stage II-IV); ‡ Loft *et al*., (1991) (benign problem); * GDG consensus; ** Chien *et al*., (2005)

Chemotherapy

Within the guideline, a review of the clinical evidence was conducted to ascertain the most effective chemotherapy regimen in patients with early disease. To assure consistency between the guideline as a whole and the economic model, it was agreed that for the purposes of economic analysis, patients in whom cancer is confined to the ovaries receive a carboplatin-based chemotherapy regimen. Dosage, duration of treatment, estimates of overall survival and progression free survival were obtained from the ICON 1 trial (Swart et al., 2007)) (Table A1.5). The study did not report major toxicities associated with carboplatin. Patients with advanced disease (i.e. where cancer is not confined to the ovaries) followed the treatment pathway outlined by 'Guidance on the use of paclitaxel in the treatment of ovarian cancer' (NICE, 2003). Similarly, estimates of overall survival, progression free survival, duration of treatment and dosages of a combination of agents were taken from Bagnall et al., (2002) (see Table A1.5 below).

Table A1.5 Dosage, duration of treatment and survival estimates assumed by the model

	Confined to the ovaries	Not confined to the ovaries
Agent (s)	Carboplatin	Paclitaxel/carboplatin
Dosage	AUC6	175 mg/m^2 AUC6
Number of cycles	6	6
Progression free survival (PFS)	67% (10 years PFS)	17.1 months (median)
Overall survival (OS)	72% (10 years OS)	37.1 months (median)
Data source	ICON 1 Trial (Swart *et al*., 2007)	ICON 3 Trial (Bagnall *et al*., 2002)

3.6.4 Supportive care and follow-up monitoring

Supportive care

No studies were found to provide estimates of healthcare resource use for the provision of supportive care specifically in this group of patients. Given the advanced stage of the disease, it was agreed that a patient will spend a third of their time at home, a third in a hospital and the latter stage in a hospice. For the purpose of this analysis, we obtained estimates of unit costs of resource use by GDG consensus.

Follow-up monitoring

Similarly, no studies were found quantifying healthcare resource use associated with the follow-up monitoring of women who had undergone treatment (surgery and chemotherapy). Other guidelines were used to identify relevant components of care and a likely schedule of follow-up monitoring for women who have undergone active treatment. The GDG agreed that follow-up monitoring should include a history and physical examination (including pelvic examination) every three months for three years and once a year for the following five years. Estimates of resource use were obtained by GDG consensus and are summarised in Table A1.6.

Table A1.6 Resource use associated with provision of supportive care and follow-up monitoring

	Number of units
Supportive care (per patient)	
Hospital stay (in days)	14
Hospice stay (in days)	14
Home stay	
GP visits (0.5/week)	1
District nurse	4
Nurse specialist	2
Follow-up monitoring (per year)	
Years 1-3	
Physical examination (including pelvic examination)	4
Years 4 – onwards	
Physical examination (including pelvic examination)	1

3.6.5 Other cancer – colorectal

It was agreed that for the purposes of this economic model estimates of survival associated with treatment for colorectal cancer will be used as proxy for the subgroup of patients in whom a non-gynaecological cancer was identified following diagnostic investigation. A summary of average survival (by stage) is reported in Table A1.7.

Table A1.7 Distribution and survival by stage (at diagnosis)

Disease stage	**Proportion** (NCIN, 2009)	**Average Survival** (Tappenden et al., 2007)
Dukes A	13.2%	11years
Dukes B	36.9%	11 years
Dukes C	35.9%	8.7 years
Dukes D	14.0%	1.4 years

3.6.6 Health benefits

The health benefits derived from using the alternative diagnostic strategies compared in the analysis were estimated in terms of the number of quality-adjusted life years (QALYs) gained. The base case analysis considered a lifetime horizon, although a shorter time horizon was considered in the sensitivity analysis.

Markov processes were used to estimate life expectancy and QALYs gained by four different patient subgroups:

- Patients who were considered to have a suspicious mass at the beginning of the model (following initial test) and have undergone an appropriate treatment (true positive)
- Patients who did not have a suspicious mass at the beginning of the model (following initial test) but have undergone treatment after being wrongly diagnosed (false positive)

- Patients who did not have a suspicious mass at the start of the model (following initial test) and were discharged (true negative)
- Patients who have a suspicious mass at the start of the model (following initial test) but were wrongly discharged following diagnostic investigation (false negative).

Estimates of life expectancy

The transition probabilities of moving across health states (Figures A1.2-A1.4) were estimated from published studies (International Collaborative Ovarian Neoplasm Group, 2002; Swart et al., 2007), which reported rates of remission, recurrence and death following chemotherapy treatment in patients with localised and advanced disease. An appropriate adjustment was conducted to obtain yearly transition probabilities of recurrence and death in this subgroup of patients (Hunink and Glasziou, 2001). Moreover, the transition probabilities were assumed to be constant throughout the time horizon of the model.

Figure A1.2 Markov process for prognosis of patient with early disease

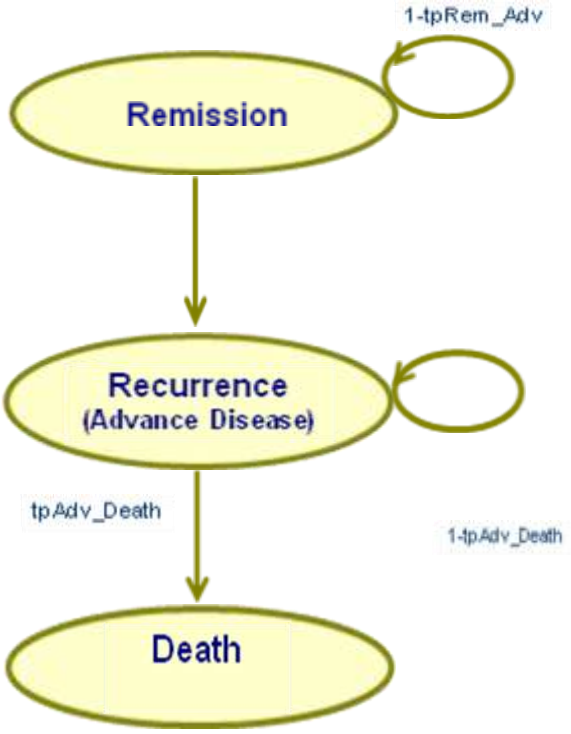


Figure A1.3 Markov process for prognosis of patient with advance disease

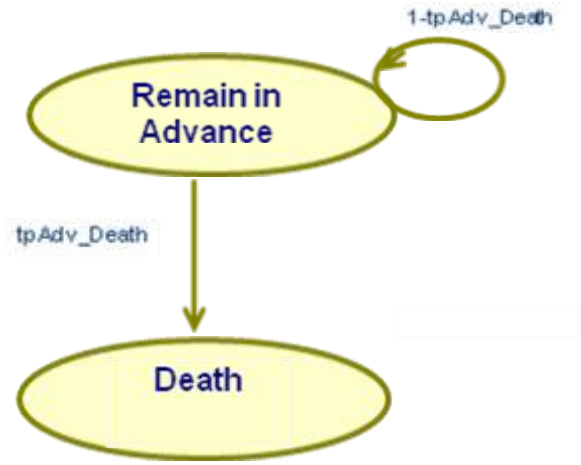
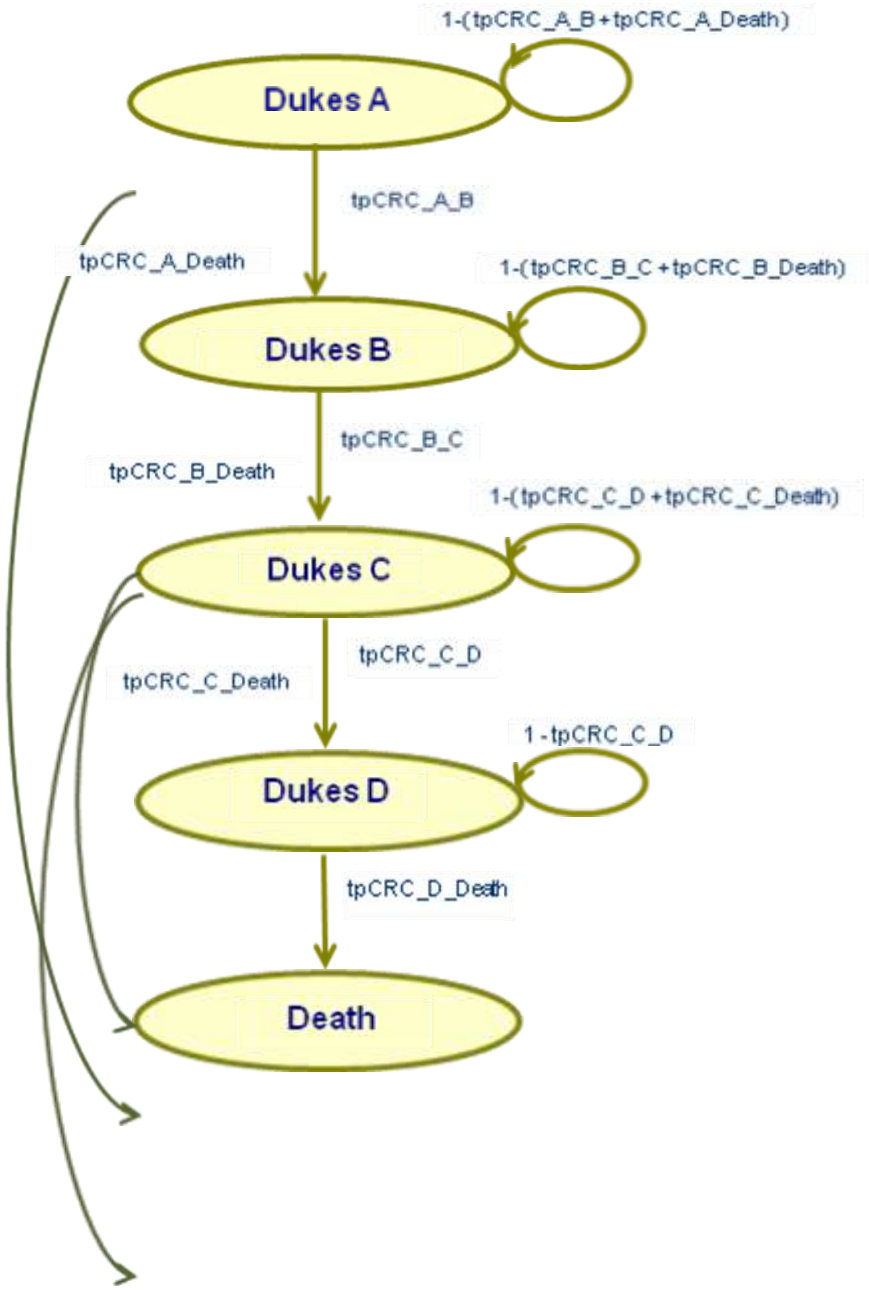


Figure A1.4 Markov process for prognosis of patient with colorectal cancer



For patients who did not have the disease, had a benign condition or required follow-up monitoring after undergoing chemotherapy, transition probabilities of moving from “alive” to “dead” from all causes were estimated using the age-related mortality rates (as reported by the Office of National Statistics, 2009).

For patients who are diagnosed with colorectal malignancy, progression from initial stage to the next or to death was captured by the transition probabilities reported in Tappenden et al., (2007).

A summary of all transition probabilities used to populate the model is reported in Table A1.8.

Table A1.8 Transition probability between health states

Transition probability	Mean	Description
Ovarian cancer		
tpRem_Adv	0.105	Probability of recurrence (early disease)
1-tpRem_Adv	0.895	Probability of remaining in remission
1- tpAdv_Death	0.797	Probability of remaining in the advanced disease state
tpAdv_Death	0.203	Probability of dying (advanced disease)
Colorectal cancer		
tpCRC_A_B	0.5829	Probability of moving from Dukes A to Dukes B
tpCRC_A_Death	0	Probability of dying (Dukes A)
tpCRC_B_C	0.6555	Probability of moving from Dukes B to Dukes C
tpCRC_B_Death	0.01	Probability of dying (Dukes B)
tpCRC_C_D	0.8668	Probability of moving from Dukes C to Dukes D
tpCRC_C_Death	0.0602	Probability of dying (Dukes C)
tpCRC_D_Death	0.3867	Probability of dying (Dukes D)

Utility estimates

The value of estimating the number of QALYs gained is that this single measure combines the gains from mortality (quantity gains) and from morbidity (quality gains) (Drummond et al., 2005). An index based on an individual's preference for a specific health state in relation to alternative health states (utility weights) were required in the model to estimate quality-adjusted life years (QALYs), which are calculated by weighting life expectancy by a measure of associated health-related quality of life. Estimates of health state utilities specific to ovarian cancer patients were obtained from published studies. There are a number of studies that report utility weights associated with diagnostic investigations and treatments of ovarian cancer. Havrilesky et al., (2009) reported utility estimates related to various heath states following false positive/negative test results and treatment with toxicities. Utility estimates obtained using the time trade-off method (TTO) tended to be slightly higher compared to those obtained using a visual analogue score (VAS). Drummond et al., (2005) noted that visual scales for comparing health state preferences are subject to inherent biases and are generally less accurate. For this reason we used utility estimates derived using the TTO method. Utility estimates associated with undergoing surgery and colorectal cancers were obtained from Grann et al., (1998) and Tappenden, et al. (2007) respectively. The utility values used in the model are summarised in Table A1.9 below.

Table A1.9 Utility values

Health state	Mean	Data Source
Diagnostic test false positive/negative result	0.88	Havrilesky *et al*., 2009
Chemotherapy (carboplatin)	0.81	Havrilesky *et al*., 2009
Chemotherapy (paclitaxel)	0.55	Havrilesky *et al*., 2009
Toxicity grade 3-4 (paclitaxel)	0.49	Havrilesky *et al*., 2009
Surgery	0.68	Grann *et al*., 1998

Recurrence	0.47	Havrilesky *et al*., 2009
Remission (early)	0.83	Havrilesky *et al*., 2009
Stable - advanced disease	0.63	Grann *et al*., 1998
Colorectal cancer (by stage)		
Dukes A	0.74	Tappenden *et al*., 2007
Dukes B	0.70	Tappenden *et al*., 2007
Dukes C	0.50	Tappenden *et al*., 2007
Dukes D	0.25	Tappenden *et al*., 2007
Supportive care	0.16	Havrilesky *et al*., 2009
Follow-up	0.99	Assumed

3.6.7 Cost estimates

The costs considered in this analysis were only those relevant to the UK NHS, in accordance with the perspective taken by the NICE Reference Case for economic evaluations. Costs were estimated based on 2008-9 prices. When costs have been taken from other sources and are applicable to a different price year, they have been inflated using the Hospital and Community Health Services Pay and Prices Index (PSSRU, 2009). The categories of costs included:

- Cost of diagnostic tests (in primary and secondary care)
- Cost of therapy (surgery, drug acquisition costs, administration costs)
- Cost of major treatment related to morbidity
- Cost of healthcare resource use associated with supportive care and follow-up monitoring

Costs of diagnostic tests

The cost estimates of diagnostic tests relevant to this analysis were obtained from various sources. Unit costs of ultrasound, CT and MRI were obtained from the NHS Reference Costs and estimated at £69, £143 and £178 respectively (HRG codes: RA24Z, RA13Z and RA01Z). The cost of pelvic examination was estimated using unit cost reported in the Personal Social Services Research Unit (PSSRU 2009) and included the cost of GP's and nurses time. Unit costs of tumour marker test (serum CA125) was estimated at £23 and obtained using GDG consensus. Unit costs of combination tests were estimated as a sum of the unit costs of the individual tests.

The cost estimates of pathological investigation were assumed to consist of the cost of percutaneous biopsy and aspiration cytology. These costs were obtained from NHS Reference costs and from GDG consensus, and were estimated to be £1,124 and £42 respectively. A summary of unit costs of diagnostic tests are presented in Table A1.10.

Table A1.10 Cost estimates of diagnostic tests

	Mean (£)	Data source
Ultrasound	69	NHS Reference Cost: HRG code RA24Z
Pelvic examination		
GP practitioner (per procedure)	52	PSSRU 2009
GP nurse (per procedure)	10	PSSRU 2009
Total	62	
Serum CA125	**23**	**GDG consensus**
Cost estimation of combination diagnostic tests		
Pelvic examination + ultrasound	115	
Pelvic examination + serum CA125	85	
Serum CA125 + ultrasound	76	
Pelvic examination + ultrasound + serum CA125	138	
CT scan	143	NHS Reference Cost: HRG code RA13Z
Biopsy		
Percutaneous biopsy	1124	NHS Reference Cost: HRG code FZ12C
Aspiration cytology	42	GDG consensus
Total	1166	
MRI	178	NHS reference Cost: HRG code RA01Z

Cost of Treatment

Chemotherapy

The drug costs were calculated for chemotherapy regimens for patients with localised and advanced disease, assuming that a patient received one dose per 3-week cycle for single or combination therapy (Table A1.11). In addition to the drug acquisition costs, the cost of administering the drug was estimated from the NHS Reference Costs. Administration of carboplatin and the carboplatin/paclitaxel combination regimens was assumed to be performed on an outpatient basis. The cost of administering these regimens was estimated using outpatient tariffs of £272 (HRG SB12Z) and £335 (HRG SB13Z) respectively. This cost includes hospital overheads, the administration costs of chemotherapy and clinical time. These assumptions were verified with the GDG.

The base case analysis used list prices for drugs obtained from the British National Formulary (BMG Group and Pharmaceutical Press, 2010). The effect of the drug discounts were explored through sensitivity analysis.

Table A1.11 Drug acquisition costs

Strategy	**Carboplatin**	**Carboplatin/paclitaxel**	
	Carboplatin	Carboplatin	Paclitaxel
List prices, £ (BNF 59, 2010)			
5 ml vial			66.85
15 ml vial	56.29	56.29	
50 ml vial			601.03
60 ml vial	260	260	
i.v. concentrate (mg/ml)	10	10	6
Recommended dose (mg/m^2)	696	660	175

Average cost per vial (£)	316.29	316.29	667.88
Number of vials	1	1	1
Average drug cost per cycle (£)	**316.29**	**316.29**	**667.88**

Surgery

Patients identified as having ovarian cancer or a benign gynaecological problem undergo a surgical procedure. The unit costs considered in this analysis were estimated by mapping the Classification of Surgical Operations and Procedures from the Office of Population, Censuses and Survey (OPCS – 4) into Health Related Groups (HRGs) and by identifying the relevant unit cost as reported in the NHS Reference Costs for the specific HRGs. OPCS – 4 codes for laparotomy for malignant and benign conditions were obtained via GDG consensus. Costs of surgical procedures for malignant and benign gynaecological problems are reported in Table A1.12.

Table A1.12 Costs of surgical procedures

	Mean (£)	**Data source**
Laparotomy **with malignancy** *(no complications)*	3,561	NHS Reference Cost: HRG code MA06Z
Laparotomy **with malignancy** *(with complications)*	3,705	NHS Reference Cost: HRG code MA06Z*
Laparotomy **without malignancy** *(no complications)*	2,967	NHS Reference Cost: HRG code MA07B
Laparotomy **without malignancy** *(with complications)*	3,101	NHS Reference Cost: HRG code MA07A

* Extra cost associated with complication was obtained using percentage change between HRG MA07A and MA07B as a proxy.

Treatment of colorectal cancer

Lifetime costs estimates of the treatment of colorectal cancer were obtained from a published study by Tappenden *et al*., (2007) and are reported in the Table A1.13 below.

Table A1.13 Lifetime costs of treatment of colorectal cancer

Disease stage	**Mean cost (£)**
Dukes A	8,299
Dukes B	12,441
Dukes C	19,077
Dukes D	11,946

Source: Tappenden *et al*., 2007

Cost of supportive care and follow-up monitoring

No published data was found that quantified healthcare resource use associated with the provision of supportive care and follow up monitoring specifically in patient subgroups identified in the model. Categories and number of units of relevant resource use items were obtained via GDG consensus. The total number of units for each category of resource use was multiplied by the cost of providing it (PSSRU, 2009). A summary of unit costs for each category of resource use are shown in Table A1.14.

Table A1.14 Unit cost of supportive care resource use

Resource	**Unit cost (£)**	**Data source**

Hospital specialist palliative care support	133	NHS Reference costs: HRG code SD03A
Hospice specialist palliative care	418	NHS Reference costs: HRG code SD01A
GP visits	58	PSSRU, 2009
District nurse	114	PSSRU, 2009
Nurse specialist	82	PSSRU, 2009
Annual follow-up monitoring		
Years 1-3	248	PSSRU, 2009
Year 4 (onwards)	62	PSSRU, 2009

3.7 Discounting

Within health economic evaluation, the discounting of costs and health outcomes is standard practice – since costs and benefits that accrue in the future are given less weight to those which occur in the present. Following NICE methodological guidance (NICE, 2008), all costs and health outcomes are discounted at 3.5% per year.

3.8 Sensitivity analysis

A series of one-way sensitivity analyses were conducted to assess the robustness of the study results. One-way sensitivity analysis describes the process of changing one parameter in the model and re-running the model to see how a change in this parameter influences overall results.

Five scenarios were considered and are detailed below:

- Nationally-agreed drug discounts in England were as follows: the cost per dose of paclitaxel is £63.15 compared to a list price of £668 per dose (NHS Purchasing and Supplies Agency, August 2009). The price of carboplatin is £23.93 compared to a list price of £316 per dose. In Wales, nationally-agreed discounts were: 97% per dose for paclitaxel and 92% for carboplatin (personal communication from the Welsh Health Supplies, August 2009). Based on these rates, the discounted cost of each regimen was calculated for England and for Wales. Whilst it is acknowledged that regional pharmacies and/or commissioners may negotiate other discounts separately, only nationally agreed discounts are considered (NICE, 2008). The average discounted cost across both regions is also reported in Table A1.15.

- The prevalence of ovarian malignancy in primary care was decreased to 0.14%.

- The prevalence of benign gynaecological problem was varied over an agreed range (20% - 30%).

- The proportion of patients who are not fit for further treatment following diagnostic investigation was decreased to 2%.

- The age at the start of the model was increased from 40 to 50 years of age.

Table A1.15 Discounted drug acquisition costs in England and Wales

Regimen	Carboplatin	Carboplatin/paclitaxel
Average cost of regimen per cycle (£)		
List price	316.29	984.17
Discount price (England)	26	89
Discount price (Wales)	25	45

However these scenarios are unlikely to happen independently; they are more likely to occur concurrently. To fully characterise this uncertainty and to estimate the effects of the parameter uncertainty on the results, a probabilistic sensitivity analysis (PSA) was undertaken.

Firstly, the stochastic parameters in the model were identified (presented in the first column of Table A1.16). These are parameters which are (arguably) measureable, but are associated with sampling uncertainty.

Secondly, these parameters were specified as distributions rather than point estimates (see fourth column of Table A1.16). Distributions associated with each of these parameters were selected according to a well developed body of methodological literature. The data required to inform these distributions was taken from the same sources as was used for the point estimates.

Parameters not chosen for PSA:

- unit costs of health professionals and drug acquisition
- estimates of test accuracy

Thirdly, the analysis was run 10,000 times. For each simulation, different values were picked from the various distributions for each stochastic parameter in the model.

Table A1.16 Parameters varied in the probabilistic sensitivity analysis

Parameter	Deterministic value	Distribution assigned	Source
Utilities			
Diagnostic test false positive/negative result	0.88		Havrilesky. *et al.,* 2009
Stable – advanced disease	0.63	Beta	Grann *et al.,* 1998
Advanced (undergoing chemotherapy)	0.55	Beta	Havrilesky. *et al.,* 2009
Advanced (undergoing chemotherapy with toxicity)	0.49	Beta	Havrilesky. *et al.,* 2009
Early (chemotherapy)	0.81	Beta	Havrilesky. *et al.,* 2009
Early (recurrence)	0.47	Beta	Havrilesky. *et al.,* 2009)

Early (remission)	0.83	Beta	Havrilesky. *et al.*, 2009
Surgery	0.68	Beta	Grann *et al.*, 1998
Colorectal cancer – Dukes A	0.74	Beta	Tappenden *et al.*, 2007
Colorectal cancer – Dukes B	0.70	Beta	Tappenden *et al.*, 2007
Colorectal cancer – Dukes C	0.50	Beta	Tappenden *et al.*, 2007
Colorectal cancer – Dukes D	0.25	Beta	Tappenden *et al.*, 2007
Supportive care	0.16	Beta	Havrilesky. *et al.*, 2009
Follow-up	0.99	Beta	Assumed
Transition probability			
tpAdv_Dead	0.203	Beta	Bagnall *et al.*, 2002
tpRem_RecAdv	0.11	Beta	Swart *et al.*, 2007
tpCRC_A_B	0.58	Dirichlet	Tappenden *et al.*, 2007
tpCRC_A_Death	0	Dirichlet	Tappenden *et al.*, 2007
tpCRC_B_C	0.66	Dirichlet	Tappenden *et al.*, 2007
tpCRC_B_Death	0.01	Dirichlet	Tappenden *et al.*, 2007
tpCRC_C_D	0.87	Dirichlet	Tappenden *et al.*, 2007
tpCRC_C_Death	0.06	Dirichlet	Tappenden *et al.*, 2007
tpCRC_D_Death	0.39	Dirichlet	Tappenden *et al.*, 2007
Proportions and rates			
Prior – disease prevalence	0.2529	Beta	Hamilton *et al.*, 2009
Rate of toxicity (alopecia in advanced stage)	0.73	Beta	Bagnall *et al.*, 2002
Rate of mortality (early) – post surgery	0.01	Beta	Venesmaa *et al.* 1992
Rate of mortality (advanced) - post surgery	0.03	Beta	Gerestein *et al.*, 2009
Rate of mortality (benign) – post surgery	0.0016	Beta	Loft *et al.*, 1991
Rate of morbidity (early) – post surgery	0.05	Beta	GDG consensus
Rate of morbidity (advanced) - post surgery	0.13	Beta	GDG consensus
Rate of morbidity (benign) – post surgery	0.05	Beta	Chien *et al.*, 1991
Proportion of patients with disease **confined** to the ovaries (undergoing treatment)	0.5	Beta	GDG consensus
Proportion of patients in whom ovarian cancer is detected (following secondary care test)	(0.35; 0.60; 0.05)	Dirichlet	GDG consensus

Proportion of patients with disease **not confined** to the ovaries (undergoing treatment)	(0.85; 0.1; 0.05)	Dirichlet	GDG consensus
Proportion of patients with benign gynaecological problem	0.85	Beta	GDG consensus
Proportion of patients with colorectal cancer	0.15	Beta	GDG consensus
Proportion of Dukes A-D	(0.13; 0.37; 0.36; 0.14)	Dirichlet	Tappenden *et al.*, 2007

4 Results

A summary of expected costs and effects associated with each diagnostic strategy in the model are presented in Table A1.17. The expected cost of the strategies varies widely, ranging from the least expensive (serum CA125) at just over £1,500 to the most expensive (combination strategy of pelvic examination plus serum CA125 plus ultrasound) at £,3160 per patient. Health outcomes, measured in terms of QALYs, ranged from 20.391 for the serum CA125 strategy to 19.524 for pelvic examination plus serum CA125 plus ultrasound combination strategy. Serum CA125 (single test) strategy on average generates 20.391 QALYs and ultrasound (single test) generates 20.387 – a difference of 0.004 QALYs is an equivalent (on average) of an additional 1.5 days of perfect health.

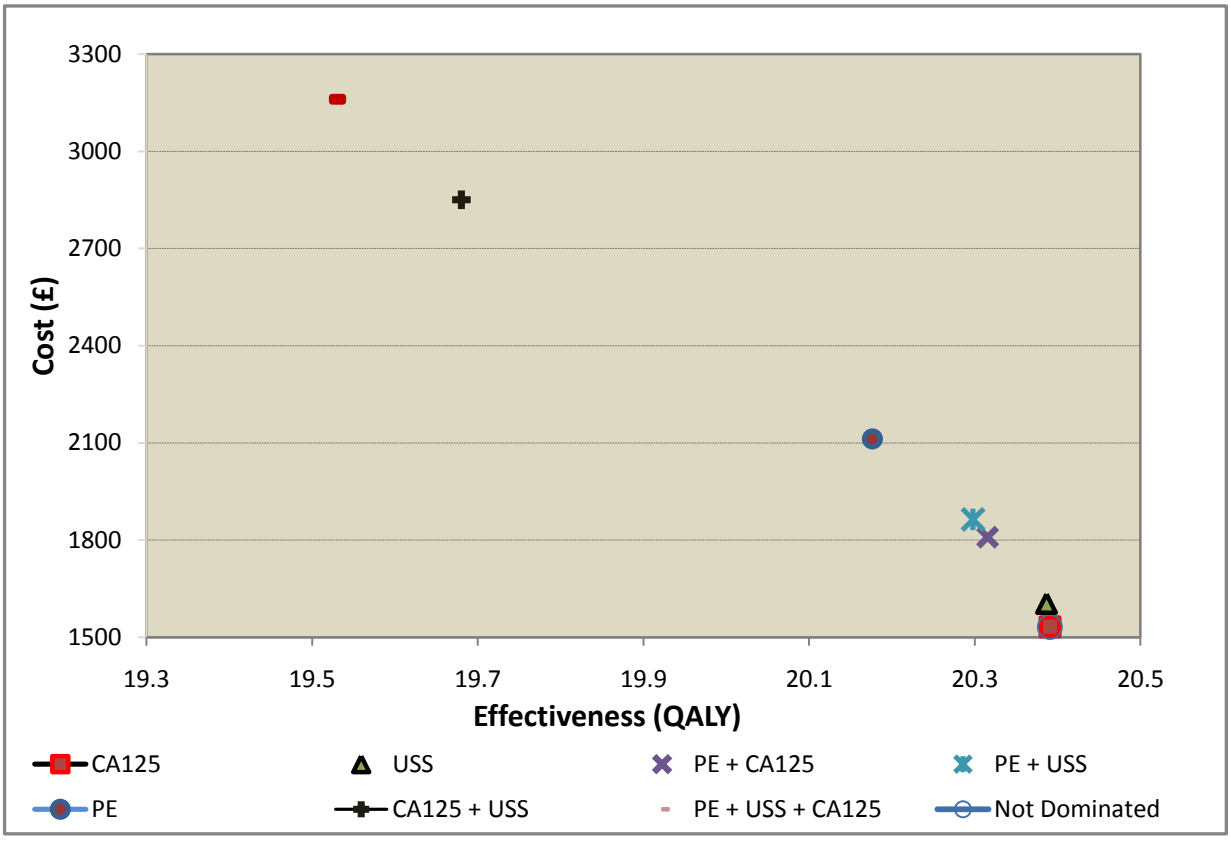
Table A1.17 Base case total expected cost and QALYs

Strategy	Cost (£)	Effectiveness (QALY)	ICER†
Serum CA125	1,532.32	20.391	
Ultrasound	1,604.24	20.387	(Dominated)
Pelvic examination + serum CA125	1,809.06	20.316	(Dominated)
Pelvic examination + ultrasound	1,864.16	20.298	(Dominated)
Pelvic examination	2,112.49	20.177	(Dominated)
Serum CA125 + ultrasound	2,850.49	19.681	(Dominated)
Pelvic examination + ultrasound + serum CA125	3,160.73	19.524	(Dominated)

†ICER – incremental cost-effectiveness ratio

All strategies in this analysis are dominated by the serum CA125 strategy. A strategy is said to be dominated if it is both more costly and less effective than its comparator. Graphical representation of the base case shown on Figure A1.5.

Figure A1.5 Cost-effectiveness plane for base-case results



4.1 Sensitivity analysis

The results of base case analysis were not sensitive to any of the five scenarios outlined above in section 3.8.

The discount on paclitaxel and carboplatin available in England and Wales is considerable; the price is about 10% of the list price. This drastically reduced the costs attributed to marginal reduction in the overall expected costs for each of the strategies, but did not alter the ranking of the cost-effective diagnostic strategies (Table A1.18).

Table A1.18 One-way sensitivity analysis – drug discounts

Strategy	Costs (£)	Costs (£)	Effectiveness (QALY)
	England	Wales	
Serum CA125	1,525.1	1,524.8	20.3909
Ultrasound	1,596.5	1,596.2	20.3867
Pelvic examination + serum CA125	1,800.9	1,800.5	20.3155
Pelvic examination + ultrasound	1,855.8	1,855.5	20.2979
Pelvic examination	2,103.8	2,103.4	20.1765
Serum CA125 + ultrasound	2,841.3	2,840.9	19.6802

Pelvic examination + ultrasound + serum CA125	3,151.4	3,151.0	19.5241

Similarly, the results of the one-way sensitivity analysis of the other scenarios (for example, changes in the prevalence, proportion of patients undergoing supportive care and starting age of the patients in the model) showed changes in the overall expected costs and health benefits but did not alter the ranking of the cost-effective diagnostic strategy. The results of deterministic sensitivity analysis are presented in Tables A1.19 and A1.20.

Table A1.19 One-way sensitivity analysis – change in prevalence

Strategy	**Prevalence of ovarian cancer 0.14%**		**Prevalence of benign condition 20%**		**Prevalence of benign condition 30%**	
	Costs (£)	**QALYs**	**Costs (£)**	**QALYs**	**Costs (£)**	**QALYs**
Serum CA125	1,525.6	20.4024	1,362.1	20.5313	1,702.6	20.2504
Ultrasound	1,597.1	20.3989	1,423.1	20.5289	1,785.4	20.2446
Pelvic examination + serum CA125	1,801.6	20.3283	1,621.7	20.4551	1,996.5	20.1760
Pelvic examination + ultrasound	1,856.6	20.3108	1,675.8	20.4368	2,052.6	20.1590
Pelvic examination	2,104.8	20.1898	1,924.9	20.3092	2,300.1	20.0438
Serum CA125 + ultrasound	2,843.2	19.6935	2,701.3	19.7818	2,999.7	19.5786
Pelvic examination + ultrasound + serum CA125	3,153.6	19.5374	3,023.9	19.6159	3,297.6	19.4323

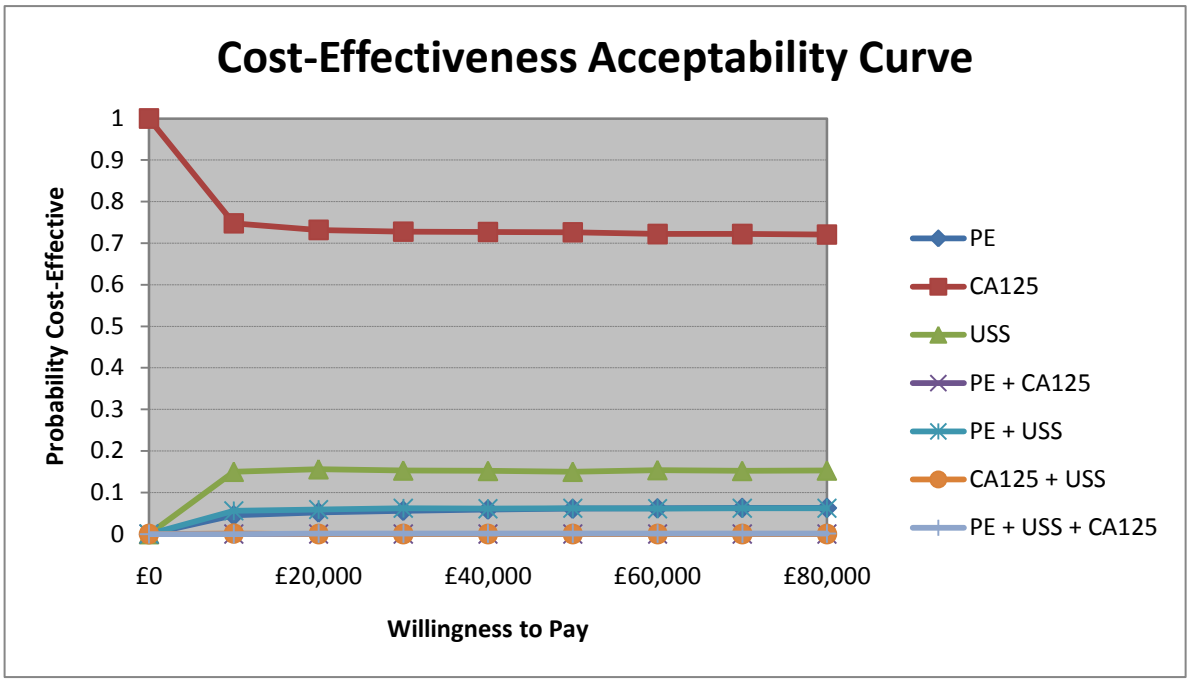
Table A1.20 One-way sensitivity analysis – proportion estimates and starting age

Strategy	**Prop. Supportive Care 2%**		**Starting age 50 years**	
	Costs (£)	**QALYs**	**Costs (£)**	**QALYs**
Serum CA125	1,532.7	20.3909	1,531.2	17.9052
Ultrasound	1,604.6	20.3868	1,603.2	17.9019
Pelvic examination + serum CA125	1,809.5	20.3156	1,808.0	17.8403
Pelvic examination + ultrasound	1,864.6	20.298	1,863.1	17.825
Pelvic examination	2,112.9	20.1766	2,111.5	17.7197
Serum CA125 + ultrasound	2,851.0	19.6803	2,849.7	17.2885
Pelvic examination + ultrasound + serum CA125	3,161.2	19.5242	3,160.0	17.153

To fully assess the effects of the parameter uncertainty on the results, the base case model was estimated using probabilistic sensitivity analysis. As with the deterministic results, the results of PSA showed serum CA125 as the dominant strategy. The corresponding cost-

effectiveness acceptability curve (CEAC) shows that, at a threshold of £20,000 per QALY, the probability that the serum CA125 strategy is the most cost effective option is almost 73%. Moreover, the serum CA125 strategy had the highest probability of being the most cost-effective when compared to other strategies, at any level of willingness-to-pay per additional QALY gained (Figure A1.6).

Figure A1.6 Cost-effectiveness acceptability curve for base case results



PE = pelvic examination; CA125 = serum CA125; USS = ultrasound

5 Discussion

The aim of this study was to assess the cost-effectiveness of diagnostic strategies for women presenting with symptoms suggestive of ovarian cancer in primary care. A cost-utility analysis was undertaken to estimate the incremental cost per QALY of seven diagnostic strategies, which included the downstream costs and consequences of subsequent treatments considered likely to reflect current UK clinical practice and to be consistent with recommendations made within this guideline.

The base-case results of this analysis provide a clear message for recommendations on this topic, in terms of cost-effectiveness. They show that the serum CA125 diagnostic strategy dominates all other strategies. The robustness of the model was tested using one-way sensitivity analysis. The results of the deterministic sensitivity analysis showed that although expected costs and health outcomes varied across strategies, the overall ranking of the cost-effective strategy did not change. Moreover, probabilistic sensitivity analysis was undertaken to fully assess the effects of the parameter uncertainty on the results. The results of the PSA showed serum CA125 as the dominating strategy and the corresponding cost-effectiveness acceptability curve (CEAC) shows that, at a threshold of £20,000 per QALY, the probability that the serum CA125 strategy is the most cost effective option is almost 73%.

There are a number of limitations to this analysis. The sensitivity analyses conducted were aimed at assessing only parameter uncertainty; however given the complexity of the downstream consequences associated with each strategy further analysis of the later structural assumptions would be beneficial. The costs used were often proxies for costs that

were hard to capture and may not fully capture the differences between the different diagnostic strategies, for instance the costs of pelvic examination.

Despite these acknowledged limitations, this analysis does provide some useful information which the guideline development group can use in its deliberations over the recommendations to be made on this clinical question. Serum CA125 is the most cost-effective (dominating) strategy and as shown above is more likely to be cost-effective compared to other strategies in the model.

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