NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of maximal effort cytoreductive surgery for advanced ovarian cancer

Ovarian cancer has usually reached an advanced stage when it is detected. Maximal effort cytoreductive surgery (also known as extensive or ultra-radical surgery) for advanced ovarian cancer aims to improve outcomes for people with advanced ovarian cancer by removing all or almost all visible cancerous tissue. More tissue is removed than with standard surgery. As well as removing the ovaries, fallopian tubes and womb, tissue from the spleen, liver, diaphragm, peritoneum and bowel may also be removed.

Contents

Appendix

Abbreviations

Word or phrase	Abbreviation
Confidence interval	CI
European Organisation for Research and Treatment of Cancer	EORTC
Hazard ratio	HR
Incidence rate ratio	IRR
International Federation of Gynecology and Obstetrics	FIGO
Interquartile range	IQR
Neoadjuvant chemotherapy	NACT
Odds ratio	OR
Relative risk	RR
Patient Reported Outcome Measures	PROMs
Peritoneal cancer/carcinomatosis index	PCI
Standard deviation	SD
Standard error	SE
Surgical complexity score	SCS

Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedure overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and professional opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in July 2022.

Procedure name

- Maximal effort cytoreductive surgery for advanced ovarian cancer

Professional societies

- British Gynaecological Cancer Society
- BASO – The Association for Cancer Surgery
- Royal College of Obstetricians and Gynaecologists
- Royal College of Surgeons of England
- Royal College of Surgeons of Edinburgh
- Royal College of Physicians and Surgeons of Glasgow.

Description of the procedure

Indications and current treatment

Early symptoms of ovarian cancer can be similar to those of other pelvic or abdominal conditions and include persistent bloating, pain in the pelvis and lower abdomen, urinary frequency and urinary urgency. Ovarian cancer is usually at Stage 3 or 4 when it is diagnosed and the outcome is generally poor. The overall 5-year survival rate for ovarian cancer is about 43%, and is lower for people with more advanced disease. The stage of the disease at diagnosis is the most important factor affecting outcome and is defined by the International Federation of Gynecology and Obstetrics (FIGO) system:

- Stage 1 (A to C) – the tumour is confined to the ovary.
- Stage 2 (A, B) – the tumour involves 1 or both ovaries and has extended into the pelvis.
- Stage 3 (A to C) – the tumour involves 1 or both ovaries with microscopically confirmed peritoneal metastasis outside the pelvis or regional lymph node metastasis (if cancer cells are found only in fluid taken from inside the abdomen the cancer is stage 2).
- Stage 4 (A, B) – there is distant metastasis beyond the peritoneal cavity (if ovarian cancer is only found on the surface of the liver and not within the liver itself, then the cancer is stage 3).

The FIGO stage does not take into account the distribution of disease within the abdomen or the volume of the disease. Therefore FIGO stage 3C can range from a single cancer deposit of more than 2 cm on the omentum to widespread intra-abdominal disease where cancer is present on the surface of the large bowel, small bowel, spleen, diaphragm, liver and across the peritoneum.

NICE's guideline on ovarian cancer describes the initial management options. The main treatments for advanced ovarian cancer are surgery to remove all macroscopic residual disease (also known as debulking) and chemotherapy. Standard surgery usually involves, as a minimum, bilateral salpingo-oophorectomy, total abdominal hysterectomy and omentectomy. Maximal effort cytoreductive surgery uses additional surgical procedures including upper abdominal surgery, with the aim of achieving no residual disease. The most important factor affecting outcomes after treatment are responsiveness to platinum-based chemotherapy and the amount of cancer left behind at the end of cytoreductive surgery (residual disease).

Conventional imaging techniques cannot accurately predict the distribution or volume of disease before surgery. Therefore, the only definitive assessment of the distribution or volume of disease found in the abdomen and pelvis is done at the time of surgery. Currently, no objective tools exist to select people for surgery and a decision for surgery will rest on many factors including fitness, patient choice, availability of surgeons with appropriate expertise, and resource levels.

What the procedure involves

The aim of maximal effort cytoreductive surgery for advanced ovarian cancer is to remove all identifiable disease, to improve survival compared with standard surgery. It is a development and extension of surgery for ovarian cancer.

The precise differences between standard, radical and maximal effort cytoreduction procedures are not well defined. Surgical complexity scores, such as the Aletti system, have been developed to try to quantify the complexity of surgery. Each procedure that is done during the surgery is allocated a score:

- Total hysterectomy and bilateral salpingo-oophorectomy=1
- Omentectomy=1
- Pelvic lymphadenectomy=1
- Paraaortic lymphadenectomy=1
- Pelvic peritoneum stripping=1
- Abdominal peritoneum stripping=1
- Rectosigmoidectomy anastomosis=3
- Large bowel resection=2
- Diaphragm stripping or resection=2
- Splenectomy=2
- Liver resection=2
- Small bowel resection=1

The total score can then be used to categorise the surgery into low complexity (1 to 3), intermediate complexity (4 to 7) or high complexity (8 and above).

Outcome measures

Peritoneal cancer/carcinomatosis index (PCI)

The PCI is a diagnostic and prognostic tool that is a sum of scores in 13 abdominal regions. Each region is given a score of 0 to 3 based on the largest tumour size in each region (0 = no tumour, 1 = tumours up to 0.5 cm, 2 = tumours up to 5 cm, 3 = tumours larger than 5 cm). The total score ranges from 0 to 39. Higher scores indicate more widespread or larger tumours in the peritoneal cavity.

European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire QLQ-C30

The EORTC Core Quality of Life questionnaire (EORTC QLQ-C30) is designed to measure physical, psychological and social functions in patients with cancer. The questionnaire is composed of multi-item scales and single items. All of the scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level. A high score for a functional scale represents a high level of functioning, a high score for the global health status represents a high quality of life, but a high score for symptoms represents a high level of symptomatology.

Efficacy summary

Quality of life

In a NICE-commissioned UK multicentre cohort study of 247 patients with late-stage ovarian cancer who had cytoreductive surgery of varying complexity with the aim of complete tumour clearance, quality of life improved in all groups with no clinically meaningful differences in quality of life among patients undergoing surgery of different complexities. The mean change in score from baseline in the EORTC QLQ-C30 at 6 weeks after surgery was 3.4 (SD 1.8, n=88) in the low SCS group, 4.0 (SD 2.1, n=55) in the intermediate SCS group and 4.3 (SD 2.1, n=52) in the high SCS group (p=0.048). At 12 months the mean change was 4.3 (SD 2.1, n=51) in the low SCS group, 5.1 (SD 2.2, n=41) in the intermediate SCS group and 5.1 (SD 2.2, n=35) in the high SCS group (p=0.133). In all patients, there was a small statistically significant improvement in quality of life after surgery at the 12 month follow up (p<0.001). Patients in the high SCS group had small to moderate decreases in physical (p=0.004), role (p=0.016) and emotional (p=0.001) function at 6 weeks after surgery, which resolved by 6 to 12 months (Sundar 2022).

Overall survival

In a cohort study of 1,471 patients, treatment centres were categorised by patterns of surgical practice (mainly high SCS, mainly intermediate SCS and mainly low SCS). Median survival was 23.1 months (95% CI 19.0 to 27.2 months) in the mainly high SCS centres, 22.0 months (95% CI 17.6 to 26.3 months) in the mainly intermediate SCS centres and 17.9 months (95% CI 15.7 to 20.1 months) in the mainly low SCS centres. Compared to patients in the high SCS centres, patients in the low SCS group centres had a hazard ratio of 1.21 (95% CI 1.04 to 1.40) for death (Cummins 2022).

In the cohort study of 247 patients, overall survival at 2 years was 83% in patients with no residual disease after surgery and 64% in patients with residual disease ($p<0.001$; Sundar 2022).

In a population-based cohort study of 3,728 patients with primary stage 3C or 4 cancer of the ovary, fallopian tube, peritoneum or undesignated primary site, survival improved after national guidelines for ovarian cancer were implemented. After adjusting for age and stage, the excess mortality rate ratio was 0.89 (95% CI 0.82 to 0.96, $p<0.05$). In those patients who had primary debulking surgery, median overall survival was 35 months (95% CI 32.8 to 39.2) before the guideline was implemented compared with 43 months (95% CI 40.9 to 46.4) after. The median survival where R0 (no residual tumour) was achieved was 59.0 months (95% CI 53.6 to 66.1) compared with 32.5 months (95% CI 29.9 to 34.6) for those with residual tumour (Dahm Kahler 2021).

In a population-based cohort study of 752 patients with advanced epithelial ovarian cancer, comparing those who were treated before and after a paradigm shift to upfront ultra-radical surgery reported that there was no difference in 5-year overall survival irrespective of treatment modality (HR 1.03, 95% CI 0.87 to 1.22, $p=0.75$). The subgroup of patients with high SCS had inferior survival in the later cohort (HR 1.99, 95% CI 1.12 to 3.56). The median survival for patients in whom radical resection was achieved was 58 months in the earlier cohort and 55 months in the later cohort (HR 1.31, 95% CI 0.89 to 1.92, $p=0.17$; Falconer 2020).

In a retrospective analysis of chemotherapy trials, 2,655 patients with advanced epithelial ovarian cancer or primary peritoneal cancer who had primary cytoreductive surgery to achieve complete surgical resection or less than 1 cm residual disease, median overall survival was 48.7 months in those who had low SCS surgery, 48.4 months in those who had moderate SCS surgery and 44.2 months in those who had high SCS surgery ($p=0.191$). For patients who had complete resection, median overall survival was 76.9 months compared with 40.6 months for those with residual disease ($p<0.01$; Horowitz 2015).

In a cohort study of 978 patients with advanced ovarian cancer who had primary debulking surgery, 5-year overall survival was 40% in those who were treated between 2001 and 2005, 44% in those who were treated between 2006 and 2009 and 56% for those who were treated between 2010 and 2013 (p<0.001). During this time, extensive upper abdominal procedures started to be incorporated and the goal for primary debulking surgery evolved from residual disease 10 mm or less to either complete gross resection or as minimal residual tumour as possible (Tseng 2018).

In a cohort study of 608 patients with stage 3 or 4 advanced ovarian cancer who had cytoreductive surgery, median overall survival was 48.2 months (95% CI 40.6 to 55.8 months). In patients who had primary debulking surgery and complete cytoreduction, the median overall survival had not been reached. The estimated mean overall survival was 83.9 months (95% CI 75.2 to 92.7 months). In patients who had primary debulking surgery and optimal or suboptimal cytoreduction, the median overall survival was 56.3 months (95% CI 25.8 to 86.8 months) and 15.0 months (95% CI 9.1 to 20.8 months), respectively. In patients who had interval debulking surgery, the median overall survival was 57.9 months (95% CI 43.2 to 72.7 months) in those with complete cytoreduction, 33.4 months (95% CI 25.0 to 41.7 months) for those with optimal cytoreduction and 28.4 months (95% CI 21.6 to 35.2 months) for those with suboptimal cytoreduction (Phillips 2019).

A Cochrane systematic review, including 3 studies, concluded that survival may be prolonged in woman who had ultra-radical surgery compared to standard surgery but the evidence was limited and very uncertain: HR 0.60 (95% CI 0.43 to 0.82); 2 studies, n=397 (Hiu 2022).

Progression-free survival

In the cohort study of 247 patients, progression-free survival at 2 years was 34% (95% CI 24.7 to 42.3%) in patients in the low SCS group, 47% (95% CI 35.0 to 58.6%) in the intermediate SCS group and 34% (95% CI 22.4 to 46%) in the high SCS group (p=0.109). For patients with no residual disease, progression-free survival at 2 years was 47% compared with 21% (p<0.001) for those with residual disease (Sundar 2022).

In the retrospective analysis of chemotherapy trials of 2,655 patients, median progression-free survival was 18.5 months in those who had low SCS surgery, 18.0 months in those who had moderate SCS surgery and 14.9 months in those who had high SCS surgery (p<0.01). For patients with complete resection, median progression-free survival was 28.9 months compared with 15.3 months (p<0.01) for those with residual disease (Horowitz 2015).

In the cohort study of 978 patients with advanced ovarian cancer who had primary debulking surgery, 5-year progression-free survival was 15% in those who were treated between 2001 and 2005, 16% in those who were treated between 2006 and 2009 and 20% for those who were treated between 2010 and 2013 (p=0.199; Tseng 2018).

In a cohort study of 384 patients with stage 3 or 4 ovarian cancer who had primary or interval debulking surgery, median progression-free survival was 17.2 months (95% CI 15.2 to 20.7 months) in the low SCS group compared with 21.5 months (95% CI 18.2 to 25.7 months) in the intermediate or high SCS group (p=0.038; Palmqvist 2022).

The Cochrane systematic review concluded that disease progression may be delayed in women who had ultra-radical surgery compared to standard surgery but the evidence was limited and very uncertain: HR 0.62 (95% CI 0.42 to 0.92); 1 study, n=203 (Hiu 2022).

Completeness of resection

In the population-based cohort study of 3,728 patients, the proportion of patients with no residual tumour after primary debulking surgery increased from 29% (224/968) to 53% (430/835) after the implementation of national guidelines (Dahm Kahler 2021).

In the cohort study of 247 patients, complete macroscopic tumour clearance was reported in 56% (63/113) of patients in the low SCS group, 71% (50/70) of patients in the intermediate SCS group and 63% (40/64) in the high SCS group (p=0.007; Sundar 2022). In the cohort study of 752 patients, the complete resection rate increased from 37% to 67% (p≤0.001) after the shift to upfront and ultra-radical surgery (Falconer 2020).

In the retrospective study of chemotherapy trials of 2,655 patients, those who had high SCS surgery were statistically significantly more likely to have complete resection than those who had low SCS (OR 4.17, 95% CI 2.30 to 7.56; p<0.01) or moderate SCS surgery (OR 2.66, 95% CI 1.91 to 3.70; p<0.01; Horowitz 2015).

In the cohort study of 978 patients with advanced ovarian cancer who had primary debulking surgery, the rate of complete gross resection was 29% in those who were treated between 2001 and 2005, 40% in those who were treated between 2006 and 2009 and 55% for those who were treated between 2010 and 2013 (p<0.001; Tseng 2018).

In the cohort study of 608 patients, complete cytoreduction rates were statistically significantly higher (87.7% compared with 56.7%, p<0.0001) in patients who had

ultra-radical surgery compared with those who had standard surgery (Phillips 2019).

In the cohort study of 384 patients, the rate of complete cytoreduction was 48.7% (187/384; Palmqvist 2022).

Safety summary

Unspecified complications

At least 1 complication was reported in 30% of patients in the cohort study of 247 patients. A grade 3 or higher complication (using Clavien–Dindo classification) was reported in 14% of patients. Overall complication rates were 20% in the low SCS group, 26% in the intermediate SCS group and 52% in the high SCS group ($p<0.001$). The rates of grade 3 or higher complications were 9% in the low SCS group, 13% in the intermediate SCS group and 25% in the high SCS group (p value not stated; Sundar 2022).

The overall rate of major (grade 3 to 5) complications was 15% (148/978) in the cohort of 978 patients and was similar across time periods. It was 13% (41/315) in those who were treated between 2001 and 2005, 16% (51/320) in those who were treated between 2006 and 2009 and 16% (56/343) for those who were treated between 2010 and 2013 ($p=0.440$; Tseng 2018).

The overall rate of major surgical complications was 22% (123/549) in a cohort study of 549 patients who had primary, interval or closure debulking surgery with either complete cytoreduction or cytoreduction to minimal residual disease for Stage 3c to 4 epithelial ovarian, fallopian, or primary peritoneal cancer. Of the 123 patients, 75 (61%) had a SCS of 8 or above compared with 45% (249/549) for the whole cohort ($p<0.001$). A high SCS was not identified as a factor associated with major surgical complications in multiple logistic regression analysis (OR 0.93, 95% CI 0.42 to 2.07, $p=0.863$; Angeles 2022).

Patients who had multiple bowel resections had a RR of 7.73 (95% CI 3.92 to 15.26), patients with a high SCS had an RR of 6.12 (95% CI 3.25 to 11.52), patients with diaphragmatic surgery and gastrointestinal anastomosis had an RR of 5.57 (95% CI 2.65 to 11.72), patients with any gastrointestinal resection had an RR of 4.69 (95% CI 2.66 to 8.24), patients with ultra-radical surgery had an RR of 4.65 (95% CI 2.26 to 8.79), and patients with supra-radical surgery had an RR of 4.20 (95% CI 2.35 to 7.51) of grades 3 to 5 morbidity, compared with patients who had standard surgery as defined by the NICE classification used in the study (Phillips 2019).

Mortality

Mortality was 1% (3/247) in the cohort study of 247 patients. Causes of death were disseminated intravascular coagulation and multiorgan failure, pulmonary embolism, and intra-abdominal sepsis. Of the 3 patients, 2 were in the intermediate SCS group and 1 was in the low SCS group (Sundar 2022).

Overall 30-day all-cause mortality was less than 1% (4/978) and 90-day all-cause mortality was 1% (13/975) in the cohort study of 978 patients. 90-day mortality decreased over time from 2.9% in those who were treated between 2001 and 2005, 1% in those who were treated between 2006 and 2009 and 0% for those who were treated between 2010 and 2013 (p=0.002; Tseng 2018).

Mortality caused by postoperative complications (Clavien–Dindo grade 5) was reported in 2% (10/549) of patients in the cohort study of 549 patients (Angeles 2022).

30-day mortality was less than 1% (1/384) and 90-day mortality was 1% (4/384) in the cohort study of 384 patients. The death within 30 days was caused by sepsis, multiple organ failure and cardiac arrest (Palmqvist 2022).

The weighted mean perioperative mortality was 4.6% (95% CI 4.6 to 4.7) in a systematic review of 18,579 patients (46 studies) who had primary cytoreductive surgery for ovarian cancer. The number of surgical procedures, weighted surgical complexity index, and highest procedure complexity were computable in 26 cohorts included in the review. There was no statistically significant association between the weighted mean value of these parameters and the incidence rate of mortality, although an inverse trend was observed (Di Donato 2017).

Digestive complications

Major digestive complications were reported in 9% (51/549) of patients in the cohort study of 549 patients (Angeles 2022). Return to theatre for gastric perforation, subsequent enterocutaneous fistula and tracheostomy was reported in 1 patient who had ultra-radical surgery in the cohort study of 608 patients (Phillips 2019).

Return to theatre for anastomotic leak was reported in 2 patients who had standard surgery and 2 patients who had ultra-radical surgery in the cohort study of 608 patients. Another patient in the ultra-radical surgery group was returned to theatre for anastomotic leak and sheath dehiscence (Phillips 2019). Grade 3b anastomotic leakage and suspected anastomotic leakage, treated by surgery, were reported in 1 patient each in the cohort study of 384 patients. Grade 4b

anastomotic leakage, treated by surgery followed by intensive care, was reported in 1 patient in the same study (Palmqvist 2022).

Infection

Major infectious complications were reported in 9% (49/549) of patients in the cohort study of 549 patients (Angeles 2022). Return to theatre for paraspinal infection was reported in 1 patient who had ultra-radical surgery in the cohort study of 608 patients. Another patient in this group died from pancreatitis and acute respiratory distress syndrome (Phillips 2018). Intra-abdominal abscess treated by drainage was reported in 1 patient and vaginal vault abscess treated by drainage was reported in 2 patients in the cohort study of 384 patients. Intra-abdominal abscess and stoma necrosis that needed surgical intervention were reported in 1 patient each, and sepsis with multiple organ failure needing intensive care was reported in 1 patient in the same study (Palmqvist 2022).

Infection was the most common cause of death identified in the systematic review of 18,579 patients (46 studies) who had primary cytoreductive surgery for ovarian cancer (Di Donato 2017).

Respiratory complications

Major respiratory complications were reported in 5% (28/549) of patients in the cohort study of 549 patients (Angeles 2022).

Chest drain insertion with or without bronchoscopy was reported in 1 patient who had standard surgery and 4 patients who had ultra-radical surgery in the cohort study of 608 patients. One patient in the ultra-radical surgery group died from pulmonary embolus (Phillips 2019).

Pleural fluid drainage was reported in 4% (16/384) of patients in the cohort study of 384 patients. Pulmonary failure that needed intensive care treatment was reported in 0.5% (2/384) patients in the same study (Palmqvist 2022).

Abdominal wall complications

Major abdominal wall complications were reported in 4% (24/549) of patients in the cohort study of 549 patients (Angeles 2022).

Diaphragmatic hernia was described in 4 patients after debulking surgery for advanced ovarian cancer in a case series. They were diagnosed at 5, 6, 8 and 18 months after the procedure and were treated surgically (Ehmann 2021).

Wound complications

Grade 3 wound resuturing and wound seroma were reported in 1 patient each and wound infection was reported in 2 patients in the cohort study of 384 patients. Grade 4 wound haematoma that needed to be resutured was reported in 1 patient and wound dehiscence that needed to be resutured was reported in 2 patients in the same study (Palmqvist 2022).

Lymphatic complications

Major lymphatic complications were reported in 4% (19/549) of patients in the cohort study of 549 patients (Angeles 2022).

Haemorrhagic complications

Major haemorrhagic complications were reported in 3% (18/549) of patients in the cohort study of 549 patients (Angeles 2022). Return to theatre for grade 3 haematoma or bleeding was reported in 2 patients who had standard surgery and 2 patients who had ultra-radical surgery in the cohort study of 608 patients. Intraoperative splenectomy for iatrogenic bleeding was reported in 1 patient who had ultra-radical surgery and another had to return to theatre for splenectomy, liver failure, renal failure and pancreatitis (Phillips 2019). Intra-abdominal bleeding that needed surgical intervention was reported in 0.5% (2/384) of patients in the cohort study of 384 patients. Intra-abdominal abscess and bleeding, and bleeding diaphragm that needed surgical intervention were reported in 1 patient each in the same study (Palmqvist 2022).

Urinary or renal complications

Major urinary or renal complications were reported in 2% (13/549) of patients in the cohort study of 549 patients (Angeles 2022). Grade 4 renal failure and urinary tract fistula were reported in 1 patient each who had ultra-radical surgery in the cohort study of 608 patients (Phillips 2019). Hydronephrosis, treated by nephrostomy, was reported in 0.5% (2/384) of patients in the cohort study of 384 patients. Urinary tract injury, treated by surgery, was reported in 1 patient in the same study (Palmqvist 2022).

Cardiac complications

A major cardiac event was reported in 2% (10/549) of patients in the cohort study of 549 patients (Angeles 2022). Cardiac pacing after sinus arrest was reported in 1 patient who had ultra-radical surgery in the cohort study of 608 patients (Phillips 2019).

Neurological complications

A major neurological event was reported in less than 1% (2/549) of patients in the cohort study of 549 patients (Angeles 2022).

Anecdotal and theoretical adverse events

In addition to safety outcomes reported in the literature, professional experts are asked about anecdotal adverse events (events that they have heard about) and about theoretical adverse events (events that they think might possibly occur, even if they have never happened).

For this procedure, professional experts listed the following additional anecdotal or theoretical adverse events: pancreatic leaks, pneumonia, pneumothorax, reduced immune response (secondary to splenectomy), weight loss and reduced absorption (after partial gastrectomy), chylous ascites, bile duct injury, devascularisation of the foregut, liver ischaemia, short gut syndrome.

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to maximal effort cytoreductive surgery (also known as extensive or ultra-radical surgery) for advanced ovarian cancer. The following databases were searched, covering the period from their start to 14 June 2022: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the internet were also searched. No language restriction was applied to the searches (see the literature search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The inclusion criteria were applied to the abstracts identified by the literature search. If selection criteria could not be determined from the abstracts the full paper was retrieved.

Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded if no clinical outcomes were reported, or if the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with advanced ovarian cancer.
Intervention/test	Maximal effort cytoreductive, extensive or ultra-radical surgery
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on over 12,000 patients from 9 cohort studies, 1 non-randomised comparative study, 1 systematic review and 1 case series (Sundar 2022, Soo Hoo 2015, Cummins 2022, Dahm Kahler 2021, Falconer 2020, Horowitz 2015, Tseng 2018, Angeles 2022, Phillips 2019, Palmqvist 2022, Hiu 2022, Ehmann 2021). In addition, a systematic review that includes 18,579 patients who had primary cytoreductive surgery for ovarian cancer has been included (Di Donato 2017).

Other studies that were considered to be relevant to the procedure but were not included in the main summary of the key evidence are listed in the appendix.

Summary of key evidence on maximal effort cytoreductive surgery for advanced ovarian cancer

Study 1 Sundar S (2022)

Study details

Study type	Cohort study (SOCQER-2)
Country	UK, India and Australia
Recruitment period	2015 to 2016
Study population and number	n=247 (113 low surgical complexity score [SCS], 70 intermediate SCS and 64 high SCS) Patients with late-stage ovarian cancer
Age	mean not reported; 104 (42%) patients were older than 65
Patient selection criteria	Patients with suspected or confirmed epithelial ovarian cancer with radiological spread beyond the pelvis and if primary or delayed debulking surgery was planned. Patients having neoadjuvant chemotherapy could be recruited before chemotherapy or immediately before delayed debulking surgery. Patients who did not have FIGO stage-3 or 4 epithelial ovarian cancer on histology following surgery, or who did not have debulking surgery as planned, were subsequently excluded.
Technique	Primary or delayed debulking surgery. The complexity of surgery varied across centres. Low-, intermediate-and high-SCS procedures were done in 46% (113), 28% (70) and 26% (64) of patients, respectively. Surgical complexity was defined using the validated Aletti SCS: low (score 1 to 3), intermediate (score 4 to 7) or high (score 8+). Pancreatic tail resection, cholecystectomy, resection from lesser sac and porta hepatis disease were not included in the original score and were allocated a score of 5.
Follow up	2 years
Conflict of interest/source of funding	SOCQER2 study in the UK was commissioned and funded by the National Institute for Health and Care excellence. The funder had no role in interpretation of results from the study. The SOCQERoOZ study received a research grant from Australian Society of Gynaecologic Oncologists Inc. The SOCQER2 India study was part funded by the Department of Science Technology, India -UKIERI grant and Jiv Daya Foundation, US. Authors have received honoraria, grants or fees outside the submitted work from the following companies or organisations: Astra Zeneca, MSD, GSK, Ethicon, Tesaro, Clovis, Roche, Barts Charity, The Eve Appeal. One author reported royalty from Newcastle University (Clovis Oncology) related to the work of development of rucaparib. This is unrelated to the submitted work.

Analysis

Follow-up issues: The authors stated that there was minimal missing data (more than 99% data fields complete for clinical and surgical information, 88% PROMs response) and minimal loss to follow up in the period up to 12 months after surgery. At 2 years, data were available for 90 patients and 157 patients had either had disease progression or died. The response rates at 18 and 24 months after surgery were lower in the low SCS group (70% at 12 to 18 months and 46% at 24 months) compared with more than 80% in the intermediate and high SCS groups, suggesting a biased response.

Study design issues: Prospective, non-randomised multicentre observational study. Recruitment to the study was done by research nurses. The primary outcome measure was change in the validated patient-reported outcome measure (PROM) questionnaire EORTC QLQ-C30 global score after surgical treatment, measured at 6 weeks, 6 months and 12 months after surgery. Data collection stopped upon disease progression. A sample size of 123 (41 intermediate SCS and 82 extensive SCS), was calculated for 80% power, assuming a 13-point difference in EORTC QLC-30 of clinical importance and a baseline score of 66 (SD 24) in those having high-complexity surgery. Fewer women who had high-complexity surgery and more women who had low-complexity surgery were recruited than expected, reducing the anticipated power regarding the outcomes of high-complexity surgery.

Study population issues: The median PCI at baseline was 11; 34% (85/247) of patients had PCI of 6 or less, 23% (56/247) had a PCI of 7 to 12 and 43% (106/247) had a PCI above 12. Upper abdominal disease was present in 43% (48), 63% (44) and 92% (59) of patients who had low, intermediate or high SCS procedures, respectively (p=0.001). Most patients (70%) had delayed debulking surgery. Among the 30% (75) who had primary debulking surgery, 10 (13%) patients had low, 26 (35%) had intermediate and 39 (52%) had high SCS surgery (p=0.001).

Other issues: The centre in Australia recruited 13 patients (12 with low-SCS surgery and one with intermediate-SCS surgery), but the PCI scores were not available and so those patients were not considered in the analysis of quality of life, as adjustment for disease burden was not possible.

Key efficacy findings

Number of patients analysed: 247

Mean change from baseline in EORTC QLQ-C30 global scores by SCS group

SCS score	6 weeks	6 weeks	12 months	12 months
	Mean	SD	Mean	SD
Low	3.4	1.8 (n=88)	4.3	2.1 (n=51)
Intermediate	4.0	2.1 (n=55)	5.1	2.2 (n=41)
High	4.3	2.1 (n=51)	5.1	2.2 (n=35)
p		0.048		0.133

Patients in the high SCS group had small to moderate decreases in physical (p=0.004), role (p=0.016) and emotional (p=0.001) function at 6 weeks after surgery, which resolved by 6 to 12 months. By 12 months there was no difference in physical and emotional function between the 3 groups.

At 6 weeks follow up, a negative change in EORTC QLQ-C30 global score was reported for 43 (48.9%) patients who had low-SCS surgery, 23 (41.8%) of those who had intermediate-SCS surgery and 19 (35.9%) of

those who had high-SCS surgery. There was a positive change in EORTC QLQ-C30 global score in 23 (26.1%) patients who had low=SCS surgery, 22 (40%) patients who had intermediate-SCS surgery and 23 (44.2%) patients who had high-SCS surgery (p=0.219).

At 12 months follow up, 17 (33.1%) patients who had low-SCS surgery, 8 (19.5%) patients who had intermediate-SCS surgery and 10 (28.6%) of those who had high-SCS surgery had a negative change in EORTC QLQ-C30 global score, whereas 24 (47.1%), 27 (65.9%) and 23 (65.7%) patients, respectively, had a positive change (p=0.180).

In all groups clinically meaningful and statistically significant improvements in physical function were noted at 12 months after surgery. There were no differences between the groups regarding cognitive or social function, both of which improved over time.

Complete macroscopic tumour clearance by SCS group

- Low SCS=55.8% (63/113)
- Intermediate SCS=71.4% (50/70)
- High SCS=62.5% (40/64), p=0.007

Cumulative progression-free survival at 2 years

- Low SCS=34% (95% CI 24.7 to 42.3%)
- Intermediate SCS=47% (95% CI 35.0 to 58.6%)
- High SCS=34% (95% CI 22.4 to 46%), p=0.109

Progression-free survival at 2 years by site of disease

- Pelvic disease only=57% (95% CI 36.8 to 74.4)
- Mid-abdominal disease=49% (95% CI 37.4 to 61.0%)
- Upper abdominal disease=29% (95% CI 21.4 to 36.0%), p=0.001

Progression-free survival at 2 years by residual disease status after surgery

- Residual disease=21%
- No residual disease=47%, p<0.001

Overall survival at 2 years by residual disease status after surgery

- Residual disease=64%
- No residual disease=83%, p<0.001

Key safety findings

- Proportion of patients with at least 1 minor or major complication=30%

- Proportion of patients with grade 3 or higher complication=14.2%
- Mortality=1.2% (3/247); 1 patient who had intermediate SCS surgery developed disseminated intravascular coagulation and multi-organ failure; 1 patient aged 76 years who had low SCS surgery died because of a pulmonary embolism; and 1 patient who had intermediate SCS surgery with intraoperative blood loss of 2 to 3 litres developed intra-abdominal sepsis.

Complication rates by SCS group

- Low SCS=20%
- Intermediate SCS=26%
- High SCS=52%, p<0.001

Complication rates grade 3 or higher by SCS group

- Low SCS=9%
- Intermediate SCS=13%
- High SCS=25%

Study 2 Soo Hoo S (2015)

Study details

Study type	Non-randomised comparative study (Surgery in Ovarian Cancer Quality of life Evaluation Research study [SOCQER 1])
Country	UK
Recruitment period	2011 to 2014
Study population and number	n=88 (32 benign, 32 cancer standard surgery, 24 cancer extensive surgery) Patients having primary surgery for suspected ovarian cancer or delayed debulking surgery for biopsy-confirmed diagnosis of ovarian, primary peritoneal, or fallopian tube cancer
Age	median 62 years
Patient selection criteria	All patients referred to a single Gynaecological Cancer Centre having primary surgery for suspected ovarian cancer or delayed debulking surgery for biopsy-confirmed diagnosis of ovarian, primary peritoneal, or fallopian tube cancer were eligible. Patients who had a planned surgical procedure but at laparotomy were deemed unresectable were not included in the analysis.
Technique	All patients had surgery with an intention to achieve complete cytoreduction. Neoadjuvant chemotherapy (NACT) was used as a standard approach in patients with significant ascites and low albumin level to facilitate surgery and to enhance postoperative recovery and in patients with stage 4 disease. Overall, 20 patients had primary debulking surgery, and 36 patients had platinum-based NACT followed by delayed debulking surgery. Most (88%) of the 56 patients with malignant disease completed 6 cycles of chemotherapy irrespective of aggressiveness of surgical procedure. Standard surgery was done in patients with less disease burden, ranging from FIGO stages 1 to 4 disease, whereas extensive surgery was only done for advanced-stage ovarian cancer (stage 3 and 4 disease).
Follow up	Median 8.5 months
Conflict of interest/source of funding	None

Analysis

Follow up issues: Patient-reported outcome assessment was scheduled preoperatively (baseline), at 6 weeks, and at 3, 6, and 9 months after their surgical procedure. The median questionnaire completion rates in benign, cancer standard, and cancer extensive groups were 53%, 72%, and 58%, respectively.

Study design issues: Small non-randomised feasibility study. The primary aim was to evaluate the feasibility of collecting preoperative, short- and medium-term patient-reported outcomes after extensive debulking surgery and standard surgery. Patient-reported outcome assessment was done using the validated EORTC QLQ-C30

and the ovarian cancer-specific module QLQ-OV28 questionnaires. Complete resection was defined as no visible disease at the end of the operation, whereas less than 1 cm residual disease was defined as optimal debulking; any operation with more than 1 cm residual disease was deemed suboptimal. Patients with benign and borderline tumours who had a standard surgical procedure were classified as benign. Patients with malignant disease were divided into the cancer standard surgery and cancer extensive surgery groups according to their SCS (as described by Aletti et al.) with standard surgery defined by an SCS of 3 or lower and extensive surgery by an SCS of 4 or higher.

Study population issues: Median age, body mass index, preoperative serum CA125 and albumin were comparable across the 3 groups. The median SCS score for the cancer standard surgery group was 2 (range 1 to 3). The median SCS score for the cancer extensive surgery group was 7 (range 4 to 11).

Key efficacy findings

Number of patients analysed: 88 (32 benign, 32 cancer standard surgery, 24 cancer extensive surgery)

- Complete macroscopic cytoreduction = 81% for standard surgery and 71% for extensive surgery
- Median overall survival = 35 months for standard surgery and 26 months for extensive surgery
- The median progression-free survival times = 25 months for standard surgery and 16 months for extensive surgery

Mean quality of life scores across time points, mean (SD)

Clinical outcome	Patient group	Baseline	6 weeks	3 months	6 months	9 months	p value
Global health score	Benign	55.38 (30.01)	73.89 (15.06)	77.63 (15.73)	75.69 (23.15)	70.83 (26.5)	0.26
	Cancer standard	58.33 (21.62)	58.33 (20.59)	55.63 (18.7)	60.91 (18.75)	65.1 (20)	
	Cancer extensive	63.1 (25.63)	63.64 (16.36)	53.89 (14.73)	60.42 (17.96)	63.46 (26.25)	
Functional score	Benign	71.04 (23.31)	80.89 (15.01)	86.13 (13.22)	85.72 (26.44)	79.73 (24.57)	0.13
	Cancer standard	64.71 (28.5)	68.43 (26.67)	67.63 (23.62)	73.16 (26.05)	73.89 (23.14)	
	Cancer extensive	67.94 (24.95)	48.24 (20.29)	58.93 (20.56)	62.73 (18.48)	68.49 (23.21)	
Symptom score	Benign	25.97 (16.84)	17.53 (11.71)	17.22 (10.73)	16.9 (18.87)	18.67 (15.05)	0.19
	Cancer standard	27.74 (20.17)	26.18 (16.46)	28.39 (20.62)	24.96 (17.67)	24.57 (15.89)	
	Cancer extensive	30.35 (21.61)	31.86 (11.89)	33.06 (15.57)	35.03 (17.02)	26.85 (15.12)	

Key safety findings

Surgical morbidity in patients with cancer who had standard or extensive surgery

Outcome	Standard surgery, n=32	Extensive surgery, n=24	p value
Estimated blood loss, ml			
<500	24 (75%)	4 (17%)	
500 to 999	5 (16%)	11 (46%)	
1,000 to 1,500	3 (9%)	9 (38%)	0.0001
>1,500	0 (0%)	0 (0%)	
Intraoperative blood transfusion	0 (0%)	0 (0%)	
Postoperative blood transfusion	2 (6%)	5 (21%)	0.048
Major complications (> grade 2 according to the Memorial Sloan Kettering Cancer Center grading system)			
Splenic tear	2 (6%)	0 (0%)	
Hepatic tear	0 (0%)	2 (8%)	
Bladder injury	0 (0%)	1 (4%)	
Infectious	3 (9%)	5 (21%)	0.6
Gastrointestinal	0 (0%)	1 (4%)	
Cardiopulmonary	0 (0%)	4 (17%)	
Thromboembolic	0 (0%)	0 (0%)	
Median length of stay (range), days	6 (2 to 22)	9 (6 to 17)	

During the study, 7 patients died; 6 because of disease progression and 1 death was caused by a cardiac event within 30 days of surgery in the extensive (ultraradical) surgery group. A further 10 patients had disease recurrence and had further treatment.

Study 3 Cummins C (2022)

Study details

Study type	Cohort study
Country	UK
Recruitment period	2015 to 2016
Study population and number	n=1,471 Patients with ovarian cancer stage 3, 4 or unknown
Age	110 (8%) age 0 to 49, 620 (42%) age 50 to 69, 463 (32%) age 70 to 79, 278 (19%) age 80 and over
Patient selection criteria	Female patients with ovarian cancer stage 3, 4 or unknown were included. Tumours with borderline or sex stromal or germ cell morphologies were excluded.
Technique	Centres were classified into 3 groups based on their SCS; those practicing mainly low complexity, (5/11 centres with more than 70% low SCS procedures, 759 patients), mainly intermediate (3/11, 35 to 50% low SCS, 356 patients), or mainly high complexity surgery (3/11, more than 35% high SCS, 356 patients). Rates of patients who had surgery were 43% in the mainly low SCS group, 58% in the intermediate group and 61% in the mainly high SCS group (p<0.001). Treatment of ovarian cancer was defined as the delivery of systemic anti-cancer therapy ('chemotherapy') or major surgical resection ('surgery') during the primary (first) course of treatment, defined as the 9 months following diagnosis.
Follow up	24 months
Conflict of interest/source of funding	The study received funding from NICE. The authors declared no conflict of interest.

Analysis

Study design issues: The paper describes population level outcomes for Stage 3 and 4 and unstaged ovarian cancer patients managed at the 11 centres in England that participated in the SOCQER2 study described by Sundar et al. (2022; study 1). Data on disease load and surgical procedures performed, which was available for those patients recruited to the SOCQER2 study, was used to derive a SCS for each patient. These scores were used to categorise centres by patterns of surgical practice (mainly low complexity, mainly intermediate and mainly high complexity surgery).

Study population issues: Age and morphology distribution across the cohort were similar with no statistically significant differences between the 3 SCS groups. There were statistically significant differences in deprivation (p=0.002), with the mainly low SCS group having fewer deprived patients. Differences in stage were also noted (p=0.001), with the mainly low SCS group having more unstaged patients and Stage 3 patients. The proportion of patients who were offered bevacizumab was similar across the 3 groups.

Other issues: residual disease data were not available for analysis in this cohort.

Key efficacy findings

Number of patients analysed:1,471

Median survival

- Mainly high SCS centres=23.1 months (95% CI 19.0 to 27.2)
- Mainly intermediate SCS centres=22.0 months (95% CI 17.6 to 26.3)
  Mainly low SCS centres=17.9 months (95% CI 15.7 to 20.1)

In an age and deprivation quintile adjusted by the Cox proportional hazards model, the hazard of death increased steeply with age (4.83, 95% CI 3.62 to 6.44) in patients aged 80 and over compared with patients aged less than 50 and in patients whose area of residence was in the highest Area Income Deprivation quintile relative to those in the first deprivation quintile (1.24, 95% CI 1.04 to 1.40).

Compared to patients in the high SCS centres, patients in the low SCS group centres had a hazard ratio of 1.21 (95% CI 1.04 to 1.40) for death.

Analysis of treatment by centre SCS pattern

Treatment	Mainly low SCS centres, n (%)	Mainly intermediate SCS centres, n (%)	Mainly high SCS centres, n (%)
No surgical resection or chemotherapy	217 (28.6)	94 (26.4)	93 (26.1)
Chemotherapy only	214 (28.2)	54 (15.2)	83 (23.3)
Surgical resection only	25 (3.3)	20 (5.6)	41 (11.5)
Surgical resection and chemotherapy	303 (39.9)	188 (52.8)	139 (39.0)
Total	759	356	356
% in each surgical centre grouping	51.6%	24.2%	24.2%

In logistic regression analysis, women aged 70 to 79 were much less likely (OR 0.30, 95% CI 0.20 to 0.48) and women aged 80 or over were very unlikely to undergo both surgery and chemotherapy (OR 0.05, 95% CI 0.03 to 0.09). Receiving both chemotherapy and surgery was strongly associated with age ($p<0.001$).

Key safety findings

No safety outcomes were reported.

Study 4 Dahm Kahler P (2021)

Study details

Study type	Cohort study
Country	Sweden
Recruitment period	2008 to 2016
Study population and number	n=3,728 (1,746 before and 1,982 after national guidelines were published) Women with primary stage 3C or 4 cancer of the ovary, fallopian tube, peritoneum or undesignated primary site
Age	Mean 67.4 years (range 20 to 100)
Patient selection criteria	The study included all women aged 18 or over, registered in the Swedish Quality Registry for Gynecologic Cancer 2008 to 2011 or 2013 to 2016 for primary stage 3C or 4 cancer of the ovary, fallopian tube, peritoneum or undesignated primary site. The year 2012 was excluded because the speed of implementation of the national guidelines varied across the country. Patients who did not have surgery were also included.
Technique	Patients had primary (n=1,803) or interval (n=723) debulking surgery. The guidelines recommended primary debulking surgery (to R0 if achievable) followed by standard chemotherapy. Recommended standard chemotherapy consisted of combination therapy, carboplatin and paclitaxel every 3 weeks for 6 cycles. Recommendations for neoadjuvant chemotherapy included standard chemotherapy for 2 to 3 cycles before interval debulking surgery, followed by an additional 3 to 4 cycles. In June 2015 bevacizumab was recommended to high risk groups. More complex surgical procedures were done after the implementation of the guidelines.
Follow up	Mean 33 months (range 0 to 135 months)
Conflict of interest/source of funding	None

Analysis

Follow up issues: Patients were followed up until 30 April 2019, or until death, whichever came first. Missing data was more common during the first study period and more pronounced with some of the variables, such as details on medical oncology treatment. Missing data for primary treatment was similar in the 2 cohorts (about 5%).

Study design issues: Population-based register study using data from the Swedish Quality Registry for Gynecologic Cancer. The aim of the study was to evaluate relative survival related to the choice of primary treatment and surgical outcome following the implementation of the first Swedish national guidelines for ovarian cancer, published in 2012. The cohort of patients treated between 2008 to 2011 was compared with those treated between 2013 to 2016. Mortality data for the general population in Sweden was used to estimate expected survival rates for the study population.

IP overview: Maximal effort cytoreductive surgery for advanced ovarian cancer

Study population issues: There were no statistically significant differences in age or stage distribution between the 2 cohorts at baseline. The mean follow up period was statistically significantly longer in the earlier cohort of patients compared to the later cohort.

Other issues: The use of the angiogenetic inhibitor bevacizumab increased during the study period. The use of PARP-inhibitors was introduced in Sweden in 2017 and some patients may have been offered them and not yet registered.

Key efficacy findings

Number of patients analysed: 3,728 (1,746 treated 2008 to 2011 and 1,982 treated 2013 to 2016)

- After adjusting for age and stage, survival improved in 2013 to 2016 compared with 2008 to 2011 (excess mortality rate ratio 0.89; 95% CI 0.82 to 0.96, p<0.05).

Primary debulking surgery

- Median overall survival for patients who had primary debulking surgery
  - Cohort 1=35 months (95% CI 32.8 to 39.2)
  - Cohort 2=43 months (95% CI 40.9 to 46.4)
- The median survival of the complete cohort where R0 was achieved was 59.0 months (95% CI 53.6 to 66.1) compared with 32.5 months (95% CI 29.9 to 34.6) for R>0
- 5-year relative survival for patients who had primary debulking surgery
  - Cohort 1=29.6% (95% CI 26.8 to 32.8)
  - Cohort 2=37.4% (95% CI 33.6 to 41.7)
- The excess mortality rate ratio was 0.83 after implementation (95%CI 0.76 to 0.91, p<0.001) compared to before.
- For the cohort with residual tumor, the excess mortality rate ratio was 2.16 (95% CI 1.88 to 2.49, p<0.001) compared to the R0 cohort.

Neoadjuvant chemotherapy and interval debulking surgery

- Median overall survival for patients who had interval debulking surgery
  - Cohort 1=29 months (95% CI 26.8 to 33.9)
  - Cohort 2=35 months (95% CI 31.9 to 37.6)
- The median survival of the complete cohort where R0 was achieved was 41.2 months (95% CI 36.1 to 46.4) compared with the cohort of R>0 of 27.5 months (95% CI 25.5 to 30.6)
- 5-year relative survival for patients who had interval debulking surgery
  - Cohort 1=17.5% (95% CI 13.8 to 22.2)
  - Cohort 2=20.7% (95% CI 15.9 to 27.1)
- The excess mortality rate ratio was 0.89 after implementation (95% CI 0.78 to 1.00, p=0.058) compared to before.
- For the cohort with residual tumor, the excess mortality rate ratio was 1.68 (95% CI 1.39 to 2.03, p<0.001) compared to the R0 cohort.

Chemotherapy alone

- The proportion of patients who had chemotherapy alone increased from 9.2% in cohort 1 to 17.6% in cohort 2.

- 5-year relative survival was 7.3% (95% CI 4.0 to 13.4) before and 7.1% (95% CI 3.5 to 14.3) after implementation.
- The median survival was 11 months (95% CI 9.5 to 18.7) before, compared to 17 months (95% CI 14.7 to 19.4) after.

Surgical complexity and completeness of resection

Variable, number of patients (%)	Primary debulking surgery, cohort 1, n=968	Primary debulking surgery, cohort 2, n=835	p value	Interval debulking surgery, cohort 1, n=334	Interval debulking surgery, cohort 2, n=389	p value
Surgical complexity						
Peritoneal Diaphragmal resection	38 (3.9%)	242 (29.0%)	<0.001	10 (3.0%)	58 (14.9%)	<0.001
Intestinal resections	56 (5.8%)	272 (32.6%)	<0.001	18 (5.4%)	71 (18.3%)	<0.001
Splenectomy	15 (1.5%)	117 (14.0%)	<0.001	6 (1.8%)	37 (9.5%)	<0.001
Pelvic Lymph Node Dissection	21 (2.2%)	93 (11.1%)	<0.001	4 (1.2%)	9 (2.3%)	0.40
Paraaortal Lymph Node Dissection	22 (2.3%)	89 (10.7%)	<0.001	6 (1.8%)	7 (1.8%)	1.0
Postoperative residual tumour			<0.001			<0.001
0 mm	224 (28.9%)	430 (53.3%)		105 (36.8%)	177 (50.1%)	
1 mm to 10 mm	216 (27.9%)	149 (18.5%)		61 (21.4%)	74 (21.0%)	
>10 mm	296 (38.2%)	207 (25.7%)		86 (30.2%)	90 (25.5%)	
Not evaluable	38 (4.9%)	21 (2.6%)		33 (11.6%)	12 (3.4%)	
Missing	194	28		49	36	

Key safety findings

No safety outcomes were reported.

Study 5 Falconer H (2020)

Study details

Study type	Cohort study
Country	Sweden
Recruitment period	2009 to 2011 (cohort 1) and 2014 to 2016 (cohort 2)
Study population and number	n=752 (364 in cohort 1 and 388 in cohort 2 [after paradigm shift to upfront and aggressive ultra-radical surgery]) Women with advanced epithelial ovarian cancer
Age	mean not reported
Patient selection criteria	Patients with FIGO stages 3 and 4 epithelial ovarian/fallopian tube/peritoneal cancer and cancer in the abdomen of unknown origin (epithelial ovarian cancer without a biopsy specifically from the adnexa). Exclusion criteria in cohort 2: Eastern Cooperative Oncology Group above 2, aged over 80, involvement of tumour in the root of the mesentery (with risk of resection of the superior mesenteric artery and/or vein), involvement of tumour in the pancreas, in more than just the pancreatic tail, tumour involvement of the superior mesenteric artery, coeliac trunk, portal vein, duodenum and the hepatoduodenal ligament (superficial carcinomatosis excluded), involvement of tumour in the lesser omentum with need of resection of left gastric artery (leading to gastrectomy if also splenectomy is performed), disseminated carcinomatosis in the small bowel with need of resection leading to short bowel syndrome, multiple lung metastases bigger than 1 cm, multiple liver metastasis or metastases in both liver lobes, non-resectable extra-abdominal lymph nodes, patient does not accept blood transfusion, patient does not accept stoma formation, massive comorbidity where the surgeon decides the patient inoperable or the anaesthetist decides the patient not eligible for general anaesthesia, serum albumin less than 20 g/l.
Technique	In the first cohort, surgery was done by gynaecologic oncologists, gynaecologists without training in surgical gynaecologic oncology and, in selected cases, by colorectal surgeons. There was no structured surgical management, no uniform preoperative work-up or structured postoperative management. In the second cohort, the aim was that all surgery was done independently by surgical gynaecologic oncologists. If achieving residual disease of less than 1 cm was deemed impossible at time of surgery in FIGO stage 3, surgery was discontinued except for histological verification of disease including ovarian biopsy. For FIGO stage 4, surgery was discontinued if complete resection was deemed impossible. The median SCS increased in cohort 2 from 3 to 7 (p=0.001), and the proportion of ultra-radical procedures increased.
Follow up	Median 29 months (cohort 1) and 27 months (cohort 2)
Conflict of interest/source of funding	None

IP overview: Maximal effort cytoreductive surgery for advanced ovarian cancer

Analysis

Follow up issues: median follow up was similar in the 2 cohorts.

Study design issues: registry based observational cohort study, using data from the Swedish Quality Registry of Gynecologic Cancer (with complete coverage of patients with epithelial ovarian cancer). The main aim was to assess overall survival after a structured shift to an ultra-radical upfront surgical treatment algorithm and to investigate changes in the distribution of primary treatments after this shift. The main outcome measure was 5-year overall survival.

Study population issues: The median age for each primary treatment modality was similar, except for chemotherapy only, where the median age was higher in cohort 2 ($p<0.01$). Consolidating Bevacizumab was only offered to patients in the second cohort ($p<0.01$), and only patients in the second cohort had consolidating PARP-inhibitor ($p<0.001$) in second line treatment. Of the 752 patients, 528 (70%) had surgery.

Other issues: there was no analysis of postoperative morbidity. The authors noted that survival after complete resection in the study differs substantially from previous studies and reflects the impact of an entire population on the outcomes.

Key efficacy findings

Number of patients analysed: 752 (364 cohort 1, 388 cohort 2)

- The proportion of patients in whom complete resection was achieved, increased in cohort 2 from 37 to 67% ($p\leq0.001$).
- In patients who had upfront surgery the period between surgery and start of adjuvant chemotherapy decreased in cohort 2 from 35 to 30 days ($p=0.001$).
- There was an 11% decrease in surgically treated patients in cohort 2 (from 75% to 66%) ($p<0.001$) and a corresponding increase in non-surgically treated patients (24% compared with 33%).

Overall survival

- There was no difference in total 5-year overall survival irrespective of treatment modality (Hazard Ratio [HR] 1.03, 95% CI 0.87 to 1.22; $p=0.75$).

- The subgroup of patients with high SCS had inferior survival in the second cohort, HR 1.99 (95% CI 1.12 to 3.56)

- Median overall survival for patients who did not have surgical treatment
  - Cohort 1=8 months
  - Cohort 2=12 months, HR 0.76 (95% CI 0.58 to 1.01; $p=0.06$).
- Median overall survival for patients who had surgical treatment
  - Cohort 1=39 months
  - Cohort 2=39 months, HR 0.94 (95% CI 0.75 to 1.18; $p=0.59$)

- Median overall survival for patients with residual disease at end of surgery
  - Cohort 1=29 months

  - Cohort 2=23 months, HR 1.33 (95% CI 0.99 to 1.80; p=0.06)
- Median overall survival for patients in whom radical resection was achieved
  - Cohort 1=58 months
  - Cohort 2=55 months, HR 1.31 (95% CI 0.89 to 1.92; p=0.17)

- When adjusting for age, stage, timing of surgery, SCS, complete resection and histology, surgically treated patients in the second cohort had a statistically significantly higher hazard of death, HR 1.40, (95% CI 1.07 to 1.84; p=0.02). Non-surgically treated patients in the second cohort had a non-statistically significant lower hazard of death, HR 0.85 (95% CI, 0.72 to 1.02; p=0.09), adjusted for age and stage.

Frequency of ultra-radical procedures to achieve complete resection of tumour by cohort (where radical resection was accomplished)

Procedure and surgical complexity, no. (%) (if not stated otherwise)	Cohort 1, n=101	Cohort 2, n=172	p value
Diaphragmatic resection/stripping	10 (9.9)	99 (57.6)	<0.001
Posterior modified exenteration	18 (17.8)	62 (36.0)	0.001
Splenectomy	5 (5.0)	44 (25.6)	<0.001
Large bowel resection apart from posterior modified exenteration	14 (13.9)	31 (68.9)	0.40
Stoma in total	13 (12.9)	20 (11.6)	0.85
Small bowel resection	7 (6.9)	37 (21.5)	0.001
Lymph node resection above renal veins	2 (2.0)	16 (9.3)	0.02
Cardiophrenic lymph node resection	0 (0)	24 (14.0)	<0.001
Cholecystectomy	0 (0)	22 (12.8)	<0.001
Resection of distal pancreas	2 (2.0)	0 (0)	0.14
SCS, median (IQR)	3 (2 to 6)	7 (4 to 10.5)	<0.001
SCS group (according to Mayo clinic SCS)			
Low (3 or less)	57 (56.4)	35 (20.3)	<0.001
Medium (4 to 7)	28 (27.7)	60 (34.9)	0.23
High (8 or more)	16 (15.8)	77 (44.8)	<0.001
Time from diagnosis to death, no. (%)			
Within 30 days	1 (1.0)	0	0.37
Within 60 days	1 (1.0)	0	0.37
Within 90 days	1 (1.0)	1 (0.6)	0.47

Key safety findings

No safety outcomes were reported.

Study 6 Horowitz N (2015)

Study details

Study type	Cohort study (retrospective analysis of chemotherapy trials)
Country	US
Recruitment period	Not reported
Study population and number	n=2,655 (low surgical complexity score=456, moderate=1,770 and high=429) Patients with advanced epithelial ovarian cancer or primary peritoneal cancer who had primary cytoreductive surgery to achieve complete surgical resection or less than 1 cm of residual disease
Age	Mean or median not reported
Patient selection criteria	Inclusion criteria: patients with FIGO stage 3 or 4 histologically confirmed epithelial ovarian cancer or primary peritoneal cancer who were enrolled onto the Gynecologic Oncology Group 182 study.
Technique	All patients had primary cytoreductive surgery before being randomly assigned to 1 of 5 platinum and paclitaxel–based chemotherapy regimens. Surgical complexity was based on a complexity score, calculated using a published scoring system. Each procedure was assigned a weighted score ranging from 1 to 3, and the composite surgical complement was calculated by summing the weights for each patient. Patients were classified into 3 groups: SCS low (score 1 to 3), SCS moderate (score 4 to 7), or SCS high (score 8 or above).
Follow up	Not reported
Conflict of interest/source of funding	None

Analysis

Study design issues: All patient data for the study were abstracted from a previous prospective, multicentre trial comparing different chemotherapy regimens (Gynecologic Oncology Group–182) case report forms. The main aims were to examine the effects of disease burden, complex surgery, and residual disease status on progression-free and overall survival in patients with advanced epithelial ovarian cancer or primary peritoneal cancer and complete surgical resection or less than 1 cm of residual disease after surgical cytoreduction. Progression-free survival was defined as the number of months from date of random assignment in Gynecologic Oncology Group 182 to documentation of disease progression or death, whichever came first. Overall survival was defined as the number of months between date of entry and death resulting from any cause. Patients who were still alive or alive and progression free were censored at the date of last follow-up. Initial site of disease was used to develop the preoperative disease score (low score, with pelvic and retroperitoneal spread; moderate score, with additional spread to the abdomen but sparing the upper abdomen; or high score, with upper abdominal disease affecting the diaphragm, spleen, liver, or pancreas)

Study population issues: Groups stratified by disease score included 173 low score, 845 moderate and 1,636 high score. Patients with higher disease score tended to be older than those in lower disease burden

groups (p=0.005). Of the 2,655 patients, 32% (860) had complete resection and 68% (1,795) had <1 cm of residual disease. Patients with higher surgical complexity tended to have poorer performance status (p=0.011), stage 4 disease (p=0.001), and ascites (p=0.001) compared with patients with less extensive surgery. SCS was not associated with age, adjuvant chemotherapy type, or frequency of discontinuation.

Other issues: No statistically significant treatment effects on progression-free survival or overall survival were found among the different treatment chemotherapy regimens in the original study.

Key efficacy findings

Number of patients analysed: 2,655

Median progression-free survival by disease distribution

- Low disease score=33.9 months
- Moderate disease score=23.4 months
- High disease score=15.1 months, p<0.01

Median overall survival by disease distribution

- Low disease score=86.3 months
- Moderate disease score=70.8 months
- High disease score=40.2 months, p<0.01

Median progression-free survival by completeness of resection

- Complete resection=28.9 months
- Residual disease=15.3 months, p<0.01

Median overall survival by completeness of resection

- Complete resection=76.9 months
- Residual disease=40.6 months, p<0.01

Median progression-free survival by SCS

- Low SCS=18.5 months
- Moderate SCS=18.0 months
- High SCS=14.9 months, p<0.01

Median overall survival by SCS

- Low SCS=48.7 months
- Moderate SCS=48.4 months
- High SCS=44.2 months, p=0.191

Association of SCS with resection status

- Those with high SCS were statistically significantly more likely to have complete resection than those with low SCS (OR 4.17, 95% CI 2.30 to 7.56; p<0.01) or moderate SCS (OR 2.66, 95% CI 1.91 to 3.70; p<0.01).
- About 40% of the patients with high disease score who had complete resection had high SCS. Within the group of patients with low or moderate disease scores, SCS was not a differentiating factor for obtaining complete resection (p=0.76 overall).

Association of disease score with survival in patients with complete resection

- In patients with a complete resection, those with an initial high disease burden still had a worse progression-free survival (median 18.3 months compared with 33.2 months for those with low or moderate disease scores, p<0.001) and overall survival (median 50.1 months compared with 82.8 months for those with low or moderate disease scores, p<0.001) than patients starting with smaller volume disease.
- The progression-free survival in the 199 patients with high disease score and complete resection was 18.3 months compared with 14.8 months in those who had <1 cm residual disease (p<0.001). Overall survival was 50.1 months in those with complete resection and 39.5 months in those with <1 cm residual disease (p<0.001).

Predictors of survival identified in multivariable analysis

- The mutually contingent effects of disease score and residual disease were statistically significant predictors of progression-free survival and overall survival.
- After controlling for disease score, residual disease, an interaction term for disease stage and SCS, performance status, age, and cell type, SCS was not an independent predictor of either progression-free survival or overall survival.

Key safety findings

No safety outcomes were reported.

Study 7 Tseng J (2018)

Study details

Study type	Cohort study
Country	US
Recruitment period	2001 to 2013
Study population and number	n=978 (Group 1: 2001 to 2005, n=315; group 2: 2006 to 2009, n=320; group 3: 2010 to 2013, n=343) Patients with advanced ovarian cancer who had primary debulking surgery
Age	Median 61 years (range 19 to 95 years)
Patient selection criteria	All patients with FIGO 2009 stage 3b to 4 ovarian, fallopian tube or primary peritoneal carcinoma, who had primary debulking surgery at a single centre with the intent of maximal cytoreduction between 1/1/2001 and 31/12/2013. Patients who had exploratory laparotomy for anticipated debulking but who were ultimately declared unresectable due to extensive disease burden, were still included in the analysis. The study was restricted to high-grade epithelial histologies. Those who had neoadjuvant chemotherapy or presented for management of recurrent disease were excluded.
Technique	In 2001, extensive upper abdominal procedures started to be incorporated into the debulking armamentarium. In 2006, the goal for primary debulking surgery evolved from residual disease 10 mm or less to either complete gross resection or as minimal residual tumour as possible. During 2010 to 2013, 3 additional changes were gradually adopted: routine performance of cardiophrenic lymph node resection, use of specific selection criteria for neoadjuvant chemotherapy, and implementation of earlier operative start times. Almost all patients had postoperative primary platinum/taxane-based chemotherapy (n=949, 99%). Intraperitoneal chemotherapy was administered in 34% (n=322) of patients.
Follow up	Median 77.7 months (range 1.3 to 198 months)
Conflict of interest/source of funding	Outside the submitted work, 1 author is on the Medical Advisory Boards of Bovie Medical Co. and Verthermia Inc. The other authors have no conflict of interest.

Analysis

Follow up issues: the paper states that 3 patients were excluded from the denominator for 90-day all-cause mortality data because of short follow up.

Study design issues: Retrospective single centre cohort study, using the Memorial Sloan Kettering Cancer Center Gynecology Service database to identify patients. Records for individual patients were reviewed and clinical variables were abstracted. The study timeline was divided into 3 periods based on the implementation of changes in the approach to ovarian cancer debulking, and patients were stratified into groups based on the year of their primary surgery: 2001 to 2005 (Group 1, n=315), 2006 to 2009 (Group 2, n=320), and 2010 to

2013 (Group 3, n=343). Complete gross resection was defined as no visible disease remaining at the end of the surgical procedure. Minimal residual disease was defined as one or more tumour nodules 1 to 10 mm in maximal dimension remaining at the completion of surgery, and suboptimal debulking was defined as any residual tumour nodule more than 10 mm in maximal dimension remaining at the completion of surgery.

Study population issues: Of the 978 patients, 794 (81%) had stage 3 disease (stage 3b, n=33 [3%]; stage 3c, n=761 [78%]), and 19% (n=184) had stage 4 disease. Most patients had disease of serous histology (n=869, 89%). Among those with known BRCA status, 28% (n=144) had a BRCA mutation. 81% (n=792) of patients had carcinomatosis and 60% (n=585) had bulky upper abdominal disease. Compared to Group 1, those who had primary debulking surgery during the latter 2 time periods had higher American Society of Anesthesiologists scores (p<0.001), higher-stage disease (p<0.001), and more often had carcinomatosis (p=0.015) and bulky UAD (p=0.009). There was no statistically significant difference in age, preoperative serum albumin, histology, or rates of postoperative chemotherapy use between groups.

Other issues: although postoperative chemotherapy regimens were all platinum/taxane-based, exact regimens were variable. Perioperative care and postoperative treatment were standardised.

Key efficacy findings

Number of patients analysed: 978

- Complete gross resection rates=42% (408/978)
  - Group 1 (2001 to 2005)=29% (92/315)
  - Group 2 (2006 to 2009)=40% (129/320)
  - Group 3 (2010 to 2013)=55% (187/343), p<0.001
- Median progression-free survival=18.2 months (95% CI 17.3 to 19.9 months)
  - Group 1=16.9 months
  - Group 2=17.3 months
  - Group 3=21.1 months
- 5-year progression-free survival=16.9% (95% CI 14.6 to 19.4%)
  - Group 1=15%
  - Group 2=16%
  - Group 3=20%, p=0.199
- Median overall survival=55.4 months (95% CI 52 to 59.6 months)
  - Group 1=49.4 month
  - Group 2=53.7 months
  - Group 3=68 months
- 5-year overall survival rate=46.5% (95% CI 43.3 to 49.7%)
  - Group 1=40%
  - Group 2=44%
  - Group 3=56%, p<0.001

Suboptimal debulking rates decreased over time in those with the highest tumour burden from 36% (Group 1) to 18% (Group 3).

Progression-free survival stratified by residual disease

Residual disease	Median progression-free survival, months (95% CI)	5-year progression-free survival rate (85% CI)	Hazard ratio (95% CI)	p value
Complete gross resection	26.5 (24 to 29.1)	25.3% (21 to 29.7%)	1	<0.001
Minimal residual	16.5 (14.9 to 18.2)	12.9% (9.7 to 16.5%)	1.66 (1.42 to 1.94)	
Suboptimal	12.6 (11.2 to 14.2)	7.3% (4.2 to 11.5%)	2.61 (2.17 to 3.14)	

Overall survival stratified by residual disease

Residual disease	Median overall survival, months (95% CI)	5-year overall survival rate (85% CI)	Hazard ratio (95% CI)	p value
Complete gross resection	79.1 (68.7 to 87.1)	59.3% (54.1 to 64%)	1	<0.001
Minimal residual	52.5 (48.8 to 58.4)	42.8% (37.6% to 47.8%)	1.68 (1.41 to 2)	
Suboptimal	36.6 (32.1 to 40.2)	27.4% (21.2% to 33.9%)	2.58 (2.11 to 3.17)	

On multivariable analysis, complete gross resection was independently associated with progression-free survival (p<0.001) and overall survival (p<0.001).

Key safety findings

- 30-day all-cause mortality=0.4% (4/978)
  - Group 1=0.6%
  - Group 2=0.6%
  - Group 3=0%, p value not reported
- 90-day all-cause mortality=1.3% (13/975)
  - Group 1=2.9%
  - Group 2=1.3%
  - Group 3=0%, p=0.002
- Major (grade 3 to 5) complications=15% (148/978)
  - Group 1=13% (41/315)
  - Group 2=16% (51/320)
  - Group 3=16% (56/343), p=0.440

Study 8 Angeles M (2022)

Study details

Study type	Cohort study
Country	France and Spain
Recruitment period	2008 to 2015
Study population and number	n=549 Patients who had primary, interval or closure debulking surgery with either complete cytoreduction or cytoreduction to minimal residual disease for Stage 3c to 4 epithelial ovarian, fallopian, or primary peritoneal cancer
Age	Median 61 years (range 21 to 88 years)
Patient selection criteria	Exclusion criteria: patients with unresectable disease, with residual disease 2.5 mm or more and patients with non-epithelial subtype histology or borderline tumours.
Technique	All surgical procedures were done or supervised by experienced oncological surgeons. The surgical goal was to achieve absence of residual disease, evaluated with the completeness of cytoreduction score. Hysterectomy and bilateral salpingooophorectomy, infragastric omentectomy and pelvic plus paraaortic lymphadenectomy were systematically done during debulking surgery.
Follow up	Median 65 months
Conflict of interest/source of funding	None

Analysis

Study design issues: Retrospective multicentre study, assessing the impact on survival of major postoperative complications and to identify the factors associated with these complications in patients with advanced ovarian cancer after cytoreductive surgery. Patients were divided into 3 groups according to the timing of their surgery: primary surgery and 6 cycles of adjuvant chemotherapy (primary debulking surgery); interval debulking surgery after 3 to 4 cycles of neoadjuvant chemotherapy, then 2 to 3 cycles of adjuvant chemotherapy to achieve a total of 6 cycles (early interval debulking surgery); and delayed debulking surgery after 6 cycles of neoadjuvant chemotherapy. Surgical complexity was quantified using the Aletti score, with a value of 8 or above corresponding to high complexity.

Study population issues: 66% (355/537) of patients were classified as World Health Organization performance status 0 at baseline. Of the 549 patients, 107 (19.5%) had bevacizumab. No maintenance treatment with poly (adenosine diphosphate–ribose) polymerase (PARP) inhibitors was administered during the study period.

Other issues: the timing of initiation of adjuvant chemotherapy and the possible need for dose reductions, which can both have an impact on survival, were not recorded. Some factors that may increase the risk of postoperative complications, such as nutritional status, comorbidities, and smoking, were not assessed.

Key efficacy findings

- Number of patients analysed: 549
- Median disease-free survival
  - Whole cohort=19.4 months (95% CI 18.1 to 20.6)
  - Patients with major surgical complications=16.9 months (95% CI 13.7 to 18.4)
  - Patients without major surgical complications=20.1 months (95% CI 18.6 to 22.4), p=0.012
- Median overall survival
  - Whole cohort= 56.3 months (95% CI 50.2 to 67.4)
  - Patients with major surgical complications=48.0 months (95% CI 37.2 to 73.1)
  - Patients without major surgical complications=56.7 months (95% CI 51.2 to 70.4), p=0.112

Univariable and multivariable analyses for disease-free survival

Variable	Univariable			Multivariable		
	HR	95% CI	p value	HR	95% CI	p value
Age at diagnosis						
≤60 years	1.00					
>60 years	1.07	0.89 to 1.29	0.445			
Surgical timing						
Primary	1.00			1.00		
Early interval	1.51	1.21 to 1.89	<0.001	1.53	1.22 to 1.92	<0.001
Delayed	1.43	1.12 to 1.83		1.65	1.27 to 2.15	<0.001
FIGO stage						
3c	1.00			1.00		
4	1.27	1.01 to 1.60	0.044	1.18	0.93 to 1.50	0.185
PCI						
≤10	1.00			1.00		
>10	1.52	1.26 to 1.83	<0.001	1.40	1.11 to 1.75	0.004
Aletti score						
<8	1.00			1.00		
≥8	1.35	1.12 to 1.62	0.002	1.23	0.98 to 1.53	0.071
Completeness of cytoreduction						
0 (no residual tumour)	1.00			1.00		

1 (residual <2.5 mm)	1.56	1.19 to 2.04	0.001	1.49	1.13 to 1.95	0.004
Postoperative complications						
Less than Grade 3	1.00			1.00		
Grade 3 or higher	1.32	1.06 to 1.64	0.012	1.35	1.07 to 1.69	0.010

Univariable and multivariable analyses for overall survival

Variable	**Univariable**			**Multivariable**		
	HR	**95% CI**	**p value**	**HR**	**95% CI**	**p value**
Age at diagnosis						
≤60 years	1.00					
>60 years	1.20	0.95 to 1.51	0.125			
Surgical timing						
Primary	1.00			1.00		
Early interval	1.60	1.19 to 2.14	<0.001	1.65	1.23 to 2.23	0.001
Delayed	1.73	1.27 to 2.35		2.04	1.47 to 2.81	<0.001
FIGO stage						
3c	1.00					
4	1.01	0.75 to 1.37	0.953			
PCI						
≤10	1.00			1.00		
>10	1.43	1.13 to 1.80	0.002	1.34	1.02 to 1.77	0.038
Aletti score						
<8	1.00			1.00		
≥8	1.33	1.05 to 1.67	0.017	1.25	0.96 to 1.63	0.103
Completeness of cytoreduction						
0 (no residual tumour)	1.00			1.00		
1 (residual <2.5 mm)	1.49	1.08 to 2.04	0.013	1.34	0.97 to 1.86	0.078
Postoperative complications						
Less than Grade 3	1.00			1.00		

Grade 3 or higher	1.25	0.95 to 1.64	0.112	1.31	0.99 to 1.74	0.056

Key safety findings

- Deaths caused by postoperative complications (Clavien Dindo grade 5) = 1.8% (10/549)
- Overall rate of major complications (Clavien Dindo grade 3 to 5) = 22.4% (123/549)
- Overall rate of minor complications (Clavien Dindo grade 1 to 2) = 31.9% (175/549)
- Type of major complication
  - Digestive=9.3% (51/549)
  - Infectious=8.9% (49/549)
  - Respiratory=5.1% (28/549)
  - Abdominal wall=4.4% (24/549)
  - Lymphatic=3.5% (19/549)
  - Haemorrhagic=3.3% (18/549)
  - Urinary or renal=2.4% (13/549)
  - Cardiac event=1.8% (10/549)
  - Neurological event=0.4% (2/549)
- More than 1 type of major complication=12.0% (66/549)
- There were no statistically significant differences in baseline characteristics between patients with or without major postoperative complications.

Surgical data and adjuvant treatment of patients according to occurrence of major postoperative complications

Variable	Total (n=594)	Patients without major surgical complications (n=426)	Patients with major surgical complications (n=123)	p value
Surgical timing, n (%)				0.007
Primary	175 (31.9)	125 (29.3)	50 (40.7)	
Early interval	224 (40.8)	172 (40.4)	52 (42.3)	
Delayed	150 (27.3)	129 (30.3)	21 (17.1)	
PCI, n (%)				0.003
10 or lower	287 (52.9)	237 (56.3)	50 (41.0)	
Above 10	256 (47.1)	184 (43.7)	72 (59.0)	
Surgical procedure, n (%)				
Hysterectomy	491 (89.4)	378 (88.7)	113 (91.9)	0.319
Salpingoophorectomy	502 (91.4)	385 (90.4)	117 (95.1)	0.098
Pelvic lymphadenectomy	495 (90.2)	383 (89.9)	112 (91.1)	0.706
Aortic lymphadenectomy	488 (88.9)	380 (89.2)	108 (87.8)	0.664

Infragastric omentectomy	540 (98.4)	419 (98.4)	121 (98.4)	1.000
Small bowel resection	44 (8.0)	28 (6.6)	16 (13.0)	0.021
Large bowel resection	225 (41.0)	157 (36.9)	68 (55.3)	<0.001
If large bowel resection, rectosigmoid resection (n=225)	204 (90.7)	139 (88.5)	65 (95.6)	0.095
Multiple bowel resection	48 (8.7)	29 (6.8)	19 (15.4)	0.003
Diaphragmatic stripping	330 (60.1)	246 (57.7)	84 (68.3)	0.035
Right diaphragmatic stripping	327 (59.6)	243 (57.0)	84 (68.3)	0.025
Left diaphragmatic stripping	163 (29.7)	112 (26.3)	51 (41.5)	0.001
If diaphragm stripping, diaphragm resection (n=330)	72 (21.8)	53 (21.5)	19 (22.6)	0.837
Atypical hepatic resection	15 (2.7)	11 (2.6)	4 (3.3)	0.753
Cholecystectomy	45 (8.2)	27 (6.3)	18 (14.6)	0.003
Celiac lymph node resection	65 (11.8)	48 (11.3)	17 (13.8)	0.440
Splenectomy	127 (23.1)	80 (18.8)	47 (38.2)	<0.001
Distal pancreatectomy	31 (5.6)	18 (4.2)	13 (10.6)	0.007
Partial gastrectomy	11 (2.0)	9 (2.1)	2 (1.6)	1.000
Extensive peritonectomy	256 (46.6)	177 (41.5)	79 (64.2)	<0.001
Glissonectomy	46 (9.8)	30 (8.4)	16 (14.3)	0.069
Mesentery or bowel vaporisation	125 (22.8)	91 (21.4)	34 (27.6)	0.143
Partial abdominal wall resection	100 (18.2)	79 (18.5)	21 (17.1)	0.710
Partial cystectomy/ureteral resection	8 (1.5)	7 (1.6)	1 (0.8)	0.691
Cardiophrenic lymph node resection	10 (1.8)	9 (2.1)	1 (0.8)	0.470
Inguinal lymph node resection	13 (2.4)	6 (1.4)	7 (5.7)	0.012
Axillary lymph node resection	2 (0.4)	2 (0.5)	0 (0)	1.000
Completeness of cytoreduction score				0.701
0 (no residual tumour)	481 (87.6)	372 (87.3)	109 (88.6)	
1 (residual disease less than 2.5 mm)	68 (12.4)	54 (12.7)	14 (11.4)	
Aletti score (SCS), n (%)				<0.001
Lower than 8	300 (54.6)	252 (59.2)	48 (39.0)	
8 or above	249 (45.4)	174 (40.8)	75 (61.0)	

Multivariable logistic regression analysis to identify factors associated with major surgical complications

Variable	OR	95% CI	p value
Surgical timing			0.434

Primary	1.00		
Early interval	0.82	0.51 to 1.34	
Delayed	0.46	0.25 to 0.84	0.011
PCI 10 or lower	1.00		
PCI above 10	0.77	0.43 to 1.38	0.380
Aletti score			
Lower than 8	1.00		
8 or above	0.93	0.42 to 2.07	0.863
Small bowel resection			
No	1.00		
Yes	1.44	0.60 to 3.47	0.415
Large bowel resection			
No	1.00		
Yes	1.57	0.78 to 3.18	0.205
Multiple bowel resection			
No	1.00		
Yes	1.15	0.48 to 2.77	0.754
Diaphragmatic stripping			
No	1.00		
Yes	0.52	0.25 to 1.06	0.072
Cholecystectomy			
No	1.00		
Yes	1.21	0.58 to 2.51	0.614
Splenectomy			
No	1.00		
Yes	1.80	0.98 to 3.28	0.057
Distal pancreatectomy			
No	1.00		
Yes	1.66	0.70 to 3.96	0.251
Extensive peritonectomy			
No	1.00		
Yes	2.98	1.45 to 6.15	0.003

Study 9 Phillips A (2019)

Study details

Study type	Cohort study
Country	UK
Recruitment period	2007 to 2017
Study population and number	n=608 (453 [74.5%] standard surgery and 155 [25.5%] ultra-radical surgery according to the NICE classification described below. Patients with stage 3 or 4 advanced ovarian cancer who had cytoreductive surgery
Age	Median 64.5 years (IQR 56.7 to 72.7)
Patient selection criteria	Patients were included if they were referred from a local primary care provider to the Pan-Birmingham Gynaecological Cancer Centre, had a midline laparotomy, and had a final histological diagnosis of stage 3 or 4 epithelial ovarian, tubal, or peritoneal cancer. Quaternary referrals from outside the region were excluded from this analysis.
Technique	Patients either had primary debulking surgery or they had 3 or 4 cycles of carboplatin-based neoadjuvant chemotherapy, with an intention to consider interval debulking surgery or palliation. Typically, surgical procedures included pelvic clearance, omentectomy, and lymphadenectomy. More extensive surgery was introduced in 2008. In appropriately selected patients, gastrointestinal surgery or radical upper abdominal procedures were done if required. Extensive stripping of the para-aortic lymph nodes was not done routinely but enlarged para-aortic lymph nodes were resected. 209 (34%) patients had primary debulking surgery and 399 (66%) had interval debulking surgery. When classified using the SCS, 400 (65.8%) patients had surgery of low complexity, 140 (23.0%) patients had surgery of intermediate complexity, and 68 (11.2%) patients had surgery of high complexity.)
Follow up	Not reported
Conflict of interest/source of funding	There was no funding. 1 author has received fees for lecturing for Astra Zeneca and Roche, and 1 has received personal fees from Astra Zeneca and Roche.

Analysis

Follow up issues: 2 patients were excluded from the analysis for inadequate morbidity data.

Study design issues: Retrospective review of cases identified from a prospectively recorded gynaecological oncology multidisciplinary team database. The aim was to compare the efficacy of various classifications used to describe cytoreductive surgery on their ability to predict the development of postoperative morbidity. There were 3 categories used for the type of procedure: NICE classification of standard and ultra-radical surgery; Pomel classification into standard, radical, and supra-radical surgery; and a category that grouped patients by the presence or absence of gastrointestinal resections. The number of procedures was also used to describe

radicality, including the Aletti SCS system. Postoperative morbidity was recorded using the Memorial Sloan Kettering Cancer Center complication grading system. Only major morbidity (grades 3, 4 and 5) was recorded, with patients classified by the highest recorded complication. Morbidity was both retrospectively obtained from patients' notes and prospectively recorded following a critical incident review of major morbidity during the weekly multidisciplinary team discussion. All patients were considered on an 'intention to treat' basis to allow for complete denominator data to be available.

Study population issues: Of the 608 patients, 455 (75%) had stage 3 disease and 524 (86%) were of serous histology. Age, body mass index, and grade distributions of patients were similar in both standard and ultra-radical surgery groups (according to NICE classification).

Other issues: Certain procedures, including liver resections and partial gastrectomies, were rarely done.

For the NICE classification, standard surgery was defined as total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, pelvic or para-aortic lymphadenectomy, bowel surgery outside the definition of 'ultra-radical' (localised colonic resection, non-multiple bowel resection). Ultra-radical surgery was defined as diaphragmatic stripping, extensive peritoneal stripping, multiple resections of the bowel(excluding localised colonic resection), liver resection, partial gastrectomy, cholecystectomy, splenectomy.

For the Pomel classification, standard surgery was defined as hysterectomy, bilateral salpingo-oophorectomy, pelvic peritonectomy, total omentectomy, appendicectomy, pelvic or para-aortic lymphadenectomy. Radical surgery was defined as recto-sigmoid resection. Ultra-radical surgery was defined as diaphragmatic stripping, liver resection, cholecystectomy, splenectomy, any digestive resection excluding recto-sigmoid resection.

Key efficacy findings

- Number of patients analysed: 608
- Complete cytoreduction=65%
- Optimal cytoreduction (<1 cm)=14%
- Suboptimal cytoreduction=21%
- Complete cytoreduction rates were statistically significantly higher (87.7% compared with 56.7%, p<0.0001) in the ultra-radical group compared with the standard surgery group (using NICE classification).
- Median overall survival for all patients who had surgery=48.2 months (95% CI 40.6 to 55.8 months).
- In patients who had primary debulking surgery and complete cytoreduction, the median overall survival had not been reached as of August 2017. The estimated mean overall survival was 83.9 months (95% CI 75.2 to 92.7 months).
- In patients who had primary debulking surgery and optimal or suboptimal cytoreduction, the median overall survival was 56.3 months (95% CI 25.8 to 86.8 months) and 15.0 months (95% CI 9.1 to 20.8 months), respectively.
- In patients who had interval debulking surgery, the median overall survival was 57.9 months (95% CI 43.2 to 72.7 months) in those with complete cytoreduction, 33.4 months (95% CI 25.0 to 41.7 months) for those with optimal cytoreduction and 28.4 months (95% CI 21.6 to 35.2 months) for those with suboptimal cytoreduction.
- In patients who did not have surgery, the median overall survival was 11.7 months (95% CI 8.3 to 15.0 months).

Key safety findings

Major complications in standard and ultra-radical surgery, as defined by NICE classification

Major complication	Standard surgery	Ultra-radical surgery	Total
Grade 3 - total	12	13	25
Chest drain insertion with or without bronchoscopy	1	4	5
Return to theatre (haematoma/bleeding)	2	2	4
Return to theatre (collection)	2	2	4
Image-guided drainage (collection)	0	3	3
Return to theatre (no pathology found)	2	1	3
Return to theatre (revision of stoma)	2	0	2
oesophago-gastroduodenoscopy (bleeding)	1	0	1
Return to theatre (closure of laparostomy) and oesophago-gastroduodenoscopy (bleeding)	0	1	1
Return to theatre (removal of packs)	1	0	1
Return to theatre (wound dehiscence)	1	0	1
Grade 4 - total	2	10	12
Return to theatre (anastomotic leak)	2	2	4
Return to theatre (splenectomy, liver failure, renal failure, pancreatitis)	0	1	1
Cardiac pacing after sinus arrest	0	1	1
Intraoperative splenectomy for iatrogenic bleeding	0	1	1
Return to theatre (anastomotic leak) plus sheath dehiscence	0	1	1
Return to theatre (gastric perforation) subsequent enterocutaneous fistula and tracheostomy	0	1	1
Return to theatre spinal surgery for paraspinal infection	0	1	1
Renal failure	0	1	1
Urinary tract fistula	0	1	1
Grade 5 - total	4	2	6
Renal failure	1	0	1
Bowel ischaemia secondary to mesenteric thrombosis	1	0	1
Intra-abdominal sepsis	1	0	1
Pulmonary embolus	0	1	1
Pancreatitis and acute respiratory distress syndrome	0	1	1
Pneumonia, acute respiratory distress syndrome, and renal failure	1	0	1

Postoperative morbidity by different radicality definitions

Classification	Category of surgery	Number of patients	Major complications n (%)	% of complications detected	RR overall	95% CI
NICE	Standard	453	18 (4.1)	41.9	1.00	
	Ultra-radical	155	25 (15.1)	58.1	4.65	2.26 to 8.79
POMEL	Standard	380	8 (2.1)	18.6	0.55	0.24 to 1.25
	Radical	61	8 (13.1)	18.6	3.41	1.54 to 7.56
	Supra-radical	167	27 (16.2)	62.8	4.20	2.35 to 7.51
Gastrointestinal tract	No gastrointestinal surgery	436	12 (2.8)	27.9	0.72	0.35 to 1.48
	Gastrointestinal surgery	172	31 (18.0)	72.1	4.69	2.66 to 8.24
Multiple bowel resections	0 or 1 bowel resections	571	32 (5.6)	74.4	1.46	0.82 to 2.59
	2 or more bowel resections	37	11 (29.7)	25.6	7.73	3.92 to 15.26
Diaphragmatic surgery and colorectal anastomosis	No diaphragmatic stripping or gastrointestinal anastomosis	452	16 (3.5)	37.2	0.92	0.47 to 1.80
	Diaphragmatic stripping/resection	43	5 (11.6)	11.6	3.02	1.17 to 7.79
	Gastrointestinal anastomosis	71	13 (18.3)	30.2	4.76	2.42 to 9.37
	Diaphragmatic stripping and gastrointestinal anastomosis	42	9 (21.4)	20.9	5.57	2.65 to 11.72
Aletti	Low surgical complexity	400	12 (3.0)	27.9	0.78	0.38 to 1.61
	Intermediate surgical complexity	140	15 (10.7)	34.9	2.79	1.43 to 5.43
	High surgical complexity	68	16 (23.5)	37.2	6.12	3.25 to 11.52

Study 10 Palmqvist C (2022)

Study details

Study type	Cohort study
Country	Sweden
Recruitment period	2013 to 2017
Study population and number	n=384 Women with FIGO stage 3 to 4 ovarian cancer
Age	Median 66 years (range 20 to 89 years)
Patient selection criteria	All women aged 18 years or over registered in the Swedish Quality Register for Gynecological Cancer and diagnosed with ovarian, fallopian tube or primary peritoneal cancer, FIGO stage 3 or 4 who had primary or interval debulking surgery were included in the study. Exclusion criteria: primary or interval debulking surgery considered to be emergency surgery or surgery intended for diagnosis only when reviewed.
Technique	Patients had primary (79%) or interval (21%) debulking surgery. The degree of surgery was categorised according to Aletti and grouped into low (0 to 3; 47%), intermediate (4 to 7; 37%) and high (8 and above; 16%) SCS. In the total cohort of 384 women, 121 (32%) had an upper abdominal procedure. Most women in the primary debulking surgery group had adjuvant chemotherapy with carboplatin AUC 5 and paclitaxel 175 mg/m^2 intravenously every third week for 6 cycles, with the aim to start chemotherapy within 21 days of surgery. The treatment was evaluated at cycles 3 and 6. Women who had neoadjuvant chemotherapy had interval debulking surgery after 3 to 4 cycles of chemotherapy. Treatment was planned according to the Swedish national guidelines. Bevacizumab was implemented in 2013 for women with residual disease and for high-risk patients.
Follow up	Not reported
Conflict of interest/source of funding	None

Analysis

Follow up issues: Patients were followed until November 2020 or death, whichever came first.

Study design issues: Retrospective analysis of prospectively collected registry data. When a variable was missing in the registry, 2 doctors completed the dataset by reviewing medical records. The aim of the study was to investigate and assess complications after surgery for advanced stages of ovarian, fallopian tube and peritoneal cancer in a complete population-based cohort and to identify possible associations between severe complications and patient characteristics. Progression-free survival was chosen as the measure of survival. Some study variables were missing from the registry and medical records and there was incomplete data on comorbidities.

IP overview: Maximal effort cytoreductive surgery for advanced ovarian cancer

Key efficacy findings

Number of patients analysed: 384

- Complete cytoreduction=48.7% (187/384)
- Median progression-free survival by surgical complexity
  - Low SCS = 17.2 months (95% CI 15.2 to 20.7)
  - Intermediate or high SCS = 21.5 months (95% CI 18.2 to 25.7), log-rank test p=0.038
- Median progression-free survival according to timing of surgery
  - Primary debulking surgery = 21.4 months (95% CI 18.7 to 25.0)
  - Interval debulking surgery = 14.7 months (95% CI 12.7 to 18.3), log-rank test p<0.001

Key safety findings

- 30-day mortality=0.3% (1/384)
- 90-day mortality=1.0% (4/384)

Number of complications within 30 days of surgery

Clavien-Dindo classification	n (%)
0	272 (70.8)
1 to 2	70 (18.2)
3a	22 (5.7)
3b	14 (3.6)
4a	3 (0.8)
4b	2 (0.5)
5	1 (0.3)

There was no statistically significant difference in the proportion of patients who completed chemotherapy treatment between those who had Clavien-Dindo 0 to 2 complications (90.1% [308/342]) and those who had Clavien-Dindo 3 and above complications (83.3% [35/42]; p=0.236). Overall, 89.3% (343/384) of patients completed first line chemotherapy.

Description of most severe complication per patient within 30 days of surgery

Complication	n (%)
Clavien-Dindo 3a	22 (5.7)
Pleural fluid, drainage	16 (4.2)
Hydronephrosis, nephrostomy	2 (0.5)
Wound resutured	1 (0.3)
Wound seroma, drainage	1 (0.3)
Wound infection, cleansed	2 (0.5)
Clavien-Dindo 3b	14 (3.6)
Intra-abdominal bleeding, surgical intervention	2 (0.5)
Intra-abdominal abscess, drainage	1 (0.3)
Vaginal vault abscess, drainage	2 (0.5)
Wound hematoma, resutured	1 (0.3)
Wound dehiscence, resutured	2 (0.5)
Intra-abdominal abscess, surgical intervention	1 (0.3)
Stoma necrosis, surgical intervention	1 (0.3)
Urinary tract injury, surgical intervention	1 (0.3)
Intraabdominal abscess and bleeding, surgical intervention	1 (0.3)
Suspected anastomosis leakage, surgical intervention	1 (0.3)
Anastomosis leakage, surgical intervention	1 (0.3)
Clavien-Dindo 4a	3 (0.8)
Bleeding diaphragm, surgical intervention, intensive care	1 (0.3)
Pulmonary failure, intensive care	2 (0.5)
Clavien-Dindo 4b	2 (0.5)
Anastomosis leakage, surgical intervention, intensive care	1 (0.3)
Sepsis, multiple organ failure, intensive care	1 (0.3)
Clavien-Dindo 5	1 (0.3)
Sepsis, multiple organ failure, cardiac arrest	1 (0.3)

Uni-and multivariable logistic regression analysis of the complete cohort (n=384) with Clavien-Dindo class 3 or higher complications as endpoint

Variable	Univariable regression – OR (95% CI)	Univariable regression – p value	Multivariable regression – OR (95% CI)	Multivariable regression – p value
Preoperative albumin level (g/L)				
Less than 30	1.0		1.0	
30 or above	0.93 (0.88 to 0.98)	0.012	0.96 (0.90 to 1.02)	0.180
Primary surgery				
Interval debulking surgery	1.0		1.0	
Primary debulking surgery	3.78 (1.32 to 15.92)	0.030	4.70 (0.88 to 86.99)	0.143
Complete cytoreduction				
No	1.0		1.0	
Yes	0.49 (0.24 to 0.94)	0.036	0.47 (0.20 to 1.04)	0.068
SCS				
Low (0 to 3)	1.0		1.0	
Intermediate (4 to 7)	2.54 (1.19 to 5.67)	0.018	2.62 (1.05 to 7.21)	0.047
High (8 or above)	3.25 (1.32 to 8.02)	0.010	4.11 (1.39 to 12.94)	0.012

Study 11 Di Donato V (2017)

Study details

Study type	Systematic review
Country	Studies were in Europe, US, Asia, and Africa
Recruitment period	Search date: May 2015
Study population and number	n=18,579 (46 studies) Patients who had primary cytoreductive surgery for ovarian cancer
Age	Mean weighted median 65.9 years (range 52 to 74)
Patient selection criteria	Studies with at least 30 patients that reported 30-day mortality after primary cytoreductive surgery for ovarian/tubal/peritoneal cancer were included. Studies that used neoadjuvant chemotherapy were excluded. If a study reported data on neoadjuvant chemotherapy versus primary cytoreductive surgery, only data on primary surgery was considered. A quality score was used to assess the studies, based on type of study (prospective=2, retrospective or population=1), total number of patients per study (less than 50=1; 50 to 100=2; more than 100=3), volume of the centre (number of patients per year of study: less than 10=1; 10 to 20=2; more than 20=3). All studies with quality score of less than 4 were excluded.
Technique	Primary cytoreductive surgery.
Follow up	Postoperative period (for most studies, this was 28 or 30 days). Not reported in 10 studies.
Conflict of interest/source of funding	None for authors of review.

Analysis

Study design issues: Medline, CINAHL, and Web of Science were searched for all English-language studies containing mortality data for patients who had primary cytoreductive surgery for ovarian cancer. The primary outcome of interest was postoperative mortality. Potential predictors included complications, year of study publication, accrual interval, median age of the study cohort, body mass index of the study cohort, mean number of procedures, weighted complexity index, highest procedure complexity, and percentage of patients with stage 4 disease. A modified Aletti score was used to categorise surgical complexity. Simple Poisson regression models were used to quantify the association of each of the potential predictors with each of the outcomes.

Of the 46 studies,12 were prospective and 34 were retrospective. Most of the studies (80%) were single centre and 67% were published between 2000 and 2015.

Study population issues: FIGO stage was available for 43 patient cohorts. The weighted mean proportion of patients with FIGO stage 4 disease per cohort was 24% (range 0 to 100%).

Key safety findings

- The total number of deaths across all cohorts (n=46) was 807.
- The weighted mean perioperative mortality was 4.6% (95% CI 4.58 to 4.69).
- Simple regression identified median age and proportion of patients with stage 4 disease as statistically significant predictors of 30-day mortality.
- The number of surgical procedures, weighted surgical complexity index, and highest procedure complexity were computable in 26 cohorts. There was no statistically significant association between the weighted mean value of these parameters and the incidence rate of mortality, although an inverse trend was observed.

Distribution of the identified causes of death (n = 115) from 20 studies of 3170 patients

Cause of death	n	%
Infection	35	30.4
Sepsis	26	22.6
Surgical site infection	9	7.8
Hematologic/vascular	31	27
Pulmonary embolus	11	9.6
Deep vein thrombosis	6	5.2
Ictus	3	2.6
Haemorrhage	11	9.6
Organ failure	25	21.7
Respiratory failure	17	14.8
Renal failure	1	0.9
Liver failure	1	0.9
Multiorgan failure	6	5.2
Cardiovascular	10	8.7
Myocardial infarction	6	5.2
Congestive heart failure	4	3.5
Gastrointestinal	3	2.6
Anastomotic leak	2	1.7
Occlusion	1	0.9
Tumour progression	11	9.6

Simple Poisson regression analyses of change in predictor variable effects on mortality rate

Variable	Mean*	95% CI	IRR	95% CI	SE	Increment (%)	p	Missing values (%)
Median age (years)	65.9	65.8 to 66.0	1.109	1.1 to 1.2	0.021	10.9	<0.001	13
American Society of Anesthesiologists >3	48.2	47.8 to 48.6	1.004	1.0 to 1.0	0.018	0.4	0.829	78
FIGO stage 4 ratio	25.7	25.4 to 26.0	1.017	1.0 to 1.0	0.004	1.7	<0.001	6.5
No. of surgical procedures	3.3	3.3 to 3.4	0.832	0.7 to 1.0	0.087	-16.8	0.078	47.8
Surgical complexity	3.8	3.7 to 3.9	0.889	0.7 to 1.0	0.079	-11.1	0.186	47.8
Highest procedure complexity	2.5	2.4 to 2.6	0.847	0.7 to 1.0	0.077	-15.3	0.067	47.8
Overall complication rate	23.8	23.6 to 24.0	1.013	1.0 to 1.0	0.010	1.3	0.190	34.8
Severe complication rate	9.5	9.3 to 9.7	1.057	0.0 to 11.1	0.016	5.7	<0.001	76.0

* Proportional to number of patients in each study

Estimates on mortality rate from multiple Poisson regression model at various levels for age and FIGO stage

Age	FIGO stage 3			FIGO stage 4		
(years)	Mortality rate (%)	SE (%)	95% CI	Mortality rate (%)	SE (%)	95% CI
55	1.2	0.27	0.70 to 1.75	6.8	2.8	1.37 to 12.47
60	1.9	0.32	1.24 to 2.49	10.4	3.8	3.18 to 17.90
65	2.8	0.42	2.02 to 3.66	15.9	5.0	6.18 to 25.93
70	4.3	0.71	2.93 to 5.72	24.3	7.0	10.68 to 38.21
75	6.6	1.39	3.86 to 9.31	37.3	10.5	16.73 to 57.74

Study 12 Hiu S (2022)

Study details

Study type	Systematic review (Cochrane)
Country	Studies were in: US, France, Republic of Korea
Recruitment period	Search date: November 2021
Study population and number	n=924 (3 studies) Women with stage 3 or 4 epithelial ovarian cancer, who had ultra-radical surgery as part of upfront primary debulking surgery or interval debulking surgery
Age	Median age at diagnosis ranged from 54 to 64 years (ages across studies ranged from 24 to 90 years).
Patient selection criteria	Women diagnosed with stage 3 or 4 epithelial ovarian cancer, having ultra-radical surgery as part of upfront primary debulking surgery or interval debulking surgery (surgery halfway through the course of chemotherapy) were included. Women with other concurrent malignancies or recurrent disease were excluded.
Technique	All 3 studies compared ultra-radical or extensive surgery with standard surgery. The 2 most recent studies also included some elements of extensive surgery in the standard surgery group: segmental small bowel resection, and rectosigmoid resection and appendectomy.
Follow up	Median follow up ranged from 32 to 49 months
Conflict of interest/source of funding	None for authors of systematic review

Analysis

Study design issues: Randomised controlled trials, quasi-randomised trials, non-randomised studies, prospective and retrospective cohort studies, and case series of 100 or more patients were included. Case-control studies, uncontrolled observational studies and case series of fewer than 100 patients were excluded. To minimise selection bias, they only included studies that used statistical adjustment for baseline case mix using multivariate analyses. No RCTs or comparative observational studies were identified that used statistical adjustment that addressed recurrence rate, quality of life or (loco)regional control.

All 3 included studies reported retrospective analyses of patients identified from surgical or medical records (Aletti GD, Dowdy SC, Gostout BS et al. (2006) Aggressive surgical effort and improved survival in advanced-stage ovarian cancer. Obstetrics and Gynecology 107: 77–85; Chang SJ, Bristow RE, Ryu HS (2012) Impact of complete cytoreduction leaving no gross residual disease associated with radical cytoreductive surgical procedures on survival in advanced ovarian cancer. Annals of Surgical Oncology 19: 4059-67; Luyckx M, Leblanc E, Filleron T, et al. (2012) Maximal cytoreduction in patients with FIGO stage IIIC to stage IV ovarian, fallopian, and peritoneal cancer in day-to-day practice: a Retrospective French Multicentric Study. International Journal of Gynecological Cancer 22:1337–43).

Key efficacy findings

Survival (overall and disease- specific)
Survival may be prolonged in woman who had ultra-radical surgery compared to standard surgery but the evidence was limited and very uncertain: HR 0.60 (95% CI 0.43 to 0.82); 2 studies, n=397

Progression-free survival
Disease progression may be delayed in woman who had ultra-radical surgery compared to standard surgery but the evidence was limited and very uncertain: HR 0.62 (95% CI 0.42 to 0.92); 1 study, n=203

Key safety findings

Perioperative mortality
There were 4 deaths within 30 days of surgery in both studies and none in the ultra-radical group (2 studies, n=397)

Serious postoperative morbidity
Significant postoperative morbidity occurred in 32/84 (38.1%) women in the in ultra-radical group versus 14/119 (11.8%) women in the standard surgery group. However, the evidence was limited and very uncertain. RR 3.24 (95% CI 1.84 to 5.68); 1 study, n=203

Study 13 Ehmann S (2021)

Study details

Study type	Case series
Country	US
Recruitment period	Not reported
Study population and number	n=4 Patients with diaphragmatic hernia after debulking surgery for advanced ovarian cancer
Age	Mean 46.8 years
Patient selection criteria	Not applicable
Technique	All patients had debulking surgery, which included left diaphragm peritonectomy and splenectomy. Of the 4 patients, 2 had primary debulking surgery and 2 had interval debulking surgery.
Follow up	The hernias were diagnosed at 5, 6, 8 and 18 months after surgery.
Conflict of interest/source of funding	None

Key safety and efficacy findings

Patient 1: A 36-year-old patient had primary debulking surgery for stage 4b high-grade serous ovarian cancer. Surgery for complete gross resection included bilateral diaphragm peritonectomy, splenectomy, and cholecystectomy. Postoperative chemotherapy was completed with standard systemic paclitaxel and carboplatin. Five months later, the patient presented with a history of nausea and vomiting. CT imaging showed a left diaphragmatic hernia, with a 0.8 cm defect and incarceration of the stomach. The diaphragmatic hernia was repaired through a left thoracotomy. The patient was discharged home on postoperative day 5 and a follow-up CT scan 10 months later showed no hernia.

Patient 2: A 50-year-old patient had interval debulking surgery for stage 4b high-grade serous ovarian cancer with involved supradiaphragmatic lymph nodes. Complete gross resection was achieved. The surgery included a splenectomy, left diaphragm peritonectomy, full thickness resection of the right diaphragm, resection of right mediastinal lymph nodes and insertion of a right-sided chest tube. She had an additional 2 cycles of chemotherapy after surgery. About 18 months later, the patient was diagnosed with a left diaphragmatic Hernia, which was successfully repaired.

Patient 3: A 45-year-old patient with stage 4b high-grade serous ovarian cancer, and a history of Graves' disease status after total thyroidectomy, had primary debulking surgery including bilateral diaphragm peritonectomy, splenectomy, resection of a right mediastinal lymph node and insertion of a right chest tube. She had adjuvant chemotherapy with paclitaxel and carboplatin. Bevacizumab was added with cycle 3. About 6 months after primary surgery, a CT scan showed a small left hemidiaphragm hernia containing parts of the

stomach. The patient developed some mild symptoms, belching and infrequent right upper discomfort. Corrective surgery was done robotically after she completed maintenance therapy with bevacizumab. The patient was discharged home on postoperative day 1. On follow-up her symptoms had resolved, and the chest x-ray 2 weeks after surgery showed no signs of a diaphragmatic hernia.

Patient 4: A 56-year-old patient with stage 4b high-grade serous ovarian cancer had 3 cycles of neoadjuvant chemotherapy with paclitaxel and carboplatin, followed by interval debulking surgery with a left-sided thoracoscopic procedure, left diaphragmatic peritonectomy, full thickness resection of the right diaphragm, resection of a liver lesion, partial gastrectomy with a gastrojejunostomy, small bowel resection with a side-to-side anastomosis, splenectomy, a modified posterior exenteration with end-to-end anastomosis and diverting loop ileostomy. The residual tumour was less than 5 mm. Her past medical history was significant for hepatitis B. About 8 months later, the patient had a CT scan which showed progressive disease and an asymptomatic left diaphragm hernia containing bowel and stomach contents. The patient had a left thoracotomy, reduction of the intrathoracic stomach and repair of the left diaphragm hernia with mesh reinforcement. She was discharged on postoperative day 2. A follow-up CT scan 1.5 months later showed a repaired diaphragm.

Validity and generalisability of the studies

- There are no randomised trials comparing standard surgery against more extensive surgery.
- Studies that were done outside the UK may not be generalisable to patients who are treated for ovarian cancer in the UK.
- There are 2 prospective studies primarily aimed at assessing quality of life after the procedure, both of which included data from the UK.
- Complete cytoreduction is not always assessed accurately and the definition of optimal cytoreduction has changed over time.
- Studies have different inclusion criteria and the extent of surgery is categorised in different ways.
- Some patients had primary debulking surgery and others had interval or delayed debulking surgery after neoadjuvant chemotherapy.
- Several studies compare outcomes before and after changes in surgical treatment were implemented.
- One study used data from a randomised controlled trial that was designed to assess different chemotherapy regimens (Horowitz 2015). This study excluded patients with residual disease >1cm and only included patients who could be treated surgically.
- Adjuvant treatments for ovarian cancer have changed over time and this is also likely to have an impact on survival (for example, the use of bevacizumab).
- In 1 cohort study, 34% (322/978) of patients had intraperitoneal chemotherapy.
- There are several studies from Sweden and there is likely to be some patient overlap.
- A recent Cochrane systematic review was identified, which included 3 retrospective, non-randomised studies, all of which were published before 2013.

Existing assessments of this procedure

A consensus statement titled 'Governance models to support patient safety when undergoing maximal effort cytoreductive surgery for advanced ovarian/fallopian tube/primary peritoneal cancer – a joint statement of ACPGBI, ASGBI, AUGIS and BGCS' was published in 2022 (Maxwell-Armstrong 2022). This statement sets out a framework for joint working for gynaecological oncologists and colorectal and UGI surgeons.

The European Society of Gynaecological Oncology published guidelines on ovarian cancer surgery in 2017 (Querleu 2017). It states: 'Midline laparotomy is required to manage stage III to IV ovarian cancers (expert agreement). Complete resection of all visible diseases is the goal of surgical management. Voluntary use of incomplete surgery (upfront or interval) is discouraged (grade A). Criteria against abdominal debulking are the following (expert agreement):

- Diffuse deep infiltration of the root of small bowel mesentery
- Diffuse carcinomatosis of the small bowel involving such large parts that resection would lead to short bowel syndrome(remaining bowel G 1.5 m)
- Diffuse involvement/deep infiltration of the stomach/duodenum (limited excision is possible) and head or middle part of the pancreas (tail of the pancreas can be resected)
- Involvement of truncus coeliacus, hepatic arteries, and left gastric artery (celiac nodes can be resected).'

Related NICE guidance

Below is a list of NICE guidance related to this procedure.

Interventional procedures

- Cytoreduction surgery with hyperthermic intraoperative peritoneal chemotherapy for peritoneal carcinomatosis. NICE interventional procedures guidance 688 (2021). Available from http://www.nice.org.uk/guidance/IPG688

Technology appraisals

- Olaparib plus bevacizumab for maintenance treatment of advanced ovarian, fallopian tube or primary peritoneal cancer. NICE technology appraisal 693 (2021). Available from http://www.nice.org.uk/guidance/TA693
- Niraparib for maintenance treatment of advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy. NICE technology appraisal 673 (2021). Available from http://www.nice.org.uk/guidance/TA673
- Olaparib for maintenance treatment of BRCA mutation-positive advanced ovarian, fallopian tube or peritoneal cancer after response to first-line platinum-based chemotherapy. NICE technology appraisal 598 (2019). Available from http://www.nice.org.uk/guidance/TA598
- Bevacizumab in combination with paclitaxel and carboplatin for first-line treatment of advanced ovarian cancer. NICE technology appraisal 284 (2013). Available from http://www.nice.org.uk/guidance/TA284
- Guidance on the use of paclitaxel in the treatment of ovarian cancer. NICE technology appraisal 55 (2003). Available from http://www.nice.org.uk/guidance/TA55

NICE guidelines

- Ovarian cancer: recognition and initial management. NICE clinical guideline 122 (2011). Available from http://www.nice.org.uk/guidance/CG122

Additional information considered by IPAC

Professional experts' opinions

Expert advice was sought from consultants who have been nominated or ratified by their professional Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by professional experts, in the form of the completed questionnaires, is normally published in full on the NICE website during public

consultation, except in circumstances but not limited to, when comments are considered voluminous, or publication would be unlawful or inappropriate.

10 professional expert questionnaires were submitted and can be found on the NICE website.

Patient organisation opinions

Patient organisation submissions were received and can be found on the NICE website.

Patient commentators' opinions

NICE received 14 questionnaires from patients who had the procedure (or their carers).

Patients' views on the procedure were consistent with the published evidence and the opinions of the professional experts. See the patient commentary summary for more information.

Company engagement

A structured information request was sent to 1 company who manufactures a potentially relevant device for use in this procedure. NICE received 1 completed submission. This was considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

Issues for consideration by IPAC

Evidence on recurrent ovarian cancer has not been included.

Ongoing trials:

- Trial on Radical Upfront Surgery in Advanced Ovarian Cancer (NCT02828618); Randomised controlled trial; US, Austria, Denmark, France, Germany, Italy, Sweden, UK; n=797; estimated completion date April 2023.
- Laparoscopic cytoreduction After Neoadjuvant ChEmotherapy (LANCE); randomised controlled trial; US; n=580; estimated completion date May 2023.

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Literature search strategy

Databases	Date searched	Version/files
MEDLINE (Ovid)	14/06/2022	1946 to June 13, 2022
MEDLINE In-Process (Ovid)	14/06/2022	1946 to June 13, 2022
MEDLINE Epubs ahead of print (Ovid)	14/06/2022	1946 to June 13, 2022
EMBASE (Ovid)	14/06/2022	1974 to 2022 June 13
EMBASE Conference (Ovid)	14/06/2022	1974 to 2022 June 13
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	14/06/2022	Issue 6 of 12, June 2022
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	14/06/2022	Issue 5 of 12, May 2022
International HTA database (INAHTA)	14/06/2022	-

Trial sources searched 2021

- Clinicaltrials.gov
- ISRCTN
- WHO International Clinical Trials Registry

Websites searched

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- General internet search

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

Literature search strategy

Strategy used:
1 exp Ovarian Neoplasms/
2 ((ovar* or gynae*) adj4 (neoplasm* or cancer* or carcino* or adenocarcino* or tumour* or tumor* or malignan* or lump* or metast*)).tw.

3 (ovar* adj4 (epithel* or lin* or glandul*) adj4 (neoplasm* or cancer* or carcino* or adenocarcino* or tumour* or tumor* or malignan* or lump* or metast*)).tw.
4 "Neoplasms, Glandular and Epithelial"/
5 or/1-4 118,061
6 Cytoreduction Surgical Procedures/
7 CRS.tw.
8 (cytoreduc* or debulk* or resect* or re-sect*).tw.
9 or/6-8
10 ((ultra-radical* or ultraradical* or ultra radical* or supra-radical* or supra radical or supraradical* or extensive* or aggress* or plasma) adj4 (surg* or resect* or re-sect*)).tw.
11 (high-SCS or maxim* effort* or complex* or (high adj4 SCS)).tw.
12 10 or 11
13 9 and 12
14 5 and 13
15 plasmajet*.tw.
16 14 or 15
17 animals/ not humans/
18 16 not 17

Appendix

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the summary of the key evidence. It is by no means an exhaustive list of potentially relevant studies.

Studies published before 2013 and case series with fewer than 100 patients have been excluded.

Additional papers identified

Article	Number of patients / follow up	Direction of conclusions	Reasons for non-inclusion in summary of key evidence section
Angeles MA, Cabarrou B, Gil-Moreno A et al. (2021) Effect of tumor burden and radical surgery on survival difference between upfront, early interval or delayed cytoreductive surgery in ovarian cancer. Journal of Gynecologic Oncology 32: e78	Cohort study n=549	The benefit of complete primary debulking surgery compared with neoadjuvant chemotherapy was maximal in patients with a low SCS. In patients with low tumour burden, there was a survival benefit of primary debulking surgery over early interval or delayed debulking surgery. In women with high tumour load, delayed debulking surgery impaired the oncological outcome.	A more recent publication from the same centre is included.
Angeles MA, Rychlik A, Cabarrou B et al. (2020) A multivariate analysis of the prognostic impact of tumor burden, surgical timing and complexity after complete cytoreduction for advanced ovarian cancer. Gynecologic Oncology 158: 614–21	Cohort study n=549	In multivariable analysis, surgical complexity and cytoreduction to minimal residual disease rather than complete cytoreduction were negatively associated with disease-free survival. Primary debulking surgery offered a survival gain of almost 3 years compared to interval debulking surgery in patients with minimal or no residual disease after surgery. Primary debulking surgery should remain the	A more recent publication from the same centre is included.

		standard of care for advanced ovarian cancer.	
Angioli R, Plotti F, Aloisi A et al. (2013) Does extensive upper abdomen surgery during primary cytoreduction impact on long-term quality of life? International Journal of Gynecological Cancer 23: 442-447	Prospective non-randomised comparative study (standard surgery versus extensive upper abdomen surgery) n=80 Follow up not stated	There were no statistical differences in terms of major surgical complication rates (15% versus 10%). Both groups had same times of beginning of chemotherapy (median, 19 versus 21 days) and no severe related toxicities. Quality-of-life scores of both questionnaires were comparable between groups, except for Global Health Status in QLC-30.	Small non-randomised study
Bacalbasa N, Dima S, Balescu I et al. (2015) Results of primary cytoreductive surgery in advanced-stage epithelial ovarian cancer: a single-center experience. Anticancer Research 35: 4099–104	Cohort study n=338	A more extensive surgical approach is justified and associated with improved survival in patients with advanced-stage epithelial ovarian cancer. However, careful patient selection is needed because the general preoperative status can impact survival.	Larger or more recent studies are included.
Baldewpersad Tewarie NMS, van Driel WJ, van Ham M et al. (2021) Postoperative outcomes of primary and interval cytoreductive surgery for advanced ovarian cancer registered in the Dutch Gynecological Oncology Audit (DGOA). Gynecologic oncology 162: 331–8	Cohort study n=2,382	A higher complete cytoreduction rate was achieved in primary compared to interval debulking surgery. This is associated with a higher complication with reintervention rate in the primary debulking surgery group. The higher rate of complication with reintervention is subsequently correlated with a delay in starting adjuvant chemotherapy. Maintaining a balance in aggressiveness of surgery and outcome of the surgical procedure with respect to	The main aim was to compare outcomes after primary debulking surgery and interval debulking surgery.

		severe complications is important.	
Barlin JN, Long KC, Tanner EJ et al. (2013) Optimal (≤1cm) but visible residual disease: is extensive debulking warranted? Gynecologic Oncology 130: 284–8	Cohort study n=219	Patients cytoreduced to 1 cm or less but visible residual disease who needed upper abdominal surgery did not have a worse overall survival than those who did not need upper abdominal surgery. Overall survival was similar if residual disease involved the small bowel or not. For ovarian cancer patients with disease not amenable to complete gross resection, extensive surgery should still be considered to achieve 1 cm or less but visible residual disease status, including cases where the residual disease involves the small bowel.	Larger or more recent studies are included.
Baum J, Braicu EI, Hunsicker O et al. (2021) Impact of clinical factors and surgical outcome on long-term survival in high-grade serous ovarian cancer: A multicenter analysis. International Journal of Gynecological Cancer 31: 647–55	Non-randomised comparative study (propensity score matched) n=276	After propensity score matching and multivariable adjustment, platinum sensitivity (p=0.002) was an independent favourable prognostic factor whereas recurrence (p<0.001) and ascites (p=0.021) were independent detrimental predictors for long-term survival. More long-term survivors tested positive for mutation in the BRCA1 gene than the BRCA2 gene (p=0.016). Intraoperatively, these patients had less tumour involvement of the upper abdomen at initial surgery (p=0.024). Complexity of surgery and surgical techniques were similar in both cohorts.	Larger studies are included.
Bernard L, Boucher J, Helpman L (2020)	Cohort study	Patients who had bowel resection or repair at the	Studies with more

Bowel resection or repair at the time of cytoreductive surgery for ovarian malignancy is associated with increased complication rate: An ACS-NSQIP study. Gynecologic oncology 158: 597–602	n=4,965	time of cytoreductive surgery are at increased risk of surgical site infections, without increased risk of 30-day mortality.	outcomes have been included.
Berretta R, Capozzi VA, Sozzi G et al. (2018) Prognostic role of mesenteric lymph nodes involvement in patients undergoing posterior pelvic exenteration during radical or supra-radical surgery for advanced ovarian cancer. Archives of Gynecology and Obstetrics 297: 997–1004	Cohort study n=83	The absence of residual disease after surgery is an independent prognostic factor; to achieve this result should be recommended a radical bowel resection during debulking surgery for advanced ovarian cancer with bowel involvement.	Small retrospective study.
Boer GMN-D, Hofhuis W, Reesink-Peters N et al. (2022) Adjuvant use of PlasmaJet device during cytoreductive surgery for advanced-stage ovarian cancer: results of the PlaComOv-study, a randomized controlled trial in the Netherlands. Annals of Surgical Oncology; 2022	RCT (use of neutral argon plasma) n=327 Follow up=6 months	Adjuvant use of PlasmaJet during cytoreductive surgery for advanced-stage ovarian cancer resulted in a significantly higher proportion of complete cytoreductive surgery in patients with resectable disease and higher quality of life at 6 months after surgery.	Study focuses on the effect of using neutral argon plasma during the procedure.
Ceccaroni M, Roviglione G, Bruni F et al. (2018) Laparoscopy for primary cytoreduction with multivisceral resections in advanced ovarian cancer: prospective validation. "The times they are a-changin"? Surgical	Non-randomised comparative study n=66 Follow up=median 51 months	After strict selection, a group of patients with advanced ovarian cancer may have laparoscopic primary cytoreduction with high rates of optimal cytoreduction, satisfactory perioperative morbidity, a short interval to chemotherapy, and	Small non-randomised study focusing on laparoscopic surgery.

Endoscopy 32: 2026–37		encouraging survival outcomes.	
Chang, SJ, Bristow RE, Chi DS et al. (2015) Role of aggressive surgical cytoreduction in advanced ovarian cancer. Journal of Gynecologic Oncology 26: 336–42	Review	If the patient cannot have near optimal cytoreduction, radical cytoreductive procedures should not be done except for palliation. Multiple factors impact patient survival and complete cytoreduction to no gross residual disease is one of the most powerful determinants in survival. Although published reports supporting the positive prognostic impact of aggressive surgical effort are almost entirely retrospective, the findings of these studies provide potential evidence for the hypothesis that surgical expertise at least partly counteracts the effects of underlying tumour biology. Consequently, aggressive surgical cytoreduction can offer the best opportunity for achieving extended survival in women with advanced ovarian cancer.	Review with no meta-analysis.
Costantini B, Vargiu V, Santullo F et al. (2022) Risk factors for anastomotic leakage in advanced ovarian cancer surgery: a large single-center experience. Annals of Surgical Oncology 2022	Case series n=515	Anastomotic leakage is confirmed to be an extremely rare but severe postoperative complication of ovarian cancer surgery, being responsible for increased early postoperative mortality. Preoperative nutritional status and surgical characteristics, such as blood supply and anastomosis level, appear to be the most significant risk factors.	Study focuses on a single safety outcome (risk factors for anastomotic leakage).

Datta A, Sebastian A, Chandy RG et al. (2021) Complications and outcomes of diaphragm surgeries in epithelial ovarian malignancies. Indian Journal of Surgical Oncology 12: 822–29	Cohort study n=616	Of the 616 patients, 13% (81) had diaphragm surgery. Optimal debulking was achieved in 89% of cases. The complexity of surgery was intermediate in 64% of patients and complex in 33% as per Aletti's scoring. Median recurrence-free and overall survival were 22 (95% CI 17 to 27) and 32 months (95% CI 26 to 38) respectively.	Study focuses on a small part of the procedure (diaphragm surgery).
Davidson BA, Broadwater G, Crim A et al. (2019) Surgical complexity score and role of laparoscopy in women with advanced ovarian cancer treated with neoadjuvant chemotherapy. Gynecologic Oncology 152: 554–9	Cohort study n=282	In women with advanced epithelial ovarian cancer treated with neoadjuvant chemotherapy, older age, SCS 3 or higher, and residual disease more than 1 cm at interval debulking surgery were predictors of worse survival. Minimally invasive surgery appears safe and feasible with acceptable optimal cytoreduction rates.	Study focuses on the role of laparoscopy.
Di Donato V, Di Pinto A, Giannini A et al. (2021) Modified fragility index and surgical complexity score are able to predict postoperative morbidity and mortality after cytoreductive surgery for advanced ovarian cancer. Gynecologic Oncology 161: 4–10	Cohort study n=263	Patients with a high frailty index score who had intermediate or high-complexity surgery were at higher risk of severe complications.	Studies with more patients or longer follow up are included.
Di Donato V, Bardhi E, Tramontano L et al. (2020) Management of morbidity associated with pancreatic resection during cytoreductive surgery for epithelial ovarian cancer: A systematic	Systematic review n=701 (11 studies)	Knowledge of pancreatic surgery and management of possible complications should be present in the oncologic-gynaecologic armamentarium. All patients should be referred to specialised, dedicated, tertiary centres to reduce,	Review focuses on complications related to pancreatic surgical procedures.

review. European Journal of Surgical Oncology 46: 694–702		promptly recognise and optimally manage complications.	
Egger EK, Kohls N, Stope MB et al. (2020) Risk factors for severe complications in ovarian cancer surgery. In Vivo 34: 3361–65	Cohort study n=345	There were no complications in 114 patients, mild complications in 114 patients and severe complications in 117 patients. The risk factor evaluation identified age (p=0.049), smoking (p=0.032) and duration of surgery (p<0.0001) as statistically significant factors for severe postoperative morbidity.	Although duration of surgery was considered as a risk factor, extent of surgery was not described.
Eoh KJ, Lee J-Y, Yoon JW et al. (2017) Role of systematic lymphadenectomy as part of primary debulking surgery for optimally cytoreduced advanced ovarian cancer: Reappraisal in the era of radical surgery. Oncotarget 8: 37807–16	Case series n=158	Systematic lymph node dissection might have therapeutic value and improve prognosis for patients with optimally cytoreduced advanced ovarian cancer	Study focuses on the role of lymphadenectomy.
Fagotti A, Ferrandina MG, Vizzielli G et al. (2020) Randomized trial of primary debulking surgery versus neoadjuvant chemotherapy for advanced epithelial ovarian cancer (SCORPION-NCT01461850). International Journal of Gynecological Cancer 30:1657–64	RCT n=171	Neoadjuvant chemotherapy and primary debulking surgery have the same efficacy when used at their maximal possibilities, but the toxicity profile is different.	Study aimed to compare neoadjuvant chemotherapy followed by interval debulking surgery with primary debulking surgery.
Feldheiser A, Braicu E-I, Bonomo T et al. (2014) Impact of ascites on the	Case series n=119	The presence of a high amount of ascites at cytoreductive surgery is associated with higher	Small case series, which focuses on the impact of

perioperative course of patients with advanced ovarian cancer undergoing extensive cytoreduction: results of a study on 119 patients. International Journal of Gynecological Cancer 24: 478–87		amounts of blood transfusions. The length of hospital stay and the postoperative intensive care unit treatment are statistically significantly prolonged compared with those of patients without ascites.	ascites on the outcome of surgery.
Fotopoulou C, Jones BP, Savvatis K et al. (2016) Maximal effort cytoreductive surgery for disseminated ovarian cancer in a UK setting: challenges and possibilities. Archives of Gynecology and Obstetrics 294: 607–14	Cohort study n=118	Maximal effort cytoreductive surgery for ovarian cancer is feasible within a UK setting with acceptable morbidity, low intestinal stoma rates and without clinically relevant delays to postoperative chemotherapy. Careful patient selection, and coordinated multidisciplinary effort appear to be the key for good outcome. Future evaluations should include quality of life analyses.	Larger or more recent studies are included.
Ghirardi V, Moruzzi MC, Bizzarri N et al. (2020) Minimal residual disease at primary debulking surgery versus complete tumor resection at interval debulking surgery in advanced epithelial ovarian cancer: A survival analysis. Gynecologic Oncology 157: 209–13	Non-randomised comparative study n=207 Follow up=median 56 months	Median progression-free survival was 16 months and 19 months for primary debulking surgery and interval debulking surgery, respectively (p=0.111). Median overall survival was 41 months and 52 months for primary and interval surgery group, respectively (p=0.022).	Study focuses on comparison of primary and interval debulking surgery.
Gockley AA, Fiascone S, Hicks Courant K et al. (2019) Clinical characteristics and outcomes after bowel surgery and ostomy formation at the time of debulking surgery for	Cohort study n=554	Patients who had primary surgery were more likely to have bowel resection, compared with those who had interval surgery (37% versus 14%, p<0.001). Of the 139 (25%) patients who had bowel surgery, 25	Study focuses on a single aspect of the procedure (ostomy formation).

advanced-stage epithelial ovarian carcinoma. International Journal of Gynecological Cancer 29: 585–92		(18%) had ostomy formation. Rates of ostomy formation were similar between the groups (6% primary versus 3% interval, p=0.10). Multivariate analysis showed that a high SCS was associated with ostomy formation.	
Greggi S, Falcone F, Carputo R et al. (2016) Primary surgical cytoreduction in advanced ovarian cancer: An outcome analysis within the MITO (Multicentre Italian Trials in Ovarian Cancer and Gynecologic Malignancies) Group. Gynecologic Oncology 140: 425–9	Non-randomised comparative study n=205	Complete surgical cytoreduction was associated with oncological referral centres (60% compared with 25% in non-oncological referral centres, p<0.001). The proportion of patients who had additional surgical procedures was different (at least 1 additional procedure was done in 81% in oncological referral centres compared to 51% in the others, p<0.001). Despite the more aggressive surgery done in oncological referral centres, the perioperative outcome measures were not statistically significantly different in the 2 groups.	The main focus of the study was to assess surgical management of advanced ovarian cancer and compare outcomes for different types of treatment centres.
Hall M, Savvatis K, Nixon K, et al. (2019) Maximal-effort cytoreductive surgery for ovarian cancer patients with a high tumor burden: variations in practice and impact on outcome. Annals of Surgical Oncology 26: 2943–51	Non-randomised comparative study n=249 Follow up: mean 24 months	Incorporating surgery into the initial management of epithelial ovarian cancer, even for those patients with a greater tumour burden and more disseminated disease, may need more complex procedures and more resources in terms of theatre time and hospital stay, but seems to be associated with a significant prolongation of overall survival compared with chemotherapy alone.	Studies with more patients or longer follow up are included.
Harter P, Sehouli J, Vergote I et al. (2021)	RCT n=407	A complete resection was achieved in 76% of the	Study focuses on patients

Randomized trial of cytoreductive surgery for relapsed ovarian cancer. The New England Journal of Medicine 385: 2123-2131		patients in the surgery group who had the procedure. The median overall survival was 53.7 months in the surgery group and 46.0 months in the no-surgery group (hazard ratio for death, 0.75; 95% CI 0.59 to 0.96; p=0.02). Patients with a complete resection had the most favourable outcome, with a median overall survival of 61.9 months.	with recurrence of ovarian cancer.
Harter P, Sehouli J, Lorusso D et al. (2019) Randomized trial of lymphadenectomy in patients with advanced ovarian neoplasms. New England Journal of Medicine 380: 822–32	RCT n=647	Systematic pelvic and paraaortic lymphadenectomy in patients with advanced ovarian cancer who had undergone intraabdominal macroscopically complete resection and had normal lymph nodes both before and during surgery was not associated with longer overall or progression-free survival than no lymphadenectomy and was associated with a higher incidence of postoperative complications.	Study focuses on a single aspect of the procedure (lymphadenectomy).
Hernandez-Lopez LA, Elizalde-Mendez A (2020) How far should we go in optimal cytoreductive surgery for ovarian cancer? Chin Clin Oncol 9:70. doi: 10.21037/cco-20-40	Review	An important factor playing a role in survival and in the probability of surgical cytoreductive success is tumour biology; there has been described a clear difference between serous and mucinous tumours, but some groups advocate that maximal surgical effort in mucinous tumours may compensate morbidity with an increase in survival. The extension of resection in cytoreduction is still controversial; some authors	Review without meta-analysis.

		have confirmed that the most important factor is the residual disease and that radical surgery is superior to non-radical surgery in terms of overall survival. An important factor is for procedures to be done in specialised centres.	
Horner W, Peng K, Pleasant V et al. (2019) Trends in surgical complexity and treatment modalities utilized in the management of ovarian cancer in an era of neoadjuvant chemotherapy. Gynecologic Oncology 154: 283–89	Cohort study n=68,889	The use of neoadjuvant chemotherapy increased from 8% in 2004 to 28% in 2015 (p-trend<0.001). The proportion of moderate complexity surgeries increased from 29% to 34% and high complexity surgeries from 26% to 30% (p-trend<0.001, for both). Trends in increasing surgical complexity were seen in both neoadjuvant chemotherapy and primary surgery cohorts. The increase in surgical complexity was seen most profoundly at high-volume centres. Overall 30-day mortality decreased from 3% in 2004 to 1% in 2015; and 90-day mortality decreased from 8% to 4%. During the same time, 5-year survival increased from 40% to 49%.	Study focuses on trends in surgical complexity.
Javellana M, Hoppenot C, Lengyel E et al. (2019) The road to long-term survival: Surgical approach and longitudinal treatments of long-term survivors of advanced-stage serous ovarian cancer. Gynecologic Oncology 152: 228–34	Case control study n=123	Aggressive surgical treatment intended to achieve microscopic disease, primary debulking surgery, preservation of sensitivity to chemotherapy, and recurrence amenable to secondary debulking are associated with long-term survival.	Larger studies are included.

Kengsakul M, Nieuwenhuyzen-de Boer GM, Bijleveld AHJ et al. (2021) Survival in advanced-stage epithelial ovarian cancer patients with cardiophrenic lymphadenopathy who underwent cytoreductive surgery: a systematic review and meta-analysis. Cancers 7: 5017	Systematic review n=727 15 studies	Enlarged cardiophrenic lymph nodes in preoperative imaging is highly associated with metastatic involvement. Patients with cardiophrenic lymph nodes adenopathy had a lower survival rate, compared with patients without it. Further randomised controlled trials should be conducted to definitively demonstrate whether cardiophrenic lymph node resection at the time of cytoreductive surgery is beneficial.	Review focuses on effect of enlarged cardiophrenic lymph nodes on outcomes.
Kumar S, Long J, Kehoe S et al. (2019) Quality of life outcomes following surgery for advanced ovarian cancer: a systematic review and meta-analysis. International Journal of Gynecological Cancer 29: 1285–91	Systematic review n=1,064 5 studies	Studies on patient reported outcomes after ovarian cancer surgery are limited and potentially confounded. Quality of life after primary surgery or surgery after chemotherapy is not different. There is insufficient evidence for quality of life after extensive surgery for advanced ovarian cancer.	Review only included 2 studies comparing standard with extensive surgery, both of which were observational (Angioli et al., 2013 and Soo Hoo et al., 2015). These were not included in the meta-analysis.
Kumar A, Janco JM, Mariani A et al. (2016) Risk-prediction model of severe postoperative complications after primary debulking surgery for advanced ovarian cancer. Gynecologic Oncology 140: 15–21	Cohort study n=620 Follow up=90 days	138 (22%) of patients who had primary surgery had a grade ≥3 complication. Age (OR 1.21 per 10 years increase in age), BMI (OR 1.35 for BMI<25 kg/m^2 versus reference, OR 2.83 for BMI≥40 kg/m^2 versus reference), ASA score≥3 (OR 1.49), stage (OR 1.69 stage 4) and surgical complexity (OR 2.32 high complexity versus intermediate) were	Study includes all patients who had primary debulking surgery, only a proportion of whom had high complexity surgery.

		predictive of an accordion grade≥3 complication. Within 90 days of surgery, 55 (9%) patients died. A multivariable model included age (OR 1.76 per 10 year increase in age), ASA score≥3 (OR 3.28), preoperative albumin<3.5 (OR 4.31), and BMI (OR 2.04 for BMI<25 kg/m^2 versus reference, OR 3.64 for BMI≥40 kg/m^2 versus reference) was predictive of 90-day mortality.	
La Russa M, Liakou CG, Akrivos N et al. (2020) Learning curve for gynecological oncologists in performing upper abdominal surgery. Minerva Ginecologica 72: 325–31	Case series n=126	Surgical skills in the upper abdomen evolved, demonstrated by an increase in the percentage of patients who had primary surgery, with the surgical team doing more complex procedures, less involvement of other specialties and simultaneously achieving higher rates of complete cytoreduction.	Small study, focusing on the learning curve.
Leandersson P, Granasen G, Borgfeldt C (2017) Ovarian cancer surgery - a population-based registry study. Anticancer Research 37: 1837–45	Cohort study n=458 (with advanced disease)	Tertiary centres do more extensive surgery compared to regional hospitals without increased frequency of major complications. Tertiary centres show differences among patient selection for primary debulking surgery, as well as achieving no residual tumour.	The main aim was to compare tertiary centres with regional hospitals.
Lepinay K, Szubert S, Lewandowska A et al. (2020) An analysis of long-term outcomes in patients treated by extensive bowel resection due to advanced ovarian	Cohort study n=135	Multiple bowel resections seem to improve the overall survival rate of patients when a complete resection of cancerous tissues is achievable. Extensive surgery, including more than 2 segmental bowel	Small study, focusing on bowel resections.

cancer relative to the effectiveness of surgery. Gynecologic and Obstetric Investigation 85: 159–66		resections, should be avoided when complete resection is not feasible.	
Liakou CG, Akrivos N, Kumar B et al. (2020) Cholecystectomy as part of cytoreductive surgery for advanced ovarian cancer: perioperative outcomes. Anticancer Research 40: 2331–36	Cohort study n=144	15% of patients had a cholecystectomy. Patients who had cholecystectomy were more likely to need diaphragmatic peritonectomy, splenectomy, lesser omentectomy, excision of disease from the porta hepatis and liver's capsule ($p<0.001$). There was no difference in the cytoreductive outcomes (complete or optimal) and the rate of grade 3 to 5 complications between the 2 groups ($p=0.10$ and $p=0.06$, respectively). No direct complications related to cholecystectomy were observed.	Small study, focusing on cholecystecto my.
Liberale G, Pop C-F, Polastro L et al. (2020) A radical approach to achieve complete cytoreductive surgery improve survival of patients with advanced ovarian cancer. Journal of Visceral Surgery 157: 79–86	Non-randomised comparative study n=114	A radical approach in advanced ovarian cancer allows a higher rate of complete cytoreductive surgery impacting overall survival. However, a non-significant trend for increased mild complications rate is observed in this group.	Larger studies are included.
Lim MC, Yoo HJ, Song YJ et al. (2017) Survival outcomes after extensive cytoreductive surgery and selective neoadjuvant chemotherapy according to institutional criteria in bulky stage IIIC and IV	Case series n=279	Extensive cytoreductive surgery to minimise residual tumour and selective use of neoadjuvant chemotherapy based on the institutional criteria could result in improved survival outcomes.	Larger studies are included.

epithelial ovarian cancer. Journal of Gynecologic Oncology 28: e48			
Llueca A, Serra A, Climent MT et al. (2021) Postoperative intestinal fistula in primary advanced ovarian cancer surgery. Cancer Management and Research 13: 13–23	Case series n=107	Gastrointestinal fistula was present in 11% of patients in the study (5 colorectal and 7 small bowel). It was statistically significantly associated with PCI >20, more than 2 visceral resections, and multiple digestive resections. Overall and disease-free survival were also associated with gastrointestinal fistula. Multivariate analysis identified partial bowel obstruction and operative bleeding as independent prognostic factors for survival.	Small study, focusing on a single aspect of the procedure.
Lomnytska M, Karlsson E, Jonsdottir B et al. (2021) Peritoneal cancer index predicts severe complications after ovarian cancer surgery. European Journal of Surgical Oncology 47: 2915–24	Case series n=256	Peritoneal cancer index of 21 or more was an independent predictor of high-grade complications after ovarian cancer surgery. Increased PCI also impacted overall survival negatively, but high-grade complications did not influence overall survival.	Included patients with any kind of surgery for ovarian cancer.
Mallen A, Todd S, Robertson SE et al. (2021) Impact of age, comorbidity, and treatment characteristics on survival in older women with advanced high grade epithelial ovarian cancer. Gynecologic Oncology 161: 693–99	Case series n=351	The older cohort had worse Cumulative Illness Rating Scale-Geriatric scores (5.9 versus 4.3, p=0.0001), but no strong associations between comorbidities and treatment characteristics, but less optimal cytoreductive surgery rates (75% versus 87%; p=0.007) with similar surgical complexity and less platinum sensitivity.	Study focused on identifying comorbid conditions and treatment-related factors in older women.

Martinez A, Ngo C, Leblanc E et al. (2016) Surgical complexity impact on survival after complete cytoreductive surgery for advanced ovarian cancer. Annals of Surgical Oncology 23: 2515–21	Case series n=374	Patients who need complex surgical procedures involving 2 or more visceral resections to achieve successful complete cytoreduction have worse outcome than patients with less extensive procedures. The negative impact of surgical complexity was not significant in patients who had upfront procedures. Tumour volume and extension were associated with decreased disease-free survival in patients who had a primary surgical approach. Even though complete cytoreduction is currently the objective of surgery, tumour load remains an independent poor prognostic factor and probably reflects a more aggressive behaviour.	Larger or more recent studies are included.
Minig L, Patrono MG, Cardenas-Rebollo JM et al. (2016) Use of TachoSil ® to prevent symptomatic lymphocele after an aggressive tumor debulking with lymphadenectomy for advanced stage ovarian cancer. A pilot study. Gynecologic and Obstetric Investigation 81: 497–503	Non-randomised comparative study n=36	Using TachoSil in women with advanced stage ovarian cancer who had radical debulking with retroperitoneal lymph node dissection was associated with a non-statistically significant reduction in the incidence of symptomatic lymphocele.	Small study, assessing the use of a sponge sealant patch as part of the procedure.
Narasimhulu DM, Bews KA, Hanson KT et al. (2020) Using evidence to direct quality improvement efforts: Defining the highest impact complications after complex	Cohort study n=1,434	Anastomotic leak is the largest contributor to adverse clinical outcomes and increased resource use after complex cytoreductive surgery. Quality improvement efforts to reduce anastomotic leak	Study focuses on identifying the complications with most impact.

cytoreductive surgery for ovarian cancer. Gynecologic Oncology 156: 278–83		and its impact should be of highest priority in ovarian cancer surgery.	
Nieuwenhuyzen-de Boer GM, van der Kooy J, van Beekhuizen HJ (2019) Effectiveness and safety of the PlasmaJet R Device in advanced stage ovarian carcinoma: a systematic review. Journal of Ovarian Research 12: 71	Systematic review n=77 (5 studies)	Complete cytoreduction was obtained in 79% of the patients. Apart from 1 pneumothorax after extensive surgery, no harm or additional complications related to the use of the PlasmaJet R Device were reported. Data on disease-free survival or overall survival were not reported. The findings suggest that the device is an efficient and safe innovative surgical device for debulking surgery.	Review only included 5 small studies and was focused on a specific device that has been used for the procedure.
Nieuwenhuyzen-de Boer GM, Gerestein CG, Eijkemans MJC et al. (2016) Nomogram for 30-day morbidity after primary cytoreductive surgery for advanced stage ovarian cancer. European Journal of Gynaecological Oncology 37: 63-8	Case series n=293	30-day morbidity after primary cytoreductive surgery for advanced stage epithelial ovarian cancer could be predicted by age, haemoglobin, and World Health Organization performance status.	Larger or more recent studies are included.
Nishikimi K, Tate S, Matsuoka A et al. (2020) Aggressive surgery could overcome the extent of initial peritoneal dissemination for advanced ovarian, fallopian tube, and peritoneal carcinoma. Scientific Reports 10: 21307	Case series n=186	Upper abdominal surgery and bowel resection were done in 149 (80%) and 171 patients (92%), respectively. Residual disease ≤1 cm after surgery was achieved in 164 patients (89%). No residual disease and a high-complexity surgery significantly prolonged progression-free survival ($p<0.01$ and $p=0.02$, respectively) and overall survival ($p<0.01$ and	Larger studies are included.

		p≤0.01, respectively). The extent of initial peritoneal dissemination did not affect the prognosis when initially disseminated lesions >1 cm were resected.	
Nishikimi K, Tate S, Matsuoka A et al. (2020) Learning curve of high-complexity surgery for advanced ovarian cancer. Gynecologic Oncology 156: 54-61	Case series n=271	Proficiency in performing high-complexity surgery was achieved after approximately 50 cases and this number is greater than the number of cases needed to do moderate-complexity surgery. Acceptable rates of severe perioperative complications were observed even during the initial learning period in cases of high-complexity surgery.	Study focuses on learning curve for high-complexity surgery.
Norell CH, Butler J, Farrell R et al. (2020) Exploring international differences in ovarian cancer treatment: A comparison of clinical practice guidelines and patterns of care. International Journal of Gynecological Cancer 30: 1748–56	Review of guidelines	Findings suggest international variations in ovarian cancer treatment. Characteristics relating to countries with higher stage-specific survival included higher reported rates of primary surgery; willingness to undertake extensive/ultra-radical procedures; greater access to high-cost drugs; and auditing.	Review of clinical practice guidelines.
Norppa N, Staff S, Helminen M et al. (2022) Improved survival after implementation of ultra-radical surgery in advanced epithelial ovarian cancer: Results from a tertiary referral center. Gynecologic Oncology 165: 478–85	Non-randomised comparative study n=247 Follow up=median 34 months (2013 to 2016) and 27 months 2016 to 2019)	The change of surgical approach towards maximal surgical effort improved both progression free and overall survival. The survival benefit was unquestionable for patients with stage 3 disease but did not reach statistical significance in patients with stage 4 disease. Overall survival was influenced by residual	Studies with more patients or longer follow up are included.

		tumour and Clavien-Dindo complication grade	
Oseledchyk A, Hunold LE, Mallmann MR et al. (2016) Impact of extended primary surgery on suboptimally operable patients with advanced ovarian cancer. International Journal of Gynecological Cancer 26: 873–83	Cohort study n=96	Because of the increased morbidity of bowel resections without any evidence for improvement of survival, there should be restraint from further resection of intestines if an optimal debulking seems not feasible after removal of the major tumour bulk.	Small, retrospective study.
Park SJ, Mun J, Lee EJ et al. (2021) Clinical phenotypes of tumors invading the rectosigmoid colon affecting the extent of debulking surgery and survival in advanced ovarian cancer. Frontiers in Oncology 11: 673631	Non-randomised comparative study n=83	Clinical phenotypes based on tumour separability from the rectosigmoid colon may depend on tumour invasiveness and extensiveness in advanced ovarian cancer. Moreover, these clinical phenotypes may affect surgical outcomes and survival.	Study focuses on effect of clinical phenotypes based on tumour separability from the rectosigmoid colon.
Pinelli C, Morotti M, Casarin J et al. (2020) Interval debulking surgery for advanced ovarian cancer in elderly patients (>=70y): does the age matter? Journal of Investigative Surgery https://doi.org/10.1080/08941939.2020.1733146	Case series n=153	Older age should not preclude clinicians from offering ultra-radical resection to patients with advanced ovarian cancer after neoadjuvant chemotherapy. In our series, elderly patients had the same treatment with similar outcomes to the younger group.	Small case series, focusing on elderly patients.
Prodromidou A, Pandraklakis A, Iavazzo C (2020) The emerging role of neutral argon plasma (PlasmaJet) in the treatment of advanced stage ovarian cancer: a systematic review.	Systematic review n=77 (5 studies)	Preliminary data on the use of PlasmaJet for ablation of ovarian cancer implants in the peritoneal cavity showed its safety and presented with promising outcomes in achieving complete cytoreduction.	Review only included 5 small studies and was focused on a specific device that has been used for the procedure.

Surgical Innovation 27: 299–306			
Rausei S, Uccella S, D'Alessandro V et al. (2019) Aggressive surgery for advanced ovarian cancer performed by a multidisciplinary team: A retrospective analysis on a large series of patients. Surgery Open Science 1: 43–47	Case series n=156	5-year cancer-related survival rate was 51%: only histotype and residual tumour had a statistically significant association. The results highlight the importance of a team of gynaecologists and general surgeons with specific interests and skills to achieve cytoreduction as rapidly as possible, even when it implies very complex manoeuvres.	Larger studies are included.
Ren Y, Jiang R, Yin S et al. (2015) Radical surgery versus standard surgery for primary cytoreduction of bulky stage IIIC and IV ovarian cancer: an observational study. BMC Cancer 15: 583	Non-randomised comparative study n=353 Follow up=median 25 months	Extensive upper abdominal surgery lengthens the progression-free survival and overall survival of ovarian cancer patients with bulky upper abdominal disease.	Studies with more patients or longer follow up are included.
Rodriguez N, Miller A, Richard SD et al. (2013) Upper abdominal procedures in advanced stage ovarian or primary peritoneal carcinoma patients with minimal or no gross residual disease: an analysis of Gynecologic Oncology Group (GOG) 182. Gynecologic Oncology 130: 487–92	Cohort study n=2,655	Patients who did not need an upper abdominal procedure likely had a limited disease burden and thus, had improved survival compared to patients who had an upper abdominal procedure. In patients with a high disease burden who have minimal residual disease burden, incorporating an upper abdominal procedure without achieving complete resection had minimal survival impact. In this context, aggressive upper abdominal surgery should be reserved for those patients in whom upper abdominal disease can be	Another study using the same data, with similar conclusions, is included (Horowitz et al., 2015).

		completely resected with minimal added morbidity.	
Said SA, van der Aa MA, Veldmate G et al. (2022) Oncologic outcomes after splenectomy during initial cytoreductive surgery in advanced epithelial ovarian cancer: a nationwide population-based cohort study. Acta Obstetricia et Gynecologica Scandinavica 101: 56-67	Cohort study n=3,911	Although advanced stage epithelial ovarian cancer patients who have splenectomy during cytoreductive surgery have less favourable perioperative outcomes, no adverse impact of splenectomy was seen on survival. Splenectomy during cytoreductive surgery seems to be justified to achieve complete cytoreduction in patients with advanced stage epithelial ovarian cancer.	Study focuses on a single aspect of the procedure (splenectomy).
Sinno AK, Li X, Thompson RE et al. (2017) Trends and factors associated with radical cytoreductive surgery in the United States: A case for centralized care. Gynecologic Oncology 145: 493–99	Cohort study n=28,677 admissions	The US rate of radical cytoreductive surgery for advanced ovarian cancer is increasing. At high-volume hospitals, patients receive more radical surgery with fewer complications, supporting further study of a centralised ovarian cancer care model.	Study describes the US national trends and factors associated with cytoreductive surgical radicality.
Son J-H, Kong T-W, Paek J et al. (2019) Perioperative outcomes of extensive bowel resection during cytoreductive surgery in patients with advanced ovarian cancer. Journal of Surgical Oncology 119: 1011–15	Case series n=172	Multiple bowel resections (up to 2 segments) are feasible and can be safely performed with an acceptable complication rate in patients with advanced ovarian cancer.	Small case series, focusing on a single aspect of the procedure (bowel resection).
Szczesny W, Vistad I, Kaern J et al. (2016) Impact of hospital type and treatment on long-term survival among patients with FIGO Stage IIIC epithelial ovarian cancer: follow-	Cohort study n=174	Extensive primary surgery at a teaching hospital, platinol sensitivity, age, and performance status were predictors of survival in this cohort.	More recent studies with more patients are included.

up through two recurrences and three treatment lines in search for predictors for survival. European Journal of Gynaecological Oncology 37: 305–11			
Szubert S, Skowyra A, Wojtowicz A et al. (2021) Total colectomy as a part of ultra-radical surgery for ovarian cancer-short- and long-term outcomes. Current Oncology 28: 4223–33	Case series n=1,636	Total colectomy as a part of ultra-radical surgery for advanced ovarian cancer results in high rates of optimal debulking. However, survival benefits were observed only in patients with no macroscopic disease.	Study focuses on a single aspect of the procedure (total colectomy).
Tate S, Kato Kazuyoshi, Nishikimi K et al. (2017) Survival and safety associated with aggressive surgery for stage III/IV epithelial ovarian cancer: A single institution observation study. Gynecologic Oncology 147: 73-80	Non-randomised comparative study n=176	Outcomes improved after implementing aggressive surgery for advanced ovarian cancer, without causing a significant increase in mortality.	Small, non-randomised study with historical controls.
Torres D, Kumar A, Wallace SK et al. (2017) Intraperitoneal disease dissemination patterns are associated with residual disease, extent of surgery, and molecular subtypes in advanced ovarian cancer. Gynecologic Oncology 147: 503–8	Cohort study n=741	Intraperitoneal disease dissemination patterns are associated with residual disease, surgical complexity, and tumour molecular subtypes. Patients with upper abdominal or miliary dissemination patterns are more likely to have mesenchymal high-grade serous ovarian cancer and in turn achieve lower rates of complete resection.	The main was to investigate the association between intraperitoneal disease dissemination patterns, residual disease, surgical complexity, and molecular subtypes.
Tozzi R, Ferrari F, Nieuwstad J et al. (2020) Tozzi classification of diaphragmatic surgery	Cohort study n=170	Diaphragmatic surgery can be classified in 3 types. Type 1 operations are relatively straightforward. They do not add specific	The aim of the study was to introduce a systematic classification

in patients with stage IIIC-IV ovarian cancer based on surgical findings and complexity. Journal of Gynecologic Oncology 31: e14		morbidity to the debulking surgery and are usually associated with less complex operations. Type 2 operations are the most common. The findings on the diaphragm are extensive, a full thickness resection is often needed, and liver mobilisation is always needed. Type 3 operations are the most complex procedures and are associated with the highest risk of morbidity. Detailed knowledge of the hepatic vascular anatomy is essential.	of diaphragmatic surgery in patients with ovarian cancer based on disease spread and surgical complexity.
Turnbull HL, Akrivos N, Wemyss-Holden S et al. (2017) The impact of ultra-radical surgery in the management of patients with stage IIIC and IV epithelial ovarian, fallopian tube, and peritoneal cancer. Archives of Gynecology and Obstetrics 295: 681–7	Case series n=135 Follow up not reported	Up to 50% of patients needed at least 1 surgical procedure classified as ultra-radical. Cytoreduction to no macroscopic visible disease (complete) and to disease with greater tumour diameter of less than 1 cm (optimal) was achieved in 54% and 34% of the cases, respectively.	The main aim of the study was to estimate the proportion of patients needing ultra-radical surgery.
van de Vrie R, Rutten MJ, Asseler JD et al. (2019) Laparoscopy for diagnosing resectability of disease in women with advanced ovarian cancer. Cochrane Database Syst Rev. 23: 3(3):CD009786. doi: 10.1002/14651858.CD009786.pub3.	Systematic review n=1,563 18 studies	The studies suggest that laparoscopy can accurately diagnose the extensiveness of disease. When performed after standard diagnostic work-up fewer women had unsuccessful debulking surgery and therefore resulting in less morbidity. There will still be women having a laparotomy resulting in residual tumour of > 1 cm after surgery.	Review focuses on the use of laparoscopy to diagnose the extensiveness of ovarian cancer.
Wallace S, Kumar A, Mc Gree M et al. (2017) Efforts at maximal cytoreduction improve	Cohort study n=447	Overall survival was statistically significantly better for patients with no residual disease (p≤0.001).	Larger or more recent studies are included.

survival in ovarian cancer patients, even when complete gross resection is not feasible. Gynecologic Oncology 145: 21–26		Complete resection improved from 33% to 54% (p<0.001), and residual disease >1cm decreased from 20% to 7% (p<0.001) when comparing the 2003 to 2006 (n=202) with 2007 to 2011 (n=245) cohorts. Surgical complexity increased in the latter period (24% versus 41%). 30-day Accordion grade 3 to 4 morbidity remained consistent (19% versus 21%, p=0.60), 30-day mortality decreased (5% to 1%, p=0.035), and median overall survival improved from 36 to 40 months after cytoreduction standardisation.	
Wong DH, Mardock AL, Manrriquez EN et al. (2021) Trends in extent of surgical cytoreduction for patients with ovarian cancer. PloS one 16: e0260255	Case series n=79,400	From 2013 to 2017, there was a decrease in the proportion of cases with extended procedures (19% to 15%, p<0.001). There were significant decreases in the proportion of cases with small bowel, colon, and rectosigmoid resections (p<0.001). Patients who had extended cytoreduction were more likely treated at a high surgical volume hospital (37% vs 31%, p<0.001) over the study period. For their hospital admission, patients who had extended cytoreduction had increased mortality (1.6% versus 0.5%, p<0.001) and length of stay (10 days versus 5 days, p<0.001). With the increased use of neoadjuvant chemotherapy from 30% in 2010 to 39% in	Study describes trends in surgical treatment for ovarian cancer in the US.

		2016, it is likely there is a decreased need for extended procedures during cytoreduction.	
Xu Y, Jia Y, Zhang Q et al. (2021) Incidence and risk factors for postoperative venous thromboembolism in patients with ovarian cancer: Systematic review and meta-analysis. Gynecologic Oncology 160: 610–8	Systematic review 19 studies	Venous thromboembolism, especially subclinical venous thromboembolism, is a prevalent complication in postoperative patients with epithelial ovarian cancer. History of venous thromboembolism, advanced FIGO stages, high complexity of surgery, obesity, older age, ascites, higher ASA score, smoking history and suboptimal debulking are associated with this increased incidence of postoperative venous thromboembolism among patients with epithelial ovarian cancer.	Review focuses on a single aspect of the procedure (postoperative venous thrombo-embolism)
Ye S, Wang Y, Chen L et al. (2022) The surgical outcomes and perioperative complications of bowel resection as part of debulking surgery of advanced ovarian cancer patients. BMC surgery 22: 81	Case series n=282	Bowel resection as part of debulking surgery in patients with newly diagnosed ovarian cancer resulted in a severe morbidity rate of 9%.	Study focuses on a single aspect of the procedure (bowel resection).
Ye S, He T, Liang S et al. (2017) Diaphragmatic surgery and related complications in primary cytoreduction for advanced ovarian, tubal, and peritoneal carcinoma. BMC Cancer 17, 317 https://doi.org/10.1186/s12885-017-3311-8	Case series n=150	Diaphragm peritonectomy and diaphragm full-thickness resection as part of an extensive upper abdominal procedure resulted in an acceptable morbidity rate. Pleural effusion, pneumonia and pneumothorax were the most common pulmonary morbidities. The pleural drainage rate was not high enough to justify prophylactic chest tube	Small study, focusing on a single aspect of the procedure (diaphragmatic surgery).

		placement for all patients. However, patients who had diaphragm full-thickness resection merited special consideration for intraoperative prophylactic drainage.	