Diagnosis and Management of Epithelial Ovarian Cancer

Katherine Nixon and Christina Fotopoulou

Abstract

Ovarian cancer is the fifth most common cancer among women after breast, bowel, lung, and endometrial and remains the leading cause of death due to gynecological malignancy (Cancer.org 2016). Epithelial ovarian cancer accounts for the vast majority of ovarian malignancies with figures of around 85%. Due to its insidious nature of presentation, it is often not diagnosed until the later stages leading to a high mortality rate. Five-year survival is very much influenced by stage at diagnosis. Over the last 20 years, incidence and mortality have remained fairly static, and much research is being undertaken looking for aids to diagnosis, possible screening methods, and improvement in treatment options, both surgical and medical. In this chapter we will discuss presentation, diagnostic tools, and possible management regimes for patients with epithelial ovarian cancer.

Keywords

Epithelial • Diagnosis • Imaging • Staging • Management

Contents

K. Nixon (✉)
Department of Gynecology, Imperial College NHS Trust, Queen Charlottes and Hammersmith Hospital, London, UK
e-mail: Katherine.nixon@hotmail.co.uk

C. Fotopoulou (✉)
Department of Gynaecological Oncology, West London Gynecological Cancer Centre, Imperial College NHS Trust, Queen Charlottes and Hammersmith Hospital, London, UK
e-mail: chfotopoulou@gmail.com

D. Shoupe (ed.), *Handbook of Gynecology*,
DOI 10.1007/978-3-319-17798-4_1

1 Introduction

Epithelial ovarian cancer (EOC) is the second most common genital malignancy after uterine cancer in women and accounts for the majority of deaths from gynecological malignancies in Western countries (Jemal et al. 2007). Lifetime risk is about 1.6%; the latest data show that 1 in 43 women will develop EOC during their lifetime. Women with a mutated BRCA1 or BRCA2 gene are at increased risk ranging between 25% and 60% depending on the specific mutation.

Despite the continuous advances in diagnostics and imaging, more than 70% of the patients with newly diagnosed EOC will present with an advanced stage FIGO III and IV. This is mainly attributed to the unusual tumor biology and clinical behavior of the disease, which is typically associated with locoregional dissemination throughout the peritoneal cavity. This behavior results in a delay of symptoms until only at a later stage in a rather nonspecific pattern, including abdominal bloating and distention with pain, urinary frequency, postmenopausal bleeding, loss of appetite, and occasionally rectal bleeding (Goff 2012). This unusual natural history has therefore generated unique therapeutic strategies that highlight the important contribution of locoregional control to survival for this disease (Vaughn et al. 2011).

The last decades have brought a significant advance in the treatment of EOC, both in surgical and systemic aspects, with the development and addition to standard treatment of extensive cytoreductive techniques, refinement of surgical skills in the upper abdomen, dose-dense regimes, and novel targeted therapies. Nevertheless, the survival rate of women with EOC has changed little since the revolutionary platinum-based treatment that was introduced more than 30 years ago (Omura 1986).

Only in the recent years, targeted therapies based on the principle of antiangiogenesis (Monk 2009) and homologous recombination repair mechanisms have brought a significant efficacy in the treatment of EOC: bevacizumab, pazopanib, and olaparib have proven in a maintenance regime during and/or after successful chemotherapy their efficacy in significantly prolonging progression-free survival (PFS), but failed to significantly influence the overall survival of the patients (Janczar et al. 2009). A possible mechanism discussed for this consistent discrepancy is the high rate of crossover in the subsequent lines that contaminate any survival benefit attributed to each agent.

Great changes in the way we understand ovarian cancers have occurred in the last decade. Traditionally ovarian cancers have been categorized based on their origin either from mesothelial epithelial cells, germ cells, or stromal cells, this being based on the theory that epithelial ovarian cancers arise from the ovarian epithelium. However it is now widely believed that high-grade serous ovarian cancers more likely arise from the epithelium of the fallopian tubes and ovarian deposits are therefore secondary implants. As such these are now investigated and managed as a group with primary peritoneal carcinomas (Kurman et al. 2010). Epithelial ovarian malignancies are histologically divided into serous carcinoma, mucinous carcinoma, endometrioid carcinoma, undifferentiated carcinoma, and clear cell carcinoma. These are further divided into low-grade and high-grade subtypes with low grade tending to be more stable and high grade behaving aggressively and usually presenting at an advanced stage (Doufekas 2014).

Management and prognosis are determined by stage at presentation and histological grading following biopsy or debulking surgery. The etiology of epithelial ovarian cancers has been studied at length. Factors found to increase risk include age, with most diagnoses made after 40 years, a steep curve after 50, and peak in the 80s. Around 10% of ovarian cancers have a hereditary component with the vast majority being BRCA1 and two mutations; there is also an association with

hereditary non-polyposis colorectal cancer. Previous breast cancer, nulliparity, history of endometriosis, and long-term use of hormone replacement therapy have also all been shown to increase risk of ovarian cancer. Conversely, prolonged use of combined oral contraceptive medication, parity, and breastfeeding have been associated with risk reduction as well as history of tubal ligation and hysterectomy. Recent evidence even suggests that women who give birth to their first child in their mid-30s or later may have an even lower risk of ovarian cancer compared to those who gave birth to their first child earlier than that. Each 5-year increase in a woman's age at birth of their first child seems to correspond to a 16% lower risk of ovarian cancer. This association is not fully understood; however a possible mechanism is a progesterone-mediated effect which seems to be more prevalent and efficient in older women.

2 Presentation

Ovarian cancer often presents at a late stage and can be difficult to diagnose. This is because the signs and symptoms tend to be nonspecific and are sometimes put down to gastrointestinal upset. Common symptoms include bloating, loss of appetite, abdominal pain, disturbance in urinary or bowel habit, and weight loss. Patients may have increased abdominal girth, evidence of pelvic mass and ascites, bowel obstruction, and, depending on stage of presentation, a cachectic appearance.

Correct diagnosis is often delayed either because patients do not present to a medical professional or due to initial misdiagnosis of conditions such as irritable bowel disease, diverticular disease, and urinary tract infection.

3 Diagnosis

3.1 History and Assessment

If a diagnosis of ovarian cancer is suspected, a referral should be made to a specialist gynecological oncology center.

In clinic a full history should be taken including symptoms, age, parity, past medical history, and past surgical and gynecological history, especially focusing on risk factors, e.g., previous endometriosis or malignancies. Although the majority of patients will present postmenopausal, it is important to determine a patients' wishes with regard to fertility if premenopausal as this may influence management. Past surgical history is important as most treatment options for epithelial ovarian cancer will involve surgery and previous abdominal operations could complicate this. Different options for management will also be determined by the patients' performance status; therefore a full medical history is important to include, e.g., history of diabetes, respiratory or cardiac diseases, and smoking status. Social history should include who their support system is (family/friends), given the gravity of potential diagnosis being made. It will also contribute to the assessment of a patient's performance status; for example, someone requiring nursing home care will likely be a more complex surgical candidate than someone who is independent and living in their own home. Fragility scores predicting surgical outcome in older patients with comorbidities have not been well defined in ovarian cancer surgery; it is however the focus of various currently ongoing studies.

Examination in clinic should include patients' BMI, blood pressure, and heart rate. These simple observations will help indicate their current health status. Abdominal examination should assess for distension, presence of a mass or ascites, any tenderness, and previous scars. Vaginal examination will help with assessment of size and mobility of a pelvic mass, an indication of the likely difficulty of surgery. Rectal examination is helpful in determining any invasion of disease and to help instruct if rectal resection is likely to be necessary.

4 Bloods

Initial blood tests should include baseline full blood count, renal, and liver function and tumor markers to help determine the origin of the cancer.

Markers should be sent for cancer antigen 125 (Ca125) for ovarian pathology, carcinoembryonic antigen (CEA) for colorectal, carbohydrate antigen 19-9 (Ca 19-9) for pancreatic/gastrointestinal malignancies, and possibly alpha-fetoprotein if germ cell tumor is suspected. Ca 125 has a low sensitivity of 55% as it can be raised due to many processes in the pelvis, usually inflammation from infection or endometriosis. The ration of CA125 to CA199 could indicate a non-ovarian pathology and dictate the necessity of further investigations like colonoscopy. Some epithelial ovarian cancers will not express Ca125 and this makes them more difficult to follow-up posttreatment.

5 Imaging

Transvaginal ultrasound is the most commonly used modality for first-line imaging in epithelial ovarian cancer. It can demonstrate the presence of pelvic mass and the characteristics of the mass. It can also detect any free fluid in the pelvis and assess if the adnexal structures are fixed or mobile indicating the possible presence of adhesions. Features suggestive of malignancy include a multilocular mass, presence of papillary structures, solid areas, and a mass with increased vascularity on Doppler ultrasound. Risk of malignancy index can be used to help assess the likelihood of a mass being malignant. This is done by a simple calculation of a score given to the ultrasound findings, the menopausal status of the patient, and the Ca125 level (NICE 2011). The International Ovarian Tumor Analysis (IOTA) guidance may be used for premenopausal women (Timmerman 2010). Simple rules were applicable in 77% of adnexal masses and when inconclusive masses were considered as malignant, reporting a sensitivity of 91% and specificity of 93%. Guidance could consider supporting recruitment into ongoing trials that evaluate diagnostic tests and presurgical triage.

Magnetic resonance imaging (MRI) of the pelvis is used to correlate with USS to help further determine the nature of a mass in patients with the absence of metastatic sites and with fertility sparing wish, for additional guidance in regard to whether such an approach would be advisable or feasible.

Computerized tomography (CT) is used to evaluate stage and tumor dissemination pattern of the disease and especially identify distant intraparenchymatous metastases that would determine operability and course of optimal therapeutic approach. Additionally, chest pathology like pulmonary embolism, mediastinal lymphadenopathy, etc., can be identified and have impact on therapeutic decisions.

Epithelial ovarian cancer acts like a rash within the abdomen using the peritoneum as a vector; the disease is most commonly seen on the peritoneum covering the pelvis, bladder, para-colic areas, upper abdominal structures, and diaphragm. Omental disease can occur in deposits or forming one large "cake" of disease. Para-aortic and pelvic lymph nodes may be enlarged. CT can assess the presence of disease on the splenic surface and liver capsule plus any deposits on small/large bowel serosa, mesentery, and any more invasive lesions that may require a bowel resection to remove. CT PET (positron emission tomography) scans use a radioactive glucose solution which is injected into patients and the uptake monitored. The glucose solution is more readily taken up by cancerous cells, and therefore this imaging modality is useful in helping to locate areas of metastasis and also disease activity in lymph nodes. The rate of uptake can also advise on the potential grade of the cancer.

6 Pathology

Examination, blood results, and imaging may be sufficient to provide a working diagnosis of ovarian cancer, and even though histological diagnosis prior to primary surgery is not mandatory, it would be advisable to be available in borderline cases with atypical clinical pattern, in young women with fertility sparing wish – in which case a two-stage approach should be

followed. If ascites is present, this can be drained and samples sent for both cytology and microscopy. Biopsies may be taken from tumor deposits demonstrated on imaging on the peritoneum or omentum or sometimes from the mass itself; this is usually done under USS or CT guidance. Occasionally the histology is already known from previous surgery such as an oophorectomy for ovarian cyst at another unit, and the patient is then referred to the specialist unit for ongoing management. If a CT- or US-guided biopsy is not technically possible, then a laparoscopic histological confirmation should be performed.

7 Staging

Using the imaging a provisional staging can be made. It should be noted that full staging will come after surgery, if this takes place, once the suspicious tissues have been removed and examined histologically. Imaging may indicate affected areas which turn out to be benign after excision and vice versa.

The staging for ovarian cancer as per FIGO 2014 is as follows (Helm 2014)	
Stage I consists of tumor limited to the ovaries or fallopian tubes	
Stage IA includes the following	
Tumor limited to one ovary (capsule intact) or fallopian tube	
No tumor on the external surface of the ovary or fallopian tube	
No malignant cells in ascites or peritoneal washings	
Stage IB includes the following	
Tumor limited to both ovaries (capsules intact) or fallopian tubes	
No tumor on the external surface of the ovaries or fallopian tubes	
No malignant cells in ascites or peritoneal washings	
Stage IC includes tumor limited to one or both ovaries or fallopian tubes, with any of the following:	
Stage IC1	Surgical spill
Stage IC2	Capsule ruptured before surgery, or tumor on ovarian or fallopian tube surface
Stage IC3	Malignant cells in the ascites or peritoneal washings
Stage II tumor involves one or both ovaries or fallopian tubes, with pelvic extension (below pelvic brim) or primary peritoneal cancer	
Stage IIA	Extension and/or implants on the uterus and/or ovaries and/or fallopian tubes
Stage IIB	Extension to other pelvic intraperitoneal tissues
Stage III tumor involves one or both ovaries or fallopian tubes, or primary peritoneal cancer, with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes	
Stage IIIA1	Positive (cytologically or histologically proven) retroperitoneal lymph nodes only
Stage IIIA1(i)	Metastasis up to 10 mm in greatest dimension
Stage IIIA1(ii)	Metastasis more than 10 mm in greatest dimension
Stage IIIA2	Microscopic extrapelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes
Stage IIIB involves macroscopic peritoneal metastasis beyond the pelvis up to 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes	
Stage IIIC involves macroscopic peritoneal metastasis beyond the pelvis more than 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes. Stage IIIC includes extension of tumor to the capsule of liver and spleen without parenchymal involvement of either organ	
Stage IV	
Stage IV consists of distant metastasis, excluding peritoneal metastases, and includes the following:	
Stage IVA: Pleural effusion with positive cytology	
Stage IVB: Parenchymal metastases and metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)	

8 Management

Treatment of epithelial ovarian cancer is from a multidisciplinary approach based on input from expert gynecological oncologists, medical oncologists, pathologists, and radiologists. In comprehensive cancer centers, patients should ideally be additionally supported by a specialist nurse to help them with their treatment journey (Vernooji 2007). The mainstay of treatment is surgical cytoreduction combined with systemic agents.

9 Definition of Surgery in EOC

The large differences in current practice nationally and internationally are also being reflected in the discrepancy in the terminology used to adequately characterize the different types of surgery at the different stages of the disease. A clarification of the various definitions used broadly is necessary before proceeding so that the context is clear:

- Exploratory surgery: usually laparoscopically to assess intraperitoneal dissemination patterns; the value of this in assessing operability is highly questionable and not standard practice, unless to set histological diagnosis or in cases of unclear ascites with absent ovarian mass or peritoneal disease at imaging.
- Primary or upfront cytoreduction: tumor debulking at initial diagnosis before any systemic treatment, aiming at maximal tumor reduction and ideally total macroscopic tumor clearance.
- Interval debulking: cytoreductive surgery after usually three cycles of neoadjuvant chemotherapy.
- Second look surgery: exploratory laparotomy or laparoscopy after completion of systemic treatment to confirm response; this method is obsolete, since it has no evidence of survival benefit.
- Secondary surgery: surgery due to the first relapse. Here definition is unclear in regard to aim; usually used to describe cytoreductive effort but can also be used for palliative surgery due to symptoms at first relapse.
- Tertiary surgery: the equivalent of secondary surgery at the second relapse.
- Quaternary surgery: the equivalent of secondary surgery at the third relapse.
- Palliative surgery: surgery aiming at palliation of tumor-induced symptoms, such as bowel obstruction and intestinal perforation, where conservative management has failed.

The maximum diameter of the postoperative residual tumor after cytoreductive surgery is considered the strongest independent clinical prognostic factor (Du Bois et al. 2009). Bristow et al. published for the first time a systematic meta-analysis on this subject based on a total of 53 studies with 6885 patients overall (period: 1989–1998).

They studied the influence of surgical tumor resection on overall survival. Published studies with surgically operated patients with FIGO stage III or IV and subsequent platinum-based chemotherapy were evaluated. According to this meta-analysis, patient cohorts that had had a maximum tumor reduction rate (<2 cm) of over 75% had a median overall survival of 36.8 months. By contrast, patient cohorts with a maximum tumor reduction rate of less than 25% had a median overall survival of only 23 months. Every 10% reduction in tumor was associated with a 6.3% prolongation of median overall survival (Bristow et al. 2002).

There is internationally ongoing debate as to the best timing of surgery, whether this should be done at the outset of treatment or following a course of neoadjuvant chemotherapy. However, the general recommended course of treatment for those patients with good performance status and resectable disease is primary debulking surgery followed by adjuvant chemotherapy (Colombo et al. 2009). Neoadjuvant chemotherapy can be used if the extent of the disease at the time of presentation is deemed to be not suitable for surgical resection; the patient is not fit enough to undergo a primary debulking due to advanced age, low performance status, and comorbidities, or for bridging acute events like thromboembolic episodes. Nevertheless, practice regarding the optimal upfront approach varies strongly between centers and countries and often depends on the gynecological oncology center and experience of surgeon. Two prospective randomized trials (Vergote et al. 2010; Kehoe et al. 2015) have demonstrated lower surgical morbidity and mortality in the neoadjuvant approach; however the oncologic safety is being doubted since both trials included mainly patients who had undergone in their majority suboptimal cytoreduction with much lower resection rates then anticipated in specialized centers for the disease. For that reason, future prospective randomized trials with strictly defined surgical quality are warranted in order to

answer this question and establish optimal practice. These future trials will address additional issues such as management of fragile patients, assessment of short- and long-term quality of life scores, impact of ascites, and pleura effusion on hemodynamic management and would also have an additional translational portfolio in an attempt to identify valid biomarkers that would predict operability and clinical outcome. These are often extensive operations with the possibility of large volume shifts. Therefore, anesthetic involvement prior to proceeding is recommended and an ITU bed may be indicated. Surgery for ovarian cancer should always ideally be carried out by an experienced gynecological oncology surgeon (Eisenkop 1992; Paulsen 2006).

10 Tumor Dissemination Patterns at Relapse

A better understanding of the tumor dissemination patterns followed in the primary and subsequently in the recurrent situation of EOC is highly essential for the better understanding of the disease and may enhance the evolution and refinement of surgical and, by extension, systemic approach (Gabra 2010). Nevertheless, data correlating the tumor dissemination pattern and surgical outcome in primary and later recurrent situation at the same patient hardly exist. A prospectively maintained database evaluating the intraoperative tumor dissemination pattern and operative outcome of all women who underwent both primary and secondary tumor-debulking surgeries in the same institution within a 10-year period of time has been systematically analyzed (Braicu 2011). On the basis of 79 patients, it could be demonstrated that secondary cytoreduction appears to be associated with significantly lower optimal tumor-debulking rates compared to primary debulking, mainly attributed to less "accessible" recurring patterns such as gastrointestinal serosa, radix mesenterii, gastric serosa, and porta hepatis. Interestingly, no significant predictors of surgical outcome or tumor pattern, such as peritoneal carcinomatosis, intestinal tumor involvement, or positive lymph nodes, could be identified between primary and relapse. It appeared that a different tumor "behavior" is followed in the primary compared to recurrent situation of the disease even in the same patient, while interestingly the primary tumor patterns do not appear to have any predictive value for the tumor patterns at recurrence, apart from the predictive value of initial tumor residuals which clearly correlate with the amount of postoperative tumor residuals at relapse. Venturing even beyond surgical borders, one could say that ovarian cancer reappears under a different dissemination profile than at its initial presentation in terms of a higher "aggressivity" and higher dissemination tendency. Any potential attempts to derive clinically relevant conclusions on the outcome of the forthcoming cytoreduction depending on the outcome and tumor dissemination at the outset of the disease would rather fail. Therefore, novel biomarkers are warranted in order to predict tumor patterns followed at recurrence and hence surgical outcome.

The role of imaging is also unclear in the characterization of peritoneal carcinosis as definite basis for indication for surgery at relapse, even though PET-CT appears to have higher accuracy indices than simple CT. Results suggest that PET/CT may prove a useful tool for presurgical staging of ovarian cancer with a sensitivity and specificity of 78% and 68%, respectively. In a prospective trial correlating the PET-CT results with laparoscopic findings, PET/CT showed an adequate correlation between SUVmax values and laparoscopy findings of lesions >5 mm, but a high rate of false negative results in lesions <5 mm such as in carcinomatosis (De Iaco 2010). Clinical decision-making processes should therefore be very carefully constructed around clinical findings and symptoms and history of the disease and not on imaging alone.

Interestingly, it appears that patterns of relapse may also be altered depending on the primary mode of treatment. In a retrospective evaluation of 175 stage IIIC-IV EOC patients who were operated in an Italian gynecology cancer center with diffuse peritoneal carcinosis, patterns of relapse were stratified according to whether the patient had upfront or interval debulking surgery at initial presentation (Petrillo et al. 2013). Forty

patients received complete primary debulking surgery, and the remaining 135 were treated with neoadjuvant chemotherapy followed by interval debulking surgery with absent residual tumor after surgery. No differences were observed in the distribution of clinical pathological characteristics at the time of diagnosis between the two groups. In a median follow-up period of 31 months (range 9–150 months), the authors observed 20 (50.0%) recurrences in the upfront group compared to 103 (76.3%) in the interval debulking group. Duration of primary platinum-free interval was also significantly shorter in the interval debulking arm (13 vs. 21 months, respectively). A significantly higher percentage of patients in the interval debulking group experienced platinum-resistant recurrences and carcinomatosis at the time of relapse. Also the platinum-free interval of second relapse was significantly longer in favor of the upfront arm. This documented more "favorable behavior" of recurrent disease in EOC patients with diffuse peritoneal carcinomatosis treated with complete upfront surgical approach compared to women submitted to neoadjuvant chemotherapy needs to be prospectively validated in larger datasets; however it does give a clear signal about the highly significant impact of the quality of upfront treatment even in peritoneal disseminated disease.

11 Value of Secondary Cytoreduction

There is clear evidence that patients experiencing an early platinum resistant or even refractory EOC relapse are highly unlikely to benefit from secondary debulking surgery. Older reports could demonstrate very dismal overall survival rates of a mean value of 8 months, not adequately justifying a radical surgical approach but rather concentrating on palliation (Morris et al. 1989; Segna 1993). Anecdotal and empirical case reports may demonstrate a survival benefit in platinum-resistant patients who present with early lymph node relapse which rather represents a persistent lymph node metastasis not removed through lymph node dissection at primary surgery and hence not representing a true relapse (Chan 2007). The selection of these patients however is very challenging and no randomized data will ever exist for this special subgroup of women. Caution should be awarded to adequately judge and evaluate situations always taking into consideration the quality of surgery at primary or interval debulk and the tumor dissemination pattern at relapse.

The first systematic data analysis for secondary debulking in a platinum-sensitive setting originates from the German AGO (Arbeitsgemeinschaft Gynaekologische Onkologie) within the DESKTOP I trial (Harter et al. 2006). This was a retrospective evaluation of 267 patients which showed that patients appeared to benefit from surgery in recurrent EOC only when total macroscopic clearance was achieved. Complete tumor resection was associated with significantly longer survival compared with surgery leaving any postoperative residuals. Hence, the challenge was to accurately preoperatively identify the optimal candidates for surgery, in order to avoid surgical procedures that would not have a prognosis benefit for the patients. Based on a multivariate model, three factors were identified as independently predicting resectability, building so the so-called AGO score: good performance status, complete resection at primary surgery, and absence of ascites. The value of the AGO score lies with others also in the simplicity to use, based on easy-to-assess clinical features and not on complicated mathematic algorithms that would make its use in the daily routine very challenging. An exploratory analysis of the DESKTOP results to evaluate the role of peritoneal carcinomatosis present in recurrent EOC clearly showed that even though peritoneal carcinomatosis was a negative predictor for complete resection in the recurrent situation of the disease, it appeared to have no negative impact on survival if total macroscopic clearance could be achieved. The authors concluded that improving surgical skills might increase the patient proportion that could benefit from surgery for recurrent disease (Harter et al. 2009).

A subsequent confirmation and validation of the AGO score followed within the prospective,

multicenter DESKTOP II trial, in which the AGO score could be confirmed as a useful and reliable tool to predict complete tumor resection in more than two thirds of patients with platinum-sensitive relapsed EOC (Harter et al. 2011). Participating centers prospectively enrolled patients with platinum-sensitive first or second relapse. The AGO score was then applied to all patients, but each center was free to decide the therapeutic management. A total of 516 patients were screened within 19 months; of these, 261 patients (51%) were classified as score positive, and 129 patients with a positive score and first relapse received a secondary tumor debulking. The rate of complete resection was 76%, thus confirming the validity of this score regarding positive prediction of complete resectability in more than two thirds of patients. Interestingly on analysis poor correlation of imaging and intraoperative findings was found, both in terms of number of lesions identified and localization of tumor.

Perioperative morbidity and mortality appeared to be acceptable within the DESKTOP series with a mortality as low as 0.8% and an 11% relaparotomy rate mainly due to bowel leakage or fistula (7%). DVT rate was 2%, while 52% of the patients required a postoperative intensive care stay of a median 2 days (range: 1–20). Morbidity and mortality data of other equivalent series are in a similar level.

A subsequent multicenter randomized trial, the DESKTOP III (AGO-Ovar OP.4.), commenced in June 2010, to prospectively evaluate the impact of recurrent EOC-surgery in platinum-sensitive patients with positive AGO score (tumor-free initial surgery, good performance status, and ascites $<$500 ml). The study has completed recruiting all 409 preplanned patients and results are now awaited within the next 2–3 years. This very important study is anticipated to finally answer the question whether surgery at the relapse situation of the disease is truly associated with a benefit for survival and quality of life of the affected patients.

The equivalent American trial from the GOG (GOG 0213) has been recruiting for a longer period than the DESKTOP trial, however in a slower rhythm. A further difference is the additional randomization to systemic bevacizumab 15 mg/m^2 at maintenance. There are future plans to combine data of both trials together to achieve a larger cohort and more robust survival data.

The largest retrospective multicenter and multinational analysis worldwide showed equivalent results (Zang et al. 2011; Tian et al. 2012). Of the 1075 evaluated patients, 434 (40.4%) underwent complete resection. Total macroscopic tumor clearance was associated with a significant improvement in survival, from a median OS of 57.7 months, when compared with only 27.0 months in those with residual disease of 0.1–1 cm and 15.6 months in those with residual disease of $>$1 cm, respectively. Complete secondary cytoreduction was associated with six variables: FIGO stage, residual disease after primary cytoreduction, PFS, Eastern Cooperative Oncology Group (ECOG) performance status, CA125, and ascites at recurrence. These variables were entered into the risk model and assigned scores ranging from 0 to 11.9. Patients with total scores of 0–4.7 were categorized as the low-risk group, in which the proportion of complete cytoreduction was 53.4% compared with 20.1% in the high-risk group. In external validation, the sensitivity and specificity was 83.3% and 57.6%, respectively.

In one systematic meta-analysis by Bristow et al. where 40 cohorts of 2019 patients with recurrent EOC were identified over a period of 24 years, it could be clearly shown that, after controlling of all other disease-related factors, each 10% increase in the proportion of patients undergoing complete cytoreductive surgery was associated with a 3-month increase in median cohort survival time (Bristow 2009).

Despite the very encouraging retrospective data, it is still not clear if the actual tumor resection is significantly influencing survival or if it is just a surrogate marker of more "favorable" tumor biology and therefore associated with a better overall prognosis. The first two prospectively randomized surgical trials will definitely answer this question, change clinical practice worldwide, and set new evidence-based standards.

12 Value of Tertiary Cytoreduction

The scenery is even more vague and undefined in the second relapse of EOC. Obtaining palliation in cases of severe tumor-induced symptoms like bowel obstruction may often be the main purpose of tertiary cytoreduction (TCS); still, the potential prolongation of survival and improvement of quality of life may also constitute relevant goals even in a tertiary setting of this chronic disease. Experiences regarding TCS were recently only limited in six monocentric analyses including a small number of patients. All conclude mainly to the fact that TCS may indeed offer a survival benefit in a highly select group of recurrent EOC patients and that this benefit appears to be greatest in those patients in whom a complete gross resection can be achieved (Shih et al. 2010; Hizli et al. 2012). Leitao et al. was the first to report on 26 patients who had undergone TCS at a single institution (Leito et al. 2004). Treatment-free interval before TCS and current postoperative residual disease could be identified as independent prognostic factors for survival, whereas time to first recurrence failed to retain prognostic significance in the multivariate analysis. Interestingly, platinum resistance failed to be identified as being significantly associated with a more dismal outcome. No independent factors predicting optimal cytoreduction could be identified among common clinical factors such as advanced age, residual disease after initial surgery, time to first recurrence, time from second cytoreduction, platinum-sensitivity as well as size and site of tumor-recurrence.

A further retrospective report by Karam et al. (2007) evaluating the outcome of 47 EOC patients undergoing tertiary cytoreduction confirmed the statistically significant superior overall survival in patients with microscopic versus macroscopic residual disease (24 vs. 16 months). After controlling these analyses for age, time to progression, and optimal residual disease during TCS, the authors identified only the presence of diffuse peritoneal carcinosis, at tertiary exploration as significant predictor of a worse overall survival. In a subanalysis of patients with limited disease implants, multivariate analysis could indeed indicate that total macroscopic tumor clearance at TCS retains prognostic significance of overall survival, so that the authors concluded that size of disease implants on preoperative imaging may guide the selection of ideal candidates for TCS. Regarding the assessment of potential preoperative predictors of optimal TCS, the authors could identify only tumor size (<5 cm) as a statistically significant predictor of complete tumor resection at TCS. Other variables like presence of ascites, initial disease-free interval, age at TCS, and limited number of disease sites on preoperative imaging (i.e., <4) could not show any significant impact.

In a smaller analysis including only 20 patients, the authors concluded to opposing results, challenging the benefit of TCS in EOC (Gultekin et al. 2008). Multivariate analysis could identify neither any significant predictors for optimal cytoreduction nor any significant prognostic factors for survival. Major intrinsic pitfalls of this particular analysis are though, as emphasized by the authors themselves, the small sample of patients, rendering a multivariate analysis to have to be interpreted with caution. Furthermore, the authors defined as "optimal" cytoreduction residual disease of <2 cm, and not, as universally accepted, microscopic or <0.5 cm tumor residuals.

The largest monocentric TCS analysis evaluated 135 patients, and identified tumor involvement of the middle abdomen and peritoneal carcinomatosis as the two only parameters negatively affecting tumor resection (Fotopoulou et al. 2011).

A recent project published the largest multicentric analysis on TCS worldwide including 406 patients (median age, 55y; range,16–80) who underwent TCS between 1997 and 2011 in 12 centers across Europe, the USA, and Asia (Fotopoulou et al. Jan 2013). This represents the largest series so far in the tertiary setting of the disease and considering the fact that the conduction of any prospectively randomized trial in this advanced stage will be very challenging if not impossible, this constitutes currently the most valuable source of experience. The majority of the patients had an advanced initial FIGO stage

III/IV (69%), peritoneal carcinomatosis (51.7%), and absence of ascites (72.2%). Two hundred twenty-four (54.1%) patients underwent complete tumor resection. The most frequent tumor dissemination site was the pelvis (73%). This confirmed the knowledge from the previous results that even in the tertiary setting complete macroscopic tumor clearance plays a significant role both on overall and progression-free survival overruling the factor peritoneal carcinomatosis which failed to retain any prognostic significance on survival after controlling for tumor residual status. Median OS for patients without versus any tumor residuals was 49 versus 12 months. Most importantly, common clinicopathologic characteristics such as tumor stage, age, and histological subtype, which have been shown to be of significant predictive value at initial presentation of the disease, did not appear to be of any prognostic significance at the tertiary stage. A significant impact of third line postoperative systemic chemotherapy on overall survival was identified, emphasizing the importance of combinative systemic and surgical treatment in the fight against EOC even in this heavily pretreated patient collective. This may nevertheless constitute a selection bias since those patients who were fit enough and able to tolerate chemotherapy following radical surgery have theoretically also more favorable survival rates than patients too weak to tolerate any systemic treatment or even so advanced and multifocal metastasized that no chemotherapy was indicated. Rates of major operative morbidity and 30-day mortality were 25.9% and 3.2%, respectively, hence slightly higher than the equivalent data of secondary patients at the DESKTOP series; however here not only platinum-sensitive patients for cytoreduction were included but also palliative symptomatic patients who underwent surgery aiming at amelioration of symptoms. The most common complication was infection/sepsis by 13%, a 4.4% relaparotomy rate, but interestingly without any higher rates of thromboembolic events (2.5%).

Multivariate analysis identified platinum-resistant, tumor residuals at secondary surgery and peritoneal carcinomatosis to be of predictive significance for complete tumor resection, while tumor residuals at secondary and tertiary surgery, decreasing interval to second relapse, ascites, upper abdominal tumor involvement, and non-platinum third-line chemotherapy, significantly affected OS.

Again here, like at secondary surgery, correct selection of surgical candidates is crucial to minimize morbidity and maximizing benefit from this radical approach in a highly palliative patient cohort.

13 Beyond Tertiary Cytoreduction: Quaternary Surgery

Venturing even beyond tertiary cytoreduction, the evidence is very scarce. There are only two series internationally to systematically evaluate the results of quaternary surgery in EOC. The largest series of 49 recurrent EOC patients demonstrated that even in a quaternary setting, nearly 33% complete tumor resection rates are feasible in a highly specialized gynecologic oncologic center, despite the fact that the majority of the patients had peritoneal carcinomatosis (77.6%) (Fotopoulou et al. April 2013). According to prospectively documented intraoperative tumor mapping, patients presented with the following tumor pattern: lower abdomen 85.7%, middle abdomen 79.6%, and upper abdomen 42.9%. Median duration of surgery was 292 min and hence equivalent to the duration of primary and secondary cytoreduction. Rates of major operative morbidity and 30-day mortality were 28.6% and 2%, respectively. Also noted were highly significant differences in survival between tumor-free and not tumor-free patients. Mean OS for patients without any tumor residuals was 43 months as opposed to only 13.4 months for patients with any residual disease. Mean OS for patients who received postoperative chemotherapy ($n = 18$; 36.7%) was 40.5 months versus 12 months for those who did not, also highly a significant difference, corresponding so with the results of the TCS.

Multivariate analysis indentified multifocal tumor dissemination to be of predictive significance for incomplete tumor resection, higher operative morbidity, and more dismal survival.

Interestingly, otherwise established prognostic factors such as ascites, platinum resistance, high-grade histology, and advanced age appeared not to carry any significant impact on survival.

The second monocentric analysis includes 15 patients and originates from the Memorial Sloan Kettering Cancer Center (Shih et al. 2009). Their findings showed comparable results: the number of sites of recurrence and optimal tumor debulking were associated with a prolonged survival, especially when a total macroscopic tumor clearance could be obtained. They also reported that all other well-established predictive factors for primary ovarian cancer and first relapse such as time to recurrence and response to platinum failed to retain any prognostic value on survival.

Still, especially in this advanced situation of the disease indication for cytoreduction, aiming at a putative amelioration of survival should be done only with high caution, careful patient selection, and clear discussion with the patients about the chronic and palliative situation of the disease and weighing of risks and benefits.

14 Salvage Surgery in Acute Situations: Bowel Obstruction and Intestinal Perforation in the Era of Targeted Antiangiogenetic Agents

EOC appears to behave differently from other epithelial cancer types, since its constant, almost pathognomonic feature is its local and lymphatic dissemination to the peritoneal and pleural layers by a paucity of visceral distant metastases via hematogenous pathways. Locoregional peritoneal disease is what most patients die from, in terms of bowel obstruction, cachexia, hypoproteinemia from ascites, organ failure, and exhaustion. Attributed to this diffuse tumor dissemination pattern along the peritoneal layers, EOC patients often present with the clinical picture of impaired intestinal passage or even bowel obstruction in the advanced primary and especially relapsed EOC. The newly emerging novel implementation of targeted therapies with antiangiogenetic potential may additionally favor fistula formation or intestinal perforation. EOC complicated by such severe and acute events constitutes a therapeutic dilemma. Massive systemic and surgical pretreatment and extensive tumor dissemination combined by acute systemic inflammatory immunologic response make any surgical intervention in this setting highly challenging, while associated with high morbidity and mortality rates (Sehouli et al. 2012). Appropriate balancing of risks and benefits is required to design the optimal treatment options tailored around the individual needs. The patient communication processes are currently based on rather scattered monocentric data series, since data from large multicenter analyses are broadly lacking. Surgical interventions include various surgical techniques and strategies, such as en bloc resections of the involved intestinal package and terminal proximal ileo- or jejunostomy, since due to the severe peritoneal carcinosis and inflammation, no plane dissection with anastomotic and repair techniques is feasible. Short bowel syndrome with subsequent total parenteral nutrition (TPN) is therefore in some cases inevitable and requires high institutional and physical resources.

In cases of acute intestinal complications such as perforation and peritonitis, therapeutic approaches are rather limited. The cancer-induced tissue alterations and the overall low patient reserve constitute a major challenge for both the patients themselves and the treating physicians so that often such acute situations provoke a therapeutic nihilism and overall hesitation of active surgical measures. Retrospective analyses have shown that patients operated on in acute situations had significantly higher rates of anastomotic insufficiency compared to those operated within a planned setting, as also that the anastomotic insufficiency rate seems to be higher at primary debulking with tumor residuals compared to those without. For these reasons, even though no randomized trials exist to prove the safety or not of a primary anastomosis in an acute setting with

peritonitis, the high probability of an intestinal stoma should be preoperatively discussed with the affected patients.

EOC rarely develops true visceral metastases; organ involvement is mainly due to direct extension by continuous tumor growth of the visceral peritoneum. Based on this, tumor resection is best achieved by an extraperitoneal approach of the tumor mass and en block dissection of all the tumor-involved organs together with the adjacent peritoneum, following their dissection from the ureteric and blood vessel level in the lower abdomen and duodenum, pancreas, and biliary duct in the upper abdomen. Extensive multivisceral techniques are increasingly therefore being included in the surgical armamentarium of advanced disease management (Fotopoulou et al. 2010). This reflects also the optimal approach in acute situations. A simple local intestinal resection with reanastomosis or barrel loop ileostomy is often not feasible, since the combination of peritoneal carcinosis and peritonitis makes a dissection in the physiological planes impossible and of high risk of further injury.

A major issue is also the highly crucial role of psychosocial and nutritional support network to provide TPN at home. Multidisciplinary teams consisting of nutritional specialists, dieticians, gastroenterologists, and psycho-oncologists are therefore indispensable for the successful outcome of such surgeries.

15 Systemic Treatment of Epithelial Ovarian Cancer

15.1 Early-Stage Disease (FIGO I-IIb)

Adjuvant platinum-based chemotherapy should be discussed and offered in all cases of early ovarian cancer apart from Ia/Ib G1 not only in case of incomplete staging but also to optimally staged higher-risk early disease, such as higher grade or serous subtype (WHO 2014).

Two prospectively randomized trials examined the value of chemotherapy after surgery in early-stage ovarian cancer. ACTION and ICON1 included a broad range of early-stage patients with grade 2 and 3 stages IA/B and all grades of stages IC/IIA, in order to recruit sufficient patients. The primary analysis of ICON1 on its own, with a median follow-up of 4-years demonstrated a significant improvement in both RFS and OS in favor of immediate adjuvant chemotherapy with six cycles of single agent carboplatin (AUC 5/6). Very similar findings were reported in the ACTION trial in which the majority of patients received a platinum-based combination chemotherapy.

A recent Cochrane meta-analysis of five large prospective clinical trials (four of ten with platinum-based chemotherapy) shows that chemotherapy is more beneficial than observation in patients with early-stage ovarian cancer. Patients who received platinum-based adjuvant chemotherapy had better OS and PFS than patients who did not receive adjuvant treatment. Nevertheless, in all abovementioned trials, only approximately one third of the patients were optimally staged, the remainder having a 30% chance of being understaged and harboring occult disease. Despite this, benefit for chemotherapy in optimally staged patients cannot be excluded and adjuvant chemotherapy should be discussed and offered to all patients with high-risk early-stage ovarian cancer.

The addition of targeted therapies such as bevacizumab and other VEGF inhibitors such as nintedanib and cediranib, tyrosine kinase inhibitors, or PARP inhibitors is not of any established evidence, so far, and should not be offered outside clinical trials.

15.2 Advanced Stage Disease (FIGO IIc – IV)

Platinum-based chemotherapy ± paclitaxel is the, as per national and international guidelines dictated, first-line chemotherapy. The standard of care for most is thus carboplatin (AUC5/6) and paclitaxel (175 mg/m^2) given 3 weekly for six cycles. Dose-dense scheduling of the paclitaxel (80 mg/m^2 days 1, 8, 15 every 21 days with carboplatin AUC 5/6 on day 1) has been shown to improve overall survival in a large prospective randomized Japanese trial where Paclitaxel was applied in the dose of 80 mg/m^2. These findings

have not been confirmed yet in the Caucasian population. A similar Italian study by the MITO group has shown a better tolerability of the weekly arm; however, it failed to demonstrate any survival benefit by a paclitaxel dose of 60 mg/m^2 and hence lower to the Japanese equivalent study. The just completed UK-based ICON 8 trial will in a few years answer the question of value of dose density in first-line chemotherapy for ovarian cancer and hence potentially establish standards of care.

For those patients who develop allergy to or do not tolerate paclitaxel, the combination of docetaxel-carboplatin or pegylated liposomal doxorubicin-carboplatin can be considered as an alternative regime based on two randomized clinical trials that showed similar efficacy.

Addition of bevacizumab concurrently to chemotherapy as maintenance for up to 12 months afterward in the ICON 7 and for 15 months in the GOG 218 has been shown to significantly prolong PFS and OS in patients with documented residual disease and/or distant metastases (grade A). The antiangiogenic VEGF inhibitor, bevacizumab, has been shown to improve overall survival when given together with carboplatin and paclitaxel 3 weekly as maintenance for up to 12 months total, in a higher-risk subgroup of these patients, who have been suboptimally debulked (1 cm residual disease) or had no surgery or stage IV disease (ICON 7). However, in the GOG 262 study, no survival benefit was seen in the bevacizumab arm if patients received paclitaxel in a weekly regime, even though there was no prior randomization to bevacizumab versus placebo. The value and safety of bevacizumab in the neoadjuvant setting is currently the objective of various ongoing randomized trials.

The value of intraperitoneal (IP) chemotherapy continues to be strongly controversial despite the efficacy that has been shown in different prospective randomized trials; an effect that seems to pertain even decades later. The lack of broad acceptance seems to be due to the reported high toxicity and high drop-off rates in the IP arm, but also due to the fact that it is not clear whether the survival benefit is due to the dose-dense application of iv paclitaxel or to the IP application per se. Currently ongoing trials with dose regimes equivalent to the intravenous version will answer the question of value of IP chemotherapy.

Despite the initial high response rates to first-line platinum-based therapies, the majority of patients with EOC will experience relapse and die of the disease. Several therapeutic options are available and the decision as to which therapy to commence is dependent on the platinum-free interval (PFI), even though in the last Ovarian Cancer Consensus Conference (OCCC) in Tokyo, the consensus was to rather abandon the traditional 6-month cutoff as outdated and rather define treatment-free interval (TFI) of TFIp (platinum), TFInp (non-platinum), and TFIb (biological agent to be specified). Traditionally the platinum-free interval has been considered as a predictor of response to future platinum-based treatment, even though now-emerging theories support approaches of "platinum resensitization" by extending the platinum-free interval with agents like trabectedin.

15.3 Intermediate Platinum Response (PFS 6–12 Months)

Patients with an intermediate response to platinum (i.e., PFI between 6 and 12 months) represent a therapeutic challenge. Various trials exist addressing only this special patient subset. The Italian study group MANGO leads the OVATYON trial evaluating PLD 30 mg/m^2 1 h i.v. + carboplatin AUC 5 30–60 min i.v. on day 1 q4 weeks; treatment was allowed to six cycles or progression versus PLD 30 mg/m^2 1 h i.v. + trabectedin 1.1 mg/m^2 3 h i.v. on day 1 q3weeks, up to six cycles or progression in EOC relapse patients with a PFI of 6–12 months.

A further study is the phase III MITO-8- (Efficacy Study of Chemotherapy to Treat Ovarian Cancer Recurrence and to Prolong the Platinum Free Interval). This study aims to test the hypothesis that the artificial prolongation of the platinum-free interval with a non-platinum treatment will improve the effectiveness of overall therapy in patients with EOC progression occurring 6–12 months after first-line treatment with a

platinum derivative. The study groups MANGO and AO-Ovar are also participating, and a total number of 46 patients of the overall estimated 253 have already been recruited. In the experimental arm patients are treated with stealth liposomal doxorubicin followed at a later progression by carboplatin and paclitaxel, while in the conventional arm patients receive carboplatin and paclitaxel followed at a later progression by stealth liposomal doxorubicin.

15.4 Platinum Resistant/Refractory EOC Relapse (PFI <6 Months)

This is a difficult group in which to demonstrate benefit. Sharma et al. reported recently their experience of extended weekly carboplatin and paclitaxel in an attempt to increase response to chemotherapy in this special population. Twenty patients with platinum-resistant/refractory ovarian cancer received carboplatin AUC 3 and paclitaxel 70 mg/m^2 on day weekly. The RECIST response rate was 60% by radiological criteria (RECIST) and 76% by CA125 assessment, comparably very high for this platinum-resistant situation. Despite the dose-dense regimen in this heavily pretreated patient collective, no grade 3/4 thrombocytopenia occurred. The dynamics of response to dose-dense therapy were as rapid as with front-line therapy within the same patient. The authors state that this dose-dense regimen is routinely extended to at least 18 weekly cycles over 6 months and that it forms a highly active and tolerable cytotoxic scaffold to which molecular-targeted therapies can be added in platinum-resistant ovarian cancer.

Like in the primary also in the recurrent situation of the disease, targeted therapies are being implicated into conventional cytotoxic regimens to enhance response. Various antiangiogenics and small molecules such as sorafenib, bevacizumab, cediranib, zibotentan (ZD4054), and farletuzumab (MORAb-003) are being evaluated.

The multicenter AURELIA trial showed a significant prolongation of PFS in platinum-resistant patients who were treated with bevacizumab additionally to non-platinum monotherapy (liposomal pegylated doxorubicin or paclitaxel weekly or topotecan); however equivalent to the platinum-sensitive trials, bevacizumab failed to show any significant effect on overall survival.

16 Follow-Up

The aim of follow-up is not only to detect relapse and direct patients toward future therapeutic approaches but also to help the patients cope with the chronic effects of the anticancer treatment they had such as polyneuropathy, gastrointestinal symptoms, etc.

Duration of follow-up and intervals between follow-up visits vary according to local practices, but generally every 3 months for the first years and then every 6 months, even though there is no randomized trial to prove survival benefit of strict follow-up protocols versus an individualized patient and symptom-led approach. Rises in CA125 can be used to document progressive disease in patients who achieve a normal CA125 after primary treatment but tend to precede symptomatic relapse by a median of 4.5 months (range 0.5–29.5 months). A recent MRC/EORTC trial demonstrated no difference in overall survival between patients who received chemotherapy based on a rising CA125 and those who did not receive chemotherapy until they were symptomatic. Although the value of routine CA125 measurements was negated by this randomized controlled trial (RCT), some patients prefer to know as accurately as possible what might lie ahead and can cope with the knowledge that a rising CA125 indicates that their cancer has returned and yet immediate treatment is not necessarily of any benefit.

Participation in first-line trials also generally requires regular CA125 measurements in order to accurately determine trial end points. But rising CA125 alone without clinical or radiographic evidence of recurrence is not sufficient enough to commence systemic chemotherapy.

The results of the upcoming prospectively randomized DESKTOP III and GOG 0213 will nevertheless newly define and potentially change follow-up practice if tumor-free secondary

debulking will be shown to be associated with survival benefit, in which case tumor burden at the time of secondary surgery will impact on surgical complexity, morbidity, and overall outcome. Furthermore, in the increasingly emerging era of targeted agents and maintenance approaches, additional monitoring with CA125 may identify patients with early relapse (i.e., within 6 months) who may be suitable for phase 2 clinical trials with investigational new agents.

At follow-up visits, a careful history is imperative, together with clinical examination. CA125 measurement is not mandatory and has not been proven to be of prospective survival benefit. All patients should have the contact details of their key worker so that they can have early local review for unexpected symptoms.

17 Conclusion

To conclude, epithelial ovarian cancer is a complex disease which is difficult to detect in its early stages due to its vague symptom pattern and has a high mortality rate owing to the aggressive nature of the majority of tumors. No effective screening protocol has been designed as yet and so it continues to present at advanced stages. Work is ongoing, especially in proteomics, to discover a marker which can be used to detect cancer and then guide follow-up; however finding a universal marker is difficult due to the broad inter-tumor heterogeneity demonstrated by these cancers.

References

Braicu EI, Sehouli J, Richter R, Pietzner K, Lichtenegger W, Fotopoulou C. Primary versus secondary cytoreduction for epithelial ovarian cancer: a paired analysis of tumour pattern and surgical outcome. Eur J Cancer. 2012;48(5):687–94. Epub 2011 Jul 13.

Bristow RE, Tomacruz RS, Armstrong DK, Trimble EL, Montz FJ. Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis. J Clin Oncol. 2002; 20(5):1248–59.

Bristow RE, Puri I, Chi DS. Cytoreductive surgery for recurrent ovarian cancer: a meta- analysis. Gynecol Oncol. 2009;112(1):265–74.

Chan K, Urban R, Hu JM, Shin JY, Husain A, Teng NN, Berek JS, Osann K, Kapp DS. The potential therapeutic role of lymph node resection in epithelial ovarian cancer: a study of 13 918 patients. Br J Cancer. 2007; 96:1817–22.

Colombo PE, Mourregot A, Fabbro M, et al. Aggressive surgical strategies in advanced ovarian cancer: a monocentric study of 203 stage IIIC and IV patients. Eur J Surg Oncol. 2009;35(2):135–43.

De Iaco P, Musto A, Orazi L, Zamagni C, Rosati M, Allegri V, Cacciari N, Al-Nahhas A, Rubello D, Venturoli S, Fanti S. FDG-PET/CT in advanced ovarian cancer staging: value and pitfalls in detecting lesions in different abdominal and pelvic quadrants compared with laparoscopy. Eur J Radiol. 2011;80(2):e98–103. Epub 2010 Aug 4.

Doufekas K, Olaitan A. Clinical epidemiology of epithelial ovarian cancer in the UK. Int J Womens Health. 2014;6:537–45.

du Bois A, Reuss A, Pujade-Lauraine E, Harter P, Ray-Coquard I, Pfisterer J. Role of surgical outcome as prognostic factor in advanced epithelial ovarian cancer: a combined exploratory analysis of 3 prospectively randomized phase 3 multicenter trials: by the Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) and the Groupe d'Investigateurs Nationaux Pour les Etudes des Cancers de l'Ovaire (GINECO). Cancer. 2009; 115(6):1234–44.

Eisenkop SM, Spirtos NM, Montag TW, et al. The impact of subspecialty training on the management of advanced ovarian cancer. Gynecol Oncol. 1992; 47:203–9.

Fotopoulou C, Richter R, Braicu EI, Schmidt SC, Lichtenegger W, Sehouli J. Can complete tumor resection be predicted in advanced primary epithelial ovarian cancer? A systematic evaluation of 360 consecutive patients. Eur J Surg Oncol. 2010;36(12):1202–10. Epub 2010 Sep 22.

Fotopoulou C, Richter R, Braicu IE, et al. Clinical outcome of tertiary surgical cytoreduction in patients with recurrent epithelial ovarian cancer. Ann Surg Oncol. 2011; 18:49–57.

Fotopoulou C, Zang R, Gultekin M, Cibula D, Ayhan A, Liu D, Richter R, Braicu I, Mahner S, Harter P, Trillsch F, Kumar S, Peiretti M, Dowdy SC, Maggioni A, Trope C, Sehouli J. Value of tertiary cytoreductive surgery in epithelial ovarian cancer: an international multicenter evaluation. Ann Surg Oncol. 2013a;20(4):1348–54. Epub 2012 Oct 2.

Fotopoulou C, Savvatis K, Kosian P, Braicu IE, Papanikolaou G, Pietzner K, Schmidt SC, Sehouli J. Quaternary cytoreductive surgery in ovarian cancer: does surgical effort still matter? Br J Cancer. 2013b; 108(1):32–8.

Gabra H. Back to the future: targeting molecular changes for platinum resistance reversal. Gynecol Oncol. 2010;118:210–1.

Goff B. Symptoms associated with ovarian cancer. Clin Obstet Gynecol. 2012;55(1):36–42.

Gultekin M, Velipaşaoğlu M, Aksan G, Dursun P, Dogan NU, Yuce K, Ayhan A. A third evaluation of tertiary cytoreduction. J Surg Oncol. 2008;98(7):530–4.

Harter P, du Bois A, Hahmann M, Hasenburg A, Burges A, Loibl S, Gropp M, Huober J, Fink D, Schröder W, Muenstedt K, Schmalfeldt B, Emons G, Pfisterer J, Wollschlaeger K, Meerpohl HG, Breitbach GP, Tanner B, Sehouli J, Arbeitsgemeinschaft Gynaekologische Onkologie Ovarian Committee, AGO Ovarian Cancer Study Group. Surgery in recurrent ovarian cancer: the Arbeitsgemeinschaft Gynaekologische Onkologie (AGO) DESKTOP OVAR trial. Ann Surg Oncol. 2006;13(12):1702–10.

Harter P, Hahmann M, Lueck HJ, Poelcher M, Wimberger P, Ortmann O, Canzler U, Richter B, Wagner U, Hasenburg A, Burges A, Loibl S, Meier W, Huober J, Fink D, Schroeder W, Muenstedt K, Schmalfeldt B, Emons G, du Bois A. Surgery for recurrent ovarian cancer: role of peritoneal carcinomatosis: exploratory analysis of the DESKTOP I trial about risk factors, surgical implications, and prognostic value of peritoneal carcinomatosis. Ann Surg Oncol. 2009;16(5):1324–30.

Harter P, Sehouli J, Reuss A, Hasenburg A, Scambia G, Cibula D, Mahner S, Vergote I, Reinthaller A, Burges A, Hanker L, Pölcher M, Kurzeder C, Canzler U, Petry KU, Obermair A, Petru E, Schmalfeldt B, Lorusso D, du Bois A. Prospective validation study of a predictive score for operability of recurrent ovarian cancer: the Multicenter Intergroup Study DESKTOP II. A project of the AGO Kommission OVAR, AGO Study Group, NOGGO, AGO-Austria, and MITO. Int J Gynecol Cancer. 2011;21(2):289–95.

Helm CW, Chief Editor: Harris JE. Ovarian cancer staging. http://emedicine.medscape.com/article/2007140-overview

Hızlı D, Boran N, Yılmaz S, Turan T, Altınbaş SK, Celik B, Köse MF. Best predictors of survival outcome after tertiary cytoreduction in patients with recurrent platinum-sensitive epithelial ovarian cancer. Eur J Obstet Gynecol Reprod Biol. 2012;163(1):71–5.

http://www.cancer.org/cancer/ovariancancer/overviewguide/ovarian-cancer-overview-survival

http://www.nice.org.uk/guidance/CG122/chapter/Appendix-D-Risk-of-malignancy-index-RMI-I

http://www.who.int/selection_medicines/committees/expert/20/applications/EpithelialOvarian.pdf?ua=1

Janczar S, Graham JS, Paige AJW, Gabra H. Targeting locoregional peritoneal dissemination in ovarian cancer. Expert Rev Obstet Gynecol. 2009;4(2):133–47.

Jemal A, et al. Cancer statistics. Cancer J Clin. 2007;57(1):43–66.

Karam AK, Santillan A, Bristow RE, Giuntoli 2nd R, Gardner GJ, Cass I, Karlan BY, Li AJ. Tertiary cytoreductive surgery in recurrent ovarian cancer: selection criteria and survival outcome. Gynecol Oncol. 2007;104(2):377–80. Epub 2006 Oct 2.

Kehoe S, et al. Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): an open-label, randomised, controlled, non-inferiority trial. Lancet. 2015;386(9990):249–57.

Kurman RJ, Shih I-M. The origin and pathogenesis of epithelial ovarian cancer- a proposed unifying theory. Am J Surg Pathol. 2010;34(3):433–43.

Leitao Jr MM, Kardos S, Barakat RR, Chi DS. Tertiary cytoreduction in patients with recurrent ovarian carcinoma. Gynecol Oncol. 2004;95:181–8.

Monk BJ, Coleman RL. Changing the paradigm in the treatment of platinum-sensitive recurrent ovarian cancer: from platinum doublets to nonplatinum doublets and adding antiangiogenesis compounds. Int J Gynecol Cancer. 2009;19 Suppl 2:S63–7. doi:10.1111/IGC.0b013e3181c104fa.

Morris M, Gershenson DM, Wharton JT. Secondary cytoreductive surgery in epithelial ovarian cancer: nonresponders to first-line therapy. Gynecol Oncol. 1989;33(1):1–5.

Omura G, et al. A randomized trial of cyclophosphamide and doxorubicin with or without cisplatin in advanced ovarian carcinoma. A Gynecologic Oncology Group Study. Cancer. 1986;57:1725–30.

Paulsen T, Kjaerheim K, Kaern J, et al. Improved short-term survival for advanced ovarian, tubal, and peritoneal cancer patients operated at teaching hospitals. Int J Gynecol Cancer. 2006;16 Suppl 1:11–7.

Petrillo M, Ferrandina G, Fagotti A, Vizzielli G, Margariti PA, Pedone AL, Nero C, Fanfani F, Scambia G. Timing and pattern of recurrence in ovarian cancer patients with high tumor dissemination treated with primary debulking surgery versus neoadjuvant chemotherapy. Ann Surg Oncol. 2013;20(12):3955–60.

Segna RA, Dottino PR, Mandeli JP, Konsker K, Cohen CJ. Secondary cytoreduction for ovarian cancer following cisplatin therapy. J Clin Oncol. 1993;11(3):434–9.

Sehouli J, Papanikolaou G, Braicu EI, Pietzner K, Neuhaus P, Fotopoulou C. Feasibility of surgery after systemic treatment with the humanized recombinant antibody bevacizumab in heavily pretreated patients with advanced epithelial ovarian cancer. Ann Surg Oncol. 2012;19(4):1326–33.

Shih KK, Chi DS, Barakat RR, Leitao Jr MM. Tertiary cytoreduction in patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer: an updated series. Gynecol Oncol. 2010a;117:330–5.

Shih KK, Chi DS, Barakat RR, Leitao Jr MM. Beyond tertiary cytoreduction in patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer. Gynecol Oncol. 2010b;116(3):364–9. Epub 2009 Nov 7.

Simple ultrasound rules to distinguish between benign and malignant adnexal masses before surgery: prospective validation by IOTA group. BMJ. 2010;341.

Tian WJ, Chi DS, Sehouli J, Tropé CG, Jiang R, Ayhan A, Cormio G, Xing Y, Breitbach GP, Braicu EI, Rabbitt CA, Oksefjell H, Fotopoulou C, Meerpohl HG, du Bois A, Berek JS, Zang RY, Harter P. A risk model for secondary cytoreductive surgery in recurrent ovarian cancer: an evidence-based proposal for patient selection. Ann Surg Oncol. 2012;19(2):597–604.

Timmerman D. Simple ultrasound rules to distinguish between benign and malignant adnexal masses before surgery: prospective validation by IOTA group. BMJ. 2010;341:c6839.

Vaughan S, Coward JI, Bast Jr RC, Berchuck A, Berek JS, Brenton JD, Coukos G, Crum CC, Drapkin R, Etemadmoghadam D, Friedlander M, Gabra H, Kaye SB, Lord CJ, Lengyel E, Levine DA, McNeish IA, Menon U, Mills GB, Nephew KP, Oza AM, Sood AK, Stronach EA, Walczak H, Bowtell DD, Balkwill FR. Rethinking ovarian cancer: recommendations for improving outcomes. Nat Rev Cancer. 2011; 11(10):719–25.

Vergote et al. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. N Engl J Med. 2010;363:943–53.

Vernooij F, Heintz P, Witteveen E, et al. The outcomes of ovarian cancer treatment are better when provided by gynecologic oncologists and in specialized hospitals: a systematic review. Gynecol Oncol. 2007;105: 801–12.

Zang RY, Harter P, Chi DS, Sehouli J, Jiang R, Tropé CG, Ayhan A, Cormio G, Xing Y, Wollschlaeger KM, Braicu EI, Rabbitt CA, Oksefjell H, Tian WJ, Fotopoulou C, Pfisterer J, du Bois A, Berek JS. Predictors of survival in patients with recurrent ovarian cancer undergoing secondary cytoreductive surgery based on the pooled analysis of an international collaborative cohort. Br J Cancer. 2011;105(7):890–6. Epub 2011 Aug 30.