The Surgery of Ovarian Cancer

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Geoffrey Lane

Abstract

Surgery has remained the mainstay of treatment for ovarian cancer despite considerable advances in chemotherapy. The findings and results of the initial laparotomy have a greater bearing on the eventual outcome than do many subsequent therapeutic decisions. Hysterectomy with bilateral salpingo-oophorectomy continues to be the most cogent therapy. Both ovaries are removed because of the frequency of bilateral synchronous tumors and the possibility of occult metastases, which may be between 6 and 43 % even in a normal-looking ovary. The uterus is removed because the uterine serosa and endometrium are also frequent sites for occult metastases, and the prevalence of synchronous carcinoma of the endometrium and ovary is relatively high.

Introduction

Surgery has remained the mainstay of treatment for ovarian cancer despite considerable advances in chemotherapy. The findings and results of the initial laparotomy have a greater bearing on the eventual outcome than do many subsequent therapeutic decisions. Hysterectomy with bilateral salpingo-oophorectomy continues to be the most cogent therapy. Both ovaries are removed because of the frequency of bilateral synchronous tumors and the possibility of occult metastases, which may be between 6 and 43 % even in a normal-looking ovary. The uterus is removed because the uterine serosa and endometrium are also frequent sites for occult metastases, and the prevalence of synchronous carcinoma of the endometrium and ovary is relatively high.

The precise role of surgery in the management of the disease remains controversial. Few randomized controlled trials exist and there is a considerable difference of opinion with regard to the surgical effort required. As a result there is substantial national variation in the rates of complete surgical clearance of disease.

G. Lane, MB, BS, MD, FRCOG
Department of Gynaecological Oncology,
Guy's & St Thomas Hospitals,
Westminster Bridge Road,
London SE1 7EH, UK
e-mail: geoff.lane@gstt.nhs.uk

N. Wilkinson (ed.), *Pathology of the Ovary, Fallopian Tube and Peritoneum*,
Essentials of Diagnostic Gynecological Pathology,
DOI 10.1007/978-1-4471-2942-4_3,

NICE Guidelines

Following the publication and implementation of the national document. Improving Outcomes in Gynecological Cancers in 1999, there was an eventual shift in the management of ovarian cancers to greater specialization, with almost all cancers being treated surgically in regional cancer centers. There has also been a subtle but imperceptible drift to increasing surgical effort brought about in part by the specialization and also the introduction of neoadjuvant chemotherapy.

In April 2011, the National Institute for Health and Clinical Excellence (NIHCE) in the United Kingdom published guidelines regarding the management of ovarian cancer [1]. The publication confirmed that the overall 5-year survival of women with the disease remained less than 35 %, but with the introduction of effective chemotherapy and changes in surgical practice, there had been a twofold increase in survival over the past 30 years.

The guidelines suggest that optimal surgical staging should include a midline laparotomy to allow thorough assessment of the abdomen and pelvis; a total abdominal hysterectomy, bilateral salpingo-oophorectomy, and infracolic omentectomy; biopsies of any peritoneal deposits; and random biopsies of the pelvic and abdominal peritoneum if no disease is obvious and a retroperitoneal lymph node assessment. In early-stage disease, that is, in women with suspected ovarian cancer whose disease appears to be confined to the ovaries, the guidelines suggest that a pelvic lymph node assessment should form part of optimal surgical staging. The guidelines also, however, recommend that surgery should not include systematic retroperitoneal lymphadenectomy (block dissection of lymph nodes from the pelvic side walls to the level of the renal veins) as part of standard surgical treatment.

For advanced disease however the guidelines do not provide any additional support other than confirming that the definition of optimal debulking is no macroscopic residual disease at the end of the procedure.

The guidelines also recommend that a prospective randomized controlled trial should be undertaken to evaluate the therapeutic effect, associated risks, and cost-effectiveness of systematic retroperitoneal lymphadenectomy in those women who appear to have disease confined to the ovary and that research should be undertaken to determine the effectiveness of primary surgery in women with advanced ovarian cancer whose tumor cannot be fully excised. While these are laudable suggestions, their achievement may be difficult. Leaving resectable tumor after chemotherapy may be too difficult a pill to swallow for the majority of gynecological oncology surgeons.

The Surgery of Disease Apparently Confined to the Ovary

The diagnosis of ovarian cancer where there is no disease outside the ovary is difficult. Standard texts opine that optimal treatment should include midline laparotomy, peritoneal washings, a total abdominal hysterectomy, bilateral salpingo-oophorectomy and infracolic omentectomy with peritoneal biopsies, and a retroperitoneal lymph node assessment as noted above. However, in younger women wanting to retain their fertility and in the elderly with significant comorbidity, this approach may not be optimal.

The traditional approach to surgical management is both therapeutic and diagnostic. Surgery is carried out to remove both primary and metastatic disease even when the latter is not visible macroscopically. The diagnostic aim is to upstage the disease to facilitate optimal nonsurgical management. In our series (Hewitt M and Lane G (2006), unpublished data), in apparent stage 1 ovarian cancer, random peritoneal biopsies, removal of the omentum, and lymphadenectomy resulted in an upstaging of the disease in 12 % of 147 cases, 4 % by peritoneal biopsy alone. It is well established that lymph nodes are frequently involved in apparent stage I tumors with Burghardt et al. [2] demonstrating that in his small series of 37 patients, 24 % had positive nodes. Surprisingly, no patients in this study had positive para-aortic nodes without pelvic node involvement. A thorough investigation of the

subject has recently been carried out by Kleppe and colleagues [3]. They demonstrated that in 14 analyzed studies, the mean incidence of lymph node metastases in stages I–II epithelial ovarian cancer was 14.2 % (range 6.1–29.6 %). As expected the incidence of lymph node metastases increased with increasing grade. The lowest incidence (2.6 %) was found in the mucinous subtype and the highest (23.3 %) in the serous subtype. In unilateral tumors pelvic lymph node metastases were found on both sides in 45.2 % of cases, ipsilateral in 38.7 % and contralateral in only 16.1 %. Para-aortic lymph node metastases alone were found in 49.7 % of cases, positive pelvic nodes alone in 20.3 %, and both areas were positive in 29.9 % of the women who had nodal disease. The authors concluded that the incidence of lymph node metastases in apparently early-stage epithelial ovarian cancer is considerable, and the omission of a systematic lymphadenectomy should only be considered in grade 1 mucinous tumors.

Similar data for the omentum and for random peritoneal biopsies are more difficult to find, although in a study with very small numbers, Piver et al. [4] reported an incidence of only 3.2 % in women with apparent stage I disease.

It is clear therefore that for adequate staging, lymphadenectomy is essential. NICE guidelines [1] suggest that this is an untested procedure but agree that it is likely to be more accurate than lymph node sampling with the potential benefit for the woman of avoiding chemotherapy. The guidelines suggest that it is not warranted because of the risk of morbidity and the lack of evidence of a survival advantage.

Fertility-Sparing Surgery for Epithelial Ovarian Cancer

It is inevitable that some women of childbearing age and desirous of children will develop ovarian cancer. It is reported that between 3 and 17 % of ovarian tumors occur in women less than 40 years of age, and these women are more likely to present with earlier-stage and lower-grade disease [5–10]. Over 20 % of epithelial ovarian cancers are diagnosed at stage I [11], and about 7–8 % of stage I cancers occur in women under the age of 35 [12]. Provided that the preoperative imaging is suggestive of a malignant ovarian lesion with no disease outside the ovary, under these circumstances limited surgery might be attempted. This would include a unilateral salpingo-oophorectomy, bilateral pelvic lymphadenectomy, para-aortic lymphadenectomy, omentectomy, and peritoneal biopsies. The rationale for the lymphadenectomy is outlined above. Provided no disseminated disease is discovered and the disease is stage 1a, no further treatment should be necessary unless the histological subtype is unfavorable. This is discussed elsewhere in this book.

Fertility-sparing surgery such as this cannot of course identify all sites of metastatic disease and recurrence in a proportion of cases is inevitable. Numerous retrospective studies have investigated whether less than radical surgery can preserve fertility without compromising survival. Schilder and her colleagues [13] collated multi-institutional data on 52 patients with invasive stage IA or IC disease. Forty-two patients had stage IA disease and 10 stage IC. Twenty-five patients (48 %) had mucinous tumors, 10 (19 %) serous, 10 (19 %) endometrioid, 5 (10 %) clear cell, and 2 mixed. Nineteen patients, 11 with stage IA and 8 with IC tumors, received adjuvant chemotherapy with a platinum-containing agent and paclitaxel. Five patients (10 %) developed recurrence between 8 and 78 months following initial surgery and two died of disease within the study period, both mucinous tumors, but overall there was no statistically significant relationship between tumor substage or tumor histology and the frequency of tumor recurrence. It is interesting to note that 3 of the 5 recurrences were in the contralateral ovary. Following treatment 24 patients attempted pregnancy and 17 (71 %) conceived. Six of the 17 had received chemotherapy.

Park et al. [14] looked at women of all stages who underwent fertility-sparing surgery. Of the 62 epithelial ovarian cancers studied, 36 were stage IA, 2 were stage IB, 21 were stage IC, and one each were IIB, IIIA, and IIIC. Forty-one tumors were mucinous, 8 were endometrioid, 7 were serous, 4 were clear cell, and 2 were

mixed. Forty-eight tumors were grade I, 5 were grade II, and 9 were grade III. In this study as well as a standard staging procedure as in the previous study, 17 patients also had wedge biopsies of the other normal-looking ovary. Full staging was not carried out on each patient; however, all underwent partial omentectomy, multiple peritoneal biopsies, and washings. Pelvic and para-aortic lymphadenectomy and appendicectomy were optional. Patients with early-stage disease and high-risk factors including high-grade lesions, clear cell histological type, tumor growth through the capsule, surface excrescences, malignant cells in ascites or peritoneal washings, preoperative rupture, and dense adhesions were treated with platinum-based chemotherapy. Regular clinical follow-up was complemented by tumor marker estimation and imaging by ultrasound, computed tomography, magnetic resonance imaging, and positron-emission tomogram. Eleven cancers recurred, 7 of them mucinous tumors 5 of which were also stage I. Two stage 1A clear cell tumors also recurred and 1 stage 1C endometrioid cancer. Two of the patients who were upstaged to stages II and III due to microscopic disease had recurrence of their tumor and died of their disease 10 and 16 months after initial treatment. Of the 19 patients who attempted to conceive, 8 had received Carboplatin and Paclitaxel chemotherapy and 5 of these managed to conceive. Fifteen patients in total became pregnant and no congenital abnormalities were reported. The authors concluded that fertility-sparing surgery is effective but emphasizes the need for accurate surgical staging and that careful attention is paid to grade and histological type. In this study only 4 patients had clear cell cancers, but 2, both with stage IA disease, recurred and one died; in addition, two-thirds of women with grade III tumors also recurred. Otherwise recurrence rates were low and pregnancy was easy to achieve even after chemotherapy.

Wright and his colleagues [15] reported similar conclusions. Using the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) data, women under 50, diagnosed with epithelial ovarian cancer stages 1A to 1C, were studied [16]. In total 1,186 women with serous, endometrioid, mucinous, and clear cell tumors were studied. The study concluded that neither uterine nor ovarian preservation had an adverse impact on survival but did not formally address the impact of grade or histological subtype. The small study of Schlaerth and colleagues [17] also confirmed the safety of fertility-sparing surgery compared with the conventional approach but again was underpowered to address tumor grade and histological subtype.

Kajiyama and colleagues [18] analyzed data from multiple institutions with regard to survival. In their study no difference was found in disease-free survival and overall survival between women 40 years of age or under who underwent fertility-sparing surgery and those both under and over 40 who underwent radical surgery regardless of the stage I substage and whether there was intraoperative capsule rupture. In contrast stage IC attributable to preoperative rupture, positive ascites, or peritoneal washings appeared to be a contraindication to fertility-sparing surgery as did grade III and clear cell histology. Vergote et al. [19] concluded that mucinous histology yielded the most favorable prognosis in early-stage ovarian cancer.

During surgical staging the value of wedge biopsy of the other ovary remains unclear. It has been reported that wedge biopsy may result in mechanical infertility [20] or ovarian failure [21]. The incidence of occult metastases in the unaffected ovary is unclear. Some studies report an incidence of between 7 and 12 % in normal-looking ovaries [22, 23]. Later reports found that none of their patients who underwent fertility-sparing surgery had microscopic metastases on routine biopsies of their macroscopically normal-looking ovaries [24, 25]. Another report suggested only 2.5 % of contralateral ovaries are affected [26]. It is therefore unclear whether random biopsies are helpful or harmful, although the incidence of malignancy in 2 of 9 benign-looking cysts in the study of Park et al. [14] suggests that there should be a high index of suspicion when ovarian appearances deviate from normal.

Some studies have reported a high incidence of endometrial abnormalities in women with

endometrioid ovarian cancer and recommend that in such cases, an endometrial assessment should be undertaken [27]. There is little follow-up data to support the reported incidence of 14 % of women with stage I endometrioid ovarian cancer suffering from endometrial cancer. Endometrial sampling was carried out in 70 % of the patients undergoing fertility-sparing surgery in the study by Schlaerth and colleagues [17], but no endometrial abnormalities were found, although one patient developed an endometrial cancer 15 months postoperatively. Zaino et al. [28] discovered that 10 % of women with endometrioid ovarian cancer also had a secondary or synchronous carcinoma of the endometrium at the time of surgery. Endometrial assessment should therefore form part of the assessment when fertility-sparing surgery is considered.

At the end of childbearing, completion surgery with oophorectomy or hysterectomy should be considered. In the study of Schilder and colleagues [13], 3 of the 5 recurrences occurred in the contralateral ovary. Similarly, Morice et al. [22] found 5 of 7 recurrences in the retained adnexa. Whether completion surgery affects long-term survival is unknown, and thus the decision to undergo surgery should be individualized.

The Surgery of Germ Cell Tumors of the Ovary

Ovarian germ cell tumors account for 20–25 % of all ovarian neoplasms but only 3 % of these are malignant [29]. The age distribution of the tumors shows a sharp peak between 15 and 19 years to which teratomas and dysgerminomas contribute [30] and a secondary wider peak at ages 65–69 composed mainly of teratomas. Historically, the women and children had a poor prognosis when treated with surgery alone, but the introduction of radiotherapy and combination chemotherapy with vincristine, actinomycin D, and cyclophosphamide improved the outcome considerably [31]. Later with the addition of platinum-based regimens, a further improvement in survival rate was accomplished [32].

The preponderance of these tumors in the second and third decades of life results in decisions concerning childbearing and probabilities of recurrence. Fortunately, developments in chemotherapy have dramatically improved the prognosis for many patients who develop the more aggressive types of germ cell tumor. This permits reduced surgical aggressiveness without diminishing survival [33]. The standard surgical treatment including hysterectomy and bilateral salpingo-oophorectomy with omentectomy, lymphadenectomy, and biopsies may by safely limited to staging plus adnexectomy without significant reduction in survival rate in women who wish to retain fertility.

As with epithelial ovarian cancers, comprehensive staging is important to allow individualization of treatment. The retrospective study of Palenzuela and colleagues [34] reported on 60 patients between the ages of 0.4 and 27.9 years. Fifty-two patients presented with abdominal pain or a mass, 4 with premature puberty and 2 with dysmenorrhea. Two patients had surgery after being followed-up for gonadal dysgenesis and were suspicious for gonadoblastoma. Ten patients were in a poor prognosis group because of high levels of the tumor markers alpha-fetoprotein (AFP) and human chorionic gonadotrophin (HCG) at diagnosis. Fifty-eight patients underwent primary surgery, which included midline laparotomy, peritoneal cytology, thorough exploration of the abdomen and pelvis with lymph node biopsies, and biopsies of the contralateral ovary if necessary in addition to adnexectomy and complete intact resection with enucleation of the contralateral lesion if the tumor was bilateral. Tumors were designated Ia, Ib, or Ic if staging information was complete and Ix if not. The most common histological groups were mixed tumors most of which included yolk sac tumors and some immature teratomas. Dysgerminomas were the next most common histological type. Among the stage I tumors, 24 were observed and not given chemotherapy: None of the 8 stage Ia tumors relapsed, all stage Ic tumors relapsed as did 5 of the 13 stage Ix tumors. None of the stage Ic or Ix tumors receiving adjuvant chemotherapy relapsed. Adequate

Table 3.1 Survival according to stage in ovarian germ cell tumors

Stage	No	6 year survival %
I	41	95.1
II	16	93.8
III	58	97.3
IV	16	93.3

Table 3.2 Conception following treatment for ovarian germ cell tumors

Conception outcome	FIGO stage				Total
	I	II	III	IV	
Conceived	20	1	8	0	29
Did not conceive	7	0	2	0	9
Total	27	1	10	0	38

staging therefore may, if no disease is discovered outside the ovary, avoid chemotherapy. The authors concluded that the rate of improper surgical staging significantly increased with surgeons less experienced in gynecological surgery, and the risk of relapse in stage I tumors undergoing observation increased significantly if the tumor was improperly staged. These relapses did not appear to modify survival because chemotherapy salvaged patients after relapse.

Current platinum-based chemotherapy regimens produce excellent survival figures, even for advanced-stage disease. This study demonstrated a 93.3 % 6-year survival for stage IV tumors (Table 3.1).

To avoid the use of adjuvant chemotherapy, it is of prime importance to remove the ovarian lesion intact. This precludes the use of ovarian biopsy in stage I tumors and mandates the use of midline laparotomy to optimize the chances of intact removal of the lesion. Laparoscopic surgery therefore appears to be contraindicated.

When an ovarian lesion is removed inadvertently and intact but not staged, further staging information might be achieved laparoscopically and a negative result obviates the need for chemotherapy. The results of adjuvant chemotherapy are so good, however, that in more advanced disease, stage Ic and above, chemotherapy will be indicated in any event and further surgery might be deemed unnecessary.

Following treatment the reproductive outcome of women after conservative surgery is excellent. In the series reported by Tangir et al. [35], fertility-sparing surgery was performed in 64 of 106 patients with malignant germ cell tumors. In the study, 38 women attempted conception and 29 (76 %) achieved at least one pregnancy. Among these were 10 patients with advanced disease who were treated conservatively and of these 8 also conceived (Table 3.2). Among the women who conceived, 25 of the 29 had received combination chemotherapy.

Low et al. [36] reported similar figures. Seventy-four women underwent conservative surgery for malignant germ cell tumors of the ovary, 47 (64 %) received adjuvant chemotherapy, and of the 20 of these who attempted conception 19 succeeded.

Of 81 similar patients studied by Zanetta et al. [37] who underwent conservative surgery, 47 received adjuvant chemotherapy, 20 attempted to conceive, and 19 were successful. All 12 who did not receive chemotherapy conceived. Gershenson [38] published similar data with 16 of the 40 patients in his study attempting conception. Nine conceived naturally and 3 more conceived after fertility treatment. It was not stated how many of the 10 patients with advanced disease conceived. Research from the same authors [39] showed that 3 of 16 women who underwent conservative surgery for dysgerminoma and who were subsequently treated with bleomycin, etoposide, and cisplatin conceived.

For germ cell tumors, conservative surgery is therefore a realistic option in women desiring fertility even if chemotherapy is required.

The Surgery of Sex Cord-Stromal Tumors of the Ovary

This category of ovarian tumors includes all those that contain granulosa cells, theca cells and their luteinized derivatives, Sertoli cells, Leydig cells, and fibroblasts of gonadal stromal origin. The tumors are rare and represent approximately 7 % of all ovarian malignancies [40].

Because of their rarity the surgical management of these tumors is not well defined. Juvenile granulosa cell tumors are generally unilateral and may occur at any age, but in prepubertal girls 82 % present with isosexual pseudoprecocity [41]. Adult granulosa cell tumors are frequently found in postmenopausal women but often occur at puberty. In the postmenopausal group, surgery has generally reflected that of epithelial ovarian cancer including full surgical staging to involve omentectomy, pelvic and para-aortic lymphadenectomy, and biopsies [42, 43]. Older women and those with advanced or bilateral ovarian disease may benefit additionally from hysterectomy and bilateral salpingo-oophorectomy although there is little data to support this approach. Because the majority of tumors are unilateral, in younger patients desiring fertility and with stage Ia disease, which has an excellent prognosis [41], unilateral salpingo-oophorectomy seems appropriate.

Recent studies of both granulosa cell and Sertoli-Leydig tumors strongly suggest that lymph node metastases are rare, and therefore the use of routine lymphadenectomy is likely to produce little additional information and may be omitted from the primary or secondary staging procedure [44, 45]. This was confirmed by Thrall et al. [46] who also found in her study of 87 patients that 8.5 % of those with granulosa cell tumors were also found to have a concurrent endometrial carcinoma. An endometrial assessment is therefore essential in women with this tumor and in whom fertility-sparing surgery is considered.

Secondary surgical staging in women who have undergone ovarian cystectomy or unilateral salpingo-oophorectomy is likely to remain an important management tool. In Thrall's series (2011), of 8 women who had secondary staging 2 had residual disease, one in the residual ovary. This is similar to the series of Brown et al. [45] where 4 women had disease in residual ovarian tissue. In Thrall's series 6 of the 10 women found to have disease at secondary staging had only microscopic extraovarian disease confirming the importance of this procedure even if lymphadenectomy is not required.

The Surgery of Borderline Ovarian Tumors

There is clear evidence that there is a group of epithelial ovarian tumors whose histology and behavior falls between benign and frankly malignant ovarian neoplasms. Borderline tumors represent between 10 and 20 % of all epithelial ovarian malignancies [47]. Approximately 80 % of women have stage I disease [48], and the median age at diagnosis is 40 compared to about 60 for women with invasive carcinoma [49, 50].

Serous borderline tumors are bilateral in a third of cases [50, 51]. They are usually associated with noninvasive implants, but invasive implants occur in 20–25 % of cases [52]. Bilateral tumors and noninvasive implants do not predict a worse outcome compared with those with invasive implants [53, 54]. Invasive implants may progress to invasive carcinoma whereas noninvasive implants will remain stable and regress after removal of the main ovarian tumor [55]. Women with serous tumors without invasive implants have a 10-year survival of 95 % compared with 60–70 % in women with invasive implants [49]. Women with invasive implants develop progressive disease in about 30 % of cases while only 2 % of women without invasive implants will eventually progress [56, 57].

Mucinous tumors are either of intestinal or endocervical type [48, 54]. Tumors of intestinal type may be very large and are nearly always unilateral. In the case of bilaterality, it is important to look for a primary intestinal tumor. The endocervical subtype may be bilateral. Both subtypes may present with intraepithelial carcinoma and microinvasion of less than 10 mm^2. Extraovarian spread is infrequent and nearly always as pseudomyxoma peritonei although most of these represent dissemination from a mucinous tumor of the appendix. An appendicectomy should therefore be carried out at primary surgery for an intestinal borderline tumor. All mucinous borderline tumors have the potential to recur as invasive adenocarcinoma. This is particularly true if ovarian cystectomy rather than salpingo-oophorectomy has been performed [58].

The diagnosis of borderline ovarian tumor is difficult to make before surgery. It is also difficult

to distinguish between serous and mucinous tumors [59]. Intraoperative frozen section diagnosis is not helpful for the discrimination between borderline tumors and epithelial ovarian cancer when underdiagnosis of up to 25 % has been reported [60, 61]. It is even more difficult to determine preoperative variables that might influence prognosis and therefore alter the surgical approach accordingly. FIGO stage is the strongest prognostic factor for recurrence and survival. Micropapillary histology has been reported as an additional risk factor, but this is a postoperative diagnosis as well as being controversial as the poor prognosis is seen only with invasive implants [62–65]. In the retrospective study from the Norwegian Radium Hospital [51], by multivariate analysis the only three independent risk factors for disease-free and long-term survival were stage, histologic type, and age. Using DNA ploidy the women could be divided into risk groups with low risk being characterized by stage I disease, diploid phenotype, and age less than 40. The high-risk group who had a greater than 75 % chance of dying of the disease had aneuploid tumors stage II and III disease and age older than 70. Lymph node involvement has not been shown to be an independent risk factor. It is worthy of note that tumors with less than 10 mm^2 of invasion behave as borderline tumors and are classified as such [66–68]. Surgery is therefore essential before a diagnosis is made.

The standard surgical approach for the treatment of borderline ovarian tumors is therefore the same as for epithelial ovarian cancers including hysterectomy, bilateral salpingo-oophorectomy peritoneal biopsies, and omentectomy with appendicectomy in mucinous borderline ovarian tumors. The involvement of lymph nodes, even if the disease is upstaged as a result, appears not to influence survival [51, 69]. Lymph nodes are rarely involved with mucinous borderline tumors and lymphadenectomy may be omitted, as there is no difference in recurrence or survival rates [70].

Nearly one-third of women with borderline ovarian tumors are under 40, and therefore the preservation of reproductive function may be desirable and feasible. Relapse rates are higher following ovarian cystectomy (12–58 %) compared to bilateral salpingo-oophorectomy (0–20 %) and radical surgery (2.5–5.7 %). Multifocality may be a reason why cystectomy fails to control the disease; extensive sampling of the margin of the tumor is important [21, 24] as involved margins are also strong predictors of recurrence [71].

Many women are referred to gynecological oncology centers following the diagnosis of a borderline tumor following surgery for apparent benign disease. Staging is therefore incomplete. Occasionally surgery for a borderline tumor will unearth an unexpected malignancy when the abdomen has not been thoroughly explored. Snider et al. [72] discovered in his small series that none of 12 patients with mucinous tumors were upstaged while 4 of 13 serous tumors were upstaged although the recurrence and survival advantages were not discussed. As stage is an important prognostic indicator, the restaging of serous tumors appears worthwhile.

Early detected recurrences are curable with repeated surgery, and therefore further conservative surgery may be considered in young women wishing to retain fertility [48, 65, 70]. If invasive implants are diagnosed, this should not be recommended as women suboptimally debulked have poor survival [73].

Follow-up of borderline ovarian tumors should be lifelong as recurrences may develop after more than 15 years. In conservatively treated women, close follow-up of the remaining ovary or ovaries is essential. It is not clear whether the remaining ovary and uterus should be removed after completion of the family. For low-risk borderline ovarian tumors, this is probably unnecessary; however, it should be given strong consideration in high-risk disease. The alternatives are to await recurrence or treat radically.

The Surgery of Advanced Ovarian Cancer

NICE guidelines [1] are clear that the aim of surgery in the management of advanced, stage II–IV, ovarian cancer should be the complete resection

of all macroscopic disease [1]. Previously, the definition of optimal surgical debulking had been set at less than 2 cm residual disease, which was open to interpretation. The objective is now clear.

The spread of ovarian cancer occurs directly to adjacent tissues, through the lymphatic system and throughout the peritoneal cavity where surface deposits may be seen on all areas of the gastrointestinal tract and the omentum and peritoneal surfaces including those of the liver, spleen, and diaphragm, sometimes invading from the surface into these organs. Until recently the standard of care for all patients with advanced ovarian cancer particularly FIGO stages III and IV has been primary debulking surgery followed by Paclitaxel and Carboplatin chemotherapy [74]. However, no prospective randomized controlled trials are available, proving that primary debulking surgery improves the prognosis of patients with ovarian cancer.

The management of advanced ovarian cancer began to change soon after the publication of van der Burg and colleagues [75] who reported on 319 patients who had residual lesions greater than 1 cm after primary surgery. After three cycles of cyclophosphamide and cisplatin, the patients were randomized to undergo further debulking surgery or no surgery followed by three further cycles of chemotherapy. The authors concluded that debulking surgery significantly lengthened progression-free and overall survival. These findings were confirmed by the EORTC [76] who also concluded that neoadjuvant chemotherapy followed by interval debulking surgery was not inferior to primary debulking surgery followed by chemotherapy as a treatment option for patients with bulky stage IIIC or IV ovarian carcinoma. The study recorded a higher morbidity and mortality after primary debulking when compared with interval debulking surgery. Using an intention to treat analysis, the hazard ratios for death and progression comparing neoadjuvant chemotherapy to primary debulking was 1.01 and 0.98, respectively. Therefore to reduce morbidity and mortality, in addition to achieving the goal of optimal cytoreduction that is no macroscopic residual disease, this approach has received widespread acceptance. Image-guided core biopsies are now standard practice for diagnosis [77].

It has been long reported that survival when residual disease exceeds 2 cm diameter is poor [78]. The inability to optimally debulk has often been attributed to adverse tumor biology rather than lack of surgical effort; however, the variations in optimal debulking rates between countries such as the United Kingdom where the average optimal resection rate was only 42.9 % after neoadjuvant chemotherapy while in Belgium optimal debulking was achieved in 62.9 % of patients at primary surgery [76].

Numerous studies although retrospective in nature strongly suggest that the effort employed by the surgical team will reap benefits in terms of survival although mortality and short-term morbidity may well increase. The role of lymphadenectomy is unclear, although unlike endometrial cancer there are no reports of the procedure influencing survival in an adverse manner. Rouzier et al. [79] used SEER data to investigate the effect of lymphadenectomy on survival. The group found a beneficial effect of lymphadenectomy in epithelial ovarian cancer regardless of stage but acknowledged potential biases in their methodology including stage migration and incomplete data requiring estimation of disease extent. They also suggest that a thorough lymphadenectomy might reflect the quality of cytoreductive surgery.

Chi et al. [80] compared aggressive upper abdominal cytoreduction with earlier and less aggressive primary cytoreduction. They noted an increase in 5-year progression-free survival and overall survival from 14 to 31 % and 35 to 47 %, respectively. Peiretti and coworkers [81] reported on their experience with extensive upper abdominal surgery including diaphragm peritonectomy, splenectomy, distal pancreatectomy, partial liver resection, cholecystectomy, and gastric resection. Their findings were similar and demonstrated progression-free and overall survival figures of 19.9 and 57.6 months, respectively.

Other surrogates of maximal surgical effort including transverse colectomy [82] demonstrated median survival figures of 68.3 months. In addition Aletti and colleagues [83] showed an

improvement in survival in a subgroup of women with less than 1 cm residual disease following cytoreductive surgery when diaphragm resection was performed. This was associated with an improved survival from 28 % in those without diaphragm resection to 55 % in those where this was carried out.

Surgery for stage IV disease has also been considered futile. However, complete resection is a clear positive prognostic factor [84]. Aletti et al. [85] demonstrated an improved survival in women with stage IV disease with positive pleural cytology when the disease was optimally debulked in the abdomen. Rafil et al. [86] also showed that maximal debulking after neoadjuvant chemotherapy was associated with improved survival compared with those women with stage IV disease that were suboptimally debulked.

Therefore although there is no randomized data to confirm that maximal surgical effort results in improved outcomes, there is a groundswell of opinion which is leading the specialty in this direction.

Secondary Debulking Surgery

Routine second-look procedures have largely fallen out of favor. Secondary debulking in the presence of radiologically proven recurrence continues to hold a small but significant place in the management of advanced ovarian cancer although again there are few randomized trials to provide evidence of its efficacy.

Patients who are platinum sensitive, do not have ascites or intestinal tumor involvement, have tumor outside the upper abdomen, and have serous histology have significantly higher tumor resection rates [87]. It is probable, however, that only women who are cytoreduced to no visible disease are likely to obtain a survival advantage. An additional predictive factor of a good surgical response is a preoperative CA125 of less than 250 U/ml [88]. This does not of course preclude palliative surgery for symptom control when necessary, but it is imperative that patients undergoing surgery under these circumstances are aware of the possible morbidity without necessarily achieving prolongation of life, although increased quality is the end point under these circumstances.

Risk-Reducing Surgery

The group most likely to benefit from prophylactic oophorectomy are those women who have a particular genetic risk and those in a number of familial cancer syndromes. The lifetime risk of development of ovarian cancer has been estimated at 60 % in BRCA1 carriers and 27 % in BRCA2 carriers [89–91]. Later reports suggest that these may be overestimates [92, 93].

It is reported that the age of development of ovarian cancer in women with two or more relatives affected with the disease is younger than the median age of onset in the general population [94]. In this study, the median age at diagnosis was 47 years, 14 years earlier than the median age of sporadic ovarian cancer diagnosis in the United States. Another study examined apparent site-specific ovarian cancer, hereditary breast ovarian cancer syndrome, and Lynch II families [95]. The hereditary breast ovarian cancer syndrome patients were diagnosed on average 7 years younger than the general population mean of 59 years. Apparent site-specific family members were diagnosed 10 years younger while the Lynch II family members were diagnosed 14 years earlier than the general population mean.

There appears to be no correlation between age at presentation with ovarian cancer affecting mother and daughter and therefore probably with other relatives, but there is a relationship between sisters which should be taken into consideration when planning surgery [96].

In the United States a consensus panel has recommended prophylactic oophorectomy for a woman in a family with hereditary ovarian cancer syndrome at age 35 or when she has completed childbearing [97].

Once a genetic link has been established, the technique of oophorectomy is relatively simple. The ovaries with the Fallopian tubes may be removed through either a small low transverse

abdominal incision or more commonly laparoscopically using three or four appropriately placed 0.5–1 cm abdominal incisions [98, 99]. With the laparoscopic approach, a 24–48 hours hospital stay is usually required but may be a day case procedure with a recovery period of a few weeks.

A report by Colgan et al. [100] suggested that peritoneal lavage at the time of prophylactic oophorectomy is likely to identify occult malignancy, and the authors have recommended that this procedure is carried out whenever such surgery is performed.

Women in low-risk groups in their 40s are among the most likely to suffer from benign gynecological conditions such as prolapse, urinary incontinence, and menstrual disturbance all of which may lead to pelvic surgery. At the time of this surgery, the ovaries may be removed.

The lifetime risk of the development of ovarian cancer is widely variable throughout the world and in the United Kingdom is 1.4 %. Several studies have shown that carrying out prophylactic oophorectomy at the time of incidental benign abdominal or pelvic surgery can prevent a proportion of these cases. For example, Rozario and colleagues [101] analyzed data from 404 patients with ovarian cancer and demonstrated that if oophorectomy had been carried out on everyone who had undergone pelvic surgery over the age of 40, 10.9 % of ovarian cancers would have been avoided. This figure reduced to 6.7 % if the surgery had been carried out over 45 years and to 4 % if over 50 years.

There is now compelling evidence that serous tubal intraepithelial carcinoma (STIC) arising from the tubal fimbriae is a precursor of high-grade serous ovarian carcinoma of the ovary and possibly the peritoneum [102], and standardization of morphologic and immunohistochemical reproducibility of diagnosis is being devised [103]. The removal of the Fallopian tubes at the time of benign gynecological surgery is becoming noticeably more common and has been recommended for both low- and high-risk groups [104]. It remains to be seen whether the incidence of serous ovarian cancer reduces as a result, and further large-scale studies are required.

References

1. National Institute for Health and Clinical Excellence. NICE clinical guideline 122 – Ovarian cancer. The recognition and initial management of ovarian cancer. NHS. 2011.
2. Burghardt E, Girardi F, Lahousen M, Tamussino K, Stettner H. Patterns of pelvic and paraaortic lymph node involvement in ovarian cancer. Gynecol Oncol. 1991;40:103–6.
3. Kleppe M, Wang T, Van Gorp T, Slangen BFM, Kruse AJ, Kruitwagen RFPM. Lymph node metastasis in stages I and II ovarian cancer: a review. Gynecol Oncol. 2011;123:610–4.
4. Piver MS, Barlow JJ, Lele SB. Incidence of subclinical metastases in stage I and II ovarian cancer. Obstet Gynecol. 1978;52(1):100–4.
5. Duska LR, Chang YC, Flynn CE, et al. Epithelial ovarian carcinoma in the reproductive age group. Cancer. 1999;85:2623–9.
6. Massi D, Susini T, Savino L, Boddi V, Aminni G, Cola-francesci M. Epithelial ovarian tumours in the reproductive age group: age is not an independent prognostic factor. Cancer. 1996;77:1131–6.
7. Plaxe SC, Braly PS, Freddo JL, McLay E, Kirmani S, Howell SB. Profiles of women aged 30 – 39 and age less than 30 with epithelial ovarian cancer. Obstet Gynecol. 1993;81(5(pt 1)):651–4.
8. Smedley H, Sikora K. Age as a prognostic factor in epithelial ovarian cancer. Br J Obstet Gynaecol. 1985;92:839–42.
9. Swenerton KD, Hislop TG, Spinelli J, LeRiche JC, Yang N, Boyes DA. Ovarian carcinoma: a multivariate analysis of prognostic factors. Obstet Gynecol. 1985;65:264–70.
10. Thigpen T, Brady MF, Omura GA, et al. Age as a prognostic factor in ovarian carcinoma. The Gynecologic Oncology Group experience. Cancer. 1993;71(2 Suppl):606–14.
11. Green JA. Early ovarian cancer – time for a rethink on stage? Gynecol Oncol. 2003;90:235–7.
12. DiSaia PJ. Fertility-sparing treatment of patients with ovarian cancer. Compr Ther. 1990;16(11):35–42.
13. Schilder JM, Thompson AM, De Priest PD, et al. Outcome of reproductive age women with stage Ia or Ic invasive epithelial ovarian cancer treated with fertility-sparing surgery. Gynecol Oncol. 2002;87:1–7.
14. Park J-Y, Kim D-Y, Suh D-S, Kim J-H, Kim Y-M, Kim Y-T, Nam J-H. Outcomes of fertility-sparing surgery for invasive epithelial cancer: oncologic safety and reproductive outcomes. Gynecol Oncol. 2008;110:345–53.
15. Wright JD, Shah M, Mathew L, Burke WM, Culhane J, Goldman N, Schiff PB, Herzog TJ. Fertility preservation in young women with epithelial ovarian cancer. Cancer. 2009;115:4118–26.
16. Department of Health, National Cancer Guidance Steering Group. Improving outcomes in gynaecological cancers. Cancer Service Guidance. 1999.

17. Schlaerth AC, Chi DS, Poynor EA, Barakat RR, Brown CL. Long-term survival after fertility-sparing surgery for epithelial ovarian cancer. Int J Gynecol Cancer. 2009;19:1199–204.
18. Kajiyama H, Shibata K, Mizumo M, Umezu T, Suzuki S, Nawa A, Kawai M, Nagasak T, Kikkawa F. Long-term survival of young women receiving fertility-sparing surgery for ovarian cancer in comparison with those undergoing radical surgery. Br J Cancer. 2011;105:1288–94.
19. Vergote I, De Brabanter J, Fyles A, et al. Prognostic importance of the degree of differentiation and cyst rupture in stage I invasive epithelial carcinoma. Lancet. 2001;357:176–82.
20. Weinstien D, Polishuk WZ. The role of wedge resection of the ovary as a mechanical cause for mechanical sterility. Surg Gynecol Obstet. 1975; 141:417–8.
21. Morice P, Camatte S, El Hassan J, Pautier P, Duvillard P, Castaigne D. Clinical outcomes and fertility after conservative treatment of ovarian borderline tumours. Fertil Steril. 2001;75:92–6.
22. Brown C, Hyman J, Almadrones L, Curtin J, Hoskins W. Conservative surgical management of early epithelial ovarian cancer (EOC). Proc ASCO. 1995;14:766.
23. Munnell EW. Is conservative therapy ever justified in stage I (IA) cancer of the ovary. Am J Obstet Gynecol. 1969;103:641–53.
24. Morice P, Wicart-Poque F, Rey A, El Hassan J, Pautier P, L'homme C, et al. Results of conservative treatment in epithelial ovarian carcinoma. Cancer. 2001;92:2412–8.
25. Zanetta G, Chiari S, Rota S, Bratina G, Maneo A, Torri V, et al. Conservative surgery for stage I ovarian carcinoma in women of childbearing age. Br J Obstet Gynaecol. 1997;104:1030–5.
26. Benjamin I, Morgan MA, Rubin SC. Occult bilateral involvement in stage I epithelial ovarian cancer. Gynecol Oncol. 1999;72(3):288–91.
27. Kottmeier HL. Surgical management – conservative surgery. In: Gentil F, Junqueria AC, editors. Ovarian cancer 2. New York: Springer; 1968.
28. Zaino R, Whitney C, Brady MF, et al. Simultaneously detected endometrial and ovarian carcinomas – a prospective clinicopathological study of 74 cases: a Gynecologic Oncology Group study. Gynecol Oncol. 2001;83:355–62.
29. ACOG classification and staging of gynecological malignancies. ACOG Technical Bulletin No 155 (May 1991). Int J Gynaecol Obstet. 1992;38: 319–23.
30. Dos Santos SI, Swerdlow AJ. Ovarian germ cell malignancies in England: epidemiological parallels with testicular cancer. Br J Cancer. 1991;63:814–8.
31. Wollner N, Exelby PR, Woodruff JM, et al. Malignant ovarian tumours in childhood: prognosis in relation to initial therapy. Cancer. 1976;37: 1953–64.
32. Ablin AR, Krailo MN, Ramsay NKC, et al. Results of treatment of malignant germ cell tumours in 93 children: a report from the Children's Cancer Group study. J Clin Oncol. 1991;9:1782–92.
33. Billmire D, Vinocur C, Rescorla F, Cushing B, London W, Schlatter M, Davis M, Giller R, Lauer S, Olson T. Outcome and staging evaluation in malignant germ cell tumours of the ovary in children and adolescents: an Intergroup study. J Pediatr Surg. 2004;39:424–9.
34. Palenzuela G, Martin E, Meunier A, Beuzeboc P, Laurence V, Orbach D, Frappaz D. Comprehensive staging allows for excellent outcome in patients with localised malignant germ cell tumors of the ovary. Ann Surg. 2008;248(5):836–41.
35. Tangir J, Zelterman D, Wenging M, Schewartz PE. Reproductive function after conservative surgery for malignant germ cell tumours of the ovary. Obstet Gynecol. 2003;101:251–7.
36. Low JJG, Lewis CP, Crandon AJ, Hacker NF. Conservative surgery to preserve ovarian function in patients with malignant ovarian germ cell tumours. Cancer. 2000;89:391–8.
37. Zanetta G, Bonazzi C, Cantu MG, Binidagger S, Locatelli A, Bratini G, et al. Survival and reproductive function after treatment of malignant germ cell ovarian tumours. J Clin Oncol. 2001;19:1015–20.
38. Gershenson DM. Menstrual and reproductive function after treatment with combination chemotherapy for malignant ovarian germ cell tumours. J Clin Oncol. 1988;6:270–5.
39. Brewer M, Gershenson DM, Herzog C, Mitchell M, Silva E, Wharton J. Outcome and reproductive function after chemotherapy for dysgerminoma. J Clin Oncol. 1988;6:270–5.
40. Koonings PP, Campbell K, Mishell Jr DR, Grimes DA. Relative frequency of primary ovarian neoplasms: a 10-year review. Obstet Gynecol. 1989;74:921–6.
41. Young RH, Dickerson GR, Sculloy RE. Juvenile granulosa cell tumour of the ovary. A clinicopathological analysis of 125 cases. Am J Surg Pathol. 1984;8:575–96.
42. Gershenson DM. Management of early ovarian cancer: germ cell and sex cord-stromal tumours. Gynecol Oncol. 1994;55:S62–72.
43. NCCN. Practice guidelines in oncology v2.2011. Ovarian, fallopian tube and primary peritoneal carcinomas. 2011.
44. Abu-Rustum NR, Restivo A, Ivy J, Soslow R, Sabbatini P, Sonoda Y, Barakat RR, Chi DS. Retroperitonealnodal metastases in primary and recurrent granulosa cell tumors of the ovary. Gynecol Oncol. 2006;103:31–4.
45. Brown J, Sood AK, Deavers MT, Milojevic L, Gershenson DM. Patterns of metastasis in sex cord-stromal tumours of the ovary: can routine staging lymphadenectomy be omitted? Gynecol Oncol. 2009;113:86–90.
46. Thrall MM, Paley P, Pizer E, Garcia R, Goff BA. Patterns of spread and recurrence of sex cord-stromal tumors of the ovary. Gynecol Oncol. 2011;122(2): 242–5.

47. Lenhard MS, Mitterer S, Kumper C, et al. Long-term follow-up after ovarian borderline tumor: relapse and survival in a large patient cohort. Eur J Obstet Gynecol Reprod Biol. 2009;145:189–94.
48. Trillsch F, Mahner S, Reuttzel J. Clinical management of borderline ovarian tumors. Expert Rev Anticancer Ther. 2010;10:1115–24.
49. Sherman ME, Mink PJ, Curtis R, et al. Survival among women with borderline ovarian tumors and ovarian carcinoma: a population-based analysis. Cancer. 2004;100:1045–52.
50. Skirnisdottir I, Garmo H, Wilander E, et al. Borderline ovarian tumors in Sweden 1960–2005: trends in incidence and age at diagnosis compared to ovarian cancer. Int J Cancer. 2008;123:1897–901.
51. Kaern J, Trope CG, Abeler VM. A retrospective study of 370 borderline tumors of the ovary treated at the Norwegian Radium Hospital from 1970 to 1982. A review of clinicopathological features and treatment modalities. Cancer. 1993;71:1810–20.
52. Seidman JD, Horkayne-Szakaly I, Haiba M, et al. The histologic type and stage distribution of ovarian carcinomas of surface epithelial origin. Int J Gynecol Pathol. 2004;23:41–4.
53. Bell DA, Weinstock MA, Scully RE. Peritoneal implants of ovarian serous borderline tumors. Histologic features and prognosis. Cancer. 1988;62:2212–22.
54. Tinelli R, Tinelli A, Tinelli FG, et al. Conservative surgery for borderline ovarian tumors: a review. Gynecol Oncol. 2006;100:185–91.
55. Kurman RJ, Trimble CL. The behaviour of serous tumors of low malignant potential: are they ever malignant? Int J Gynaecol Pathol. 1993;12:120–7.
56. Morice P, Camatte S, Rey A, et al. Prognostic factors for patients with advanced stage borderline tumours of the ovary. Ann Oncol. 2003;14:592–8.
57. Oedegaard E. Ovarian carcinomas and borderline ovarian tumors – molecular markers and operative treatment. Dissertation, Faculty of Medicine, University of Oslo, 2008.
58. Trope CG, Davidson B, Paulsen T, et al. Diagnosis and treatment of borderline ovarian neoplasms, "the state of the art". Eur J Gynaecol Oncol. 2009;30:471–82.
59. Bazot M, Haouy D, Darai E, Cortez A, Dechoux-Vodovar S. Is MRI a useful tool to distinguish between serous and mucinous borderline ovarian tumours? Clin Radiol. 2013;68:e1–8.
60. Tempfer CB, Polterauer S, Bentz EK, et al. Accuracy of intraoperative frozen section analysis in borderline tumors of the ovary: a retrospective analysis of 96 cases and a review of the literature. Gynecol Oncol. 2007;107:248–52.
61. Trope CG, Kristensen G, Makar A. Surgery for borderline tumor of the ovary. Semin Surg Oncol. 2000;19:69–75.
62. Chang SJ, Ryu HS, Chang KH, et al. Prognostic significance of the micropapillary pattern in patients with serous borderline ovarian tumours. Acta Obstet Gynecol Scand. 2008;87:476–81.
63. Prat J, Nictolis M. Serours borderline tumors of the ovary: a long-term follow-up study of 137 cases, including 18 with a micropapillary pattern and 20 with microinvasion. Am J Surg Pathol. 2002;26:1111–28.
64. Seidman JD, Kurman RJ. Ovarian serous borderline tumours: a critical review of the literature with emphasis on prognostic indicators. Hum Pathol. 2000;31:539–57.
65. Silva EG, Gershenson DM, Malpica A, et al. The recurrence and the overall rates of ovarian serous borderline neoplasms with non invasive implants is time dependent. Am J Surg Pathol. 2006;30:551–9.
66. Cusido M, Balaguero L, Hernandez G, et al. Results of the national survey of borderline ovarian tumors in Spain. Gynecol Oncol. 2007;104:617–22.
67. Longacre TA, McKenney JK, Tazelaar HD, et al. Ovarian serous tumors of low malignant potential (borderline tumors): outcome based study of 276 patients with long-term (> or =5 yr) follow up. Am J Surg Pathol. 2005;29:707–23.
68. Ren J, Peng Z, Yang K. A clinicopathological multivariate analysis affecting recurrence of borderline ovarian tumors. Gynecol Oncol. 2008;110:162–7.
69. Camatte S, Morice P, Thorbury A, et al. Impact of surgical staging in patients with macroscopic "stage I" ovarian borderline tumours: analysis of a continuous series of 101 cases. Eur J Cancer. 2004;40:1842–9.
70. Cadron I, Leunen K, Van Gorp T, et al. Management of borderline ovarian neoplasms. J Clin Oncol. 2007;25:2928–37.
71. Lim-Tan SK, Cajlgas HE, Scully RE. Ovarian cystectomy for serous borderline tumours: a follow up study of 35 cases. Obstet Gynecol. 1988;72:775–81.
72. Snider DD, Stuart GC, Nation JG, Robertson DI. Evaluation of surgical staging in stage I low malignant potential ovarian tumours. Gynecol Oncol. 1991;40:129–32.
73. Crispens MA, Bodurka D, Deavers M, et al. Response and survival in patients with progressive or recurrent serous ovarian tumors of low malignant potential. Obstet Gynecol. 2002;99:3–10.
74. McGuire WP, Hoskins WJ, Brady MF, Kucera PR, Partridge EE, Look KY, Clarke-Pearson DL, Davidson M. Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin: in patients with III and stage IV ovarian cancer. N Engl J Med. 1996;334:1–6.
75. van der Burg ML, van Lent M, Buyse MBA, Kobierska A, Colombo N, Favalli G, Lacave AJ, Nardi M, Renard J, Percorelli S. The effect of debulking surgery after induction chemotherapy on the prognosis in advanced epithelial ovarian cancer. N Engl J Med. 1995;332:629–34.
76. Vergote I, Trope CG, Amant F, et al. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. N Engl J Med. 2010;363:943–53.

77. Hewitt MJ, Anderson K, Hall GD, Weston M, Hutson RC, Wilkinson N, Perren TJ, Lane G, Spencer JA. Women with peritoneal carcinomatosis of unknown origin: efficacy of image-guided biopsy to determine site specific diagnosis. Br J Obstet Gynaecol. 2007;114:46–50.
78. Hoskins WJ, McGuire WP, Brady MF, et al. The effect of diameter of largest residual disease on survival after primary cytroreductive surgery in patients with suboptimal residual epithelial ovarian carcinoma. Am J Obstet Gynecol. 1994;170:974–9.
79. Rouzier R, Bergzoll C, Brun J-L, Dubernard G, Selle F, Uzan S, Pomel C, Darai E. The role of lymph node resection in ovarian cancer: analysis of the surveillance epidemiology, and end results (SEER) database. BJOG. 2010;117:1451–8.
80. Chi DS, Eisenhauer EL, Zivanovic O, et al. Improved progression-free and overall survival in advanced ovarian cancer as a result of a change in surgical paradigm. Gynecol Oncol. 2009;114:26–31.
81. Peiretti M, Zanagnolo V, Aletti GD, Bocciolone L, Colombo N, Landoni F, Minig L, Biffi R, Radice D, Maggiomi A. Role of maximal primary cytoreductive surgery in patients with advanced epithelial ovarian and tubal cancer: surgical and oncological outcomes. Single institution experience. Gynecol Oncol. 2010;119:259–64.
82. Bristow RE, Peiretti M, Zanangnolo V, Salani R, Giuntoli II RL, Maggioni A. Transverse colectomy in ovarian cancer surgical cytoreduction: operative technique and clinical outcome. Gynecol Oncol. 2008;109:364–9.
83. Aletti GD, Dowdy SC, Podratz KC, Cliby WA. Surgical treatment of diaphragm disease correlates with improved survival in optimally debulked advanced stage ovarian cancer. Gynecol Oncol. 2006;100:283–7.
84. Wimberger P, Wehling M, Lehmann N, Kimmig R, Schmalfeldt B, Burges A, Harter P, Pfisterer J, du Boid A. Influence of residual tumor on outcome in ovarian cancer patients with stage IV disease. Ann Surg Oncol. 2010;17:1642–8.
85. Aletti GD, Podratz KC, Cliby WA, Gostout BS. Stage IV ovarian cancer: disease site-specific rationale for postoperative treatment. Gynecol Oncol. 2009;112:22–7.
86. Rafil A, Deval B, Geay J-F, Chopin N, Paoletti X, Paraiso D, Pujade-Lauraine E. Treatment of FIGO stage IV ovarian carcinoma: results of primary surgery or interval surgery after neoadjuvant chemotherapy: a retrospective study. Int J Gynecol Cancer. 2007;17:777–83.
87. Gil-Ibanez B, Oskay-Ozcelik G, Richter R, Fotopolou C, Braicu E, Neuhaus P, Lichtenegger W, Sehouli J. Predictive factors in relapsed ovarian cancer for complete tumor remission. Anticancer Res. 2011;31:2583–7.
88. Frederick PJ, Ramirez PT, Quinn L, Milam MR, Weber DM, Coleman RL, Gershenson DM, Landen CN. Preoperative factors predicting survival after secondary cytoreduction for recurrent ovarian cancer. Int J Gynecol Cancer. 2011;21:831–6.
89. Ford D, Easton DF, Bishop DT, et al. Risks of cancer in BRCA1-mutation carriers. Lancet. 1994;343:692–5.
90. Ford D, Easton DF, Stratton M, et al. Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. Am J Hum Genet. 1998;62:676–9.
91. Thompson D, Easton D, Breast Cancer Linkage Consortium. Variation in cancer risks, by mutation position, in BRCA2 mutation carriers. Am J Hum Genet. 2001;68:410–9.
92. Streuwing JP, Hartge P, Wacholder S, et al. The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Askenazi Jews. N Engl J Med. 1997;336:1401–8.
93. Whittemore AS, Gong G, Intyre J. Prevalence and contribution of BRCA1 mutations in breast cancer and ovarian cancer: results from three US population-based case–control studies of ovarian cancer. Am J Hum Genet. 1997;60:496–504.
94. Amos CI, Shaw GL, Tucker MA, et al. Age at onset for familial epithelial ovarian cancer. JAMA. 1992;286:1896–9.
95. Lynch HT, Watson P, Lynch JF, et al. Hereditary ovarian cancer: heterogeneity in age at onset. Cancer. 1993;71:573–81.
96. Houlston RS, Hampson J, Collins WP, et al. Correlation in ages at death from familial ovarian cancer among sisters. Gynecol Oncol. 1992;47:253–4.
97. NIH Consensus Development Panel on Ovarian Cancer. Ovarian cancer: screening, treatment and follow up. JAMA. 1995;273:491–7.
98. Eltabbakh GH, Piver MS, Hempling RE, et al. Laparoscopic management of women with a family history of ovarian cancer. J Surg Oncol. 1999;72:9–13.
99. Morice P, Pautier P, Mercier S, et al. Laparoscopic prophylactic oophorectomy in women with inherited risk of ovarian cancer. Eur J Gynaecol Oncol. 1999;20:202–4.
100. Colgan TJ, Murphy J, Cole DE, et al. Occult carcinoma in prophylactic oophorectomy specimens: prevalence and association with BRCA germline mutations. Am J Surg Pathol. 2001;25:1283–9.
101. Rozario D, Brown I, Fung MF, et al. Is incidental prophylactic oophorectomy an acceptable means to reduce the incidence of ovarian cancer? Am J Surg. 1997;173:495–8.
102. Kurman RJ, Shih I-M. The origin and pathogenesis of epithelial ovarian cancer: a proposed unifying theory. Am J Surg Pathol. 2010;34:433–43.
103. Visvanathan K, Vang R, Shaw P, Gross A, Soslow R, Parkash V, Shih L-M, Kurman RJ. Diagnosis of serous tubal intraepithelial carcinoma based on morphologic and immunohistochemical features: a reproducibility study. Am J Surg Pathol. 2011;35:1766–75.
104. Anderson CK, Wallace S, Guiahi M, Sheeder J, Behbakht K, Spillman M. Risk-reducing salpingectomy as preventative strategy for pelvic serous cancer. Int J Gynecol Cancer. 2013;23:417–21.