



Hematol Oncol Clin N Am
17 (2003) 945–956

HEMATOLOGY/
ONCOLOGY
CLINICS OF
NORTH AMERICA

Surgical advances in the treatment of ovarian cancer

Andrew J. Li, MD^{a,b,*}, Beth Y. Karlan, MD^{a,b,c}

^a*Division of Gynecologic Oncology, Department of Obstetrics and Gynecology,
Cedars-Sinai Medical Center, Los Angeles, CA 90048, USA*

^b*Department of Obstetrics and Gynecology, David Geffen School of Medicine at UCLA,
Los Angeles, CA 90048, USA*

^c*Women's Cancer Research Institute, Cedars-Sinai Medical Center, Los Angeles, CA 90048, USA*

Epithelial ovarian cancer remains the most lethal of all the gynecologic malignancies. Although this disease is among the most chemosensitive of all adult solid cancers, surgery remains the cornerstone of management. Initial surgical exploration is crucial for comprehensive staging and tumor cytoreduction and affords prognostic determination and adjuvant therapy planning. Although most of the 24,000 new cases of ovarian cancer each year still are diagnosed with advanced stage disease, multiple surgical advances have prolonged survival and improved patient quality of life. Definitions of “optimal” surgical cytoreduction are evolving, as are new roles for laparoscopy and fertility-sparing procedures. The identification of increased ovarian cancer risk associated with genetic mutations in ovarian cancer susceptibility genes has broadened the role of prophylactic surgery in the prevention of this disease. This article focuses on advances in surgical management of epithelial ovarian cancer, with emphasis on cytoreduction, prophylactic oophorectomy, and conservative surgical procedures.

Surgical standards in cytoreduction

The definition of an optimal surgical tumor cytoreduction continues to evolve. First recognized by Meigs [1] in 1934, cytoreductive surgery was believed to potentiate the effects of postoperative radiation therapy in advanced stage ovarian carcinomas. It was not until 1975, however, that Griffiths [2] published his seminal report showing the inverse correlation of patient survival with residual tumor diameter. Subsequently, Wharton and Herson [3] reported that patients

* Corresponding author. 8700 Beverly Boulevard, Suite 160W, Los Angeles, CA 90048.

E-mail address: Andrew.Li@cshs.org (A.J. Li).

with residual disease greater than 2 cm had no better survival than patients who had undergone biopsy alone, setting this parameter as the standard goal for cytoreduction. In a large meta-analysis of 53 studies examining surgical cytoreduction in stage III and IV ovarian carcinomas, Bristow et al [4] noted that 79% of the authors used a criterion of less than or equal to 2.0 cm to define maximal cytoreductive surgery. From these data, these investigators determined that each 10% increase in maximal cytoreduction was associated with a 5.5% increase in median survival time and confirmed that maximal cytoreduction is one of the most powerful determinants of survival among patients with advanced disease (Fig. 1) [4].

Many authors have challenged 2.0 cm as the standard by which optimal cytoreduction is determined. Hacker et al [5] reported in 1983 that patients whose largest residual lesions were no greater than 5 mm showed superior survival (median survival 40 months compared with 18 months in patients whose lesions were <1.5 cm and 6 months for patients with nodules >1.5 cm). Patients with cancers completely resected to no visible residual disease have an even better prognosis, with approximately 60% of patients being disease-free at 5 years [6]. These findings have been validated further by Eisenkop et al [7], who reported a median and estimated 5-year survival of 54 months and 48% in a cohort of 163 patients, of whom 85.3% underwent removal of all visible tumor, 13.5% had cytoreduction to less than 1 cm residual disease, and 1.2% had unresectable bulky disease (Fig. 2).

Despite these data, there is no consensus establishing a clear parameter for optimal cytoreduction. In a survey addressed to gynecologic oncologists in the

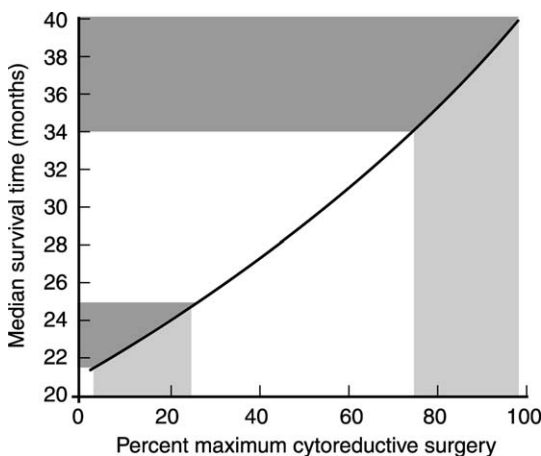


Fig. 1. Simple linear regression analysis: de-logged median survival time plotted against percent maximal cytoreductive surgery. Gray area, maximal cytoreductive surgery <25% and >75%; crosshatched area, corresponding range of median survival times. (From Bristow RE, Tomacruz RS, Armstrong DK, Trimble EL, Montz FJ. Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis. *J Clin Oncol* 2002;20:1428–59; with permission.)

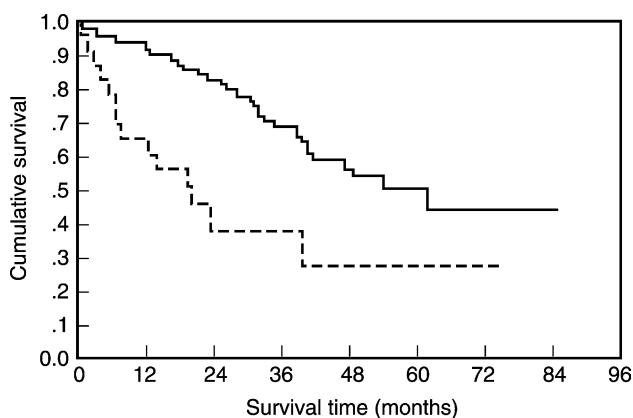


Fig. 2. Survival by cytoreductive outcome. Disease-free, solid; not disease-free, dashed (1–10 mm residual disease). $P = 0.001$. (From Eisenkop SM, Friedman RL, Wang HJ. Complete cytoreductive surgery is feasible and maximizes survival in patients with advanced epithelial ovarian cancer: a prospective study. *Gynecol Oncol* 1998;69:103–8; with permission.)

United States, 12.0% of respondents defined optimal cytoreduction as no residual disease; 13.7% used a 5-mm threshold; 60.8% used a 1-cm threshold; and 12.6% used a 1.5- to 2.0-cm threshold [8]. In a phase III chemotherapy trial (#182), the Gynecologic Oncology Group has stratified patients into no gross residual disease and a separate category of optimal cytoreduction defined as less than 1.0 cm. Although the parameters of an optimal procedure continue to change, it seems that aggressive surgical cytoreduction resulting in microscopic residual disease affords the best prognosis for overall survival.

Although most gynecologic oncologists are in consensus regarding maximal cytoreductive effort at initial diagnosis, some controversy exists for women with stage IV disease. More recent data indicate, however, a significant survival advantage for optimal tumor removal even in stage IV patients with extraperitoneal metastases. A retrospective review of 71 women with stage IV disease in China found a 14.1% 5-year survival in patients who were optimally cytoreduced to less than 1 cm of residual disease compared with 0% 5-year survival in patients who were not; this was reflected by a median survival of 23 months in the optimal cohort versus 9 months in the suboptimal cohort. These findings were identified only in patients who were stage IV by pleural effusions or malignant supraclavicular lymph nodes, however; patients with parenchymal liver disease did not exhibit similar patterns of survival [9]. Bristow et al [10] identified a 50.1-month median survival in patients who were optimally cytoreduced of extrahepatic and parenchymal liver disease compared with 27.0 months in patients with optimal extrahepatic disease but suboptimal residual hepatic tumor. Patients with suboptimal extrahepatic and suboptimal hepatic residual disease had a median survival of only 7.6 months. These findings were confirmed with another retrospective review of 37 women in the United Kingdom with stage IV disease. In this report, optimal cytoreductive surgery to residual disease either

less than 2 cm or less than 1 cm was highly significant for prolonged survival; in contrast to the Chinese study, a more favorable survival also was identified with optimal cytoreduction in the 23 cases with liver metastases, with a hazard ratio of 1.74 (95% confidence intervals 1.08 to 2.82) [11].

In the largest retrospective study examining women with stage IV epithelial ovarian cancer, Akahira et al [12] reported on data abstracted from 225 patients from 24 Japanese institutions. The most common site of extraperitoneal disease was pleural effusion (39.6%), and 31.1% were optimally cytoreduced to less than 2 cm of residual disease. Multivariate analysis revealed that performance status, histology, and residual disease after cytoreductive surgery were independent prognostic predictors of outcome. The overall median survival for optimally debulked patients was 32 months compared with 16 months for suboptimally reduced patients ($P < 0.0001$) [12]. Although these studies are all retrospective in nature and do not use consistent parameters of optimal residual disease, they do suggest that despite the presence of extraperitoneal metastases, aggressive cytoreduction is associated with prolongation of survival.

Despite these and other advances in the treatment of ovarian cancer, most women with advanced stage disease experience recurrence. In contrast to initial diagnosis, management of recurrent disease is less clear, and the role of tumor reductive surgery in this setting continues to evolve. Several more recent studies indicate, however, that successful cytoreductive surgery extends survival in selected women with recurrent disease. Eisenkop et al [13] examined 106 patients with a disease-free interval greater than 6 months after primary treatment who underwent re-exploration. All patients were without radiographic evidence of unresectable hepatic or extra-abdominal metastases. The authors identified a majority (82.1%) of patients who successfully underwent cytoreduction of all visible tumor; on multivariate analyses, their survival was more than doubled (median 44.4 months) compared with patients with macroscopic residual disease (median 19.3 months) [13]. Independent predictors of complete cytoreduction were identified as the largest size of recurrent tumor (< 10 cm [90%] versus > 10 cm [66.7%]), the use of salvage chemotherapy before secondary surgery (chemotherapy given [64.3%] versus chemotherapy not given [93.8%]), and preoperative Gynecologic Oncology Group performance status.

These findings have been confirmed by several other studies. Zang et al [14] reported on a retrospective cohort of 60 patients with recurrent epithelial ovarian cancer and a disease-free interval of at least 6 months. In this report, optimal secondary cytoreduction was achieved in 38.3% of patients, with disease removed to less than 1 cm. Median survival was nearly doubled (19 months versus 8 months) in patients successfully cytoreduced. In a second retrospective study of 46 Australian patients with recurrent disease, Tay et al [15] found that patients successfully cytoreduced to no residual disease at secondary exploration had a median survival of 38 months versus 11 months for patients with any residual disease. Survival was extended dramatically when the initial disease-free interval was greater than 24 months (median 39 months) compared with disease-free intervals of less than 12 months (median 6 months). Finally, in the largest

prospective study with 149 patients, Scarabelli et al [16] reported that residual tumor after secondary surgery was the most strongly predictive factor for survival (hazard ratio 2.65, 95% confidence interval 1.43 to 4.92). Disease-free intervals of greater than 12 months were associated with extended survival (62.9% survival at 2 years) compared with patients with disease-free intervals of less than 12 months (22.3% survival at 2 years). Taken together, these data underscore the utility of secondary cytoreduction at time of recurrence and suggest that optimal candidates are patients with prolonged initial disease-free intervals and limited volume of recurrent disease.

Prophylactic surgery

Prophylactic surgical extirpation of a healthy organ to reduce the risk of disease is a relatively new concept and has gained significant attention as genetic mechanisms of epithelial ovarian carcinogenesis become more defined. Of all women who develop ovarian cancer, approximately 10% of cases result from a hereditary cancer predisposition related to a germline mutation in *BRCA1*, *BRCA2*, or the DNA mismatch repair genes associated with the human non-polyposis colon cancer syndrome. The identification of these genes and the increasing availability of genetic testing have underscored the need for advances in early detection and prevention of this disease. Because present screening techniques continue to show poor sensitivity and specificity, prophylactic oophorectomy often is recommended after completion of childbearing to reduce risk of carcinogenesis in women at high risk.

Until more recently, data supporting prophylactic oophorectomy were limited to small studies and decision-analysis models [17–19]. These reports now have been validated by two large studies strongly supporting a significant role for oophorectomy in the prevention of ovarian cancer. Kauff et al [20] designed a prospective study of 170 carriers of *BRCA* mutations with a mean follow-up of 2 years. In the 98 women who underwent prophylactic salpingo-oophorectomy, early staged tumors were identified in 3 patients at the time of surgery (3.1%), and primary peritoneal cancer developed in 1 patient during follow-up (1.0%). Of the 72 women who underwent surveillance only, epithelial ovarian or primary peritoneal cancer developed in 5 (6.9%). The time to breast cancer or *BRCA*-related gynecologic cancer was significantly longer in the salpingo-oophorectomy group, with a hazard ratio for subsequent breast cancer or *BRCA*-related gynecologic cancer of 0.25 (95% confidence interval 0.08 to 0.74) (Fig. 3) [20].

A second, multicenter, retrospective analysis of 551 women with either *BRCA1* or *BRCA2* mutations confirmed the risk reduction with prophylactic surgery. Among 292 women who underwent surveillance, 58 (19.9%) developed ovarian cancer during a mean follow-up of almost 9 years. In contrast, among 259 women who underwent bilateral prophylactic oophorectomy, stage I cancers limited to the ovaries were identified at the time of surgery in 6 women (2.3%), and a primary peritoneal cancer subsequently developed in 2 (0.8%). With the

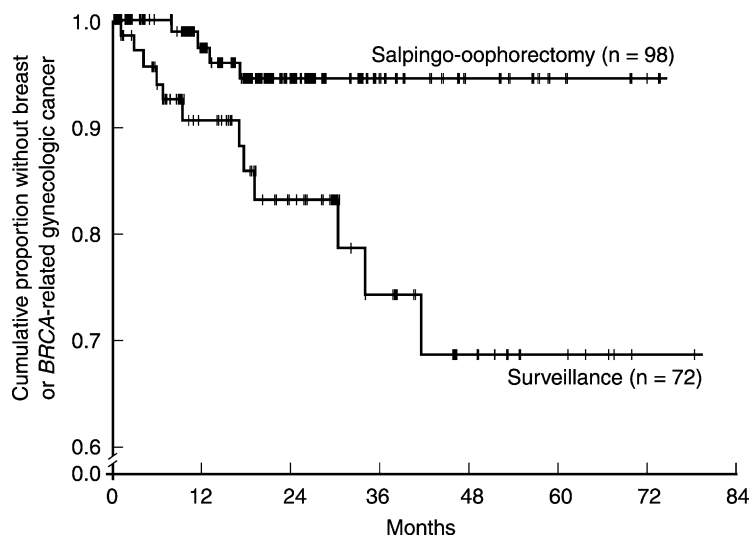


Fig. 3. Kaplan-Meier estimates of the time to breast cancer or *BRCA*-related gynecologic cancer among women electing salpingo-oophorectomy versus surveillance for ovarian cancer. $P = 0.006$ by the log-rank test for the comparison between the actuarial mean times to cancer. (From Kauff ND, Satagopan JM, Robson ME, Scheuer L, Hensley M, Hudis CA, et al. Risk-reducing salpingo-oophorectomy in women with a *BRCA1* or *BRCA2* mutation. *N Engl J Med* 2002;346:1609–15; with permission.)

exclusion of the six women whose cancer was diagnosed at surgery, prophylactic oophorectomy significantly reduced the risk of epithelial ovarian cancer (hazard ratio 0.04, 95% confidence interval 0.01 to 0.16) [21].

What other gynecologic organs are susceptible to *BRCA* mutation-induced carcinogenesis? Numerous case reports identify primary fallopian tube cancers arising in women harboring *BRCA1* and *BRCA2* mutations [22–24]. These anecdotal reports were validated in a large genetic epidemiologic study from Canada, where 44 women with pathologically confirmed primary fallopian tube carcinoma were identified and underwent genetic testing. Of these women, five were positive for a mutation in *BRCA1* (11%), and two were positive for a *BRCA2* mutation (5%). Of 18 women diagnosed at or before age 55, 5 were positive (28%). Two of the seven mutation carriers had a strong family history of breast and ovarian cancer, and three carriers had a modest family history [25]. Based on these data and their own observations, Paley et al [26] suggested that hysterectomy should be considered with bilateral salpingo-oophorectomy at the time of surgical prophylaxis to ensure removal of the entire fallopian tube. Uterine cancer itself is not associated with *BRCA1* or *BRCA2* mutations. Levine et al [27] examined 199 Ashkenazi Jewish women with endometrial cancer and did not identify an increased frequency of *BRCA* mutations above baseline for this population. No significant relative risk of endometrial cancer associated with *BRCA* mutations was identified. For women with uterine cancers of papillary serous histology,

Goshen et al [28] examined 56 women with these malignancies and did not find any clear examples of hereditary breast-ovarian cancer syndrome; none of the 56 patients was found to carry a *BRCA1* or *BRCA2* mutation. Taken together, these data suggest that complete bilateral salpingo-oophorectomy is appropriate in counseling women at high risk for gynecologic malignancies associated with *BRCA* mutations, but the role of prophylactic hysterectomy is controversial.

Careful pathologic evaluation of all specimens is mandatory to exclude subclinical disease. Agoff et al [29] identified additional cases of fallopian tube carcinoma in situ after modification of pathologic sampling techniques at their institution. Malignant cells found unexpectedly in the peritoneal washings of two patients led to the detection of previously unrecognized subclinical cancers. Colgan et al [30] examined peritoneal lavage cytology in 35 high-risk women undergoing prophylactic salpingo-oophorectomy. Malignant cells were identified in three cases, and occult ovarian and tubal carcinomas were confirmed in two of these cases. Whether pathologists adopt more comprehensive sampling or re-examine specimens with malignant cells identified in lavages, it must be recognized that many *BRCA*-associated cancers may be occult, and careful histopathologic evaluation is necessary.

Although the psychological effects of prophylactic surgery have not been well elucidated, studies have begun to address the impact on quality of life. Swisher et al [31] queried 30 women undergoing prophylactic oophorectomy and 30 women undergoing ovarian cancer surveillance and determined that few women undergoing prophylactic surgery had regret about their decision, although many would have liked more information before surgery. In the women undergoing surveillance, half expressed some regret, and 10% were frankly dissatisfied. Tiller et al [32] prospectively examined 95 women initially assessed at a familial cancer clinic. Of the 22 women who underwent prophylactic oophorectomy, a significant reduction in ovarian cancer anxiety was observed, and 86.4% reported a high degree of satisfaction with their decision to have the procedure. As the benefits associated with prophylactic bilateral salpingo-oophorectomy with or without hysterectomy have now been validated in large studies, other reports indicate that the psychological impacts are commensurate with the low risks of the procedure and the significant risk reduction of gynecologic malignancies.

Conservative and fertility-sparing surgery

Standard staging for epithelial ovarian cancer is surgical and encompasses a midline laparotomy incision with peritoneal cytology, thorough inspection of all the visceral and parietal peritoneal surfaces with biopsy of any abnormality, total abdominal hysterectomy and bilateral salpingo-oophorectomy, omentectomy, and bilateral pelvic and para-aortic lymphadenectomies [33]. Although radical resection of the pathologic adnexa is always indicated, data suggest that alternative surgical approaches in the management of epithelial ovarian cancer may be considered in special cases.

Several studies support conservative surgical staging to preserve fertility in women who desire childbearing when disease is confined to one ovary. Brown et al [34] examined 127 patients who underwent surgical staging for stage I epithelial ovarian cancer. Sixteen patients, all younger than age 40 at diagnosis, had preservation of the uterus and contralateral ovary at the time of staging. Based on high-risk factors, 37% of these women were administered platinum-based chemotherapy. After a median follow-up of 66 months, 88% were alive without disease. Two experienced recurrence of their disease in the remaining ovary and subsequently died of disease. Of the 92 women who underwent standard staging with hysterectomy and bilateral oophorectomy, 87% were alive without disease; 15% recurred, and 8 patients have died of disease. In the conservative surgery group, five patients had a total of eight successful pregnancies, two after adjuvant chemotherapy. Twelve surviving patients in the conservative group were found to have proven fertility or normal menstrual function after completing therapy [34].

Morice et al [35] confirmed these findings in a larger study of 25 women conservatively treated for epithelial ovarian carcinoma. After a median follow-up of 47 months, 72% were alive and disease-free. Of the seven patients who recurred, three had stage IA disease, and four had stage IC or higher. The 5-year survival for patients with stage IA disease was 90% (95% confidence interval 60% to 95%). When stratified according to tumor grade, the disease-free survival at 5 years for patients with stage IA disease was 89% (95% confidence interval 58% to 96%) in patients with grade 1 disease and 71% (95% confidence interval 36% to 88%) in patients with grade 2 disease. Morice et al [35] concluded that conservative surgery may be considered in patients with early stage disease who desire childbearing potential but should be limited to patients with grade 1 disease limited to the ovary.

If a decision is made to preserve the uterus and contralateral ovary for disease apparently limited to one ovary, comprehensive surgical staging including bilateral lymph node sampling still is indicated. Cass et al [36] reviewed 96 patients with disease clinically confined to one ovary and determined patterns of lymph node sampling and metastases. They determined that 15% of the group had microscopic metastatic disease to the lymph nodes, all of whom had grade 3 tumors. Of patients, 42 had node sampling only on the side ipsilateral to the neoplastic ovary, 4 (10%) of whom had metastatic disease. Of patients, 54 had bilateral sampling performed, 10 (19%) of whom had metastases. Of these 10 patients, isolated ipsilateral node metastases were seen in 5 (50%) cases. Isolated contralateral node metastases were seen in three (30%) cases, and bilateral metastases were seen in two (20%). Cass et al [36] concluded that bilateral lymph node sampling increased the identification of nodal metastases and recommended bilateral pelvic and para-aortic node sampling to stage ovarian carcinoma accurately.

The role of laparoscopy in ovarian cancer also continues to evolve. Because many adnexal masses are evaluated initially through the laparoscope, some oncologists may elect to complete surgical staging without a laparotomy incision.

Scribner et al [37] analyzed the first 100 cases of planned laparoscopic pelvic and para-aortic lymph node dissections performed for staging of gynecologic cancers. Laparoscopy was completed in 70.9% of the group. Although the number of pelvic, common iliac, and para-aortic lymph nodes did not differ statistically between patients who underwent laparoscopy compared with patients who underwent conversion to laparotomy, two deaths did occur; one from a vascular injury on initial trocar insertion and a second from a pulmonary embolism after laparotomy for bowel herniation through a trocar incision.

Many investigators also have examined the use of laparoscopy in reassessment or second-look surgery in patients without clinical evidence of disease after surgical cytoreduction and chemotherapy. Although the role of second-look surgery is controversial, the laparoscopic technique is feasible and approximately equivalent to laparotomy in detecting persistent disease. Casey et al [38] reviewed 57 laparoscopic and 69 open reassessment procedures at Cedars-Sinai Medical Center and determined that the ability to detect disease was 52.6% and 53.6%. In patients who underwent laparoscopic surgery, Casey et al [38] identified less blood loss, decreased hospital stay, less financial burden, and no increase in patient morbidity. Husain et al [39] reported on their experience with 150 patients at Memorial Sloan-Kettering Cancer Center. Of patients, 69 (46%) were found to have pathologically negative results of second-look surgery, comparable to rates identified in reassessment surgery by laparotomy. Eighteen patients (12%) underwent conversion to laparotomy—four for repair of bowel or bladder injuries and the remainder for secondary cytoreduction. Only one case was identified in which adhesions limited laparoscopic evaluation. Clough et al [40] designed a prospective comparative study with 20 patients who initially underwent reassessment laparoscopy followed by immediate comparative laparotomy. They identified the positive predictive value of laparoscopy to be 100% (6 of 6 cases) and the negative predictive value to be 86% (2 false-negative cases of 14). The presence of adhesions in this series limited complete intraperitoneal investigation to 41% for laparoscopy compared with 95% for laparotomy. Although post-operative adhesions may present a limiting factor for complete evaluation, these data validate the feasibility and accuracy of laparoscopy in reassessment surgery.

Preliminary data further support a role for laparoscopy in the surgical management of recurrent disease. Successful tumor removal of a solitary adrenal metastasis and a solitary splenic metastasis has been reported [41,42]. The splenectomy was performed using hand-assisted laparoscopy, which is an alternative approach that preserves the tactile advantages of open surgery. Pelosi et al [43] described their preliminary experience with this approach, which permits the insertion of a hand into the abdomen through a glove-sized incision while maintaining the pneumoperitoneum. Their data suggest that hand-assisted laparoscopy may be feasible and expeditious and may replace an extended open laparotomy incision or an excessively tedious laparoscopic exercise in the evaluation and management of pelvic malignancies [43].

Laparoscopic procedures with known epithelial ovarian cancers should be approached with caution. The risk of port-site metastases is well documented,

usually identified within weeks after initial laparoscopy [44–46]. Anecdotally the presence of large-volume disease and ascites seems to contribute to port-site spread. These metastases do not seem to result from the type or pressure of pneumoperitoneum; studies in animal models have not shown adverse effects on weight of omental metastases or number of peritoneal metastases in carbon dioxide versus gasless laparoscopy or midline laparotomy [47]. Pneumoperitoneal pressure was not found to affect tumor growth in a similar rat model [48]. Although a laparoscopic approach may be feasible for ovarian cancer staging, it is not without its inherent risks, and its role remains controversial. In women with known metastatic disease or ascites, surgical exploration and cytoreduction should be undertaken with the standard midline laparotomy incision.

Summary

Surgical intervention remains a key component in the diagnosis and management of epithelial ovarian carcinomas. Although the parameters defining “optimal” tumor cytoreduction continue to evolve, data validate the concept of complete operative tumor resection to no visible residual disease in all stages of ovarian cancer to prolong disease-free and overall survival. In select patients, recurrent disease also may be managed with surgical cytoreduction. At the other end of the spectrum, prophylactic bilateral salpingo-oophorectomy has been shown conclusively to reduce the risk of ovarian cancer in women at high risk. Although *BRCA1*-associated and *BRCA2*-associated gynecologic cancer syndromes do not seem to include uterine malignancies, the role of hysterectomy to remove the fallopian tube completely is controversial. Finally, new data support the concept of conservative, fertility-sparing surgery in a select group of women with early-stage disease. Although laparoscopy may be feasible in staging women with disease apparently limited to an ovary, further studies are necessary before it can be considered routinely as an alternative to standard laparotomy.

References

- [1] Meigs JV. Tumors of the female pelvic organs. New York: Macmillan; 1934.
- [2] Griffiths CT. Surgical resection of tumor bulk in the primary treatment of ovarian carcinoma. *Natl Cancer Inst Monogr* 1975;42:101–4.
- [3] Wharton JT, Herson J. Surgery for common epithelial tumors of the ovary. *Cancer* 1981;48:582–9.
- [4] 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):1428–59.
- [5] Hacker NF, Berek JS, Lagasse LD, Nieberg RK, Elashoff RM. Primary cytoreductive surgery for epithelial ovarian cancer. *Obstet Gynecol* 1983;561:413–20.
- [6] Pecorelli S, Odicino F, Maisonneuve P, Creasman W, Shepard J, Sideri M, et al. Carcinoma of the ovary: annual report on the results of treatment of gynaecological cancer. *J Epidemiol Biostat* 1998;3:75–102.
- [7] Eisenkop SM, Friedman RL, Wang HJ. Complete cytoreductive surgery is feasible and max-

- imizes survival in patients with advanced epithelial ovarian cancer: a prospective study. *Gynecol Oncol* 1998;69:103–8.
- [8] Eisenkop SM, Spirtos NM. What are the current objectives, strategies, and technical capabilities of gynecologic oncologists treating advanced epithelial ovarian cancer? *Gynecol Oncol* 2001; 82(3):489–97.
- [9] Zang RY, Zhang ZY, Cai SM, Li ZT, Chen J, Tang MQ, et al. Cytoreductive surgery for stage IV epithelial ovarian cancer. *J Exp Clin Cancer Res* 1999;18(4):449–54.
- [10] Bristow RE, Montz FJ, Lagasse LD, Leuchter RS, Karlan BY. Survival impact of surgical cytoreduction in stage IV epithelial ovarian cancer. *Gynecol Oncol* 1999;72(3):278–87.
- [11] Naik R, Nordin A, Cross PA, Hemming D, De Barros Lopes A, Monaghan JM. Optimal cytoreductive surgery is an independent prognostic indicator in stage IV epithelial ovarian cancer with hepatic metastases. *Gynecol Oncol* 2000;78(2):171–5.
- [12] Akahira JI, Yoshikawa H, Shimizu Y, Tsunematsu R, Hirakawa T, Kuramoto H, et al. Prognostic factors of stage IV epithelial ovarian cancer: a multicenter retrospective study. *Gynecol Oncol* 2001;81(3):398–403.
- [13] Eisenkop SM, Friedman RL, Spirtos NM. The role of secondary cytoreductive surgery in the treatment of patients with recurrent epithelial ovarian carcinoma. *Cancer* 2000;88(1):144–53.
- [14] Zang RY, Zhang ZY, Li ZT, Chen J, Tang MQ, Liu Q, et al. Effect of cytoreductive surgery on survival of patients with recurrent epithelial ovarian cancer. *J Surg Oncol* 2000;75(1):24–30.
- [15] Tay EH, Grant PT, Gebiski V, Hacker NF. Secondary cytoreductive surgery for recurrent epithelial ovarian cancer. *Obstet Gynecol* 2002;99(6):1008–13.
- [16] Scarabelli C, Gallo A, Carbone A. Secondary cytoreductive surgery for patients with recurrent epithelial ovarian carcinoma. *Gynecol Oncol* 2001;83(3):504–12.
- [17] Schrag D, Kuntz KM, Garber JE, Weeks JC. Decision analysis—effects of prophylactic mastectomy and oophorectomy on life expectancy among women with BRCA1 and BRCA2 mutations. *N Engl J Med* 1997;336:1465–71.
- [18] Grann VR, Panageas KS, Whang W, Antman KH, Neugut AI. Decision analysis of prophylactic mastectomy and oophorectomy in BRCA1-positive or BRCA2-positive patients. *J Clin Oncol* 1998;16:979–85.
- [19] Struewing JP, Watson P, Easton DF, Ponder BA, Lynch HT, Tucker MA. Prophylactic oophorectomy in inherited breast/ovarian cancer families. *J Natl Cancer Inst Monogr* 1995;17:33–5.
- [20] Kauff ND, Satagopan JM, Robson ME, Scheuer L, Hensley M, Hudis CA, et al. Risk-reducing salpingo-oophorectomy in women with a BRCA1 or BRCA2 mutation. *N Engl J Med* 2002; 346(21):1609–15.
- [21] Rebbeck TR, Lynch HT, Neuhausen SL, Narod SA, Veer LV, Garber JE, et al. Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations. *N Engl J Med* 2002;346(21):1616–22.
- [22] Ansink AC, Burger CW, Seynaeve C. Occult cancer in the fallopian tube in patients with a BRCA-1 germline mutation. *Gynecol Oncol* 2001;83(2):445.
- [23] Sobol H, Jacquemier J, Bonaiti C, Dauplat J, Birnbaum D, Eisinger F. Fallopian tube cancer as a feature of BRCA1-associated syndromes. *Gynecol Oncol* 2000;78(2):263–4.
- [24] Herbert-Blouin MN, Koufogiannis V, Gillett P, Foulkes WD. Fallopian tube cancer in a BRCA1 mutation carrier: rapid development and failure of screening. *Am J Obstet Gynecol* 2002;186(1): 53–4.
- [25] Aziz S, Kuperstein G, Rosen B, Cole D, Nedelcu R, McLaughlin J, et al. A genetic epidemiological study of carcinoma of the fallopian tube. *Gynecol Oncol* 2001;80(3):341–5.
- [26] Paley PJ, Swisher EM, Garcia RL, Agoff SN, Greer BE, Peters KL, et al. Occult cancer of the fallopian tube in BRCA-1 germline mutation carriers at prophylactic oophorectomy: a case for recommending hysterectomy at surgical prophylaxis. *Gynecol Oncol* 2001;80(2):176–80.
- [27] Levine DA, Lin O, Barakat RR, Robson ME, McDermott D, Cohen L, et al. Risk of endometrial carcinoma associated with BRCA mutation. *Gynecol Oncol* 2001;80(3):395–8.
- [28] Goshen R, Chu W, Elit L, Pal T, Hakimi J, Ackerman I, et al. Is uterine papillary serous adenocarcinoma a manifestation of the hereditary breast-ovarian cancer syndrome? *Gynecol Oncol* 2000;79(3):477–81.

- [29] Agoff SN, Mendelin JE, Grieco VS, Garcia RL. Unexpected gynecologic neoplasms in patients with proven or suspected BRCA-1 or -2 mutations: implications for gross examination, cytology, and clinical follow-up. *Am J Surg Pathol* 2002;26(2):171–8.
- [30] Colgan TJ, Boerner SL, Murphy J, Cole DE, Narod S, Rosen B. Peritoneal lavage cytology: an assessment of its value during prophylactic oophorectomy. *Gynecol Oncol* 2002;85(3):397–403.
- [31] Swisher EM, Babb S, Whelan A, Mutch DG, Rader JS. Prophylactic oophorectomy and ovarian cancer surveillance: patient perceptions and satisfaction. *J Reprod Med* 2001;46(2):87–94.
- [32] Tiller K, Meiser B, Butow P, Clifton M, Thewes B, Friedlander M, et al. Psychological impact of prophylactic oophorectomy in women at increased risk of developing ovarian cancer: a prospective study. *Gynecol Oncol* 2002;86(2):212–9.
- [33] Leblanc E, Querleu D, Narducci F, Chauvet MP, Chevalier A, Lesoin A, et al. Surgical staging of early invasive epithelial ovarian tumors. *Semin Surg Oncol* 2000;19(1):36–41.
- [34] Brown CL, Dharmendra B, Barakat RR. Preserving fertility in patients with epithelial ovarian cancer: the role of conservative surgery in treatment of early-stage disease. In: Society of Gynecologic Oncologists' 31st annual meeting abstract book. Chicago (IL): Society of Gynecologic Oncologists; 2000. p. 121.
- [35] Morice P, Wicart-Poque F, Rey A, El-Hassan J, Pautier P, Lhomme C, et al. Results of conservative treatment in epithelial ovarian carcinoma. *Cancer* 2001;92(9):2412–8.
- [36] Cass I, Li AJ, Runowicz CD, Fields AL, Goldberg GL, Leuchter RS, et al. Pattern of lymph node metastases in clinically unilateral stage I invasive epithelial ovarian carcinomas. *Gynecol Oncol* 2001;80(1):56–61.
- [37] Scribner DR, Walker JL, McMeekin SD, Gold MA, Mannel RS. Laparoscopic pelvic and paraaortic lymph node dissection: analysis of the first 100 cases. *Gynecol Oncol* 2001;82(3):498–503.
- [38] Casey AC, Farias-Eisner R, Pisani AL, Cirisano FD, Kim YB, Munderspach L, et al. What is the role of reassessment laparoscopy in the management of gynecologic cancers in 1995? *Gynecol Oncol* 1996;60(3):454–61.
- [39] Husain A, Chi DS, Prasad M, Abu-Rustum N, Barakat RR, Brown CL, et al. The role of laparoscopy in second-look evaluations for ovarian cancer. *Gynecol Oncol* 2001;80(1):44–7.
- [40] Clough KB, Ladonne JM, Nos C, Renolleau C, Validire P, Durand JC. Second look for ovarian cancer: laparoscopy or laparotomy? A prospective comparative study. *Gynecol Oncol* 1999;72(3):411–7.
- [41] Einat S, Amir S, Silvia M, Moshe I. Successful laparoscopic removal of a solitary adrenal metastasis from ovarian carcinoma: a case report. *Gynecol Oncol* 2002;85(1):201–3.
- [42] Yano H, Iwazawa T, Kinuta M, Nakano Y, Tono T, Matsui S, et al. Solitary splenic metastasis from ovarian cancer successfully treated by hand-assisted laparoscopic splenectomy: report of a case. *Surg Today* 2002;32(8):750–2.
- [43] Pelosi MA, Pelosi 3rd MA, Eim J. Hand-assisted laparoscopy for pelvic malignancy. *J Laparoendosc Adv Surg Tech A* 2000;10(3):143–50.
- [44] Leminen A, Lehtovirta P. Spread of ovarian cancer after laparoscopic surgery: report of eight cases. *Gynecol Oncol* 1999;75(3):387–90.
- [45] Hopkins MP, von Gruenigen V, Gaich S. Laparoscopic port site implantation with ovarian cancer. *Am J Obstet Gynecol* 2000;182(3):735–6.
- [46] Viala J, Morice P, Pautier P, Castaigne D, Vanel D. CT findings in two cases of port-site metastasis after laparoscopy for ovarian cancer. *Eur J Gynaecol Oncol* 2002;23(4):293–4.
- [47] Lecuru F, Agostini A, Camatte S, Robin F, Aggerbeck M, Jais JP, et al. Impact of pneumoperitoneum on tumor growth. *Surg Endosc* 2002;16(8):1170–4.
- [48] Agostini A, Robin F, Jais JP, Aggerbeck M, Vilde F, Blanc B, et al. Impact of different gases and pneumoperitoneum pressures on tumor growth during laparoscopy in a rat model. *Surg Endosc* 2002;16(3):529–32.