The Journal of
OBSTETRICS AND GYNECOLOGY of India

J Obstet Gynecol India Vol. 59, No. 3 : May/June 2009 pg 209-216

Review Article

In Pursuit of Optimal Cytoreduction in Ovarian Cancer Patients: The Role of Surgery and Surgeon

Lele Shashikant [1], Kesterson Joshua P [2]

[1] Fellow, Division of MFM/OBGYN, [2] Assistant Professor

Division of Gynecologic Oncology, Roswell Park Cancer Institute, Buffalo, NY 14263

Abstract

The standard of care for women with advanced stage epithelial ovarian cancer (EOC) involves surgery followed by adjuvant platinum-based combination chemotherapy. One of the goals of surgery is to resect all macroscopic disease. In this review we will discuss the justification for an aggressive surgical approach, including a discussion of factors limiting its implementation and suggestions for providing appropriate surgical intervention for all women with EOC.

Key words : epithelial ovarian cancer, surgery, cytoreduction, optimal

Introduction

Ovarian cancer affects more than 204,000 women worldwide every year[1]. A majority of the cases are epithelial in origin and will be diagnosed at an advanced stage. The standard of care for women with advanced stage epithelial ovarian cancer (EOC) involves surgery followed by adjuvant platinum-based combination chemotherapy. The goal of the initial surgical intervention is to properly stage the patient and resect all macroscopic disease. In this review we will discuss the evolution of the current recommended therapy for initial surgical intervention for an advanced stage EOC. Included in this review is the correlation between surgical cytoreduction and patient outcomes, mechanisms which may account for this favorable association and an analysis of means by which women are burdened with sub-standard care, including the inferior outcomes resultant from not being operated on by a trained specialist. Suggestions for broadening the catchment area of women with EOC who are offered the best care are presented.

Paper received on 27/03/2009 ; accepted on 23/04/2009

Correspondence :
Lele Shashikant
Chair, Division of Gynecologic Oncology
Roswell Park Cancer Institute
Elm & Carlton Streets
Buffalo, NY 14263
Phone: (716) 845-5776
Fax: (716) 845-7608
Email: shashi.lele@roswellpark.org

Origin and Evolution of Surgical Cytoreduction

The beneficial effects of surgical cytoreduction of tumor volume in patients with ovarian cancer originally came from a report by Munnell in 1968[2]. He noted that patients who had a greater volume of their tumor removed had an improved survival. Subsequently, in 1969, Elclos and Quinlan reported an improved survival in patients with advanced stage ovarian cancer who had their disease reduced to non-palpable implants compared to

those left with palpable disease at the completion of surgery. Seven years later, Griffiths reported an inverse correlation between the size of residual tumor implants and survival [4]. He observed an increase in median survival times of 18, 29, and 39 months for those patients cytoreduced to 0.6-1.5, <0.5, and 0 cm of residual disease, respectively. An essential finding of his paper was that an inability to reduce the remaining tumor to less than 1.5 cm lesions did not result in an improved survival. Similarly, Hacker et al observed more than a doubling of survival from 18 months to 40 months when comparing those cytoreduced to 0.5-1.5 cm versus those with less than half a centimeter of residual disease [5]. Patients left with greater than 1.5 cm of disease at the completion of surgery survived a median of only six months. These investigators and their studies were the early pioneers in establishing a new paradigm for the initial surgical management of advanced EOC. They demonstrated that the optimal cytoreduction of tumor burden was associated with markedly improved survival outcomes. Furthermore, they made evident that the quantity of tumor removed was not the origin of improved outcomes, but rather what the original tumor quantity could be reduced to with surgical intervention.

Since those key studies by Munnel, Griffiths, and Hacker et al, multiple retrospective studies have confirmed more favorable outcomes experienced by those patients left with minimal residual tumor at the completion of the initial cytoreductive effort [5-11]. In 2002, Bristow et al published the results of their analysis of the effect of maximal cytoreductive surgery for patients with advanced EOC [7]. In a meta-analysis which included over 6,800 patients in 53 studies, they observed a statistically significant positive correlation between the percent of maximal cytoreduction and surgery. When comparing those in the upper and lower quartile of maximal cytoreduction, they noted a difference in median survival of 33.9 months versus 22.7 months, respectively. Further analysis showed that each 10% increase in maximal cytoreduction was associated with a 5.5% increase in median survival.

Despite these early and subsequent studies, others have suggested that the extensiveness of the tumor spread and involvement of upper abdominal organs is a more significant prognostic marker of a particular patient's ovarian cancer aggressiveness [12]. To test the relative contribution of a tumor's inherent biology versus the contribution of aggressive cytoreduction to outcomes, Eisenkop et al designed a thought-provoking analysis [13]. Patients with stage IIIC EOC at the time of initial cytoreductive surgery were assigned numeric scores to quantify the extent of the disease. The completeness of cytoreduction was also assessed. They showed that the completeness of cytoreduction had a more significant influence on survival than on the extent of disease prior to surgery. They concluded that the extensiveness of cytoreductive efforts should be dictated by surgeon's experience and the patient's ability to tolerate an extensive surgery and not the extensiveness of the pre-surgical disease, including extra-ovarian organ involvement.

Cytoreduction in Stage IV EOC Patients

Patients with either hepatic parenchymal metastases or malignant pleural effusions are classified as stage IV. The role of cytoreduction in patients with stage IV disease has been debated in the literature in the recent past, with some proponents of neoadjuvant chemotherapy in this subset of patients. Some studies have failed to show any survival advantage for stage IV patients undergoing attempted cytoreduction[14,15]. However, these studies were limited by relatively small numbers of patients or low percentages of optimal cytoreduction. The beneficial effects of debulking for stage IV patients appears to be, similar to stage III disease, proportionally correlated with the adequacy of cytoreduction. Additional studies with larger numbers of patients and higher rates of adequate cytoreduction have demonstrated markedly improved survival in women with stage IV disease who were optimally cytoreduced when compared to those who were left with larger amounts of the residual disease [6,16-18]. Even in patients with unresectable liver parenchymal lesions, optimal debulking of the extrahepatic lesions has been shown to be associated with an improved survival [6]. Thus, the evidence supports attempted cytoreduction as initial therapy in stage IV patients, with the goal of removing all macroscopic disease, as it is associated with an improved survival when compared to those patients with suboptimal cytoreduction.

Cytoreduction in the Setting of Neoadjuvant Chemotherapy

The beneficial effect of cytoreduction seems to persist in the setting of neoadjuvant chemotherapy. Neoadjuvant chemotherapy refers to the administration of chemotherapy for a set number of cycles followed by an attempted cytoreduction. In a study reported by Shibata et al of patients treated with neoadjuvant

chemotherapy for six cycles, the patients subsequently undergoing optimal cytoreduction survived over twice as long as those who were suboptimally cytoreduced after neoadjuvant chemotherapy[19]. Extensive analysis regarding the impact of residual disease in patients treated with neoadjuvant chemotherapy is difficult to perform because most studies evaluating neoadjuvant chemotherapy do so in comparison to those patients treated initially by surgery followed by adjuvant chemotherapy and do not substratify populations with and without minimal residual disease after cytoreduction in regards to their outcomes. Enthusiasm for neoadjuvant chemotherapy as the equivalent of initial cytoreduction should be tempered by a thorough analysis of the optimal cytoreduction rates of the control group, by the percentage of patients with minimal disease at the initiation of and completion of interval surgery, as well as the selection criteria used to select which women to exclude from operative intervention[20]. Optimal cytoreduction appears to be beneficial at interval surgery, but more so as the initial treatment of women with advanced stage EOC.

What is *Optimal* Cytoreduction?

The interpretation of the word *optimal* in gynecologic oncology has evolved, with variable acceptance within the field, as have the studies over the last three decades [21]. When comparing the survival benefits observed for patients debulked to =2 cm of residual disease with the poorer survival for patients with >2 cm implants, the categories of *optimal* and *suboptimal* were used [10]. However, subsequent studies have demonstrated that the inverse relationship between residual disease and survival in ovarian cancer is not binary, with a 2cm cutoff, but rather a continuum [7]. Chi et al have demonstrated that a favorable correlation between the size of the residual implants and outcomes continues to exist for implants measuring less than 2 cm [8]. They analyzed 465 Stage IIIC EOC patients who underwent cytoreductive surgery at Memorial Sloan-Kettering Cancer Center. There was a difference in survival in inverse relation to residual disease: no gross residual, 106 months; =0.5 cm, 66 months; 0.6-1 cm, 48 months; 1-2 cm, 33 months; >2 cm, 34 months. Similarly, Eisenhauer et al. reported on 296 patients with Stage IIIC-IV ovarian cancer who received adjuvant intravenous platinum-taxane chemotherapy [22]. Patients who were cytoreduced to no visible disease had improved progression-free survival and overall survival compared to the patients with 1-10 mm of residual disease and >10 mm residual disease.

Currently, the Gynecologic Oncology Group (GOG) defines *optimal* as residual disease =1 cm in maximal diameter. However, as *optimal* by definition means 'the best' and outcomes are better for patients with no macroscopic disease compared to those with larger implants, the *optimal*, or best, surgery is the one which leaves no residual disease and should be the surgeon's goal.

Theoretical Mechanistic Support for Cytoreduction

There are several theoretical mechanisms by which cytoreduction may exert its beneficial effect. One such mechanism is via surgery's ability to reduce the number of chemoresistant clones. In 1979, Goldie and Coldman reported their mathematical model for the development of the number of chemoresistant clones in a tumor [23]. They reported that as the cell number in a tumor increased so too would the resistant cells within the tumor, and thus the expectation of a cure with chemotherapy would decrease. Thus surgical intervention may serve to reset the tumor's inherent biology, increasing the probability that adjuvant cytotoxic chemotherapy will be effective. Additionally, reducing the tumor's initial large volume to small implants will decrease the proportion of tumor which is poorly vascularized, thus decreasing the chance that tumor cells will be unexposed to intravenously administered chemotherapy.

Removal of ovarian tumor may improve host immunity by subtracting from the host certain cells which have known immunosuppressive properties. Ovarian cancer tumors have been shown to contain an immunosuppressive subset of lymphocytes known as Tregulatory cells. A high proportion of Tregulatory cells has been associated with inferior clinical outcomes in ovarian cancer patients [24-26]. Additionally, ovarian tumors produce immunosuppressive cytokines. Merogi et al noted the expression of transforming growth factor-beta1 and interleukin-10, which were associated with a significant reduction in tumor-infiltrating lymphocytes and CD8+ Tcells [27]. Ovarian cancers have also been shown to secrete large amounts of vascular endothelial growth factor, believed to play a role in ascites genesis as well as metastatic tumor spread [28]. As a majority of patients present with disease beyond the ovary, including ascites, omental caking and peritoneal implants, removal of these sites of disease improves patient comfort and quality of life.

Predictors of Suboptimal Initial Cytoreduction

Considering the extensiveness of surgery required to achieve optimal cytoreduction in some patients as well as the lack of survival benefit for patients left with bulky disease despite cytoreductive efforts, attempts have been made to predict which patients may not be optimally cytoreduced and thereby possibly withheld from initial cytoreductive efforts. Recently, investigators from Denmark reported the results of their study designed to identify PET/CT characteristics predictive of incomplete primary surgical cytoreduction in advanced ovarian cancer [29]. After multivariate analysis, the presence of large bowel mesenteric implants (LBMI) was the only independent predictor of incomplete cytoreduction. However, one must consider that there was no predictor which consistently identified unresectable disease. In fact, 18% of the patients with LBMI underwent complete debulking.

Salini et al conducted a retrospective analysis of stage IIIC and IV EOC patients with conventional markers of surgically unresectable disease (i.e. large volume ascites, omental extension to spleen >1 cm, liver parenchymal disease >1 cm, porta hepatis involvement >1 cm, diaphragmatic disease >1 cm, peritoneal carcinomatosis >1 cm in the abdomen and pelvis and suprarenal para-aortic lymphadenopathy >1 cm) to evaluate the predictive utility of these criteria [30]. Optimal cytoreduction was defined as residual disease =1 cm. Over 90% of the patients with ascites, carcinomatosis or diaphragmatic disease were optimally cytoreducted. A majority of the patients with splenic involvement, liver or porta hepatis involvement were optimally cytoreduced. Patients with two, three, or four 'unresectable' disease sites were optimally cytoreduced in 94%, 82% and 93% of the cases, respectively.

Investigators at Memorial Sloan-Kettering Cancer Center evaluated the ability of pre-operative CA-125 to predict primary cytoreductive outcomes in patients with advanced ovarian, tubal and peritoneal cancer [31]. They reviewed the records of 277 patients to assess their cytoreductive outcomes, i.e. no gross residual disease, less than one centimeter of residual disease, or greater than one centimeter of residual disease, in relation to preoperative CA-125. They noted that there was no CA-125 level, above which was predictive of cytoreductive outcome. They did observe that patients with CA-125 values greater than 500 U/mL were more likely to require extensive upper abdominal surgery to achieve residual disease status of less than one centimeter, suggesting that CA-125 increases in relation to tumor burden.

These studies highlight important points regarding the prediction of the ability to optimally cytoreduce a patient. There is no way to accurately and reliably predict preoperatively what a patient's residual disease status will be at the completion of surgery. To forego a primary cytoreduction based on *unresectable* disease as determined by imaging or laboratory values is to deny those patients that can be optimally debulked an intervention associated with improved clinical outcomes, most importantly, prolonged overall survival. Physicians should also be aware of the possibility of the need for extensive and radical procedures to achieve no residual disease burden. In the study by Chi et al they noted that 50% of the cases with CA-125 values >500 U/mL required extensive upper abdominal procedures to achieve residual disease less than one centimeter, however it should be noted that over one quarter of the patients with CA-125 <500 U/mL also required similar interventions to achieve the same post-operative disease state [31]. Any decision to forego an attempted primary cytoreduction should not be based on preoperative predictors of *unresectable* disease.

The Role of Surgeon Specialty in the Initial Surgical Management

Given that the initial treatment of EOC involves surgical staging with an attempt to reduce the patient to no residual disease as these interventions result in superior outcomes, the question then becomes, 'Who is best qualified to treat these patients?'. Investigators from the Netherlands attempted to answer this question [32]. They reviewed the records of 680 patients diagnosed with EOC over a four year period and compared the outcomes of patients operated on by gynecologic oncologists versus those operated on by general gynecologists. Gynecologic oncologists were more likely to appropriately stage their patients and were twice as likely to remove all macroscopic tumor. These differences contributed to improved five year survival rates for early and late stage patients (86% vs. 70% and 21% vs. 13%, respectively).

Similarly, Chan et al attempted to estimate the influence of gynecologic onocologists on the treatment and outcomes of patients with ovarian cancer [33]. Using the California Cancer Registry, they compared the outcomes of patients seen initially by a gynecologic oncologist versus those seen by others. Women seen by a

gynecologic oncologist were more likely to have surgery as their initial treatment (92% vs. 69%), be staged, and receive chemotherapy (90% vs. 70%). Patients who saw a gynecologic oncologist and received chemotherapy had an improved survival compared to those who did not see a gynecologic oncologist and received chemotherapy. On multivariate analysis, there was a survival benefit seen when initial care was delivered by a gynecologic oncologist, when controlled for age, stage, and grade. However, this favorable effect was lost when controlled for surgery, staging and chemotherapy, suggesting that the outcome benefits attributed to seeing a gynecologic oncologist were due to their more prevalent implementation of surgery and chemotherapy in the initial management strategy.

In a meta-analysis of 19 articles, in an attempt to assess the effect of specialized care for ovarian cancer, Vernooij et al reported that gynecologic oncologists were more likely to debulk to less than two centimeters of residual disease and to no macroscopic disease status [34]. While it is difficult to group all studies together for analysis, considering that each study controlled for and evaluated different variables, it appears that there are subgroups of ovarian cancer patients who have an improved survival when operated on by gynecologic oncologists. One of these subpopulation appears to be elderly women, a group more likely to develop ovarian cancer. Earle et al, using the Surveillance, Epidemiology, and End Results (SEER) program, assessed the association between specialty care and outcomes in women with ovarian cancer aged 65 and older [35]. Patients with advanced stage disease were more likely to undergo a debulking procedure if seen by a gynecologic oncologist than if seen by a general gynecologist or a general surgeon. Similarly, the patients seen by a gynecologic oncologist were more likely to receive postoperative chemotherapy. Advanced age should not be a contraindication to aggressive cytoreduction as elderly patients with multiple comorbidities are capable of undergoing optimal cytoreduction with a low rate of complications [36].

The means by which patients receive improved outcomes when cared for by a gynecologic oncologist are multifocal with one benefit being the improved rates of optimal cytoreduction. As advanced ovarian cancer may involve the organs and structures of the upper abdomen, the ability to achieve an optimal cytoreduction in these patients will be dependent on the surgeon's ability to successfully remove these tumor sites [37]. To do so safely requires proficiency in a variety of techniques, including diaphragm stripping and resection, splenectomy, distal pancreatectomy, liver resection and cholecystectomy. Improved rates of optimal cytoreduction, and thus outcomes, have been generated via the incorporation of these techniques[38]. For a surgeon to operate on a woman with EOC without proficiency in these techniques is to risk a suboptimal cytoreduction, a patient life-shortening and potentially avoidable complication.

These studies highlight the fact that the patients seen for initial treatment by a gynecologic oncologist are more likely to be treated surgically, appropriately staged, and to receive adjuvant chemotherapy. As these factors all favorably affect patient survival, all women with the diagnosis of, or clinical suspicion of, ovarian cancer should be referred to a gynecologic oncologist with experience in operating on women with ovarian cancer. The Society of Gynecologic Oncologists (SGO) and the American College of Obstetricians and Gynecologists (ACOG) have recommendations for referral for a woman with a newly diagnosed pelvic mass (Table 1) [39].

Table 1. Society of Gynecologic Oncologists and American College of Obstetricians and Gynecologists Referral Guidelines for a Newly Diagnosed Pelvic Mass.

Premenopausal (<50 years)

- CA-125 levels greater than 200 U/mL
- Ascites
- Evidence of abdominal or distant metastasis
- Family history of breast or ovarian cancer in first-degree relative

Postmenopausal (>50 years)

- Elevated CA-125 levels
- Ascites
- Nodular or fixed pelvic mass
- Evidence of abdominal or distant metastasis·

Family history of breast or ovarian cancer in first-degree relative (ACOG Committee Opinion: number 280, December 2002)

Impact of Site of Initial Care

Not only does the surgeon's expertise play a pivotal role in optimizing outcomes for ovarian cancer patients, but so too does the site of care. Hillner et al. conducted a comprehensive review of the available literature to search for evidence that outcomes of cancer patients were affected by hospital or physician volume or specialty [40]. They noted that most studies showed a positive relationship between higher volume and better outcomes. Schrag et al investigated the association between hospital procedure volume and outcomes for ovarian cancer patients over 65 years of age [41]. Patients treated at high-volume hospitals had decreased two-year mortality when compared to those treated at low and intermediate-volume hospitals. Investigators from Finland noted similar results with five-year relative survival rates being the highest for the patients operated on in the highest volume hospitals when compared to those operated on in hospitals with decreased surgical volume [42]. Patients with advanced stage disease operated on at teaching hospitals have been shown to have an improved survival when compared to those operated on at community hospitals [43]. Goff et al evaluated the extensiveness of surgery for patients with ovarian cancer in an attempt to identify factors associated with comprehensive surgical staging [44]. After analyzing 10,432 hospital admissions over a three year period, they noted that women at teaching hospitals, in urban locales, and with higher surgical volume were more likely to receive comprehensive surgery. These results are further supported by Norwegian investigators who showed that patients operated on at teaching hospitals had improved short-term survival as well as increased rates of tumor debulking to zero centimeters [45]. All of these studies support the referral of patients with suspected ovarian cancer to appropriate centers where multidisciplinary teams and resources, including surgeons specializing in gynecologic oncology, are available to initiate proper initial treatment.

Conclusion

The standard of care for women with advanced stage EOC involves surgery followed by combination platinum-based chemotherapy. Surgery allows for a tissue diagnosis of the type of cancer, the opportunity to appropriately stage the patient to assess the extent of disease, as well as the chance to provide symptomatic relief from tumor which may be compressing or involving adjacent organs. Most importantly, surgery in advanced stage EOC allows for efforts to optimally cytoreduce the patient, an outcome which has repeatedly been shown to be associated with improved endpoints, including chemosensitivity, progression-free survival and overall survival. Acknowledging that, in the absence of effective screening strategies for diagnosis at an earlier stage, the only physician-dependent means by which to favorably impact patient survival is to provide surgery which leaves no or minimal residual disease at the completion of surgery and to follow that surgery with the administration of appropriate cytotoxic therapy.

Recognizing that primary cytoreductive surgery offers the best chance for improved survival for women with advanced EOC, the issue then becomes how to best provide this standard of care for all women with ovarian cancer. Studies have consistently shown a positive effect of surgeon specialty and site of surgery on implementation of the standard of care. Surgeons specially trained in gynecologic oncology are more likely to achieve optimal cytoreduction, adequately stage their patients and initiate chemotherapy. To deny a woman with ovarian cancer an initial consultation with a trained gynecologic oncologist is to decrease her chance of extended survival. Formalized training programs need to be developed to provide surgeons the instruction and experience in the techniques required to obtain the minimal residual disease amount in patients with ovarian cancer. Public and physician awareness efforts should be undertaken, disseminating the association of specialty training and outcomes in EOC. Quality of care for these women can be improved on a national scale via appropriate referral patterns to specialized centers with trained gynecologic oncologists, allowing the greatest number of women access to the best-available care.

References

1. IARC.GLOBOCAN.2002: Cancer incidence, mortality and prevalence worldwide (2002 estimates).[cited 2009 March 27]. Available from: http://www-dep.iarc.fr/
2. Munnell EW. The changing prognosis and treatment in cancer of the ovary. A report of 235 patients with primary ovarian carcinoma 1952-1961. Am J Obstet Gynecol 1968;100:790-805
3. Elclos L, Quinlan EJ. Malignant tumors of the ovary managed with postoperative megavoltage irradiation. Radiology 1969;93:659-63
4. Griffiths CT. Surgical resection of tumor bulk in the

primary treatment of ovarian carcinoma. Natl Cancer Inst Monogr 1975;42:101-4

5. Hacker NF, Berek JS, Lagasse LD et al. Primary cytoreductive surgery for epithelial ovarian cancer. Obstet Gynecol 1983;61:413-20
6. Bristow RE, Montz FJ, Lagasse LD et al. Survival impact of surgical cytoreduction in stage IV epithelial ovarian cancer. Gynecol Oncol 1999;72:278-87
7. Bristow RE, Tomacruz RS, Armstrong DK et al. Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: a meta-analysis. J Clin Oncol 2002;20:1248-59
8. Chi DS, Eisenhauer EL, Lang J et al. What is the optimal goal of primary cytoreductive surgery for bulky stage IIIC epithelial ovarian carcinoma (EOC)? Gynecol Oncol 2006;103:559-64
9. Eisenkop SM, Spirtos NM, Montag TW et al. The impact of subspecialty training on the management of advanced ovarian cancer. Gynecol Oncol 1992;47:203-9
10. Hoskins WJ, McGuire WP, Brady MF et al. The effect of diameter of largest residual disease on survival after primary cytoreductive surgery in patients with suboptimal residual epithelial ovarian carcinoma. Am J Obstet Gynecol 1994;170:974-80
11. Boente MP, Chi DS, Hoskins WJ. The role of surgery in the management of ovarian cancer: primary and interval cytoreductive surgery. Semin Oncol 1998;25:326-34
12. Hoskins WJ, Bundy BN, Thigpen JT et al. The influence of cytoreductive surgery on recurrence-free interval and survival in small-volume stage III epithelial ovarian cancer: a Gynecologic Oncology Group study. Gynecol Oncol 1992;47:159-66.
13. Eisenkop SM, Spirtos NM, Friedman RL et al. Relative influences of tumor volume before surgery and the cytoreductive outcome on survival for patients with advanced ovarian cancer: a prospective study. Gynecol Oncol 2003;90:390-6.
14. Bonnefoi H, A'Hern RP, Fisher C et al. Natural history of stage IV epithelial ovarian cancer. J Clin Oncol 1999;17:767-75.
15. Goodman HM, Harlow BL, Sheets EE et al. The role of cytoreductive surgery in the management of stage IV epithelial ovarian carcinoma. Gynecol Oncol 1992;46:367-71.
16. Akahira JI, Yoshikawa H, Shimizu Y et al. Prognostic factors of stage IV epithelial ovarian cancer: a multicenter retrospective study. Gynecol Oncol 2001;81:398-403
17. Curtin JP, Malik R, Venkatraman ES et al. Stage IV ovarian cancer: impact of surgical debulking. Gynecol Oncol 1997;64:9-12.
18. Naik R, Nordin A, Cross PA et al. Optimal cytoreductive surgery is an independent prognostic indicator in stage IV epithelial ovarian cancer with hepatic metastases. Gynecol Oncol 78:171-5.
19. Shibata K, Kikkawa F, Mika M et al. Neoadjuvant chemotherapy for FIGO stage III or IV ovarian cancer: Survival benefit and prognostic factors. Int J Gynecol Cancer 2003;13:587-92.
20. Bristow RE, Eisenhauer EL, Santillan A et al. Delaying the primary surgical effort for advanced ovarian cancer: a systematic review of neoadjuvant chemotherapy and interval cytoreduction. Gynecol Oncol 2007;104:480-90.
21. Eisenkop SM, Spirtos NM, Lin WC. "Optimal" cytoreduction for advanced epithelial ovarian cancer: a commentary. Gynecol Oncol 2006;103:329-35.
22. Eisenhauer EL, Abu-Rustum NR, Sonoda Y et al. The effect of maximal surgical cytoreduction on sensitivity to platinum-taxane chemotherapy and subsequent survival in patients with advanced ovarian cancer. Gynecol Oncol 2008;108:276-81.
23. Goldie JH, Coldman AJ. A mathematic model for relating the drug sensitivity of tumors to their spontaneous mutation rate. Cancer Treat Rep 1979;63:1727-33.
24. Curiel TJ, Coukos G, Zou L et al. Specific recruitment of regulatory T cells in ovarian carcinoma fosters immune privilege and predicts reduced survival. Nat Med 2004;10:942-9.
25. Sato E, Olson SH, Ahn J et al. Intraepithelial CD8+ tumor-infiltrating lymphocytes and a high CD8+/ regulatory T cell ratio are associated with favorable prognosis in ovarian cancer. Proc Natl Acad Sci U S A 2005;102:18538-43.
26. Wolf D, Wolf AM, Rumpold H et al. The expression of the regulatory T cell-specific forkhead box transcription factor FoxP3 is associated with poor prognosis in ovarian cancer. Clin Cancer Res 2005;11:8326-31.
27. Merogi AJ, Marrogi AJ, Ramesh R, et al: Tumor-host interaction: analysis of cytokines, growth factors, and tumor-infiltrating lymphocytes in ovarian carcinomas. Hum Pathol 1997;28:321-31.
28. Santin AD, Hermonat PL, Ravaggi A et al. Secretion of vascular endothelial growth factor in ovarian cancer. Eur J Gynaecol Oncol 1999;20:177-81.
29. Risum S, Hogdall C, Loft A et al. Prediction of suboptimal primary cytoreduction in primary ovarian cancer with combined positron emission tomography/computed tomography—a prospective study. Gynecol Oncol 2008;108:265-70.
30. Salani R, Axtell A, Gerardi M et al. Limited utility of conventional criteria for predicting unresectable disease

in patients with advanced stage epithelial ovarian cancer. Gynecol Oncol 2008;108:271-5.

31. Chi DS, Zivanovic O, Palayekar MJ et al. A contemporary analysis of the ability of preoperative serum CA-125 to predict primary cytoreductive outcome in patients with advanced ovarian, tubal and peritoneal carcinoma. Gynecol Oncol 2009;112:6-10.
32. Engelen MJ, Kos HE, Willemse PH et al. Surgery by consultant gynecologic oncologists improves survival in patients with ovarian carcinoma. Cancer 2006;106:589-98.
33. Chan JK, Kapp DS, Shin JY et al. Influence of the gynecologic oncologist on the survival of ovarian cancer patients. Obstet Gynecol 2007;109:1342-50.
34. Vernooij F, Heintz P, Witteveen E et al. The outcomes of ovarian cancer treatment are better when provided by gynecologic oncologists and in specialized hospitals: a systematic review. Gynecol Oncol 2007;105:801-12.
35. Earle CC, Schrag D, Neville BA et al. Effect of surgeon specialty on processes of care and outcomes for ovarian cancer patients. J Natl Cancer Inst 2006;98:172-80.
36. Sharma S, Driscoll D, Odunsi K et al. Safety and efficacy of cytoreductive surgery for epithelial ovarian cancer in elderly and high-risk surgical patients. Am J Obstet Gynecol 2005;193:2077-82.
37. 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.
38. Chi DS, Franklin CC, Levine DA et al. Improved optimal cytoreduction rates for stages IIIC and IV epithelial ovarian, fallopian tube, and primary peritoneal cancer: a change in surgical approach. Gynecol Oncol 2004;94:650-4.
39. ACOG Committee Opinion: number 280, December 2002. The role of the generalist obstetrician-gynecologist in the early detection of ovarian cancer. Obstet Gynecol 2002;100:1413-6.
40. Hillner BE, Smith TJ, Desch CE. Hospital and physician volume or specialization and outcomes in cancer treatment: importance in quality of cancer care. J Clin Oncol 2000;18:2327-40.
41. Schrag D, Earle C, Xu F et al. Associations between hospital and surgeon procedure volumes and patient outcomes after ovarian cancer resection. J Natl Cancer Inst 2006;98:163-71.
42. Kumpulainen S, Grenman S, Kyyronen P et al. Evidence of benefit from centralised treatment of ovarian cancer: a nationwide population-based survival analysis in Finland. Int J Cancer 2002;102:541-4.
43. Tingulstad S, Skjeldestad FE, Hagen B. The effect of centralization of primary surgery on survival in ovarian cancer patients. Obstet Gynecol 2003;102:499-505.
44. Goff BA, Matthews BJ, Larson EH et al. Predictors of comprehensive surgical treatment in patients with ovarian cancer. Cancer 2007;109:2031-42.
45. Paulsen T, Kjaerheim K, Kaern J et al. Improved short-term survival for advanced ovarian, tubal, and peritoneal cancer patients operated at teaching hospitals. Int J Gynecol Cancer 2006;16 Suppl 1:11-7.