Review Article

Maximal cytoreductive effort in epithelial ovarian cancer surgery

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The surgical management of advanced epithelial ovarian cancer involves cytoreduction, or removal of grossly-evident tumor. Residual disease after surgical cytoreduction of ovarian cancer has been shown to be strongly associated with survival. The goal of surgery is "optimal" surgical cytoreduction, which is generally defined as residual disease of 1 cm or less. However, the designation of "optimal" surgical cytoreduction has evolved to include maximal surgical effort and no gross residual disease. In order to achieve this, more aggressive surgical procedures such as rectosigmoidectomy, diaphragm peritonectomy, partial liver resection, and video-assisted thoracic surgery are reported and increasingly utilized in the surgical management of advanced ovarian cancer. The role of maximal surgical effort also extends to the recurrent setting where the goal of surgery should be complete cytoreduction. Patient selection is important in identifying appropriate candidates for surgical cytoreduction in the recurrent setting. The purpose of this article is to review the role of maximum surgical effort in primary and recurrent ovarian cancer.

Key Words: Ovarian cancer, Cytoreduction

INTRODUCTION

Worldwide, ovarian cancer is diagnosed in over 200,000 women yearly and accounts for over 125,000 deaths.[1] Stage of disease with Internal Federation of Gynecology and Obstetrics (FIGO) criteria is closely associated with survival. Unfortunately, the majority of cases diagnosed are advanced stage with evidence of abdominal dissemination of disease. The standard management of ovarian cancer involves a combination of initial maximal cytoreductive surgery followed by taxane-platinum based chemotherapy.

The use of maximal surgical cytoreduction in the management of epithelial ovarian cancer (EOC) was first proposed in the 1930s, but it was not supported by published data until the 1970s. The theory behind tumor cytoreduction is that of the "Gompertzian" cell growth curve. According to this theory, when tumors are small, growth rate is faster and similarly, log-kill of tumors is greater as well. Maximum tumor removed with cytoreduction theoretically improves chance of response to chemotherapy. In addition, bulky tumors are commonly present in ovarian cancer. With poor blood supply, these large tumor masses do not receive optimal distribution of chemotherapy. As a result, removal of these bulky tumors would result

in improved delivery of chemotherapy to residual tumor cells.

The objective of this review is to discuss the overwhelming evidence supporting maximal surgical effort in EOC. The role of surgical cytoreduction in both primary and recurrent disease will be discussed, with an emphasis on complete cytoreduction.

PRIMARY DISEASE

The concept of surgical cytoreduction in the management of ovarian cancer was first correlated with outcome in 1975 by Griffiths.[2] In this cohort of 102 patients, those with no gross residual disease had a mean survival of 39 months, patients with residual disease ≤ 0.5 cm had a mean survival of 29 months, patients with residual disease greater than 0.5 cm but ≤ 1.5 cm had a mean survival of 18 months, and patients with residual disease greater than 1.5 cm had a mean survival of 11 months. Residual disease greater than 1.5 cm had no correlation with survival. Multiple variables were assessed and only residual disease and histologic grade were independent prognostic factors.

The Gynecologic Oncology Group (GOG) designates "optimal" cytoreduction as residual disease ≤ 1 cm. This threshold was further evaluated by Hoskins et al.[3] Patients with stage III disease enrolled in GOG protocols 52 and 97 were analyzed for survival based on residual disease. These cooperative, randomized trials compared adjuvant cisplatin and cyclophosphamide in patients with at least stage III disease and residual disease ≤ 1 cm (GOG 52) or residual disease of greater than 1 cm (GOG 97) after primary cytoreduction. Survival was sig-

nificantly improved in patients with no gross residual disease compared with residual disease less than 2 cm and patients with ≥2 cm. Among the patients with suboptimal debulking (>1 cm), survival was significantly improved in those with residual disease <2 cm compared with patients with residual disease >2 cm. Residual disease greater than 2 cm did not affect survival. There did not appear to be a difference in survival between the patients with residual disease ≤1cm in protocol 52 and the patients in protocol 97 with residual disease between 1 cm and 2 cm. However, this may be due to a small number of patients in GOG 97 with residual disease <2 cm.

A meta-analysis of 6,885 patients with stage III or IV EOC evaluated various prognostic factors for survival.[4] There was a positive correlation between maximal surgical cytoreduction and median survival, even with multivariate analysis. Each 10% increase in maximal cytoreduction was associated with a 5.5% increase in median survival time. All patients were treated with adjuvant platinum-based chemotherapy. Patient cohorts with >75% maximal cytoreduction had a median survival of 34 months, compared with 23 months for patient cohorts with ≤25% maximal cytoreduction. The majority of studies included in this meta-analysis defined maximal cytoreduction as residual disease of 1 or 2 cm.

The goal of cytoreduction has evolved towards maximal cytoreduction in the management of primary ovarian cancer. Several reports have suggested that no gross residual should be the goal of primary cytoreduction surgery for EOC.[5-8] Table 1 lists these reports with survival based on residual disease. As mentioned previously, Hoskins et al. reported on stage III patients enrolled in two multi-center randomized clinical trials and found a 5-year survival rate of 60% in patients with no gross residual disease.[3] More contemporary studies such as Chi et al.[6] and du Bois et al.[8] report median survival of 106 months and 99 months, respectively, in patients with no gross residual disease. Chi et al.[6] evaluated 465 patients with bulky stage IIIC disease and residual disease was a significant prognostic factor on univariate and multivariate analysis. No gross

residual disease had the longest survival compared with residual disease ≤1 cm and residual disease >1 cm. du Bois et al.[8] evaluated 3,126 patients enrolled in 3 multi-center prospective randomized trials. Similarly, no gross residual disease was associated with the longest progression-free and overall survival, compared with residual disease ≤1 cm and residual disease >1 cm.

With the extent of surgical cytoreduction shifting towards maximal cytoreduction, the types of surgical procedures performed for debulking of primary ovarian cancer has also evolved. The limitations against complete cytoreduction has included disease involving the rectosigmoid colon and bulky upper abdominal disease including diaphragmatic, splenic, and portal metastases. For stage IV disease, liver parenchymal involvement and lung metastases can preclude maximal cytoreduction.

Bulky disease involving the cul-de-sac can require an en-bloc resection with low-anterior resection in order to achieve complete gross resection of disease. Various reports have demonstrated the feasibility and acceptable complication rates associated with rectosigmoid resection.[9-14] A review of patients with advanced EOC who underwent low anterior resection and anastomosis during primary cytoreduction demonstrated a low complication rate, with 3 patients (5%) developing a pelvic abscess and 1 patient (1.7%) developing an anastomotic leak.[12] A recent report of 19 patients who underwent extended left colectomy during primary cytoreduction for EOC described acceptable postoperative quality of life and no delay in administration of adjuvant chemotherapy.[15] In that report, 18 patients received intraperitoneal chemotherapy and the complications which may have been related to the colectomy included 1 patient with bacteremia. There were no postoperative pelvic abscesses in the cohort.

Upper abdominal disease (UAD) has been perceived as a rate-limiting factor in achieving complete gross resection in surgical cytoreduction of primary EOC. In addition to omentectomy, extensive upper-abdominal procedures such as diaphragm peritonectomy, splenectomy, partial liver resection, and distal pancreatectomy has been reported in the surgical cytoreduction of primary EOC.[16-19] These procedures have been described in the gynecologic oncology literature.[20] A retrospective review of 262 patients with stage IIIC and IV disease analyzed a cohort of patients divided into 3 groups: patients that required extensive upper abdominal procedures to achieve optimal debulking, patients who underwent optimal debulking with standard surgical techniques, and patients who underwent suboptimal debulking.[17] The patients in the first two groups had similar median overall and progression-free survival. Patients in the third group had significantly worse outcome. A recent report from the same institution included 490 patients with stage IIIC EOC that were divided into 3 groups: patients with no UAD, patients with UAD ≤1cm, and patients with bulky UAD >1 cm.[18] Patients with bulky UAD were more likely to have large-volume ascites and sub-

Table 1. Maximal primary cytoreduction

Author	Year	Residual disease	No.	Median survival (mo)	5-yr survival (%)
Hoskins[3]	1994	No gross	41		60
		≤1 cm	62		35
		1-2 cm	12		35
		≥2 cm	65		<20
Chi[6]	2006	No gross	67	106	
		≤0.5 cm	70	66	
		0.6-1 cm	99	48	
		1-2 cm	53	33	
		>2 cm	176	34	
du Bois[8]	2010	No gross	1,046	99.1	
		≤1 cm	975	36.2	
		>1 cm	1,105	29.6	

optimal debulking. A follow-up report on the clinical outcomes of these patients demonstrated that for patients with bulky UAD, patients who underwent optimal debulking had significantly improved progression-free and overall survival compared with the patients who underwent suboptimal debulking.[21] These reports suggest that bulky UAD should not preclude extensive surgical procedures to achieve maximal cytoreduction.

Stage IV disease presents another obstacle toward maximal surgical cytoreduction in primary ovarian cancer. Early reports suggested that even with stage IV disease, optimal cytoreduction may be associated with improved outcome.[22-24] However, many of these reports defined "optimal" cytoreduction as residual disease of less than 2 cm. Furthermore, these early reports identified pleural cavity disease by positive cytology alone. The optimal method to evaluate disease in the pleural cavity is with video-assisted thoracic surgery (VATS). Recent reports suggest the utilization of VATS to guide management of primary ovarian cancer.[25-27] Findings with VATS can quantify intrathoracic disease and allow for intrathoracic cytoreduction to achieve maximal cytoreduction.

RECURRENT DISEASE

The role of surgical cytoreduction for EOC in the recurrent setting is controversial. While there are no prospective trials demonstrating a survival benefit with surgical cytoreduction in recurrent EOC, multiple retrospective series have reported improved survival with optimal surgical cytoreduction.

In the setting of first recurrence, secondary surgical cytoreduction should be considered if optimal debulking can be achieved. The definition of optimal debulking in the recurrent setting has evolved. The first report on secondary surgical cytoreduction included 32 patients. The median survival was 20 months for patients who underwent optimal debulking (defined as ≤1.5 cm), compared with 5 months for patients who underwent suboptimal debulking.[28] Subsequently, other definitions of residual disease have been shown to be associated with a significant survival benefit including 2 cm,[29-32] 1 cm,[33-37] 5 mm,[38-40] and no gross residual disease.[41-52] A recent meta-analysis of 40 studies on cytoreductive surgery in recurrent EOC included 2,019 patients.[53] The median disease-free interval (DFI) was 20.2 months and median survival after recurrence was 30.3 months. On multivariate analysis, only complete cytoreductive surgery was independently associated with post-recurrence survival. Table 2 outlines the studies that specifically assessed maximal cytoreduction and no gross residual disease after secondary cytoreduction.

In several studies on secondary cytoreduction, other clinical variables were found to be independently associated with survival on multivariate analysis. These include age,[41,51] initial stage (IIIC vs. IV),[41] ascites ≤1 liter,[41] histology (all other vs mucinous/clear cell),[41] disease-free interval >12 months,[48] limited sites (1-2) of recurrence,[48,50] tumor size <6 cm,[48] diag-

Table 2. Maximal secondary cytoreduction

Author	Year	Residual disease	No.	Median survival (mo)
Eisenkop[41]	1995	No gross residual	139	40
		Any residual	24	14
Cormio[42]	1999	No gross residual	15	32
		Any residual	6	9
Eisenkop[43]	2000	No gross residual	31	44.4
		Any residual	11	19.3
Gadducci[44]	2000	No gross residual	17	37
		Any residual	13	19
Scarabelli[45]	2001	No gross residual	53	30
		Residual ≤1 cm	51	14
		Residual >1 cm	45	8
Tay[46]	2002	No gross residual	19	38
		Any residual	27	11
Gronlund[47]	2005	No gross residual	16	51.8
		Any residual	22	19.9
Onda[48]	2005	No gross residual	26	52
		Any residual	18	22
Benedetti Panici[49]	2007	No gross residual	37	61
		Any residual	10	19
Salani[50]	2007	No gross residual	41	50
		Any residual	14	7.2
Oksefjell[51]	2009	No gross residual	68	54
		Residual ≤2 cm	33	27.6
		Residual >2 cm	95	8.4
Tian[52]	2010	No gross residual	51	63.2
		Residual ≤1 cm	46	31.1
		Residual >1 cm	26	15.6

nosis to recurrence time >18 months,[50] and treatment-free interval <24 months.[51] Patient selection is critical in determining candidates for secondary cytoreduction. A proposed guideline for selection of patients who may benefit from secondary surgical cytoreduction includes disease-free interval and number of sites of recurrence.[39] In general, patients that are considered candidates for secondary cytoreduction have platinum-sensitive disease (recurrence beyond 6 months after completion of adjuvant platinum-based chemotherapy).

The literature on surgical cytoreduction for EOC beyond the secondary setting is limited. For recurrence after secondary cytoreduction, studies on survival benefit of tertiary cytoreduction also focus on residual disease as the most important prognostic factor. The first report included 26 patients with recurrent EOC who underwent tertiary surgical cytoreduction at a single institution.[54] Multivariate analysis revealed two significant prognostic factors associated with survival: residual disease and treatment-free interval. Patients with residual disease of ≤0.5 cm had a median survival of 36.3 months after time of tertiary cytoreduction compared with 10.6 months for patients with residual disease >0.5 cm. An update of this cohort was published in 2010.[55] This updated cohort was composed of 77 patients, including the original 26

patients. Only residual disease was a significant prognostic factor with multivariate analysis. The definition of optimal cytoreduction was extended to no gross residual disease. Patients who had no gross residual disease after tertiary cytoreduction had a median survival of 60.4 months after time of tertiary cytoreduction compared with 27.9 months for patients who had residual disease of ≤0.5 cm, and 13.6 months for patients with residual disease >0.5 cm. The only factor associated with achieving no gross residual disease with tertiary cytoreduction was sites of disease (single vs multiple). Other factors such as optimal secondary cytoreduction, time to second recurrence, treatment-free interval, and platinum sensitivity, were not significant on multivariate analysis.

The other report of tertiary cytoreduction in recurrent EOC included a cohort of 47 patients from two institutions.[56] Again, optimal cytoreduction (defined as no gross residual disease in this report) was associated with improved survival. Patients with microscopic residual disease had a median survival of 24 months compared with 16 months for patients with macroscopic residual disease. The only factor predictive of achieving optimal cytoreduction was size of tumor implants <5 cm on preoperative imaging. Furthermore, presence of diffuse disease or carcinomatosis was associated with poor survival. After multivariate analysis, the survival benefit of tertiary cytoreduction to no gross residual disease was only significant in patients with limited disease (defined as <10 sites).

The data for surgical cytoreduction for recurrence of EOC after tertiary cytoreduction is even more limited. To our knowledge, there is only one retrospective study addressing this setting.[57] The cohort included only 15 patients, and again the extent of surgical cytoreduction was associated with survival. Patients with residual disease of ≤1 cm had a median survival of 34.8 months after quaternary cytoreduction compared with 10.1 months for patients with residual disease of >1 cm. The number of sites at quaternary cytoreduction was also associated with improved survival with 49.9 months for single site of disease versus 19.5 months for multiple sites of disease. Interestingly the median time to third recurrence was 14.4 months and the median time from tertiary to quaternary cytoreduction was 24.5 months. In addition, the median treatment-free interval for the cohort was only 3.7 months. This suggests that the patients in this cohort had a favorable disease-free interval after tertiary cytoreduction and that even after documented third recurrence, patients were likely treated with chemotherapy first prior to consideration of quaternary cytoreduction.

The evidence supporting maximal cytoreduction of recurrent EOC is based on retrospective reports. The results reveal that the goal of surgical cytoreduction in recurrent EOC should be no gross residual disease. Patient selection is important as all retrospective studies have inherent selection bias. Clinical factors such as disease-free interval and number of sites of disease should be considered.

CONCLUSION

As treatment modalities improve, survival from advanced-stage EOC is improving. There is overwhelming evidence supporting the use of maximal cytoreductive effort in EOC. From the abundance of reports, residual disease after surgical cytoreduction is likely the most important prognostic factor. In order to achieve maximal cytoreduction, aggressive surgical procedures have been shown to be appropriate in the management of EOC. Surgical cytoreduction in recurrent EOC is limited to retrospective studies. With appropriate patient selection, maximal cytoreductive effort also is associated with survival benefit after recurrence. An ongoing GOG prospective study will aid in delineating the role of surgical cytoreduction in recurrent ovarian cancer.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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