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Role of aggressive surgical cytoreduction in advanced ovarian cancer

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Ovarian cancer is the eighth most frequent cancer in women and is the most lethal gynecologic malignancy worldwide. The majority of ovarian cancer patients are newly diagnosed presenting with advanced-stage disease. Primary cytoreductive surgery and adjuvant taxane- and platinum-based combination chemotherapy are the standard treatment for advanced ovarian cancer. A number of studies have consistently shown that successful cytoreductive surgery and the resultant minimal residual disease are significantly associated with survival in patients with this disease. Much has been written and even more debated regarding the competing perspectives of biology of ovarian cancer versus the value of aggressive surgical resection. This review will focus on the current evidences and outcomes supporting the positive impact of aggressive surgical effort on survival in the primary management of ovarian cancer.

Keywords: Cytoreduction Surgical Procedures; Neoplasm, Residual; Ovarian Neoplasms

INTRODUCTION

Worldwide ovarian cancer is the second leading cause of gynecologic cancer-related deaths behind cervical cancer [1]. Approximately 240,000 new cases of ovarian cancer are diagnosed annually, accounting for about 4% of female cancers, and about 152,000 women die as a result of this disease. The majority of newly diagnosed ovarian cancer patients present with advanced-stage disease. Primary cytoreductive surgery followed by taxane- and platinum-based combination chemotherapy is the cornerstone of management for advanced ovarian cancer, and optimal cytoreduction is one of the most significant predictors of survival [2]. The prognosis of advanced ovarian cancer is significantly improved with no gross residual disease (NGR) after surgery, and the contemporary surgical objective is toward removing all visible disease. To achieve this, some surgeons perform aggressive surgical resections and they advocate that aggressive surgical effort can compensate for tumor biology and patients undergoing ultraradical procedures enjoy the longest survival time with acceptable operation-related morbidities [3-11]. On the contrary, others stress that the prognosis of ovarian cancer depends on the biologic behavior of the tumor rather than surgical intervention. According to these investigators, it is the less advanced initial disease status that allows both optimal cytoreduction and improved survival, and for many surgeons and patients, aggressive surgery is accompanied by substantial morbidity, effecting quality of life and costs [12-14].

The uncertain conclusion from a recent Cochrane Review on the effectiveness of aggressive surgery for advanced ovarian cancer reflects a lack of robust phase III data in this field [15]. However, recent years have witnessed the appearance of a number of studies on not only the feasibility but also the favorable survival outcomes associated with extensive tumor

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resection. Although there is no randomized controlled trial supporting the benefit of radical procedures, the body of indirect data from a number of contemporary studies strongly supports the concept of aggressive surgical cytoreduction. This review will focus on our current understanding of the correlation between aggressive surgical cytoreduction and improved survival.

IMPORTANCE OF COMPLETE CYTOREDUCTION

Since the landmark study by Griffiths [16] demonstrating survival benefit of maximal tumor debulking, a number of investigators validated the efficacy of cytoreductive surgery and optimal cytoreduction was defined as leaving residual cancer no larger than 1 to 2 cm in the largest diameter. In the mid-1990s, Hoskins et al. [17] demonstrated that the less residual disease (RD) is achieved after primary cytoreductive surgery, the better survival outcome is obtained. More recently the objective of surgery is evolving to reach the lowest residual tumor possible. In 2010, the Gynecologic Cancer InterGroup stated that the ultimate goal of cytoreductive surgery is to remove all macroscopic lesions and patients with NGR should be considered to achieve optimal cytoreduction [18]. Around the same time, the Cochrane Review by Elattar et al. [19] proposed that all surgical attempts should be made to resect all visible tumors. These same authors suggested the surgical community should consider adopting the terms complete cytoreduction, near optimal (for cases with RD <1 cm) and suboptimal (RD >1 cm) given the survival benefits of less than complete cytoreduction. A recent meta-analysis clearly shows the positive impact of complete cytoreduction to NGR on survival among patients with advanced ovarian cancer who underwent primary cytoreductive surgery [20]. The authors searched the PubMed and the Cochrane Library between January 1996 and July 2011 using common keywords related to surgery and ovarian cancer. Included studies met all of the following criteria: (1) primary epithelial ovarian, fallopian tube, or peritoneal carcinoma; (2) International Federation of Gynecology and Obstetrics (FIGO) stages IIB to IV disease; (3) primary cytoreductive surgery; (4) adjuvant chemotherapy administered when both taxane and platinum agents were available; (5) RD reported using the criteria of no gross (microscopic) RD, RD 0 to 1.0 cm, RD 0.1 to 1.0 cm, or RD >1 cm; and (6) survival analysis according to the aforementioned RD criteria. Among 1,203 articles, a total of 18 consisting of six retrospective studies and 12 randomized controlled trials for adjuvant chemotherapy were included in the final analyses. On multiple linear regression analysis, the proportion of patients left with NGR was an important independent predictor of survival and each 10% increase in complete cytoreduction rate resulted in a concomitant 2.3 months prolongation in median survival time. These results underline the importance of complete surgical cytoreduction. These data do not diminish the benefits of cytoreduction to minimal gross RD relative to suboptimal debulking, when NGR is not possible.

CRITICISMS OF RADICAL SURGERY

If surgery is undertaken, its goal is to remove as much of the gross tumor as possible and the operating surgeon should attempt to achieve complete cytoreduction. In those with less extensive tumor spread, complete cytoreduction can be easily achieved with relatively simple surgery, and most physicians agree to do this. Two-thirds of ovarian cancer patients present with advanced disease typically characterized by ascites, omental cake, peritoneal implants, and retroperitoneal lymph node metastases. When cancer extensively involves diaphragm, liver, spleen, pancreas, stomach, or bowel, complex surgical procedures are required to obtain NGR. However, there is no consensus on the appropriate extent of surgical resection to which the surgeon should do to achieve complete cytoreduction.

Opponents of aggressive surgery advocate that despite the importance of RD as a prognostic factor is well established, it is the inherent tumor biology to determine the resectability of the tumor, not surgical aggressiveness. Two ancillary data analyses of the Scottish Randomized Trial in Ovarian Cancer (SCOTROC)-1 and the Gynecologic Oncology Group (GOG) 182 trials are often cited as supporting this concept [14,21]. In 2005, Crawford et al. [14] reported the results of subanalysis on SCOTROC-1 trial data. The authors retrospectively reviewed the clinical data on 889 patients with FIGO stage IC to IV ovarian cancer. A prognostic score system reflecting each patient' s presurgery biologic characteristics based on FIGO stage, tumor histology, presurgery cancer antigen 125 (CA-125), and omental cake was established using multivariate Cox model. The authors reported three main results: (1) non-UK patients underwent more radical surgery and had more optimal cytoreduction (RD ≤2 cm) than UK patients; (2) optimal debulking was associated with increased progression-free survival (PFS) mainly for patients with less extensive disease (with low prognostic score); and (3) non-UK patients had more favorable PFS compared with UK patients who had similar RD and debulkability. These investigators concluded that survival benefit associated with optimal surgery is limited to patients with less aggressive disease and tumor biology is a

major survival determinant.

More recently, Horowitz et al. [21] reported similar results. The authors retrospectively reviewed the GOG 182 trial data on 2,655 patients with FIGO stage III or IV ovarian cancer. PFS and overall survival (OS) were analyzed based on three indices: preoperative disease score (DS), surgical complexity score (CS), and RD. The DS was defined as follows: DS low, with pelvic and retroperitoneal spread; DS moderate, with additional spread to the abdomen but sparing the upper abdomen; or DS high, with the presence of upper abdominal disease affecting the diaphragm, spleen, liver, or pancreas. PFS and OS were decreasing with increasing DS, and patients with high DS had the worst PFS and OS. In patients with NGR, the high DS still had a worse influence on PFS and OS than those with low-moderate DS. After adjusting for RD and DS, CS was not an independent predictor of survival. These investigators suggested that, although complete cytoreduction to NGR is achieved, initial tumor burden is a powerful determinant in survival and aggressive surgery alone does not seem to have a positive impact.

However, both studies suffer from several flaws. Although the authors stress that the results are based on the prospectively collected surgical data from the large, multi-institutional RCTs, both studies are essentially retrospective re-analyses and have inherent biases which may influence the results.

First, patients with less advanced stage disease—cases of stage IC-IIIB disease for Crawford study and stage IIIIA-IIIB disease for Horowitz study—were included in both studies. These patients are likely to be easily managed and have the best surgical outcomes with relatively simple procedures. Second, the index of surgical aggressiveness employed in both studies was not objective. In the Crawford study, optimal surgery was defined as RD <2 cm and RD was regarded as a surrogate of aggressive surgery. However, RD is only the result of aggressive surgery, not aggressive surgery itself. Horowitz et al. [21] employed CS as a surrogate of aggressive surgery. Although the score is reproducible and reflects the surgical complexity well, high CS does not always mean aggressive surgical effort. For example, if a patient with stage IIIB disease involving the diaphragm undergoes the following procedures—total hysterectomy, bilateral salpingo-oophorectomy, omentectomy, pelvic/para-aortic lymphadenectomy, pelvic peritoneal stripping, segmental resection of the jejunum, and ileocecal resection, CS is 8 and the patient is found to have minimal RD on the diaphragm. According to Horowitz et al. [21], the DS is high, CS is high, the patient has minimal RD, and the surgery does not overcome the tumor biology. However, most experienced surgeons would consider that in that case, the DS is not high, CS is not high, and the patient is likely to have NGR employing upper abdominal procedures. Third, the quality of surgical care seems to be unsatisfactory. In the Crawford study, the mean operation time is about 120 minutes. Although the length of surgery is not a surrogate of the surgical complexity, it is hard to imagine the possibility of performing aggressive surgery such as extensive upper abdominal and pelvic procedures within 2 hours. Despite that, the rates of optimal cytoreduction were only 57.4% to 71.3%. In the Horowitz study, only 16% of patients had high CS and 32.4% had NGR. Fourth, both studies do not consider the disparity among surgeons and institutions. Recent studies show that patients treated by surgeons and hospitals who frequently utilize the radical procedures have better surgical outcomes and prognosis. All of these factors diminish the ability to demonstrate a benefit to aggressive surgical cytoreduction.

Morbidity associated with aggressive surgery is an important issue. Some surgeons utilize radical procedures such as diaphragm peritonectomy/resection, liver resection, splenectomy, distal pancreatectomy, subtotal colectomy, or multiple bowel resections for complete cytoreduction. Although these procedures are performed even by highly experienced gynecologic oncology surgeon, a considerable number of patients may experience severe perioperative complications. Aletti et al. [22] retrospectively review the data from three centers and reported that the 30-day morbidity and 3-month mortality rates were 18.4% (95% confidence interval [CI], 15.1 to 21.9) and 4.5% (95% CI, 3.3 to 6.9), respectively. Based on their risk prediction models, the calculated risk of complications ranged from 4.5% to 54.3% with significantly influencing on quality of life and costs.

EVIDENCES SUPPORTING RADICAL SURGERY

There are three major limitations of radical debulking surgery: first, direct evidence from randomized trials as to whether extensive surgery itself actually improves survival is nonexistent; second, radical cytoreductive surgical procedures are associated with a predictable risk of morbidity and mortality; and third, complete tumor resection in non-expert centers is only achievable in a minority of patients with advanced ovarian cancer. Some physicians have abandoned radical surgery claiming that it is ineffective, that tumor biology determines not only but surgical outcome as well, and that the associated morbidity risk is too high. However, for more than a decade, a number of studies have consistently illustrated that aggressive surgery can largely make up for differences in tumor biology. While it is apparent that approximately one third of patients

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may experience perioperative complications, the survival benefit from aggressive surgery would seem to make these morbidities tolerable. Additionally analysis of risk factors such as age, performance status, nutrition, and obesity can allow surgeons to sensibly triage those patients at highest risk of serious morbidity to alternative primary treatment. Contemporary studies from experienced centers clearly indicate that complete cytoreduction can be achieved in up to 60% of patients with FIGO stage IIIC-IV ovarian cancer, such that the feasibility argument is highly related to center expertise [23]. With these issues in mind, we will now take a look at recent evidences supporting the survival benefit from aggressive surgical cytoreduction.

1. Comparison after dedicated switch in surgical approach

Our starting point for the first question may well be as to whether individual surgeons and institutions can improve the proportion of patients achieving optimal cytoreduction by adopting systematic and programmatic change in surgical approach. Studies from both the Memorial Sloan-Kettering Cancer Center and Horst Schmidt Klinik are good examples to clearly illustrate that such a paradigm shift can result in the improved OS of patients with advanced ovarian cancer [9,24]. Chi et al. [24] from the Memorial Sloan-Kettering Cancer Center evaluated the effect of the incorporation of radical procedures into the surgical management of advanced ovarian cancer on both optimal cytoreduction and survival. These investigators reviewed 378 stage IIIC and IV ovarian cancer patients who had primary cytoreductive surgery in two different time periods based on before and after the incorporation of extensive upper abdominal surgery. One hundred and sixty-eight patients undergoing standard surgery (group 1) and 210 patients undergoing extensive upper abdominal surgery (group 2) were identified and compared. By instituting a more comprehensive approach to removal of upper abdominal disease through the use of such procedures as diaphragm peritonectomy and/or resection, splenectomy, distal pancreatectomy, partial liver resection, cholecystectomy, and porta hepatis tumor resection, the proportion of patients achieving NGR increased from 11% to 27% without significantly increasing postoperative complications. The median OS time was significantly improved in group 2 patients compared to group 1 patients (54 months vs. 43 months, p=0.03). These investigators suggested that the incorporation of extensive upper abdominal procedures was associated with increased optimal cytoreduction rates and significantly improved survival.

Harter et al. [9] from the Horst Schmidt Klinik published similar findings. Their institution employed the quality management programs on the surgical management of ovarian cancer since 2001. These authors reported their experience with 396 patients with stage IIB and IV ovarian cancer who had primary surgery according to the timeline change of the quality management program. As aggressive surgical procedures—bowel resection, diaphragm resection, splenectomy, and liver resection—were more and more utilized over time, the rates of complete cytoreduction increased from 33% to 62%. Survival analysis revealed that the more increasing surgical aggressiveness was instituted, the longer the median OS time was observed (26 months vs. 37 months vs. 45 months, p<0.003). These studies strongly suggest that implementing aggressive surgical approach is associated with a significant increase in the complete debulking rate and improved OS in patients with advanced ovarian cancer.

2. Evaluation across surgeons and institutions

Recently, several investigators have demonstrated that there are wide disparities in optimal surgery rates and survival across the operating surgeons and institutions. Aletti et al. [7] published a landmark study that drew a sharp distinction in patients' survival outcome among the operating surgeons. A total of 144 stage IIIC ovarian cancer patients with peritoneal carcinomatosis treated from 1994 to 1998 were retrospectively reviewed. In multivariate analysis, the size of RD (p<0.001) and the performance of radical surgery (p=0.047) were the only independent factors predicting patient survival. The authors further analyzed patients' survival according to the operating surgeons. Controlling for other factors, the 5-year OS rate was 44% compared with 17% for patients treated by surgeons who had a high propensity for utilizing radical and nonradical procedures, respectively (p<0.001). This study presents empirical evidence to support that radical surgery to achieve lowest RD can minimize the effect of tumor burden.

Several other retrospective series validate the contribution of radical surgery on survival outcome [11,25]. Chang et al. [11] reviewed 203 patients with stage IIIC and IV ovarian cancer. In both the entire cohort of 203 patients and subgroup of 139 stage IIIC patients with carcinomatosis, NGR and the performance of radical surgery were significantly associated with the longest PFS and OS. The volume of RD and the performance of radical surgery were found to be independent factors affecting survival outcome after controlling for other factors. A recent French multicenter study is very much like that of the above study [25]. Luyckx et al. [25] examined 527 patients with stage IIIC and IV ovarian cancer from seven centers in France. On multivariate analysis, ultraradical procedures as well as RD were independent factors influencing survival.

Wimberger et al. [26] conducted an exploratory analysis of the surgical data of 798 patients with FIGO IIB-IV ovarian

cancer from a prospectively randomized phase III study of the Arbeitsgemeinschaft Gynaekologische Onkologie Ovarian Cancer Study Group (AGO-OVAR) to evaluate the various prognostic factors for surgical outcome. Patients treated in centers with surgeons who performed comprehensive debulking surgery had a high rate of complete cytoreduction (32.8% vs. 22.9%, p=0.007) and showed incrementally improved OS (45.2 months vs. 35.0 months, p=0.045) compared with those treated in other centers. After controlling for other factors, the type of center remained one of independent prognostic factors. The authors concluded that complete cytoreduction was highly achievable in experienced centers capable of performing aggressive surgery.

Most evidence suggests that advanced ovarian cancer patients treated at the high-volume hospitals and by high-volume surgeons have better outcomes than those treated at the low-volume hospitals and by low-volume surgeons [27-32]. High-volume surgeons tend to operate at high-volume hospitals and perform more extensive ovarian cancer surgery. Recently, Bristow et al. [32] demonstrated that there was a significant disparity in survival among even high-volume hospitals. These investigators conducted a retrospective population-based analysis on a total of 9,933 patients with ovarian cancer in southern California. Hospitals were classified into three groups: (1) National Cancer Institute-designated Comprehensive Cancer Centers (NCI-CCC; n=5); (2) non-NCI-CCC high-volume hospital (n=29); and (3) non-NCI-CCC low-volume hospital (n=158). There were significant differences in survivals according to hospital types. Patients treated at NCI-CCC had the longest median survival time compared with those treated at other hospitals (77.9 months vs. 51.9 months vs. 43.4 months, p<0.001). Treatment at NCI-CCC was an independent predictor of favorable survival after adjusting other variables. This study implies that specialized centers and high-volume surgeons are more likely to provide guideline-adherent care and this is intimately linked with improved survival.

CONCLUSIONS

If the patient cannot undergo near optimal cytoreduction, radical cytoreductive procedures should not be performed except for palliation. To avoid unnecessary surgery, many attempts have been made to predict surgical outcome, and various models predicting preoperatively optimal/suboptimal cytoreduction have been developed based on physical examination, computed tomography imaging, serum CA-125, and other clinical features [33-41]. However, the accuracy of these models has been challenged in determining whether the disease can be successfully resected. Some investigators underscore the importance of inherent biologic condition of the tumor in determining the surgical success and have published the papers on predicting optimal/suboptimal debulking at the gene expression level [42-45]. If tumor biology determines the surgical resectability and the surgical outcomes, biomarkers associated with surgical outcomes could potentially be developed and feasibly used to tailor aggressive surgical intervention to the individual patient. Although some studies on The Cancer Genome Atlas (TCGA) gene expression data from patients with high-grade serous ovarian cancer showed the promising results, the majority of studies are limited by design, include heterogeneous samples and lack adjustment for major confounding factors [45]. In our view, there are no up-to-date, clear, specific models predicting surgical outcome, so it is believed that further experimentation with various clinical and molecular signatures is worthwhile.

It is clear that multiple factors impact patient survival and complete cytoreduction to NGR is one of the most powerful determinants in survival. Complete debulking rates differ markedly according to the specialty of operating surgeon and institution. The philosophy of the surgeon and institution on what qualifies as unresectable disease also differs and will undoubtedly affect both surgical outcome and survival. Of course, aggressive surgery cannot completely compensate for tumor biology. However, although published reports supporting the positive prognostic impact of aggressive surgical effort are almost entirely retrospective, the findings of these studies provide potential evidence for the hypothesis that surgical expertise at least partly counteracts the effects of underlying tumor biology. Consequently, aggressive surgical cytoreduction can offer the best opportunity for achieving extended survival in women with advanced ovarian cancer.

CONFLICT OF INTEREST

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

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