Chapter 12

Patient Selection for Ovarian Cancer Debulking Surgery

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Abstract

Complete surgical cytoreduction is the most important adverse prognostic factor for survival in ovarian cancer. To achieve this, surgeons often have to perform radical and ultraradical procedures with associated significant postoperative morbidity and mortality. Adverse events are most pronounced in patients with borderline or suboptimal capacity to withstand the stress related to surgery. In frail, elderly, malnourished patients, surgeons face limitations to exercise maximum surgical effort; therefore, alternative treatment strategies are required. Neoadjuvant chemotherapy offers a safe and effective way to enhance recovery after delayed debulking surgery in patients who are not optimal candidates for primary debulking surgery.

Keywords: debulking surgery, ovarian cancer, neoadjuvant chemotherapy, nutrition, age

1. Introduction

Primary debulking or cytoreductive surgery followed by adjuvant chemotherapy has long been the mainstay of treatment for patients with advanced ovarian cancer. The goal of surgery is complete cytoreduction with no visible residual cancer as it is associated with better survival compared with residuals 0–1 cm or >1 cm [1–6]. During the past two decades, new surgical techniques were incorporated into the armamentarium of gynecologic oncologists to address disease located in the upper abdomen. Such paradigm shift in surgical philosophy has resulted in higher rate of complete cytoreduction, and this has translated into survival benefit [7]. Upper abdominal resection (the so-called ultraradical debulking) should only be performed if complete cytoreduction is achievable as even the presence of minimal residual disease will adversely affect the survival of patients [8].

For long, upfront surgery had been the standard approach for patients with advanced ovarian cancer; however, a new treatment strategy using neoadjuvant chemotherapy followed by delayed primary surgery has emerged two decades ago and been supported by retrospective

studies [9–11]. However, Bristow et al. in their meta-analysis demonstrated inferior outcomes for patients undergoing neoadjuvant chemotherapy, although this analysis was heavily biased by the retrospective nature of the studies included [12].

In 2010, Vergote et al. published a prospective, randomized, multi-institutional study on neoadjuvant chemotherapy followed by delayed primary surgery vs. upfront surgery followed by adjuvant chemotherapy. Although the study was heavily criticized by proponents of upfront surgery, it supported a new treatment paradigm by demonstrating equivalent survival with significantly reduced morbidity and mortality for patients undergoing neoadjuvant chemotherapy followed by delayed primary surgery [2]. Kehoe et al. in their prospective, randomized CHORUS trial corroborated these findings [4].

Since the publication of these trials, professional debate has been going on whether to offer primary surgery or neoadjuvant chemotherapy for patients with advanced ovarian cancer and what is the appropriate rate of upfront surgery in cancer centers [13–15]. There has been an apparent dichotomy between highly specialized, quaternary referral centers and smaller units with lower surgical volume and less generous resources. Unfortunately, most cancer centers fail to publish their denominator data, i.e., their referral pathways, the background ovarian cancer population of their catchment area, and the percentage of patients not taken to theater or not receiving any treatment, which brings a significant selection bias into these publications and scientific debates. This makes both the interpretation of the published data and their extrapolation to day-to-day practice difficult [16].

Both EORTC55971 and CHORUS trials have received extensive criticism. Indeed, significant recruitment bias was observed in both studies: patients with large tumor load, unresectable disease, and poor performance status were overrepresented in these studies, and, therefore, many clinicians have been reluctant to extrapolate the results into clinical practice. Furthermore, the rate of complete/optimal resection in these studies was low; in the EORTC55971 trial, <1 cm residual cancer was achieved in only 41.6% of the patients in the upfront surgery arm. Although it improved to 80.7% in the neoadjuvant chemotherapy arm, this surprisingly did not translate into survival benefit [2]. The CHORUS trial reported similar results at 41 and 73%, with no therapeutic advantage associated with such increase [4].

In view of this criticism, the survival results of two subsequent randomized trials, the SCORPION study from Italy and the JCOG0602 study from Japan, are highly awaited [17, 18]. Both studies confirmed significantly reduced morbidity and mortality associated with delayed primary surgery following neoadjuvant chemotherapy compared with upfront debulking surgery. In the Italian study, 91 and 90.4% of the patients with large-volume stage 3C and 4 ovarian cancer had <1 cm residual disease after surgery, in the upfront surgery and neoadjuvant chemotherapy arms, respectively. In the upfront surgery arm, 53% of the patients developed major postoperative complications compared with 6% of the neoadjuvant chemotherapy arm.

In the Japanese trial, 37% of the patients with primary debulking achieved residual disease <1 cm and 82% of those undergoing delayed surgery after neoadjuvant chemotherapy. Interestingly, one-third of the patients in the upfront surgery arm received an interval debulking

surgery, bearing in mind that the use of preoperative laparoscopy to select out unresectable cases was not permitted in the study protocol. Severe complications developed in 5% of the patients in the neoadjuvant chemotherapy arm vs. 15% of the patients in the upfront surgery arm. Survival data for both studies are awaited to confirm superiority of neoadjuvant chemotherapy for the patient cohorts represented in the study.

Despite all criticism, clinical uptake of neoadjuvant chemotherapy has increased worldwide; in the USA, it has increased from 9% in 2003 to 23% in 2013 [19]. Recently, in their joint clinical practice guideline, the Society of Gynecologic Oncology and the American Society of Clinical Oncology have promoted a more selective approach for patients with advanced ovarian cancer, recommending upfront surgery or neoadjuvant chemotherapy for patients with different clinical characteristics [20, 21].

In clinical practice, upfront surgery and neoadjuvant chemotherapy are not equivalent alternatives for all patients. The aim of this review is to aid the readers to find the most appropriate way to treat their patients by analyzing the factors affecting clinical outcome in ovarian cancer.

2. Selecting the right patient for the right treatment

There are numerous clinicopathological factors influencing the outcome of ovarian cancer patients:

- **Patient-related factors:** age, performance status, comorbidities, nutritional status
- **Cancer-related factors:** grade, stage, tumor extent and size, platinum resistance, molecular subtype
- **Treatment-related factors:** residual cancer after surgery, time from surgery to chemotherapy, complications during treatment
- **Institutional factors:** surgical philosophy and skills, available resources, availability of multidisciplinary team

2.1. Age

Age is an independent prognostic factor for survival for patients with advanced ovarian cancer, but age itself also has an impact on patients' ability to cope with stress related to major surgical interventions [22]. The reserves of the cardiovascular, renal, pulmonary, central nervous, and skeletomuscular systems progressively decline in the elderly, and their physiological response to stress is different. Due to altered physiology of the elderly, the pharmacokinetics and pharmacodynamics of medications especially anesthetics are altered.

Mahdi et al. in their review of postoperative outcome of ovarian cancer patients found that patients older than 70 but particularly those over 80 years of age more frequently developed chronic kidney failure, cardiorespiratory diseases, and neurological deficit [23]. Compared with patients <60 years of age, the odds ratio for 30-day mortality after surgery was 3.7, 3.1, and 9.3, for patient aged 60–69, 70–79, and ≥80, respectively. While 1% of the patients younger

than 60 died after operation, 9% of the over 80s suffered fatal complications postoperatively. There was no significant difference in the mortality of patients younger or older than 70 years who received neoadjuvant chemotherapy and underwent delayed primary surgery. Similarly, patients younger than 60 developed less postoperative complications than those aged 60–69, 70–79, and ≥80 (25% vs. 34%, 35%, and 39%, respectively).

Although old age alone is not a contraindication for debulking surgery, but it is an important surrogate to take into account when planning treatment for advanced ovarian cancer. Patients over 80 years with extensive disease requiring four-quadrant resection may benefit from alternative treatment approach, such as neoadjuvant chemotherapy with delayed debulking surgery or, if frail with multiple comorbidities, primary chemotherapy with no surgical intervention.

2.2. Nutritional status

Poor nutritional status has long been demonstrated to be an adverse prognostic factor for postoperative complications, due to reduced immunity and impaired repair capacity [24–28]. Cancer-related hypoalbuminemia is a multifactorial condition related to reduced protein intake, cancer-related systemic inflammation, and muscle protein depletion and is a marker for malnutrition [29]. Patients with advanced ovarian cancer often present with ascites, and in two-thirds of the patients, it is associated with cachexia, loss of muscle weight, and hypoproteinemia-hypoalbuminemia [30].

It has been demonstrated that ovarian cancer patients with hypoalbuminemia (defined as the serum albumin level less than 35 g/L) were 5–10 times more likely to develop severe complications after debulking surgery than those with a normal albumin level. The mortality rates for patients with a low and normal serum albumin level are 12 and 2.5%, respectively [22, 23, 31, 32]. Ovarian cancer patients with a low serum albumin level have a significantly higher anastomotic leakage rate than those with normal levels (18–21% vs. 0–3.4%), and the rate of wound-related complications, infections, and septicemia is also significantly higher [33, 34].

Global clinical assessment of ovarian cancer patients is paramount in diagnosing malnutrition; a single measurement of BMI is unreliable due to excess weight associated with ascites and generalized edema. A low serum albumin level is associated with malnutrition and is an easy test prior to surgery; it is a strong predictor for postoperative morbidity. As two-thirds of ovarian cancer patients are malnourished, it is important to explore the ways to improve nutrition and albumin levels prior to cytoreductive surgery.

Total parenteral nutrition (TPN) for 10 days prior to surgery reduced postoperative complications in gastrointestinal cancer patients with severe undernutrition (defined as the serum albumin level < 30 g/L or 15% weight loss during the past 6 months or BMI < 18) [35]. Geisler et al. demonstrated that in 50% of the severe malnourished ovarian cancer patients showed nutritional improvement on TPN. This translated into less postoperative complications compared with those not responding to TPN [36].

Neoadjuvant chemotherapy offers an alternative approach for patients with nutritional compromise. After two to three cycles of neoadjuvant chemotherapy, the serum albumin level shows

improvement, patients start gaining weight, and their performance status improves [37]. This allows the surgeon to exercise maximum surgical efforts during delayed cytoreduction.

2.3. Tumor extent

The relationship between tumor extent and tumor biology remains unclear. Eisenhauer et al. found that surgical resection counterweighed the presence of bulky upper abdominal disease and concluded that large tumor load did not indicate poor tumor biology [38]. Others, however, found that extensive disease cannot be "downgraded" by radical surgery and patients with high peritoneal cancer index will have poorer survival even if completely cytoreduced [39, 40]. Vergote et al. in their seminal EORTC55971 study found that patients with largest tumor diameter > 5 cm had better survival in the neoadjuvant chemotherapy arm [2]. It does not mean of course that maximum surgical effort should not be applied, as optimally cytoreduced patients consistently perform better than those with residual disease >1 cm [41]. In elderly or frail patients, however, even if it is technically resectable, four-quadrant disease distribution may render patients unsuitable for primary debulking surgery. Aletti et al. found in their study of patients with advanced ovarian cancer that those older than 75 years of age with high initial tumor load (or stage IV disease) plus poor performance or nutritional status were at significantly higher risk for postoperative complications with minimal survival benefit after undergoing complex radical surgery [42]. Delay in starting chemotherapy or dose delays occur more often in the elderly after primary debulking surgery, and this translates into poorer survival [43]. It is imperative, therefore, to find alternative treatment routes in elderly patients with large tumor volume and four-quadrant disease distribution. In such cases, neoadjuvant chemotherapy offers an effective and safe alternative.

2.4. Stage 4 disease

Patients with stage 4 ovarian cancer represent a heterogeneous group with extraperitoneal metastases. According to recent FIGO staging, stage 4A includes patients with pleural effusion and positive peritoneal cytology. For note, the false-negative rate of pleural cytology is high; in a literature review on the use of video-assisted thoracoscopy in ovarian cancer patients with pleural effusion, 23% of the patients with negative pleural cytology had macroscopic disease found in the pleural cavity [44]. The presence of microscopic disease has not been assessed and can potentially be even more frequent. Patients with plural effusion represent a high-risk subgroup for postoperative complications with potential prolonged recovery and delayed administration of chemotherapy, and, therefore, application of neoadjuvant chemotherapy is a considerable strategy.

Stage 4B includes all other types of extraperitoneal metastases including splenic, hepatic, or lung parenchymal disease and lymph node metastases outside the abdominal cavity including the mediastinum, groin, axilla, and neck.

There seems to be an agreement that patients with stage 4 disease by virtue of solitary splenic parenchymal metastasis can easily be cytoreduced (dependent on the peritoneal disease of

course), so can be those with liver metastases in favorable anatomical positions. Controlling the peritoneal disease by complete cytoreduction in stage 4 disease appears to be associated with survival benefit [6]. This effect can only be observed in patients with complete macroscopic cytoreduction within the peritoneal cavity but not in those with any residual disease [45].

On the other hand, those with extensive mediastinal, axillary, or supraclavicular nodes or multiple, unresectable hepatic metastases represent a disease with different biological behaviors, and complete cytoreduction is not achievable; therefore, alternative treatment strategies must be considered [20, 21]. Furthermore, approximately 5% of the patients will progress through chemotherapy so patients with unresectable extraperitoneal disease should not be exposed to primary radical peritoneal resection [4, 17].

In these patients, neoadjuvant chemotherapy offers a safe and effective treatment alternative. Firstly, patients with platinum-refractory disease will not receive an unnecessary peritoneal surgical debulking with the associated morbidity. Furthermore, neoadjuvant chemotherapy effectively eliminates pleural effusion and ascites, improves performance status and serum albumin level, and, therefore, provides the surgeon with an opportunity to exercise maximum surgical effort with acceptable morbidity [37, 46].

The EORTC55971 trial confirmed that neoadjuvant chemotherapy results in superior survival compared with primary debulking surgery in the management of patients with stage 4 disease [2]. In such clinical scenario, the joint ASCO/SGO guideline also recommends the use of neoadjuvant chemotherapy [20, 21].

3. Conclusions

With no doubt, the presence of any residual disease after cytoreductive surgery remains the most important adverse prognostic factor that clinicians have to control over. Therefore, complete macroscopic clearance of the peritoneal cavity should always be the aim of surgery. Preoperatively, patients should undergo holistic assessment by gynecologic oncologist with regard of the disease distribution, extent, stage, and resectability; the patients' physical and emotional capacity to cope with the burden of surgery; and their nutritional status. All efforts should be focused on optimizing patients to tolerate the maximal surgical effort with acceptable morbidity and mortality. While primary debulking surgery remains the standard approach for patients with stage 3 ovarian cancer with optimal age, performance status, and nutritional status, there is growing evidence that neoadjuvant chemotherapy offers a safe and effective alternative for patients with less favorable characteristics.

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