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Review

Predictors of optimal cytoreduction in patients with newly diagnosed advanced-stage epithelial ovarian cancer: Time to incorporate laparoscopic assessment into the standard of care

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HIGHLIGHTS

- Laparoscopy offers assessment for optimal surgery in advanced ovarian cancer.
- Fagotti laparoscopy-based score is a useful predictor of optimal cytoreduction.
- A PIV of ≥8 is the best predictor of suboptimal cytoreduction in advanced ovarian cancer.

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ABSTRACT

The standard management of advanced-stage ovarian cancer has been a subject of debate, and much controversy remains as to whether patients should have primary cytoreductive surgery followed by chemotherapy or neoadjuvant chemotherapy followed by interval cytoreductive surgery. In addition, there is increasing evidence that the patients who ultimately gain the most benefit from surgery are those with no residual disease at the completion of surgery (R0 resection). Therefore, to determine the best therapeutic strategy (primary cytoreductive surgery vs. neoadjuvant chemotherapy) for an individual patient, it is critically important to estimate the likelihood that primary cytoreductive surgery will leave no macroscopic residual disease. A number of studies have evaluated the use of serologic markers, such as CA-125, and imaging modalities, such as computed tomography (CT) or positron emission tomography/CT (PET/CT), to determine which patients are ideal candidates for primary cytoreductive surgery. More recently, laparoscopy has been proposed as a reliable predictor of R0 resection. In this report, we provide a review of the existing literature on the proposed criteria to predict the outcome of cytoreductive surgery and the role of laparoscopy-based scores in the management of advanced ovarian cancer.

Contents

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1. Introduction

Patients with advanced epithelial ovarian cancer have traditionally been treated with primary cytoreductive surgery followed by platinum- and taxane-based chemotherapy. The most important prognostic factor for survival in such patients is the amount of residual tumor after surgery, so the goal is to achieve optimal cytoreduction. However, the definition of optimal cytoreduction has changed over the years. Currently, the Gynecologic Oncology Group defines optimal cytoreduction as a post-operative surgical residuum of ≤1 cm in largest diameter [1]. Some patients with advanced epithelial ovarian cancer undergo extensive cytoreductive surgery and still have suboptimal residual disease, often in the setting of high morbidity and with no ultimate improvement in overall survival [2].

Recently, attention has focused on the incremental benefits of residual disease under 1 cm, specifically, no macroscopic residual disease (R0 resection). Chang et al. [3] reviewed 18 studies with a total of 13,257 patients and found that each 10% increase in the proportion of patients undergoing R0 cytoreduction was associated with a significant and independent 2.3-month increase (95% confidence interval [CI] = 0.6–4.0, P = 0.011) in cohort median survival; each 10% increase in the proportion of patients undergoing cytoreduction to ≤1 cm residual disease was associated with a 1.8-month increase (95% CI = 0.6–3.0, P = 0.004) in cohort median survival. Therefore, preoperative identification of patients most likely to have R0 resection is of paramount importance.

In another study, Horowitz et al. [4], collected data from 2655 patients with epithelial ovarian cancer or primary peritoneal cancer enrolled in the Gynecologic Oncology Group 182 study and explored the effects of disease distribution and complexity of surgery on progression free survival (PFS) and overall survival (OS). In that study, a total of 860 patients (32.4%) achieved R0, and 1795 patients (67.6%) had residual disease <1 cm (not including R0). The authors showed that for those with low or moderate preoperative disease, aggressive cytoreductive surgery is important because it is associated with superior PFS and OS. The authors go on to suggest a "paradigm shift, in which, if R0 is difficult to attain at primary cytoreduction, use of neoadjuvant chemotherapy with interval debulking to allow for R0 may be superior to primary surgery".

Numerous studies have been performed to establish the factors that most accurately predict which patients will experience optimal cytoreduction, with "optimal" defined various ways, following primary cytoreductive surgery. Various factors, including circulating biomarkers, imaging studies, and laparoscopy-based scores have been assessed. Here, we present a review of the different criteria that have been proposed to predict the outcomes of cytoreduction, and we summarize the reported data on laparoscopy-based assessment as predictors of optimal cytoreduction in patients with advanced epithelial ovarian cancer.

1.1. Serum biomarker levels

The most commonly studied serum biomarker for ovarian cancer is CA-125. Chi et al. [5] reported that preoperative serum CA-125 levels greater than 500 U/mL predicted suboptimal cytoreduction. In 100 consecutive patients with stage III ovarian carcinoma, optimal cytoreduction (residual tumor ≤1 cm) was achieved in 33 of 45 patients (73%) with a CA-125 level < 500 U/mL, compared to only 12 of 55 patients (22%) with a CA-125 level > 500 U/mL (P < 0.001). The same investigators later reported an analysis of preoperative CA-125 level as a predictor of the outcome of cytoreductive surgery in patients with advanced ovarian cancer after the incorporation of extensive upper abdominal surgery [6]. That retrospective study included 277 patients with stage III/IV ovarian, tubal, or peritoneal carcinoma who underwent primary cytoreductive surgery. Sixty-eight patients (25%) had R0 resection, 153 (55%) had residual tumor ≤ 1 cm, and 56 (20%) had residual tumor > 1 cm. There was no threshold CA-125 level that accurately predicted cytoreductive outcome.

In a subsequent meta-analysis, Kang et al. [7] analyzed 14 studies with 2192 patients to assess the performance of CA-125 at various cut-off levels as a predictor of the outcome of cytoreductive surgery. Preoperative serum CA-125 level had a low positive likelihood ratio and a high negative likelihood ratio in predicting cytoreductive outcome in advanced ovarian carcinoma. However, a preoperative serum CA-125 level > 500 U/mL was strongly associated with suboptimal cytoreduction (odds ratio, 3.69; 95% CI, 2.02–6.73).

1.2. Preoperative imaging studies

1.2.1. CT and MR imaging

The imaging modality most commonly used to predict the outcome of cytoreductive surgery is computed tomography (CT). Nelson et al. [8] scored CT scans on the basis of the criteria in Table 1, as cytoreducible (no disease remaining in criteria site) or not cytoreducible (at least 1 site of disease remaining) by standard surgical techniques. Optimal cytoreduction (residual tumor < 2 cm) was accomplished in 23 of 24 patients with disease scored as cytoreducible and in 6 of 18 patients with disease scored as not cytoreducible. The CT findings accurately predicted surgical outcome with a sensitivity of 92.3% and a specificity of 79.3%. In 2000, Bristow et al. [9] proposed another CT-based predictive model based on retrospective analysis of 41 preoperative CT scans for 25 radiographic features by two radiologists without knowledge of the operative findings. Twenty of 41 patients (49%) had optimal primary cytoreduction (residual tumor < 1 cm). Thirteen radiographic features met the inclusion criteria (specificity of ≥75%, a PPV ≥ 50%, and a NPV ≥ 50%), and were each assigned 1 or 2 points (Table 1), and a Gynecologic Oncology Group performance status score ≥ 2 (assigned 2 points), was used to calculate a Predictive Index score. A Predictive Index score ≥ 4 had the highest overall accuracy, at 92.7%, and identified patients undergoing suboptimal cytoreduction with a sensitivity of 100%.

Dowdy et al. [10] published results of a retrospective analysis in which 87 preoperative CT scans were reviewed for 17 criteria indicating disease extent by 2 radiologists without knowledge of operative outcome. Sixty-two patients (71%) had optimal cytoreduction (residual tumor < 1 cm). The authors found that a model based on diffuse peritoneal thickening and ascites, had 68% PPV, 52% sensitivity and was associated with a low rate of optimal cytoreduction (32%). (Table 1)