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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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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.

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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 2,655 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 1,795 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.

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 2,192 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).

Preoperative imaging studies

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), were 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)

Positron emission tomography/CT

Hynninen et al. [11] prospectively studied 41 women with ovarian cancer who underwent preoperative fluorodeoxyglucose (FDG) PET/CT followed by diagnostic high-dose contrast-

enhanced CT. The results of PET/CT and CT were compared with systematically recorded findings on primary surgery/diagnostic laparoscopy or interval surgery. The sensitivity of PET/CT and CT in the detection of unresectable disease was poor in certain areas of the peritoneal cavity (64% for PET/CT and 27% for CT in the small bowel mesentery; 65% for PET/CT and 55% for CT in the right upper abdomen). In the overall site-based analysis, the sensitivity for PET/CT and CT was 51% and 41%; respectively, whereas the specificity was 89% and 92% and the accuracy was 64% and 57%; respectively. Preoperative contrast-enhanced CT suggested extra-abdominal disease spread in 61% patients and PET/CT in 78% patients. Fruscio et al. [12] also evaluated patients with suspected advanced ovarian cancer with preoperative 18-FDG PET/CT. The patients were divided into 3 groups on the basis of clinical and PET/CT findings: group A, stage III by both clinical and PET findings; group B, stage III by clinical findings and stage IV by PET/CT; and group C, stage IV by both clinical and PET/CT findings. Twenty-five patients had their disease upstaged to stage IV by PET/CT. The proportion of patients with residual tumor <1 cm was similar in groups B and C and was significantly higher in groups B and C than in group A. Similarly, complete response to adjuvant chemotherapy was achieved more frequently in patients in group A.

CT in combination with CA-125

Suidan et al. [13] published a prospective, nonrandomized, multicenter trial of preoperative CT of the abdomen and pelvis in combination with serum CA-125 level to predict suboptimal primary cytoreduction (≥1 cm residual disease) in patients with stage III-IV disease. Of 350 patients, 261 had optimal cytoreduction, and 89 had suboptimal cytoreduction. A CT scan of the abdomen and pelvis was obtained within 35 days before surgery, and serum CA-125 level was measured within 14 days of surgery. The results showed that the following criteria were associated with suboptimal cytoreduction: age ≥60 years, CA-125 level ≥500 U/mL, American Society of Anesthesiologists Physical Status 3 or 4, retroperitoneal lymph nodes above the renal hilum (including supradiaphragmatic) >1 cm, diffuse small bowel adhesions/thickening, perisplenic lesion >1 cm, small bowel mesentery lesion >1 cm, lesion in the root of the superior mesenteric artery >1 cm, and lesser sac lesion >1 cm. On the basis of these findings, the authors developed a predictive model in which the rate of suboptimal cytoreduction was directly proportional to a predictive value score.

Conclusions regarding findings on preoperative imaging

Although CT-based predictive models have been demonstrated to be accurate in original cohorts, they have not assessed for external validity. A significant factor affecting prediction is reliance on surgical expertise and the intraoperative experience to affect the primary endpoint, namely, R0 resection. In general, since the prevalence of R0 resection is relatively low, predictive models will struggle affirming this endpoint without high reproducible algorithms to assess disease distribution.

Laparoscopy-based assessment

The rationale for a laparoscopic evaluation prior to cytoreductive surgery includes: 1) this approach could spare patients an unnecessary laparotomy resulting in suboptimal cytoreduction; 2) patients deemed not to be candidates for cytoreduction could proceed

immediately to neoadjuvant chemotherapy without having to recover from laparotomy; 3) laparoscopy allows collection of tissue for definitive diagnosis and for molecular analyses.

Early studies

The first reported study evaluating laparoscopy prior to cytoreduction was published by Vergote et al. in 1998 [14]. This was a retrospective analysis of 285 patients with advanced ovarian carcinoma. The authors stratified patients into 3 groups according to year of treatment and treatment approach. The first group consisted of 112 patients treated during 1980–1988 who underwent primary debulking surgery. Eighty-two percent had residual tumor <0.5 cm (<1 gm residual tumor) after surgery. The second group consisted of 173 patients treated during 1989–1997 who were surgically evaluated and assigned to receive primary chemotherapy (43%) or primary debulking surgery (57%). The actuarial 3-year crude survival rate for the patients who had primary debulking surgery was higher for patients treated in 1989–1997 (42% ± 4.6%) than for those treated in 1980–1988 (26% ± 4.3%). Finally, the third group consisted of 77 patients treated during 1993–1998 who had clinical and radiological findings suggestive of advanced ovarian carcinoma that might be inoperable (not surgically cytoreducible to no macroscopic disease) and underwent open laparoscopy. Primary debulking surgery was performed in 28 of the 77 patients (36%). Seventy-nine percent of these patients with obvious metastatic disease on radiological examination had their disease cytoreduced to less than 0.5 cm largest residual tumor mass. In 31 (63%) of the 49 patients given neoadjuvant chemotherapy on the basis of the laparoscopy findings, interval debulking surgery was performed after 3 courses of chemotherapy.

In 2005, Fagotti et al. [15] reported on 65 patients who underwent preoperative clinical-radiological evaluation followed by laparoscopy and then laparotomy. Parameters analyzed during each laparoscopic procedure were ovarian masses (unilateral or bilateral), omental cake or nodules, peritoneal and diaphragmatic carcinomatosis, mesenteric retraction, bowel and stomach infiltration, liver metastases, and bulky lymph nodes. At the end of each laparoscopic procedure, the surgeon indicated the likelihood that optimal cytoreduction was possible based on the absence of standard criteria of unresectability. Optimal debulking was achieved in 34 of the 39 patients (87%) whose disease was judged completely resectable on the basis of laparoscopy findings. The overall accuracy rate of laparoscopy in predicting optimal cytoreduction was 90%. The NPV of clinical-radiological evaluation was 73%, whereas the NPV of laparoscopy was 100% (i.e., in no case when disease was judged incompletely resectable on the basis of laparoscopy findings was disease judged completely resectable at laparotomy). The PPVs of clinical-radiological evaluation and laparoscopy were both 87%.

This work was updated in 2006 when Fagotti et al. [16] proposed a Predictive Index Value (PIV) based on objective parameters determined at pre-cytoreduction laparoscopy. In this study, 64 patients underwent laparoscopy followed by standard laparotomy, and laparoscopy findings were used to estimate the chances of optimal cytoreduction (residual tumor ≤1 cm) according to the criteria used in the prior study (Table 2). The scores for the individual items were summed to obtain an overall score, the PIV. The overall accuracy of the model in

predicting surgical outcome was approximately 75% with the percent of cases correctly identified as suboptimal (sensitivity) increasing with the PIV cutoff level, and the likelihood that a patient would have a suboptimal surgical result (PPV) being 100% with a PIV ≥8. This was the first study to support the concept that laparoscopic rather than radiological features could predict the chance of optimal cytoreduction in patients with clinically advanced ovarian cancer. Each laparoscopic parameter used in the model was chosen not on the basis of a direct correlation with the chances of optimal cytoreduction, but rather to describe the intra-abdominal distribution of disease.

Angioli et al. [17] published an evaluation of the role of diagnostic open laparoscopy in predicting which patients are the best candidates for R0 resection. In this trial, 87 patients with advanced ovarian cancer underwent diagnostic laparoscopy. Fifty-three patients (61 %) were judged candidates for R0 resection and therefore underwent primary cytoreductive surgery. The optimal debulking rate in this group was 96%. The 34 patients not judged candidates for R0 resection underwent neoadjuvant chemotherapy. Twenty-five patients had a partial response and were therefore scheduled for interval debulking surgery. The optimal debulking rate in this group was 80%. No major perioperative complications due to laparoscopy occurred. Brun et al. [18] evaluated the utility of Fagotti criteria in a cohort of 55 patients with stage III-IV ovarian cancer. Of the 55 patients, 26 patients had primary cytoreductive surgery after diagnostic laparoscopy, and the remaining 29 patients were treated with neoadjuvant chemotherapy. A PIV of ≥8 was associated with suboptimal cytoreduction with sensitivity, specificity, PPV, NPV, and accuracy values of 46%, 89%, 89%, 44%, and 60%, respectively.

Prospective validation of a laparoscopy-based score to predict optimal (<1cm residual) primary cytoreduction

In 2008, Fagotti et al. [19] reported prospective data on 113 patients who underwent laparoscopy and had the likelihood of optimal cytoreduction evaluated using the PIV score [15]. Of note, this study included patients with suboptimal response after neoadjuvant chemotherapy prior to interval debulking surgery. Such patients did not undergo laparoscopy prior to determination of the plan for neoadjuvant chemotherapy. The overall accuracy rate of the laparoscopy-based score in predicting optimal cytoreduction ranged from 77.3% to 100%. The results confirmed that at a PIV of ≥8, the probability of optimal cytoreduction (residual tumor ≤1 cm) at laparotomy was 0; 40.5% of the patients had a PIV of ≥8 and avoided unnecessary exploratory laparotomy.

In 2011, the same group of investigators [20] prospectively estimated the learning curve for determining the PIV. The authors compared the scores for each laparoscopic parameter assigned by fellows and senior surgeons. Ninety consecutive women with suspected advanced ovarian/peritoneal cancer underwent laparoscopy by a fellow and a senior surgeon sequentially with independent assignment of scores for disease distribution. The median PIV was 6 (range, 0-10) for the fellows and 6 (range, 0-14) for the senior surgeons. The diagnosis of primary ovarian/peritoneal cancer was confirmed histologically in 82 of 90 patients (91%). Of the 82 patients with ovarian/peritoneal cancer, 65 (79%) had stage IIIC disease, and 17 (21%) had stage IV disease. Forty-eight patients were considered candidates for

optimal cytoreduction (PIV<8) and underwent immediate laparotomy, and all 48 patients had optimal intraperitoneal cytoreduction (<1 cm residual tumor). Fellows in gynecologic oncology with at least 12 months' experience assigned laparoscopy-based scores similar to those of senior surgeons.

A potential concern about implementing preoperative laparoscopic assessment as part of standard practice is the feasibility of this approach not only at major academic institutions but also at other sites. To determine the reproducibility of laparoscopic assessment, Fagotti et al. performed a prospective, multicenter trial (Olympia–MITO 13) [21], in which application of the laparoscopy-based PIV was evaluated in 4 satellite centers. A total of 120 patients with clinical suspicion of advanced ovarian, fallopian tube, or primary peritoneal cancer underwent staging laparoscopy at the satellite centers, the procedures were recorded and blindly reviewed at the coordinator center afterwards. The most difficult feature to assess was mesenteric retraction, which was not evaluable in 31 of 120 cases (25.8%). The rate of evaluation of the remaining variables ranged from 99.2% (peritoneal carcinomatosis) to 90% (bowel infiltration). An accuracy rate of 80% or greater was reached in 3 of the 4 satellite centers.

These studies have validated a laparoscopy-based scoring system that allows surgeons to determine with great accuracy at the time of initial diagnosis of advanced-stage ovarian cancer the likelihood that optimal cytoreduction is possible. These studies have also demonstrated that use of this scoring system is reproducible at other institutions.

Use of laparoscopy-based scores to predict optimal interval cytoreduction

Patients with suboptimal cytoreduction following interval cytoreductive surgery have worse survival than patients with optimal cytoreduction. In patients with partial response to neoadjuvant chemotherapy, it would be valuable to determine whether laparotomy would be of benefit or patients should continue with additional chemotherapy.

In 2010, Fagotti et al. [20] published results of a prospective study of laparoscopy in patients with advanced ovarian cancer prior to scheduled interval cytoreductive surgery. The aims of this study were to determine if laparoscopy could contribute to better identification of patients who would benefit from interval cytoreductive surgery and to identify the most appropriate cut-off value of PIV to identify patients unlikely to benefit. A total of 111 consecutive patients with advanced ovarian cancer underwent neoadjuvant chemotherapy, and all patients were evaluated for radiological and serological response before interval cytoreductive surgery was attempted. A total of 13 patients had disease progression and were excluded from the analysis. The remaining 98 patients who had a stable disease, complete or partial radiological and serological response were eligible for this trial and underwent laparoscopy after completion of neoadjuvant chemotherapy (median number of cycles, 4; range, 3-6). The results also showed that the addition of laparoscopy to the serological criteria used by the Gynecologic Cancer Intergroup Committee reduced the rate of exploratory laparotomy from 30% to 13% and reduced the rate of inappropriate lack of exploration. The most appropriate cut-off value of PIV to identify patients unlikely to benefit from cytoreductive surgery was PIV >4, which had a PPV of 100%. In other words, at a PIV

>4, the probability of optimally resecting the disease at laparotomy was equal to 0. In that study, the definition of optimal cytoreduction was a disease residual <1cm.

In 2011, Chéreau et al. [23] reported on 70 patients who underwent laparoscopy at the time of ovarian cancer diagnosis and were judged to be candidates for interval cytoreductive surgery after neoadjuvant chemotherapy. Among these patients, 52 ultimately underwent interval cytoreductive surgery and were thus eligible for this study; 18 patients did not undergo interval cytoreductive surgery and were excluded because of the absence of a response to chemotherapy as indicated by findings on CA-125 testing and CT. Resection was defined as optimal (residual disease <1 cm) or suboptimal according to the criteria of Fagotti et al. [21]. With a cut-off PIV of ≤4, sensitivity and PPV were 95% and 82%; respectively. The authors concluded that the laparoscopy-based score of Fagotti et al. [20] has an important role in the prediction of optimal cytoreduction among women undergoing interval cytoreductive surgery.

Prognostic value of a laparoscopy-based score

In 2013, Fagotti et al. [24] reported on 300 women with FIGO stages IIIC and IV ovarian, fallopian tube, or primary peritoneal carcinoma. One hundred forty-eight women (49.3%) were considered suitable for primary debulking surgery, and the remaining 152 patients (50.7%) underwent neoadjuvant chemotherapy. After primary debulking surgery, 92 patients (62.1%) had no gross residual disease, 41 (27.7%) had residual disease ≤1 cm, and 15 (10.2%) had residual disease >1 cm. There were no complications related to the laparoscopic procedure. The median PFS in women with R0 resection at primary debulking surgery was 25 months (95% CI, 15.1-34.8 months), which was significantly longer than the median progression-free survival in patients with less than R0 resection on primary debulking surgery and patients who underwent interval debulking surgery after chemotherapy(P=0.0001). In the overall population, the median survival from the day of histological diagnosis to the date of recurrence was 15 months (95% CI, 13.9-16.0 months), and the median overall survival from the day of histological diagnosis was 38 months (95% CI, 33.0-42.9 months).

Vizzielli et al. [25] evaluated 348 patients who underwent laparoscopy before primary cytoreductive surgery or neoadjuvant chemotherapy. Patients were stratified into 3 groups: PIV ≥8, indicating high tumor load; PIV 4 to 6, indicating intermediate tumor load; and PIV <4, indicating low tumor load. Primary debulking surgery was attempted in 165 women (47.4%); the remaining 183 women (52.6%) underwent neoadjuvant chemotherapy. Among the 165 patients who underwent primary cytoreduction R0 was achieved in 102 patients (61.8%), optimal cytoreduction (residual tumor ≤1 cm) in 48 patients (29.1%), and suboptimal cytoreduction (residual tumor >1 cm) in 15 patients (9.1%).

Ongoing clinical trials of preoperative laparoscopy in patients with advanced ovarian cancer

The goal of the SCORPION trial (NCT01461850) [26] is the evaluation and comparison of the surgical complications of primary surgery and IDS. This trial includes patients with advanced ovarian cancer (FIGO stage IIIC) who have PIV scores of 8 through 12. Patients

are randomized to primary debulking surgery followed by adjuvant chemotherapy or neoadjuvant chemotherapy followed by interval debulking surgery and subsequent additional chemotherapy. In this study, all patients undergo diagnostic laparoscopy, and a PIV is assigned. The primary outcome of the study is the evaluation and comparison of early surgical complications of primary surgery and interval debulking surgery.

Another important ongoing study is the Mission Trial [27]. The main objective of this multicenter phase II study is to assess the feasibility and early complication rates of total laparoscopic or robotic interval debulking surgery in patients with advanced ovarian cancer who experience a clinical complete or partial response to neoadjuvant chemotherapy. The secondary objectives are to assess perioperative outcomes, patterns of recurrence, progression-free survival, overall survival, and quality of life. All surgical procedures start with a diagnostic laparoscopy to confirm preoperative findings. In case of evidence of partial response by laparoscopy, the surgical approach will be chosen according to the surgeon's preference, and in case of complete response, minimally invasive surgery (laparoscopic/robotic) cytoreduction will be performed. Rutten et al. [28] are conducting a trial to evaluate the value of laparoscopy prior to primary debulking surgery leaving residual tumour of > 1 cm in women with advanced ovarian cancer. Participants are randomized between upfront surgery or diagnostic laparoscopy. Depending on the result of the laparoscopy, patients undergo surgery within three weeks, followed by six courses of platinum based chemotherapy or are treated with neoadjuvant chemotherapy followed by interval debulking 3-4 weeks after three courses of chemotherapy, followed by another three courses of chemotherapy. Primary outcome measure is the proportion of patients with residual >1cm.

Cochrane Review (2014)

A recent Cochrane Review evaluated the accuracy of diagnostic laparoscopy to determine the resectability of disease in patients suspected of having a diagnosis of advanced ovarian cancer [29]. Between 27% and 64% of patients were considered to have too extensive disease to undergo laparotomy after laparoscopic assessment. They also found that the other 36% to 73% were considered suitable for laparotomy and they underwent this surgery. At laparotomy, between 4% and 31% were found to have residual tumor remaining after surgery, suggesting that they could have been spared a laparotomy. The authors concluded that although diagnostic laparoscopy may seem better than standard diagnostic staging alone, it should not be considered a standard procedure in clinical practice. The authors do recognize that there were several weaknesses in this review including the fact that they could not correct for factors leading to bias, significant heterogeneity with regard to each of the following, criteria for clinical or radiologic staging, differences in endpoint of debulking surgery, and methodological quality assessment for the studies included in their analysis.

The Anderson Algorithm

Capitalizing on the experience of endoscopic preoperative triage assessment, investigators at the University of Texas, M.D. Anderson Cancer Center are leveraging laparoscopy as a means of surgical triage, to provide organ specific tumor sampling (primary tumor, omentum, two additional metastatic sites) and to investigate novel therapeutics [30]. Currently, “window of opportunity” trials are being conducted for those patients deemed

primary cytoreduction candidates by offering pharmacodynamic translational studies to novel single agents over a brief exposure period (7-10 days) deemed safe for pre-operative administration. For those in whom neoadjuvant chemotherapy is planned, similar studies in combination with chemotherapy are being conducted. In both protocol queues, matched organ-specific tumor sampling is undertaken for analysis of tumor tissue target engagement, modulation, and adaptive response.

Conclusion

Existing studies point to a highly valuable role for laparoscopy for objectively assessing the feasibility of optimal primary and interval cytoreductive surgery for patients with advanced-stage ovarian cancer (FIGO stages III and IV). The Fagotti laparoscopy-based score is a useful predictor of optimal cytoreduction. Moreover, standardized use of the Fagotti score should be enforced to ensure that results are concordant across different centers, with a PIV of ≥ 8 demonstrated to have the best accuracy in identifying disease dissemination and predicting suboptimal cytoreduction. Furthermore, following completion of the ongoing clinical trials, we expect use of this laparoscopy-based scoring system to become completely standard.

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Highlights

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

Table 1

CT-based models to predict the likelihood of optimal cytoreduction in patients with advanced ovarian cancer

Model	CT Findings Included in Model
Nelson (7)	• Attachment of the omentum to the spleen • Disease >2 cm in: – Mesentery – Liver surface or parenchyma – Diaphragm – Gallbladder fossa – Suprarenal paraaortic nodes – Pericardial nodes – Pulmonary or pleural nodules
Bristow (8)	• 2 points for each of the following: – Peritoneal thickening – Peritoneal implants ≥2 cm – Small bowel mesentery disease ≥2 cm – Large bowel mesentery disease ≥2 cm – Omental disease extension to stomach, spleen, or lesser sac – Extension to pelvic sidewall, parametria, or hydroureter – Large-volume ascites (seen on all cuts) – Suprarenal paraaortic lymph nodes ≥1 cm • 1 point for each of the following: – Diaphragm or lung disease ≥2 cm or confluent plaque – Inguinal canal disease or lymph nodes ≥2 cm – Liver lesion ≥2 cm on surface or parenchymal lesion of any size – Porta hepatic or gallbladder fossa disease ≥1 cm – Infrarenal paraaortic lymph nodes ≥2 cm
Dowdy (9)	• Diffuse peritoneal thickening, defined as peritoneum >4 mm thick in at least 2 of the following 5 areas: – Lateral colic gutters – Lateral conal fascia – Anterior abdominal wall – Diaphragm – Pelvic peritoneal reflections • Ascites present on at least two-thirds of the CT cuts

Table 2

Laparoscopic features and corresponding scores used to calculate the Fagotti score to predict the likelihood of optimal cytoreduction [20]

Laparoscopic Feature	Score 0	Score 2
Peritoneal carcinomatosis	Carcinomatosis involving a limited area (along the paracolic gutter or the pelvic peritoneum) and surgically removable by peritonectomy.	Unresectable massive peritoneal involvement as well as with a miliary pattern of distribution.
Diaphragmatic disease	No infiltrating carcinomatosis and no nodules confluent with the most part of the diaphragmatic surface.	Widespread infiltrating carcinomatosis or nodules confluent with the most part of the diaphragmatic surface.
Mesenteric disease	No large infiltrating nodules and no involvement of the root of the mesentery as would be indicated by limited movement of the various intestinal segments.	Large infiltrating nodules or involvement of the root of the mesentery indicated by limited movement of the various intestinal segments.
Omental disease	No tumor diffusion observed along the omentum up to the large stomach curvature.	Tumor diffusion observed along the omentum up to the large stomach curvature.
Bowel infiltration	No bowel resection was assumed and no miliary carcinomatosis on the ansae observed.	Bowel resection assumed or miliary carcinomatosis on the ansae observed.
Stomach infiltration	No obvious neoplastic involvement of the gastric wall.	Obvious neoplastic involvement of the gastric wall.
Liver metastases	No surface lesions.	Any surface lesion.