New Insights in Laparoscopic Assessment for Primary Cytoreduction in Advanced Ovarian Cancer

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ABSTRACT

In patients with potentially resectable advanced ovarian cancer, primary cytoreductive surgery followed by chemotherapy remains the treatment of choice. The aim of debulking surgery is to leave no visible macroscopic tumor, as complete debulking is the most important prognostic factor in patients with advanced ovarian cancer. Suboptimal primary debulking surgery should be avoided in order to decrease surgery related complications with no benefit in overall survival. Standard preoperatively evaluation, which usually includes physical examination, tumour markers, ultrasound and CT scan, has a low sensibility to predict when optimal debulking surgery can be performed. Laparoscopy has been increasingly incorporated as a useful tool in patients with advanced ovarian cancer but indications and limitations of this approach should be well known by gynecologic oncologists.

Keywords: Advanced ovarian cancer; Laparoscopy; Staging; Cytoreduction
INTRODUCTION

The standard treatment of ovarian cancer is primary cytoreductive surgery followed by chemotherapy. The aim of debulking surgery is to leave no visible macroscopic tumour, as complete debulking is the most important prognostic factor in patients with advanced ovarian cancer. Our definition of optimal cytoreduction that uses 1 cm of residual tumor as a cut-off has shifted to the more strict criteria of no gross residual disease. Since ovarian cancer is typically diagnosed in an advanced stage [1], achieving this goal is possible only in a limited number of cases, the success rate of optimal or complete cytoreductive surgery varying a lot among reporting institutions, from 15% to 85% [2,3].

In order to increase the percentage of complete or optimal debulking, neoadjuvant chemotherapy followed by interval cytoreduction surgery has developed as an alternative. An EOTRC prospective, randomized, controlled trial of 632 eligible patients with stage IIIC/IV epithelial ovarian cancer [4] showed that survival after platinum-based neoadjuvant chemotherapy followed by interval debulking surgery was similar in terms of survival to standard approach of primary cytoreduction surgery followed by chemotherapy. Therefore, a selection as correct as possible of patients in which optimal cytoreduction is possible would avoid unnecessary explorative laparotomies and delay in starting chemotherapy, while at the same time improve on the number of patients who undergo neoadjuvant chemotherapy, but who would have benefit from primary surgery. However, we do not possess decisive tools to make this management decision with certainty.

Thus far, the accuracy of conventional staging including physical examination, ultrasound, tumor markers and radiologic assessment by computer tomography, magnetic resonance or positron emission tomography, in order to preoperatively identify patients with unresectable tumours, which could be spared an unnecessary laparotomy, has been unsatisfactory. Several preoperative predictive models have been proposed based on clinical and CT findings and serum tumor markers. The validity of four predictive models based on preoperative CT scans, published previously by Nelson, Bristow, Dowdy and Qayyum [5-8], was evaluated in a multicentre study by Gemer et al. [9], reporting a sensibility to predict suboptimal cytoreduction ranged between 64% and 79% meaning 21% to 36% of the patients would be submitted to unnecessary laparotomy. Apart from Dowdy’s criteria [7], the accuracy rates of CT predictors of suboptimal cytoreduction in the original cohorts could not be confirmed in this cross validation, leading to a lack of wide acceptance. The use of preoperative CA-125 has also been evaluated in this setting, with a cut-off value of 500 U/mL used by most researchers. Combined predictive models have also been reported. In a prospective, non-randomized, multicenter trial of patients who underwent primary cytoreduction for stage III-IV ovarian, fallopian tube, and peritoneal cancer, Suidan et al. [10], identified nine criteria associated with suboptimal cytoreduction, three clinical and six radiologic and developed a predictive model in which the suboptimal rate was directly proportional to a predictive value score. This model had an overall predictive accuracy of 0.758.
Given the poor predictive value of tumor markers and radiologic evaluation to determine who is a candidate for primary cytoreduction surgery, the direct assessment of the abdominal cavity is needed. Laparotomy is the most accurate way to evaluate tumor burden, but it is an aggressive approach for a staging procedure and initiation of chemotherapy tends to be delayed compared with laparoscopic staging [11]. The idea of using laparoscopy to assess operability in advanced ovarian cancer patients arose from the concept that the vast majority of unresectable advanced ovarian cancer is not optimally cytoreduced due to the presence of extended mesenteric implants, large involvement of small bowel or upper abdomen, such as unresectable liver metastasis, which are parameters easily assessable by laparoscopy. Advantages of laparoscopy include direct and magnified vision of the anatomy and of the metastasis of the upper abdomen, possibility to obtain tissue for definitive diagnosis, shorter operative time, less morbidity and quicker initiation of chemotherapy. However, a gynecologic oncologist should make this assessment before neoadjuvant chemotherapy is administered.

QUALITATIVE LAPAROSCOPIC ASSESSMENT OF ADVANCED OVARIAN CANCER PRIMARY CYTOREDUCTION

In a multicentre study of 77 patients with stage III-IV ovarian cancer, Vergote et al. first reported in 1998 [12] the use of open laparoscopy in evaluating operability in advanced ovarian cancer. 28 patients were selected for primary surgery and the cytoreductive surgery was optimal (<0.5 cm largest residual tumour) in 79% of these 28 patients.

A prospective study of 64 patients with suspected advanced ovarian or peritoneal cancer was designed by Fagotti et al. [13] to investigate the role of laparoscopy in predicting chances of optimal cytoreductive surgery. A subjective clinical and radiological judgment of possible optimal cytoreduction was performed preoperatively and then, all patients were submitted to both open laparoscopy and standard laparotomy. As expected, the number of not valuable parameters in the laparoscopic group was higher than in the laparotomy one. Laparoscopy was not helpful in defining the possibility of optimal surgery in 13/64 patients. However, the presence of peritoneal or diaphragmatic carcinomatosis and mesentry disease were completely identified by laparoscopy. On the other hand, the state of lymph nodes was the least accurate parameter investigated by laparoscopic approach. A comparison on the surgical outcome estimation according to clinical-radiologic, laparoscopic and combined clinical-radiologic-laparoscopic versus laparotomy evaluation was performed. Laparoscopy predicted suboptimal debulking in 100% of cases, while the conventional staging assessed it only in 73% of cases. The rate of unnecessary laparotomy due to suboptimal debulking was 13% for both the conventional evaluation and the laparoscopic one and it was not improved by the combination of the clinical-radiologic and laparoscopic estimation. As a conclusion, the patients considered eligible for primary cytoreductive surgery after the conventional staging would probably not benefit of a laparoscopy, which seems not to add any information.
In 2006, Deffieux et al. reported the use of explorative laparoscopy in 15 patients presenting advanced ovarian cancer whose preoperative clinical and radiologic evaluation was unsatisfactory to define the possibility of achieving a complete cytoreduction [14]. Unresectable carcinomatosis was defined as one or more of the following conditions: massive involvement of liver pedicle, infiltration of the diaphragmatic muscle near the sub-hepatic vessels, massive involvement of the bowel or mesentery. From the 10 patients considered to have resectable disease at laparoscopy, complete cytoreduction was achieved of laparotomy in 9 cases (90%). Although this study involves few patients, it confirms that laparoscopy can help avoid unnecessary laparotomy in selected cases when there is inadequate information from conventional staging.

In a series of 87 patients with advanced ovarian cancer who underwent diagnostic open laparoscopy and from whom 61% were considered candidates for complete primary cytoreduction surgery, Angioli et al. [15] reported complete primary cytoreductive surgery in 96% of patients whose diagnostic open laparoscopy showed resectability to absent residual tumor. Prior to introduction of staging laparoscopy by this group, primary debulking surgery was attempted in 95% of patients with an optimal cytoreduction rate of 46%.

Brun et al. [16] reported a lower percentage of complete primary cytoreduction surgery after laparoscopic evaluation of 55 patients with stage III/IV ovarian cancer, of whom 26 (47.2%), all with stage III cancer were treated with primary debulking surgery. In this group, complete cytoreduction was achieved only in 54% of cases and optimal cytoreduction in 69%. No attempt was made to compare the predictive value of imaging methods and laparoscopy.

Another retrospective study by Nezhat et al. [17] assessed the value of laparoscopy in selected patients with advanced ovarian, fallopian tube or peritoneal cancer, candidates for optimal primary cytoreduction surgery. Only the patients who were found eligible by clinically and by imaging techniques were submitted to exploratory laparoscopy. 32 patients underwent laparoscopic evaluation and 11 (34.3%) of them also to laparotomy for cytoreduction, with 72.7% optimal reduction.

**LAPAROSCOPY-BASED PREDICTIVE MODEL**

Standardization is essential to obtain comprehensiveness and reproducibility in surgery. The management of ovarian cancer and the assessing of the intra abdominal extension and resectability are no exception to this rule. FIGO classification does not distinguish localized carcinomatosis and easily resectable from extensive intra abdominal disease inaccessible to complete surgical resection. It is essential to develop more precise tools today to assess the extension of carcinomatosis. Several staging scores have been described for ovarian cancer, with two major interests: to be a prognostic factor and to evaluate the possibility of complete cytoreduction.
Fagotti Score

After publishing in 2005 a study demonstrating that exploratory laparoscopy could be a reliable alternative to laparotomy for assessing the chance of optimal cytoreduction surgery in advanced ovarian cancer, Fagotti et al. reanalyzed the same population in order to develop a laparoscopy-based quantitative model, which could be validated by other research groups [18]. In 64 patients who underwent both laparoscopy and standard laparotomy, sequentially, 8 laparoscopic features were investigated as indicators of surgical outcome, of which 7 met the criteria of specificity, positive predictive value, negative predictive value and accuracy established for inclusion: presence of omental cake, extensive peritoneal and diaphragmatic carcinomatosis, stomach and bowel infiltration, liver metastasis and mesenteric retraction. Each of these laparoscopic features received a predictive index score of 2 and a total Predictive Index Value (PIV) for each patient was calculated based on their presence or absence. At a cut-off PIV ≥8, no patients likely to be optimally cytoreduced would be left unexplored, but the rate of unnecessary laparotomy increases up to 30%.

The same group led by Fagotti undertook a subsequent study published in 2008 [19] to validate the performance of the previous described laparoscopic model in a larger prospective series of advanced ovarian cancer patients. 113 patients underwent both laparoscopy and standard longitudinal laparotomy. In both approaches the same 7 parameters defined in the previous mentioned study [13] were evaluated. By summing the scores relative to all these parameters, the laparoscopic total Predictive Index Value (PIV) has been calculated. The accuracy of laparoscopy compared to laparotomy was >85% for almost all features, with the worst performance for bowel and stomach infiltration. Median PIV was 8. As in the previous study, the primary endpoint of the laparoscopic model was to minimize the rate of inappropriate unexploration. 49.6% of patients were optimally cytoreduced. At a predictive index cut-off of 8, the probability of optimally resecting the disease is 0, whereas the rate of performing unnecessary laparotomy is 40.5%, therefore the model has provided the same results as in the previous series [13], except for the higher percentage of unnecessary laparotomy, 40.55 vs. 30%.

In a retrospective study with 55 patients with high suspicion of advanced ovarian cancer and without previous chemotherapy, Brun et al. [20] validated this prediction model and also suggested a simplified one including only 4 parameters: diaphragmatic carcinosis, mesenteric retraction, stomach infiltration and liver metastasis. Using the Faggotti Predictive Index Value (PIV), 11% of patients with a predictive index value of ≥8 had an optimal cytoreduction, while 56% of patients with a score <8 had a suboptimal resection. In this study the modified laparoscopic model using only 4 parameters was at least as accurate as Fagotti’s score in selecting patients for optimal cytoreductive surgery, with 78% of patients with a score <4 optimally resected.
Updated Fagotti Score

Since the Fagotti laparoscopic predictive index was designed and validated before the introduction of upper abdominal surgery in the surgical management of advanced ovarian cancer, the same group reports on the use of an updated Fagotti score after this change in cytoreductive surgery [21]. In a retrospective analysis, Petrillo et al. were interested in whether a predictive index $>10$ could be a better marker to discriminate between complete and incomplete debulking. They retrospectively analyzed 234 patients with advanced ovarian cancer who received Staging Laparoscopy (S-LPS) followed by a maximal laparotomy surgical effort, after the introduction of upper abdominal surgery. S-LPS was not feasible in 3, 6% of patients due to adhesions. S-LPS identified the presence of mesenteric retraction and extensive small bowel involvement as criteria of unresectability in around 10% of the patients, directly selecting these women for neoadjuvant chemotherapy without a laparotomy attempt of primary debulking. In the model the six following laparoscopic parameters were included: massive peritoneal involvement and/or a miliary peritoneal carcinomatosis; wide spread infiltrating carcinomatosis and/or confluent nodules to the most part of the diaphragmatic surface; tumour diffusion along the omentum up to the large stomach curvature, possible large/small bowel resection (excluding recto-sigmoid involvement); neoplastic involvement of the stomach, and/or lesser omentum, and/or spleen; liver surface lesions larger than 2 cm. All these parameters reached specificity $\geq75\%$, a PPV $\geq50\%$, a NPV $\geq50\%$ and accuracy $\geq60\%$ to identify incomplete cytoreduction, and, as a consequence, a predictive score of 2 was assigned to all of them. A high agreement between S-LPS and laparotomy findings was observed, ranging from 88.6% for bowel infiltration and 97% for peritoneal carcinomatosis. The laparoscopic predictive index model was designed to minimize the rate of inappropriate unexploration and the cut-off value for this goal was a PIV $\geq10$, which corresponded to a PPV of 100%. Using this cut-off value, 33.2% of the patients were submitted to inappropriate laparotomy, as complete debulking was not achieved. The authors conclude that a future predictive model, which will reduce the suboptimal debulking while maintaining a PPV of 100%, is needed.

PCI Score Validation

Gouy et al. [22], in a prospective study with 29 patients with advanced ovarian cancer undergoing a laparoscopy and complete cytoreductive surgery by laparotomy the same day, evaluated the accuracy and reproducibility of the Peritoneal Cancer Index (PCI), described by Sugarbaker [23]. The PCI score was evaluated by a senior surgeon and by a junior surgeon at three time points on the same day: during laparoscopy, at the beginning of the laparotomy and at the end of it. The study showed that the PCI score is reproducible with high concordance between 2 surgeons during laparoscopy and laparotomy after a short learning curve. It also showed that the laparoscopic PCI score was underestimated by 2 points compared to the initial laparotomy and by 3 points compared to the end of the laparotomy, information which the authors concluded
that would be useful in the future in order to define a cut-off for the laparoscopic PCI score that would contraindicate cytoreductive surgery. In this study the use of laparoscopic PCI score to evaluate the resectability of the disease was not assessed.

**COCHRANE REVIEW**

In 2014, a Cochrane Review [24] having as objective to determine the value of open laparoscopy in predicting the resectability of advanced ovarian cancer was published. Seven studies, with a total of 364 patients suspected of advanced ovarian cancer (FIGO stage IIB-C, IIIA to C, IV) scheduled for primary debulking surgery after conventional staging, were included. The test under evaluation was an additional open diagnostic laparoscopy and the reference standard was the laparotomy. In all studies the patients received a laparotomy when the laparoscopy indicated resectable disease. Between 27% and 64% of the women had too extensive disease to warrant laparotomy. The other 36% to 73% underwent laparotomy. The laparoscopy had a false negative test result in 4% to 31% of these patients, meaning they received unnecessary laparotomy. In the two studies that performed a laparoscopy and a laparotomy in all included patients, all women diagnosed at laparoscopy with disease too extensive to be optimally debulked were diagnosed as indeed having unresectable disease at laparotomy. Given the heterogeneity of the clinical and radiological staging criteria used for inclusion, the authors of the review were not able to draw conclusions about the additional value of laparoscopy after conventional staging. Other weaknesses of the review were the small number of studies which all suffered of bias or applicability concern, heterogeneous population and difference in endpoint of debulking surgery. As a conclusion, based on available data, laparoscopy should not be a standard procedure in advanced ovarian cancer staging and using a prediction model does not increase sensitivity.

**IMPACT OF THE USE OF STAGING LAPAROSCOPY ON PROGNOSIS OF PATIENTS WITH ADVANCED OVARIAN CANCER**

To determine the role of Staging Laparoscopy (S-LPS) in advanced ovarian cancer management, it was necessary to also investigate whether the introduction of this approach would have a negative impact on prognosis. For this purpose Fagotti et al. [25] analysed retrospectively 300 consecutive patients with IIIC/IV ovarian cancer submitted to staging laparoscopy that were included in a retrospective study published in 2013. No complications related to the surgical procedure were registered. 148 (49.3%) women were considered suitable for primary debulking surgery and the remaining 152 (50.7%) were submitted to neoadjuvant chemotherapy, based on the previous described Fagotti laparoscopic scoring system, using a cut-off value of 8 [18,19]. All women were assessed for intraperitoneal extension of disease and chances of optimal cytoreduction only by laparoscopy, without other preoperative criteria. The percentages of complete (residual tumor, RT=0) and optimal (RT<1cm) cytoreduction of PDS and Interval Debulking Surgery (IDS) were 62.1% and 57.5%, 27.7% and 22.5%, respectively. The median progression free survival in women with RT=0 at PDS was 25 months. The authors conclude that including S-LPS in a tertiary referral center for the management AEOC does not appear to have a negative impact in terms of survival.
CURRENT STUDIES ON DIAGNOSTIC LAPAROSCOPY ADDED VALUE IN ADVANCED OVARIAN CANCER STAGING

As studies about the added value of additional laparoscopy in advanced ovarian cancer staging are lacking, in Netherlands Rutten et al. [26] designed a multicentre prospective randomized trial which aims to assess whether adding laparoscopy to the conventional staging of patients suspected of advanced ovarian cancer prevents unsuccessful laparotomies. Patients planned for Primary Debulking Surgery (PDS) after conventional staging consisting of medical history, physical examination, ultrasound, CA 125 and CEA serum levels, chest X-ray and abdomino pelvic CT, will be randomized to primary debulking surgery or an additional diagnostic laparoscopy followed by either PDS or NACT and interval debulking surgery. The primary outcome measure is the rate of suboptimal debulking surgery. Secondary outcome measures will be progression-free and overall survival, the number of complete and optimal debulking surgery, costs and quality of life. The trial protocol was published in 2012 and it is ongoing.

Fagotti et al. [19] described an objective predictive score with the purpose of minimizing the rate of inappropriate unexploration (the false positive results), but with a high percentage of unnecessary laparotomy, 30% [13] and 40.5% [20]. Since at present the false positive results of the diagnostic laparoscopy are not a main concern, as it was showed by Vergote et al. [12] that survival after neoadjuvant chemotherapy and interval surgery is not considered inferior to primary debulking surgery followed by chemotherapy, we must focus on lowering the percentage of unnecessary laparotomy.

As only one study [13] evaluated the additional value of diagnostic laparoscopy compared with conventional staging to assess the resectability of advanced ovarian cancer, more prospective studies are needed in order to answer the question whether diagnostic laparoscopy can avoid unnecessary laparotomy. Some abdominal regions are difficult to assess by laparoscopy: the retrohepatic area, tendinous part of the diaphragm, suprahepatic veins and retroperitoneal space, and for their evaluation imaging plays an important role in avoiding unnecessary laparotomy. The presence of adhesions may impede the evaluation of the entire abdominal cavity. The radiologic exploration is able to balance these laparoscopic disadvantages, so it is imaginable that the integration of laparoscopic evaluation and radiologic assessment could achieve the reduction in the number of patients submitted to suboptimal laparotomy.

Although, based on the recent Cochrane Review, laparoscopy should not be a standard procedure in advanced ovarian cancer staging and using a prediction model does not increase sensitivity [26], the most recent National Comprehensive Cancer Network guideline accepts the use of laparoscopy as a tool in the management of ovarian cancer, as it states: “Minimally invasive surgical approaches may be useful when evaluating whether maximum cytoreduction can be achieved in patients with newly diagnosed or recurrent ovarian cancer. If clinical judgment
indicates that maximum cytoreduction cannot be achieved, neoadjuvant chemotherapy should be considered”. In France, as recommended in the Nice Saint-Paul-de-Vence Consensus [27], laparoscopy is considered the best tool to evaluate resectability before primary cytoreductive surgery and the use of a predictive score (PCI or Fagotti) is advised.

CONCLUSION

Advanced ovarian cancer has been historically excluded of minimal invasive techniques. Nevertheless, to achieve better prediction for primary debulking surgery laparoscopy has become a useful tool to be considered by gynaecological oncologists. Future investigation should focus on the combination of the clinical, radiologic and laparoscopic information, in order to determine the best therapeutic strategy for each patient.

References


