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A Laparoscopy-Based Score To Predict Surgical Outcome in Patients With Advanced Ovarian Carcinoma: A Pilot Study

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Background: Our objective was to set up a more objective quantitative laparoscopy-based model in predicting the chances of optimal cytoreductive surgery in advanced ovarian cancer patients.

Methods: Sixty-four advanced ovarian cancer patients were submitted to both laparoscopy and standard longitudinal laparotomy sequentially, to define the chances of optimal debulking surgery (residual disease ≤1 cm). Three patients could not be evaluated by laparoscopy because of the presence of multiple and tenacious adherences. Sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy were calculated for each laparoscopic parameter. On the basis of the statistical probability of each factor to predict surgical outcome, seven laparoscopic features were selected for inclusion in the final model. Each parameter was assigned a numerical score based on the strength of statistical association, and a total predictive index value was tabulated for each patient. Receiver operating characteristic curve analysis was used to assess the ability of the model to predict surgical outcome.

Results: After debulking surgery, 41 (67.2%) of 61 patients were left with optimal residual disease. The presence of omental cake, peritoneal carcinosis, diaphragmatic carcinosis, mesenteric retraction, bowel and/or stomach infiltration, and liver metastases satisfied the basic inclusion criteria and were assigned a final predictive index value of 2. In the final model, a predictive index score ≥8 identified patients undergoing suboptimal surgery with a specificity of 100%. The positive predictive value was 100%, and the negative predictive value was 70%.

Conclusions: The reliability of laparoscopy in assessing the chance of optimal cytoreduction can be improved by using a simple scoring system.

Key Words: Predictive index score—Laparoscopy—Ovarian cancer—Cytoreduction.

Residual disease after primary surgery still represents one of the most important prognostic factors in advanced ovarian cancer patients.[1] Several studies have been published in the last few years investigating preoperative parameters, particularly radiological features, that could be able to predict the chances of optimal cytoreduction in this group of patients, with a wide variety of results.[2–4]

To explore alternative approaches to this issue, we previously demonstrated that exploratory laparoscopy could be a suitable and reliable alternative to laparotomy for assessing the chance of optimal cytoreduction (residual disease [RD] ≤1 cm) in clinically advanced ovarian cancer cases.[5] However, because of the intrinsic limits of the subjective evaluation, when we considered the possibility of extending this proce-

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dure to other institutions, it seemed quite difficult to share the final laparoscopic decision making on possible/impossible optimal cytoreduction. Other relevant issues were related to the surgeons' experience and skill in recognizing laparoscopic criteria of unresectability and to their subjective aggressiveness and background in the field of primary cytoreduction.

The aim of this study was to set up a more objective quantitative model, likely to be shared and possibly validated by other research groups, thus making this approach more reliable in predicting the chances of optimal cytoreductive surgery in patients with advanced ovarian cancer. Therefore, according to the confidence of this procedure, as previously demonstrated,[5] we reanalyzed the same study population to develop an independent laparoscopic model based on a scoring system.

PATIENTS AND METHODS

This study included the population accrued between March and November 2003 at the Division of Gynecologic Oncology of the Catholic University of Rome in the pilot study regarding the role of laparoscopy in assessing the chance of optimal cytoreductive surgery in patients with advanced ovarian cancer.[5] Inclusion criteria were the following: clinical and instrumental (computed tomography, ultrasonography, or both) suspicion of diffuse disease of ovarian or peritoneal origin (i.e., presence of omental cake; cul-de-sac nodularity; fixed mass; peritoneal bulky carcinomatosis; diaphragmatic bulky disease; tumor involvement of the spleen, liver, bowel, or mesentery; or bulky lymph nodes). However, no clinical or radiological parameters, such as Gynecologic Oncology Group performance status, preoperative serum CA-125 levels, or the presence of large-volume ascites, were considered when the chances of optimal cytoreductive surgery were assessed in this study. All patients signed written informed consent agreeing to undergo all the procedures described and for their data to be used prospectively.

Sixty-four patients underwent both laparoscopy and standard vertical laparotomy, sequentially. Laparoscopic surgery was performed as previously described.[5] During each approach, patients were evaluated for optimal debulking. In the absence of standard criteria of unresectability, assessed by both laparoscopy and laparotomy (i.e., foreshortened bowel/mesentery, diaphragmatic bulky disease, portal triad disease, deep vascular infiltration by metastatic lymph nodes, or unresectable upper abdominal metastases[6,7]), an optimal debulking was attempted.

In particular, the presence of diaphragmatic bulky disease observed by laparoscopy was not considered as a single parameter of unresectability by itself but as information regarding massive disease possibly involving the retrohepatic area, the tendineous part of the diaphragm, or the suprahepatic veins. Moreover, lymph nodal status was assessable by laparoscopy in a very low percentage of cases (8%) in this series.[5] As a consequence, although deep vascular infiltration by metastatic lymph nodes can be a reason for unresectability in advanced ovarian cancer patients, lymphnodal evaluation was excluded from the analysis because of the failure of laparoscopy to carefully assess the retroperitoneal space in this group of patients.

Standard surgery (including total abdominal hysterectomy with bilateral salpingo-oophorectomy; appendectomy; total infragastric omentectomy; peritonectomy limited to the pelvis, the paracolic gutters, and the infiltrated diaphragmatic areas; bowel resection limited to the rectosigmoid, as necessary; and removal of bulky lymph nodes to the infrarenal para-aortic level) was completed to a minimal residual disease <1 cm. Optimal debulking was judged unfeasible in 18 patients; in these cases, cytoreductive surgery was abandoned for neoadjuvant chemotherapy followed by interval debulking surgery.

Selection of Laparoscopic Features

Eight laparoscopic features were investigated as potential indicators of surgical outcome: presence of ovarian masses (unilateral or bilateral); omental cake with tumor diffusion to the small and large curvature of the stomach; extensive carcinomatosis of the diaphragm, peritoneum, bowel, and liver; and large- and/or small-bowel infiltration necessitating resection. Moreover, the foreshortened mesentery of the small bowel was evaluated by folding back the various intestinal segments were possible, whereas lymph nodal status, which was assessable in a very low percentage of cases (8.2%), was not included in the scoring system (Table 1).

Data Analysis

Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall accuracy were calculated for each laparoscopic parameter. Sensitivity was defined as the number of suboptimally debulked patients who were correctly

TABLE 1. *Laparoscopic parameters assigned a predictive index score*

Predictive index parameter[a]	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	Point value
Ovarian masses (unilateral or bilateral)	60	29	29	60	39	0
Omental cake	57	81	63	77	73	2
Peritoneal carcinosis	69	79	67	81	75	2
Diaphragmatic carcinosis	69	84	65	80	80	2
Mesenteric retraction	50	95	85	77	78	2
Bowel infiltration	70	89	78	84	82	2
Stomach infiltration	11	100	100	82	82	2
Liver metastases	35	94	75	76	76	2

PPV, positive predictive value; NPV, negative predictive value.
[a] Lymph-nodal status was not included for low percentages of assessment.

identified (true positives) divided by the total number of suboptimally debulked patients (true positives + false negatives). Specificity was defined as the number of optimally cytoreduced patients who were correctly identified (true negatives) divided by the total number of optimally cytoreduced patients (true negatives + false positives). PPV was calculated as the number of true positives divided by the total number of positive results (true positives + false positives), and NPV was defined as the number of true negatives divided by the total number of negative results (true negatives + false negatives). Accuracy was calculated as the number of true positives plus true negatives (total number correct) divided by the total number of patients studied.

Three minimum criteria were chosen for inclusion of each laparoscopic feature in the final model: specificity ≥75%, PPV ≥50%, and NPV ≥50%.[4] A specificity cutoff value of 75% was selected to minimize the number of false-positive results (i.e., patients predicted to have a suboptimal outcome but who would in fact have an optimal surgical result). Laparoscopic findings meeting these criteria were assigned a predictive index score of 1. To maximize the number of patients whose surgical status was correctly identified by the model, an additional predictive index point was assigned to the parameters that, in addition to the above-mentioned criteria, had also an overall accuracy of > 60% in predicting surgical outcome. Finally, each laparoscopic feature, except for the presence of ovarian masses, received a predictive index score of 2 (Table 1).

By using this scoring system, a total predictive index value (PIV) for each of the assessable patients was tabulated (Fig. 1). Sensitivity, specificity, PPV, NPV, and accuracy were calculated for each PIV of ≥0 through 10 (Table 2). Receiver operating characteristic curve analysis was used to assess the ability of the model to identify patients who were most likely to have optimal or suboptimal surgical results.[8]

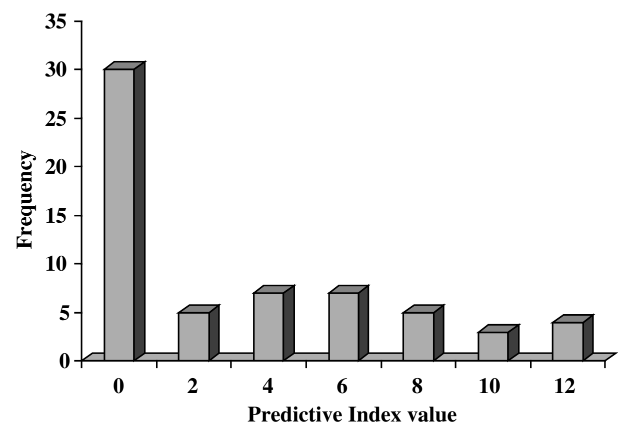

FIG. 1. Frequency distribution of predictive index value for 61 patients with advanced ovarian carcinoma.

RESULTS

Patient characteristics are listed in Table 3. Three cases (4.7%) could not be evaluated by laparoscopy because of the presence of multiple and tenacious adherences hindering access to the abdominopelvic cavity. They could not receive any predictive index score and were excluded from the study. After debulking surgery, 41 (67.2%) of 61 patients were left with optimal residual disease (RD ≤1). The median PIV in 61 laparoscopically assessable patients was 0 (range, 0–6) in RD ≤1 cm and 6 (range, 4–12) in RD > 1 cm.

Four cases had unresectable, bulky para-aortic lymph nodes deeply infiltrating the aortic and/or the vena cava wall. Three cases (75%) were identified before surgery by computed tomographic scan, whereas no case was recognized by laparoscopy.

TABLE 2. *Predictive index model*

PIV	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	Unnecessarily explored (%)	Inappropriately unexplored (%)
0	78	66	58	83	70	17	42
≥2	74	76	65	83	75	17	35
≥4	61	87	74	79	77	21	26
≥6	43	95	83	73	75	27	17
≥8	30	100	100	70	74	30	0
≥10	17	100	100	66	69	34	0

PIV, predictive index value; PPV, positive predictive value; NPV, negative predictive value.

TABLE 3. *Clinicopathologic characteristics of the patients*

Variable	Data
No. of patients	64
Age, y (mean ± SD)	57.4 ± 12.7
CA-125 level, U/mL (mean ± SD)	790 ± 1680
GOG performance status	
0	27 (42.2%)
1	25 (39.1%)
2	10 (15.6%)
3	2 (3.1%)
Primary diagnosis	42 (65.6%)
Interval debulking surgery	19 (29.7%)
Recurrence	3 (4.7%)
Ascites	
Yes	20 (31.3%)
No	44 (68.7%)
Histotype	
Benign	6 (9.4%)
Serous	42 (65.6%)
Endometrioid	3 (4.7%)
Mucinous	1 (1.6%)
Clear cell	2 (3.1%)
Undifferentiated	2 (3.1%)
Sarcoma	1 (1.5%)
Other	7 (11%)
Grade (only ovarian cancer)	
1–2	7 (11%)
3	43 (67.2%)
FIGO stage (only ovarian cancer)	
I–II	9 (17.6%)
III–IV	42 (82.4%)

GOG, Gynecologic Oncology Group; FIGO, International Federation of Gynecology and Obstetrics.

The presence of ovarian masses failed to reach the minimum criteria for inclusion because of low specificity (29%) and PPV (29%), and it was not assigned any predictive index score. However, the presence of omental cake; peritoneal, diaphragmatic, and superficial liver carcinosis; mesenteric retraction; and bowel and/or stomach infiltration satisfied the basic inclusion criteria (see Patients and Methods) and were subjectively assigned a predictive index score of 1. All these parameters had also an overall accuracy of ≥60% and were therefore assigned a final predictive index score of 2 (Table 1).

By using this scoring system, individual PIVs were tabulated for each of the 61 patients according to the presence or absence of some specific features and ranged from 0 to 12 points (Fig. 1). Individual PIVs demonstrated the largest concentration of cases in the group with a predictive index of 0 (n = 30). The sensitivity, specificity, PPV, and NPV and the accuracy of each PIV of 0 through 10 are shown in Table 2. The discriminating performance of the PIV was confirmed by a receiver operating characteristic curve analysis in which the area under the curve was .797 (data not shown).

The overall accuracy rate of the model in predicting surgical outcome was approximately 75% (range, 74%–77%), corresponding to a wide range of PIV (from ≥2 to ≥8). In this situation, sensitivity and specificity ranged from 74% to 30% and from 76% to 100%, respectively. In other words, the percentage of cases correctly identified as suboptimal surgery (sensitivity) increased with the PIV cutoff level, and the likelihood that a patient would have a suboptimal surgical result (PPV) increased to 100% in the case of a PIV ≥8 (P = .00056). However, the highest NPV, that is, the likelihood of having an optimal cytoreduction, was 83% and corresponded to a PIV of 0 or 2.

As previously discussed,[5] we included two other measures we deem more clinically relevant in this evaluation: (1) the rate of inappropriate lack of exploration, i.e., the ratio of patients thought to have unresectable disease but who will in fact undergo optimal surgery if operated on, and (2) the rate of unnecessary exploration, i.e., the ratio of patients thought to have resectable disease but who will actually be left with suboptimal residual disease. The calculated values for each PIV of 0 through 10 are listed in Table 2.

DISCUSSION

This is the first study that supports the ability of a PIV, based on laparoscopic rather than radiological features, to predict the chance of optimal cytoreduction in clinically advanced ovarian cancer patients. In this study, we calculated a PIV for each patient after assigning a score to the presence or absence of specific features documented at laparoscopy. Each laparoscopic parameter used in the model was not chosen on the basis of a direct correlation with the chances of optimal cytoreduction, but rather to fully describe the intra-abdominal diffusion of the disease. Thus, in no case they should be deemed as indices of inoperability by themselves: only the combination of them, expressed by the PIV, could be considered as an indirect sign of the biological aggressiveness of the tumor.

The association between each PIV and the chance of performing an optimal debulking was analyzed to provide clinicians with more useful parameters in terms of decision making, such as the rate of inappropriate lack of exploration and the rate of unnecessary exploration. The potential clinical usefulness of such a model is represented by a certain degree of flexibility to adjust for acceptable rates of unnecessary exploration and inappropriate lack of exploration, based on patient desire, surgeon experience, and the risk of surgical morbidity. For instance, if a very low rate of inappropriate lack of exploration is required, then the PIV ≥8 proves to be the most appropriate, because its application will result in no risk of leaving unexplored patients likely to be optimally cytoreduced, despite an obvious increase in the rate of unnecessary exploration (up to 30%). Alternatively, in the case of some specific clinical conditions, such as the presence of various comorbidities and poor performance status in elderly patients, in whom a less aggressive surgical approach can be an option, a low rate of unnecessary exploration might be advisable. In this case, one should select a PIV of ≤2, because the higher risk of inappropriate lack of exploration (35%–42%) is likely to be balanced by the documented efficacy of neoadjuvant chemotherapy in this type of tumor.[9–12]

In this context, the variability of the histotype and stage of the disease in the study group should be considered as a common event in clinical practice. In fact, the extension of the disease can be overestimated in a certain proportion of cases by preoperative evaluation, and the histological diagnosis is not usually available before surgery. In these cases, laparoscopy can be a valuable opportunity to obtain a more objective diagnosis of the origin and diffusion of the disease.

As far as the effect of such a model in clinical practice, it could be argued that it might be different according to the relevance of optimal debulking reported in different centers. In this series, all stage I and II and 19 stage III and IV (45%) cases were optimally resected to RD ≤1 cm (total degree of optimal debulking, 55%). Moreover, five cases were debulked to RD ≤2 cm (total degree of cytoreduction, 65%). The percentage of optimal cytoreduction observed in our study does not seem very different from that in the largest series reported in the United States. In particular, a meta-analysis by Bristow et al.[13] on 6885 ovarian cancer patients showed percentages of optimal cytoreduction ranging from 8% to 85%. Although single-institutional series[1] report percentages of optimal debulking up to 98.8%, we believe that this discrepancy can be related both to a different approach to the disease (i.e., a balance between optimal residual tumor and acceptable morbidity) and to the small number of cases in this study. However, in no case can the lower percentage of optimal cytoreduction in our study be ascribed to the use of laparoscopy, because all patients were submitted to laparotomy before the final judgment of optimal resectability. Finally, it can be argued that laparoscopy in advanced ovarian cancer could be useless for surgeons achieving a very high percentage of optimal cytoreductive surgery, whereas it could represent a valuable opportunity for groups that sustain a less aggressive approach. In fact, it could obtain a more direct anatomic view of the extension/resectability of the disease and could be an easy way to obtain a tissue sample for histological diagnosis, at a minimum.

In this context, the advantages of a minimally invasive surgical procedure are easily conceivable, such as either to quickly switch to an open laparotomy in the case that optimal cytoreduction is judged achievable or to quickly start neoadjuvant chemotherapy in the case that the tumor is deemed unresectable.

As far as the learning curve is concerned, exploratory laparoscopy for this type of study can be considered a very easy approach: our technique has been rather uniform over the years. We soon concluded that the retroperitoneal space could not be properly evaluated by this type of approach, and we focused our efforts on the assessment of intraperitoneal diffusion of the disease. In particular, the confidence with this technique has changed our interpretation of laparoscopic features over time. For instance, the presence of a massive diaphragmatic tumor in the assessable laparoscopic area can be interpreted as an indication of disease, possibly involving the retrohepatic area, the tendineous part of the diaphragm, or the suprahepatic veins, in most cases. Thus, surgery can be scheduled according to the laparoscopic results by hypothesizing the potential need for extended resections and the expected rate of morbidity.

Preoperative staging laparoscopy is a well-known procedure for disease of different origins, such as gastric or cervical cancer,[14–17] to define the best medical, surgical, or integrated treatment for advanced cancer patients. Conversely, few data are available in the present literature for ovarian cancer.[5,9] The largest amount of information belongs to the field of radiology, which deeply investigated the possibility of detecting bulky disease at specific nonresectable sites by computed tomographic and magnetic resonance imaging techniques to avoid unnecessary laparotomies in patients with clinically advanced ovarian cancer. However, the results of these studies vary widely according to different centers, the number of cases, selection of patients, and imaging features and still do not reach acceptable percentages when corrected for these biases.[2–4,18,19]

We previously published the results achieved by the subjective laparoscopic evaluation in terms of chances of optimal cytoreduction in clinically advanced ovarian cancer.[5] The aim of this study was to set up a more objective quantitative model that will likely be shared and possibly validated by other research groups. Improvements in the predictive performance of this model will be anticipated by both the prospective use of this scoring system and the integration with clinical and radiological evaluation. A pilot study is now ongoing in our division to address these issues.

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