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A laparoscopic risk-adjusted model to predict major complications after primary debulking surgery in ovarian cancer: A single-institution assessment

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HIGHLIGHTS

- Prediction of postoperative complications may be helpful to individualized the primary treatment in AEOC women.
- AEOC patients with high risk for postoperative complications could be identified preoperatively.
- This study develops a laparoscopic adjusted score to predict post-operative complications in AEOC patients undergoing PDS.

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ABSTRACT

Objective. To develop and validate a simple adjusted laparoscopic score to predict major postoperative complications after primary debulking surgery (PDS) in advanced epithelial ovarian cancer (AEOC).

Methods. From January 2006 to June 2015, preoperative, intraoperative, and post-operative outcome data from patients undergoing staging laparoscopy (S-LPS) before receiving PDS (n = 555) were prospectively collected in an electronic database and retrospectively analyzed. Major complications were defined as levels 3 to 5 of MSKCC classification. On the basis of a multivariate regression model, the score was developed using a random two-thirds of the population (n = 370) and was validated on the remaining one-third patients (n = 185).

Results. Major complication rate was 18.3% (102/555). Significant predictors included in the scoring system were: poor performance status, presence of ascites (>500 cm^3), CA125 serum level (>1000 U/ml), and high laparoscopic tumor load (predictive index value, PIV ≥8). The mean risk of developing major postoperative complications was 3.7% in patients with score 0 to 2, 13.2% in patients with score 3 to 5, 37.1% in patients with score 6 to 8. In the validation population, the predicted risk of major complications was 17.8% (33/185) versus a 16.7% (31/185) observed risk (C-statistic index = 0.790).

Conclusion. This new score may accurately predict a patient's postoperative outcome. Early identification of high-risk patients could help the surgeon to adopt tailored strategies on individual basis.

1. Introduction

Treatment of advanced stage epithelial ovarian cancer (AEOC) consists of primary debulking surgery (PDS) followed by platinum-based chemotherapy, according to several Society guidelines [1,2]. Successful cytoreduction to minimal residual tumor burden is the most important determinant of prognosis [3]. However, extensive surgical procedures to achieve complete tumor resection are obviously associated with postoperative morbidity and mortality, thus fuelling concerns about the optimal balance between efficacy and safety [4,5]. Reported 30-day morbidity after PDS for AEOC ranges from 11 to 67% whereas postoperative mortality rates vary between 0 and 6.7%, with a mean of 2.8% [5]. Moreover, patients with postoperative complications experience delays in initiation of chemotherapy, and may not be able to receive planned therapy, thus showing decreased survival [6]. At present, neoadjuvant chemotherapy (NACT) is the preferred therapy for AEOC patients that have preoperatively identified unresectable disease, stage IV disease,

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high tumor load, significant medical co-morbidities, or poor performance status [7,8], as suggested by recent randomized clinical trials (RCTs) [9–11]. While many studies have focused on predicting the ability to resect tumor to no gross residual disease [12–14], the patient's ability to tolerate surgery without significant morbidity is another important factor in triaging AEOC patients for initial surgical management [15]. Indeed, if patients at high risk for postoperative complications could be identified preoperatively, the clinician could use this information to personalize decisions regarding upfront surgical cytoreduction versus neoadjuvant chemotherapy.

In this context, prediction models for early post-operative morbidity could facilitate computation of surgical outcome in daily clinical practice and provide objective parameters to identify those patients who might benefit from alternative treatment approaches. We currently know few studies on risk-adjustment model for surgical outcome in AEOC patients [7,15–18] and, although recent evidences hypothesized the routinely use of the S-LPS in the work-up of AEOC [19], no papers have investigated the role of S-LPS as objective tool to pre-operatively predict post-operative major complications.

The aim of this study was to develop and validate a simple laparoscopic adjusted score to predict post-operative complications in AEOC patients undergoing PDS.

2. Material and methods

From January 2006 to June 2015 all patients with primary surgery for AEOC were retrieved from the Catholic University of the Sacred Heart (CUSH) of Rome and Campobasso - Registry database.

Patients with AEOC, defined as International Federation of Gynaecology and Obstetrics (FIGO) stage III/IV, who underwent S-LPS followed by PDS, were eligible for this study. General case notes, surgical reports and pathology reports were reviewed.

The study was performed according to the standards outlined in the Declaration of Helsinki. Women gave their written informed consent to their data be used retrospectively for scientific purposes, and the IRB approval was obtained.

Standard preoperative work-up of the patients consisted of patients' history, physical examination, thorax-abdomen and pelvic CT-scan and staging laparoscopy (*S*-LPS) to evaluate intra-abdominal dissemination of tumor according to Fagotti's score [20–23]. Blood samples for measurement of CA125 and routine blood tests were withdrawn within 1 week prior to surgery.

2.1. Surgical procedure

Experienced surgeons who had completed the training program in ovarian cancer surgery performed all surgical procedures. Each surgeon operates on at least 15 patients with AEOC/year, and his/her work is regularly peer reviewed. The laparoscopic score (i.e.: predictive index value, PIV) was calculated based on 7 parameters (presence of omental cake, peritoneal and diaphragmatic extensive carcinomatosis, mesenteric retraction, bowel and stomach infiltration, spleen and/or liver superficial metastasis), according to previous published data [20 − 23].

PDS was performed using an abdominal midline incision and included total hysterectomy, bilateral salpingo-oophorectomy, and omentectomy together with resection of all visible/palpable tumor nodules. The aim of PDS was no residual disease at the end of the procedure. Bowel resection, pancreas resection, splenectomy, diaphragmatic stripping/resection, partial liver resection and lymphadenectomy were performed, if needed to reach such goal.

2.2. Histopathological assessment

Histology was classified as Type I and Type II according to Kurman criteria [24]. Stage of disease was determined according to FIGO guidelines.

2.3. Study parameters and outcome measures

Preoperative parameters for analysis were patients' age, body mass index (BMI), clinical condition according to the Eastern Cooperative Oncology Group (ECOG) performance scale, presence of ascites prior to surgery, CA125 and albumin serum level. Ascites was defined as the presence of pelvic fluid on ultrasound, CT-scan and/or at S-LPS $>500\ cm^3$. Intra-operative laparoscopic parameters were calculated according to previous published data [20–23]. In particular, women were stratified into three different groups: high tumor load (HTL) for PIV ≥8, intermediate tumor load (ITL) for PIV equal to 6 or 4, and low tumor load (LTL) for PIV <4 [21]. Postoperative parameters for analysis were residual disease (RT), histology, and FIGO stage. To assess the extent of surgical procedures, the surgical complexity score (SCS) described by Aletti and colleagues was adopted [8]. Based on number and complexity of the surgical procedures performed, patients were assigned to one of three groups: low-, intermediate and complex surgery. Severity of peri-operative complications was graded on a 1–5 scale according to the Memorial Sloan Kettering Cancer Center (MSKCC) surgical secondary events grading system [25,26]. Major complications were defined for MSKCC grade ≥3 points. More in depth, we intended as major post-operative complications (grade 3 or more) all secondary events required surgical intervention, in line with the original intent of the MSKCC classification. In this context, we consider as major complications not all pleural effusion but only those events required post-operative placement of pleuric drainage. Moreover, according to inner policy of our Institution, we do not routinely proceed to intra-operative insertion of thoracic drainage in case of diaphragmatic surgery in order to spare about 50% of patients with an unnecessary and/or uncomfortable procedure [11,27]. Operative mortality was defined as in-hospital death (irrespective of the duration of stay) or death occurring within 30 days after surgery (grade 5). The primary outcome measure was 30-day morbidity. Patients were discharged if meeting the following criteria: absence of fever (<37.5 °C) for >48 h, regular blood parameters, good pain control with oral analgesics, adequate oral food intake and mobilization.

After PDS, women received platinum-based chemotherapy for a planned six cycles. Initiation of chemotherapy was defined as the time until receipt of the first cycle of chemotherapy after surgery. Since the overall survical (OS) could depend from several factors, such as different protocols of chemotherapy or surgery at the time of recurrence, we focused our attention on progression free survival (PFS), which seems mainly related to the primary management of the disease and its related complications. Progression-free survival (PFS) was defined as the time interval from date of S-LPS to the date of recurrence determined by CA-125 serum levels and/or CT scan.

2.4. Statistical analysis

Descriptive data are reported as mean (standard deviation), median (range) or number of patients and percentage. Categorical variables were compared by the Chi-square test, continuous variables by the Student's *t*-test and the nonparametric Mann–Whitney *U* test. The significant level was set at 0.05. To identify the predictive parameters to include in the scoring system, a univariate analysis using major complications as dependent variable was performed. To obtain a simple and easily applicable pre-operative score, the number of potential predictors was a priori restricted to the parameters with the best performance ($p < 0.2$) at multivariate analysis. Overlapping factors were removed based on their strong correlation and subsequent overfitting risk (i.e. albumin vs ascites and SCS vs. laparoscopic tumor load). A standard approach to develop the prediction score was utilized [28–30]. The study population was randomly divided in a “derivation group” ($n = 370$) representing two-thirds of overall patients, and in a “validation group” ($n = 185$).