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Is complete cytoreductive surgery feasible in this patient with ovarian cancer?

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ABSTRACT

Background: Post-operative residual tumor size is the main prognostic factor in advanced epithelial ovarian cancer. Our objective was to develop a score for predicting the feasibility of complete cytoreductive surgery in patients with advanced epithelial ovarian cancer.
Material and methods: Using data from a retrospective cohort of 123 patients with advanced ovarian cancer, we developed a score for predicting complete cytoreductive surgery, by performing multiple logistic regression after a jackknife procedure.
Results: Three criteria were independently associated with incomplete cytoreductive surgery confirmed by surgery: age >60 years (adjusted odds ratio [aOR], 6.37; 95% confidence interval [95%CI], 1.9–21.3), diaphragmatic carcinomatosis by computed tomography (aOR, 3.34; 95%CI, 1.1–9.9), and a Peritoneal Cancer Index >10 by diagnostic laparoscopy (aOR, 3.8; 95%CI, 1.4–10.2). A 10-point score was developed based on these three criteria. The area-under-the-curve of the score was 0.76 (95%CI, 0.67–0.86). The score discriminated between groups with low and high risks of incomplete cytoreductive surgery (4.4% [95% CI, 0–10.5] and 42.9% [95% CI, 26.3–59.4], respectively). Using a cutoff of 4, sensitivity of the score was 92.8% (95%CI, 83.2–100) and specificity was 77% (95%CI, 67.1–84.9) for predicting incomplete cytoreductive surgery.
Conclusion: This easy-to-calculate score may prove useful to identify patients with ovarian peritoneal carcinomatosis in whom complete cytoreductive surgery is feasible.

1. Introduction

Residual tumor size is the main prognostic factor in patients with advanced epithelial ovarian cancer [1–3]. Complete cytoreductive surgery (CC-0) produces the best outcomes, albeit at the cost of substantial morbidity [4]. On the other hand, suboptimal cytoreductive surgery has only dubious benefits yet carries the same risk of complications [2,5]. Therefore, accurately identifying those patients who would not benefit from initial surgery is crucial. When used in isolation, clinical features, laboratory findings, and radiological scores perform poorly for predicting the feasibility of CC-0. Laparoscopy has been proposed to assess tumor spread and resectability. Laparoscopy avoids unnecessary laparotomy and predicts the outcome [6,7]. Fagotti et al. and, subsequently, Brun et al. developed laparoscopic scores for describing tumor spread [8,9]. These laparoscopic scores, which use four to seven items, have good specificity for ruling out the feasibility of CC-0 but lack sensitivity (positive predictive value [PPV] for CC-0, 57%, when Brun's score is < 4). Other groups have developed scores for predicting resectability based on a combination of clinical, laboratory, computed tomography (CT), and laparoscopy findings [10].

Here, our objective was to develop a new tool for predicting the

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feasibility of CC-0 in patients with advanced epithelial ovarian cancer. We used a combination of clinical, laboratory, radiological, and laparoscopic criteria to create this feasibility score.

2. Material and methods

2.1. Study design and patients

We conducted a single-center retrospective study in consecutive patients managed for advanced epithelial ovarian cancer at the Women's Oncologic Surgery Center of the Georges Pompidou Teaching Hospital (Paris, France) between January 1, 2005, and January 30, 2013. Ethical committee approved the study (CEROG 2015-GYN-0101).

We included patients who had epithelial cancer of the ovary, tube, or peritoneum classified as advanced based on FIGO criteria (stages III or IV) and who underwent either primary or interval cytoreductive surgery. We excluded patients with early cancer (FIGO stage I or II) in order to focus on the patients for who the prediction of resectability is important. We also excluded patients who did not have cytoreductive surgery to ensure a strong gold standard.

2.2. Preoperative workup

All patients underwent the following investigations: thorough physical and gynecological examination, serum CA-125 assay (U/mL), nutritional assessment including a serum albumin assay (g/dL), and CT of the chest, abdomen, and pelvis with contrast agent injection. CT was performed using a 64-detector spiral machine (Lightspeed VCT, GE Healthcare, Chalfont St. Giles, UK), after injection of an iodinated contrast agent (1.5 mL/kg of iomeprol 350 mgI/mL, Iomeron®, Bracco, Milan, Italy). Slices 1.25-mm in thickness were acquired at the arterial phase for the chest and portal venous phase for the abdomen and pelvis. Then, 2.5-mm slices were reconstructed in the transverse, coronal, and sagittal planes for the analysis. Bowel opacification was obtained by oral administration of at least 500 mL of diluted barium sulfate suspension within 1 h before CT study. Positron emission tomography after an injection of 18F-fluorodeoxyglucose (FDG-PET) was performed if deemed appropriate. The CT and FDG-PET images were reviewed by radiologists experienced in ovarian disease during a meeting attended also by surgeons, medical oncologists, and pathologists. Finally, preoperative laboratory tests and evaluation by an anesthesiologist with determination of the ASA score were performed.

A staging laparoscopy was performed within 21 days after the imaging studies, under general anesthesia, using an umbilical port for the optical system and a 5-mm trocar on the midline. Patient who had previous abdominal surgery were also referred for staging laparoscopy. Each abdominal and pelvic sector was explored systematically. A standardized form was used to describe the sites involved with cancer and to determine the Peritoneal Cancer Index (PCI) [11]. The histological diagnosis was obtained by examining peritoneal cytology samples and biopsies of the main tumor and/or peritoneal foci and/or adnexectomy.

2.3. Patient selection for cytoreductive surgery

The choice between primary surgery and interval surgery was based on the clinical data (most notably general health) and on the radiological and laparoscopy findings, which were discussed during a meeting attended by surgeons, radiologists, medical oncologists, and pathologists. Cytoreductive surgery was deemed contraindicated in patients with any of the following CT and/or laparoscopy criteria: massive involvement of the hepatic pedicle, bowel involvement requiring extensive small-bowel resection, need for more than two gastrointestinal resections and/or mesenteric resection, suprarenal lymphadenopathy, and massive involvement of the retroperitoneum.

For primary cytoreduction, the surgical protocol varied with the spread of the disease. Residual tumor size was estimated after surgery was completed, using the completeness of cytoreduction score (CCR score) [12]. After surgery, six cycles of paclitaxel and carboplatin chemotherapy were given.

For interval cytoreduction, three to four chemotherapy cycles were given at 3-week intervals. The response was assessed based on the physical findings, CA-125 levels, and imaging studies (whole-body CT with or without PET-CT). Patients with a partial or complete response were scheduled for laparotomy. Laparoscopy was performed at the beginning of the procedure to confirm the feasibility of cytoreductive surgery.

2.4. Statistical analysis

We compared patients whose CCR score was CC-0, indicating complete cytoreduction (e.g., "no visible residual tumor") to those whose CRC score was CC-1 or CC-2, indicating incomplete cytoreduction with persistence of visible tumor nodules at completion of surgery. For between-group comparisons of qualitative variables, we chose the chi-square test or, when the expected sample size was too small, Fisher's exact test. The univariate analysis of quantitative variables relied on Student's *t*-test or, when variances were unequal (as evaluated by ANOVA), Welch's *t*-test. Variables significantly associated with incomplete cytoreduction were dichotomized on either side of the best cutoffs identified by receiver-operating characteristic (ROC) curves.

Variables yielding P values <0.20 by univariate analysis were entered into a multivariate model using descending stepwise logistic regression. The combination of variables exhibiting the strongest independent association with CC-0 at the P level of <0.05 was identified.

Jackknife resampling was performed to assess the robustness of the multivariate model [13]. This resampling procedure allows the identification and elimination of any unstable variables. Robustness of the confidence intervals of the logistic regression model coefficients was tested by rebuilding the model N times, each time using N-1 patients (with a different patient dropped each time). Robust 95% confidence intervals were then obtained by computing the mean of the results from the N iterations. Once a stable logistic regression model was obtained, the concordance statistic with its 95%CI was computed. The C-statistic (concordance statistic) is a generalization of the area under the ROC curve. For binary outcomes, the C-statistic is identical to the area under the ROC curve.

The stable logistic regression model was used to build a score based on the rounded values of the β coefficients with a multiplicative factor in order to produce a simple scale. The C-statistics of the rounded score and logistic regression model were compared to verify that the score derived from the model was not statistically different from the logistic regression model. The probability of incomplete cytoreduction associated with each value of the score was computed as $P = 1/[1 + \exp -(\alpha - \beta \times \text{score})]$. The sensitivity and specificity of various score cut-offs were computed.

Stata software version 13.0 (Stata Corp., College Station, TX, USA) was used for the statistical analysis.

3. Results

3.1. Patients

Table 1 lists the main patient characteristics. During the study