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Nomogram for predicting incomplete cytoreduction in advanced ovarian cancer patients☆

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HIGHLIGHTS

- 343 consecutive advanced-ovarian cancer patients undergoing PET/CT before primary surgery were analyzed.
- Using surgical aggressiveness and PET/CT features, a nomogram for predicting incomplete cytoreduction was developed.
- Nomogram performance was good across individual surgeons of heterogeneous surgical aggressiveness.

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ABSTRACT

Objective. Accurately predicting cytoreducibility in advanced-ovarian cancer is needed to establish preoperative plans, consider neoadjuvant chemotherapy, and improve clinical trial protocols. We aimed to develop a positron-emission tomography/computed tomography-based nomogram for predicting incomplete cytoreduction in advanced-ovarian cancer patients.

Methods. Between 2006 and 2012, 343 consecutive advanced-ovarian cancer patients underwent positron-emission tomography/computed tomography before primary cytoreduction: 240 and 103 patients were assigned to the model development or validation cohort, respectively. After reviewing the detailed surgical documentation, incomplete cytoreduction was defined as a remaining gross residual tumor. We evaluated each individual surgeon's surgical aggressiveness index (number of high-complex surgeries/total number of surgeries). Possible predictors, including surgical aggressiveness index and positron-emission tomography/computed tomography features, were analyzed using logistic regression modeling. A nomogram based on this model was developed and externally validated.

Results. Complete cytoreduction was achieved in 120 patients (35%). Surgical aggressiveness index and five positron-emission tomography/computed tomography features were independent predictors of incomplete cytoreduction. Our nomogram predicted incomplete cytoreduction by incorporating these variables and demonstrated good predictive accuracy (concordance index = 0.881; 95% CI = 0.838–0.923). The predictive accuracy of our validation cohort was also good (concordance index = 0.881; 95% CI = 0.790–0.932) and the predicted probability was close to the actual observed outcome. Our model demonstrated good performance across surgeons with varying degrees of surgical aggressiveness.

Conclusion. We have developed and validated a nomogram for predicting incomplete cytoreduction in advanced-ovarian cancer patients which may help stratify patients for clinical trials, establish meticulous preoperative plans, and determine if neoadjuvant chemotherapy is warranted.

Introduction

Epithelial ovarian cancer comprises 25% of malignancies in the female genital tract and is the most common gynecological cause of death in developed countries [1]. It is the second most common gynecological malignancy in Korea where an estimated 1300 new cases develop annually [2]. Primary cytoreductive surgery followed by taxane/

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platinum-based chemotherapy is the first-line therapy for ovarian cancer. Maximal cytoreduction is one of the most important prognostic factors for treating advanced-ovarian cancer; patients who demonstrate complete cytoreduction (i.e. no macroscopic residual tumor left) demonstrate the best prognosis after adjuvant chemotherapy [3,4].

Accurately predicting incomplete cytoreduction is needed in advanced-ovarian cancer cases for several reasons [5]. First, if a patient is at high-risk of incomplete cytoreduction, alternative treatments such as neoadjuvant chemotherapy could be an option. For such cases, cytoreductive surgery following neoadjuvant chemotherapy seems to reduce operative morbidity and increase rates of complete cytoreduction [4,6]. Second, it may help to predict the surgical requirements to achieve complete cytoreduction. If greater surgical skill and multi-disciplinary resources are required to achieve complete cytoreduction, surgeons can consider whether to refer a patient to colleagues with more experience and resources. Third, further clinical trials are needed to confirm the efficacy of neoadjuvant chemotherapy in patients at high-risk of incomplete cytoreduction. In such trials, adequate stratification based on properly assessed surgical respectability will be necessary. As a triage tool, modeling can be useful for patient stratification in such trials.

Biochemical markers and diagnostic imaging features are predictors of cytoreducibility [7–10]. Although models that incorporate these predictors have been developed [8,9,11], they cannot be independently validated [11] because of differences in individual surgical policies or skills [12]. To address the limitations of previous models, we assessed surgical aggressiveness of individual surgeons and developed a predictive nomogram for incomplete cytoreduction in advanced-ovarian cancer patients after primary surgery. Moreover, we used positron-emission tomography/computed tomography to identify predictors of cytoreducibility [13,14]. This hybrid system more accurately detects extrapelvic metastasis in comparison with conventional imaging [15–20].

Methods

Patients

Patients included in this analysis were treated at our institution from 2006 to 2013 with a suspicious ovarian cancer on the basis of physical examination, ultrasound, computed tomography, presence of ascites or increased cancer antigen-125 (CA-125) level [21,22]. Initial preoperative positron-emission tomography/computed tomography has been recommended to all suspicious ovarian cancer patients and was performed on all patients except those who refused this procedure. All eligibility criteria for inclusion in our present study had to be met: age >18 and <80 years; pathologically confirmed ovarian cancer; positron-emission tomography/computed tomography performed 4 weeks prior to surgery; primary staging and subsequent cytoreductive surgery; and postoperative diagnosis of stages III–IV cancer according to the International Federation of Gynecology and Obstetrics (FIGO). We excluded patients who did not receive primary treatment at our institution, patients who received neoadjuvant chemotherapy, and patients with a history of other malignancies. Neoadjuvant chemotherapy was administered at the physician's discretion, especially for patients who were unable to receive surgical procedures due to poor physical condition or extraabdominal disease. Indication for neoadjuvant chemotherapy in our institution is described in the Supplemental Methods. In our institutional database of 444 advanced-ovarian cancer patients, 343 patients were eligible for this study. Before analysis, patients were allocated at a 7:3 ratio to either the model development (n = 240; January 2006 to June 2011) or validation cohort (n = 103; July 2011 to August 2013) (Supplemental Fig. S1).

Clinicopathological data were collected from the medical records. Surgical staging was determined according to FIGO guidelines. If indicated, patients received ≥6 cycles of taxane/platinum-based systemic chemotherapy after surgery. Surgical exploration of the abdominal cavity was performed systematically as described previously [23]. Visual estimation of tumor spread was based on the consensus of two operators. Multiple biopsies were obtained to confirm the results of macroscopic evaluation. After surgery, details regarding the presence, location, number, and size of the residual tumor were also recorded and illustrated on a surgical documentation form. This study was approved by our institutional review board (S2013-1521-0001).

PET/CT scanning procedure

Patients were instructed to avoid strenuous exercise for 24 h before positron-emission tomography/computed tomography in order to minimize radiotracer uptake into the muscles. They were also instructed to fast ≥6 h prior to the injection of ^{18}F-fluorodeoxyglucose, which was produced in our center's radiopharmacy using standard synthetic techniques. Furosemide (40-mg tablet) and duspatalin (135-mg tablet) were orally administered just before venous blood glucose measurement. Venous blood glucose levels were maintained <140 mg/dl. All patients were injected with 0.2 mCi/kg ^{18}F-fluorodeoxyglucose and allowed to rest in a sitting or supine position for approximately 60 min prior to scanning. The patients were then positioned in the scanner with their arms above their heads. Positron-emission tomography/computed tomography scans from the base of the skull to the mid-thigh were performed using Discovery STE (GE Healthcare, Waukesha, WI), Biograph Truepoint 16 (Siemens/CTI, Knoxville, TN), or Biograph Truepoint 40 (Siemens/CTI) scanners. The scanners obtained combination multislice computed tomography and positron-emission tomography tomographs. The computed tomography data were used for attenuation correction. A total of five to six bed positions for 2–3 min per position were acquired for emission scanning (3 min/bed with the Discovery STE and Biograph Truepoint 16; 2 min/bed with the Biograph Truepoint 40). All scans were reconstructed using an ordered-subsets expectation maximization algorithm (20 subsets and two iterations for the Discovery STE; 16 subsets and two iterations for the Biograph Truepoint 16; 21 subsets and three iterations for the Biograph Truepoint 40). Calibration of each scanner against dose calibrators and well counters was routinely performed. The measured standardized uptake value of the phantom was within the acceptable range of 90–110%. The mean standardized uptake value of the liver was also calculated by drawing a three-dimensional region of interest with a 3-cm diameter within the normal inferior right lobe. Further details with regard to the criteria used to interpret positron-emission tomography scans are described in the Supplemental Methods.

Statistical analysis

The following variables were assessed to identify predictors of incomplete cytoreduction: age, parity, menopausal status, American Society of Anesthesiology physical status, preoperative serum CA-125, serum albumin, and platelet count. We evaluated the extent of each surgery using surgical complexity score [24]. Based on the number and complexity of the surgical procedures, patients were assigned to three groups: low, intermediate, or high (Supplemental Table 1). The surgical aggressiveness index of the individual surgeons was calculated using the following formula: *Surgical aggressiveness index of surgeon A = (number of high-surgical complexity score surgeries of surgeon A/total number of surgeries of surgeon A) × 100*. The index was calculated using all primary cytoreductive surgeries for advanced ovarian cancer patients (excluding cervical or corpus cancer or early ovarian cancer) during the study period (2006–2013).

Complete cytoreduction was defined as 'no gross residual tumor' [25]. Age, parity, preoperative serum CA-125, preoperative serum albumin, preoperative platelet count, surgical aggressiveness index, and