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Development of a prediction model for residual disease in newly diagnosed advanced ovarian cancer

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HIGHLIGHTS

- Preoperative factors may predict cytoreduction for advanced ovarian cancer.
- Age, ECOG status, CT findings may predict complete or suboptimal cytoreduction.

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ABSTRACT

Objectives. To construct a tool, using computed tomography (CT) imaging and preoperative clinical variables, to estimate successful primary cytoreduction for advanced epithelial ovarian cancer (EOC).

Methods. Women who underwent primary cytoreductive surgery for stage IIIC/IV EOC at Mayo Clinic between 1/2/2003 and 12/30/2011 and had preoperative CT images of the abdomen and pelvis within 90 days prior to their surgery available for review were included. CT images were reviewed for large-volume ascites, diffuse peritoneal thickening (DPT), omental cake, lymphadenopathy (LP), and spleen or liver involvement. Preoperative factors included age, body mass index (BMI), Eastern Cooperative Oncology Group performance status (ECOG PS), American Society of Anesthesiologists (ASA) score, albumin, CA-125, and thrombocytosis. Two prediction models were developed to estimate the probability of (i) complete and (ii) suboptimal cytoreduction (residual disease (RD) > 1 cm) using multivariable logistic analysis with backward and stepwise variable selection methods. Internal validation was assessed using bootstrap resampling to derive an optimism-corrected estimate of the c-index.

Results. 279 patients met inclusion criteria: 143 had complete cytoreduction, 26 had suboptimal cytoreduction (RD > 1 cm), and 110 had measurable RD ≤ 1 cm. On multivariable analysis, age, absence of ascites, omental cake, and DPT on CT imaging independently predicted complete cytoreduction (c-index = 0.748). Conversely, predictors of suboptimal cytoreduction were ECOG PS, DPT, and LP on preoperative CT imaging (c-index = 0.685).

Conclusions. The generated models serve as preoperative evaluation tools that may improve counseling and selection for primary surgery, but need to be externally validated.

1. Introduction

Epithelial ovarian cancer (EOC) is the leading cause of death from gynecologic malignancy in the United States, with an estimated 21,980 new diagnoses and 14,270 deaths in 2014 [1]. Reduction of disease to as minimal residual as possible at the time of primary surgery has been consistently shown to confer improved survival [2,3], and aggressive surgery confers survival advantage only if optimal cytoreduction is achieved [4]. Surgical reduction to no gross residual disease confers the greatest survival benefit [5–7]. For those unable to tolerate primary cytoreductive surgery or with disease initially too extensive to optimally debulk, neoadjuvant chemotherapy coupled with interval debulking surgery has emerged as a viable method of treatment with comparable outcomes [8,9]. However, a means of accurately and consistently predicting those who would be able to achieve optimal cytoreduction, and therefore benefit from upfront cytoreductive surgery, has been elusive.

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Limited usefulness and lack of validation have prevented previously proposed algorithms from becoming widely adapted [10]. A multi-institutional attempt to validate our previously-published model, in addition to several other models, was unable to replicate reported accuracy rates during cross-validation [11]. There are several issues likely contributing to the limited efficacy of tools developed thus far. These include limiting the goal of the models at predicting suboptimal resection, varying rates of complete and optimal cytoreduction across institutions, and variations in neoadjuvant chemotherapy referral practices. Additionally, in terms of computed tomography (CT) technology, older generation CT scanners had thicker slice thickness and limited image resolution, and lacked multiplanar reformatting capability, which has likely contributed to the lower sensitivities of the CT evaluation in older studies. CT techniques have been continuously evolving, and with newer multidetector row scanners the image resolution has improved and thinner sections with multiplanar reformatting have enabled better evaluation of horizontally-oriented structures such as diaphragm, hepatic and splenic hilum, and pelvic peritoneum [12,13].

We recently reexamined the use of preoperative CT findings, with the inclusion of more contemporary imaging in our patient population, to determine high tumor dissemination and likelihood of requiring extensive surgery to achieve low residual disease and found that diaphragmatic disease and omental caking are highly predictive of these outcomes. These and other factors also appear to be predictive of higher surgical complexity [14]. In addition to predictive findings on imaging, clinical factors have also been identified as potentially important factors predictive of initial disease burden. Thrombocytosis appears to be associated with extensive initial disease burden, measurable residual disease, and postoperative complications such as ileus and surgical site infection [15]. Additionally a recent study detailed use of CT and preoperative clinical factors as well as molecular markers to predict resectability. One model used extent of disease at presentation, stage, preoperative CA-125, ascites, and age to predict complete cytoreduction with a sensitivity of 83% and specificity of 75%. However, the authors felt that the addition of molecular markers or more advanced imaging studies could further increase accuracy and appropriate triage of patients to aggressive cytoreductive surgery [16]. A recent paper outlines the potential use for tumoral FABP4 as a molecular marker predictive of residual disease [17].

We aimed to utilize contemporary imaging technology, with the incorporation of objective preoperative clinical factors, to develop tools that can help estimate the likelihood of either complete or suboptimal cytoreduction when considering primary cytoreductive surgery for apparent advanced-stage EOC patients. Such a tool would provide women and their gynecologic oncologist information for counseling and informed decision-making regarding initial treatment strategies, upon external validation.

2. Methods

Women who underwent primary cytoreductive surgery for advanced stage (IIIC/IV) EOC, including primary peritoneal and fallopian tube carcinomas, at the Mayo Clinic between 1/2/2003 and 12/30/2011 and had preoperative CT imaging of the abdomen and pelvis within 90 days prior to their surgery were included. CT examination was performed at the Mayo Clinic in 102 patients and in an outside institution in 177 patients. Most CT scanners used modern technology including multi-detectors of 8 to 128 multi-detector rows and section thickness of 3–5 mm. All CT exams were reviewed digitally on axial and coronal planes using a custom-built viewing software (QREADS®). Patients with inadequate CT images to evaluate the characteristics described below, or pelvic and/or abdominal imaging other than CT, were excluded. Those with recurrent disease, were diagnosed by prior laparoscopy or laparotomy, had non-epithelial histology, or who had received neoadjuvant chemotherapy were also excluded. Complete cytoreduction was defined as no visible residual disease, optimal as ≤1 cm deposits of visible residual disease, and suboptimal as >1 cm residual disease. Perioperative National Surgical Quality Improvement Program (NSQIP) defined variables were identified with potential influence over the outcomes of interest. These included, but were not limited to, age, body mass index (BMI), Eastern Cooperative Oncology Group performance status (ECOG PS), American Society of Anesthesiologists (ASA) score, albumin, CA-125, and thrombocytosis (platelets $>450 \times 10^9$/L). Data was retrospectively abstracted by a registered nurse abstractor. All CT images were reviewed by a single radiologist (BK) and evaluated for the presence of large-volume ascites, bowel involvement, omental cake, diffuse peritoneal thickening (DPT), pleural effusion, lymphadenopathy (LP), and diaphragm, liver, or splenic involvement. Ascites was defined as present if noted on at least 2/3 of CT slices; diffuse peritoneal thickening was defined as >4 mm of peritoneal involvement at two separate sites (evaluated sites being the lateral colic gutters, lateral conal fascia, anterior abdominal wall, diaphragm, and pelvic peritoneal reflections), as previously described [18]; diaphragm involvement as >1 cm cumulative disease (i.e. 1 cm deposits or multiple deposits equaling >1 cm total disease on the diaphragm), and lymphadenopathy as lymph nodes measuring ≥2 cm in the paraaortic or pelvic nodal basins. The complexity of surgery was determined using the Aletti score, which assigns points based on surgical procedures performed and categorizes the total points as low, intermediate, or high complexity surgery [19]. This study was approved by the Mayo Clinic Institutional Review Board (IRB).

Statistical analyses were performed using the SAS version 9.3 software package (SAS Institute, Inc.; Cary, NC) and version 3.0.2 of the R package (REF) [20]. Standard descriptive statistics (mean and standard deviation (SD) or median and interquartile range (IQR)) were used to summarize continuous variables and frequency and percentage for categorical variables. Separate analyses were performed to identify factors associated with a) complete cytoreduction (versus all others) and b) suboptimal cytoreduction (versus all others). First, each of the demographic, perioperative patient, and preoperative CT characteristics was evaluated univariately using logistic regression. Second, multivariable models were fit using stepwise and backward variable selection methods considering all variables with a P value <0.20 based on univariable analysis. Variables with a P value <0.05 were retained in the final model; in addition we forced in variables considered to have clinical relevance. Associations were summarized using the odds ratios (OR) and corresponding 95% confidence intervals (CIs) estimated from the final multivariable model. Restricted cubic splines were used to model the potential non-linear relationship for age. A nomogram was created using the R 'design' package. Discrimination was assessed using the c-index, a measure of a model's predictive accuracy that is equivalent to the area under receiver operating characteristic curve. The apparent performance of the model, as measured by the c-index estimated directly from the data set that was used to develop the model, is a biased optimistic estimate of discrimination. Therefore, a nearly unbiased optimism-corrected estimate of c-index was derived using 300 bootstrap resamples, as a method of internal validation (REF) [21]. Calibration was assessed by comparing the predicted probabilities estimated from each final model with the actual observed proportion of patients with complete cytoreduction and suboptimal cytoreduction, respectively. Sensitivity and specificity estimates were derived based on varying the presence/absence of the combination of factors in each prediction model used to define a positive test.

3. Results

3.1. Patient characteristics and debulking status

During the study years, 621 women underwent primary debulking for advanced stage (IIIC/IV) EOC. A total of 279 patients met inclusion criteria; 1 patient was without consent to obtain the CT image and 341 patients were excluded due to no imaging study, inadequate