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Risk stratification and outcomes of women undergoing surgery for ovarian cancer

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HIGHLIGHTS

- Surgery for ovarian cancer is associated with substantial morbidity.
- Performance of extended cytoreductive procedures is the strongest risk factor for complications.
- Alternative treatment strategies may be considered in women with ovarian cancer at high risk for complications.

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ABSTRACT

Objective. Cytoreduction for ovarian cancer is associated with substantial morbidity. We examined the outcome of patients undergoing surgery for ovarian cancer to determine if there are sub-groups of patients who may benefit from alternative treatments.

Methods. The National Surgical Quality Improvement Program database was used to identify women who underwent surgery for ovarian cancer from 2005–2012. Multivariable logistic regression models were used to examine the effect of age, race, functional status, ASA class, preoperative albumin and performance of extended cytoreductive procedures on morbidity, mortality and resource utilization.

Results. A total of 2870 women were identified. The perioperative complication rate increased from 9.5% in women <50 years, to 13.4% in those age 60–69 years, and 14.6% in women ≥70 years (P < 0.0001). Similarly, complications rose from 7.3% in those who did not require any extended procedures to 12.9% after 1 procedure, 28.4% for those who had 2, and 30.0% in women who underwent ≥3 extended procedures (P < 0.0001). In a series of multivariable models, the number of extended cytoreductive procedures performed and preoperative albumin were the factors most consistently associated with morbidity. Using a series of model fit statistics, compared to chance alone, the ability to predict any complication increased by 27.4% when procedure score was analyzed, 22.0% with preoperative albumin, 11% with age, and 4% with functional status.

Conclusions. While preoperative clinical and demographic factors may help predict the risk of adverse outcomes for women undergoing surgery for ovarian cancer, performance of extended cytoreductive procedures is the strongest risk factor for complications.

1. Introduction

Primary cytoreduction followed by platinum-based combination chemotherapy is the standard of care for the treatment of advanced stage, epithelial ovarian cancer [1]. Surgical cytoreduction entails salpingo-oophorectomy, typically with hysterectomy, omentectomys and resection of gross tumor within the abdominal cavity. Resection of tumor may require small or large bowel resection as well as removal of other solid organs, including the liver and spleen [2–4]. Multiple

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studies have demonstrated that the amount of residual tumor after completion of the surgery is associated with long-term prognosis [4–7]. Patients who are suboptimally cytoreduced prior to chemotherapy have decreased survival [2,8,9].

Although cytoreductive surgery has numerous benefits, the operation is associated with significant morbidity [10–13]. A number of prior studies have attempted to define factors that are associated with excessive morbidity in women undergoing cytoreduction [12]. Several reports have noted that advanced age is associated with adverse outcomes [11,12,14]. However, some studies have suggested that chronologic age alone should not be a contraindication to cytoreduction and that measures of performance status and functional reserve are of greater importance [15,16].

In addition to age, the extent of cytoreductive surgery appears to influence outcomes. Prior work has shown that complications increase with the number of radical procedures performed [12]. Given the increased morbidity associated with factors such as the requirement for more extensive cytoreductive surgery and advanced age, some reports have suggested that patients with these factors may benefit from alternative treatment strategies such as neoadjuvant chemotherapy.

The objective of our study was to examine the influence of age, functional status, and extent of cytoreduction on perioperative morbidity in women with ovarian cancer. Specifically, we utilized a large, population-based database that prospectively collects detailed clinical characteristics and outcomes for patients from throughout the United States.

2. Materials and methods

2.1. Data source and patient selection

We examined the American College of Surgeons' National Surgical Quality Improvement Program (NSQIP) database [17,18]. The NSQIP database is a risk-adjusted, nationally validated and prospectively maintained surgical outcomes registry. It contains more than 240 clinical variables, including preoperative patient characteristics, intraoperative variables and 30-day postoperative outcomes. All data is abstracted from medical records by trained registrars using a highly structured sampling schema. The Columbia University Institutional Review Board deemed the study exempt.

Women ≥18 years of age with ovarian cancer (ICD-9 183.x) recorded from 2005–2012 were included. The study cohort was limited to only those patients who underwent an ovarian cancer directed surgery defined hysterectomy, oophorectomy, cystectomy or tumor cytoreduction (Supplemental Table 1).

The type and number of additional extended procedures each patient underwent were recorded. The procedures of interest included lymphadenectomy, small bowel resection, colectomy, rectosigmoid resection, hepatic resection, bladder resection, diaphragm resection and cytoreduction. In addition to individual procedures, a composite score based on the number of the above extended procedures each patient underwent was calculated. The procedure score was categorized as: 0 procedures, 1 procedure, 2 procedures, and ≥3 procedures [12].

2.2. Clinical and demographic characteristics

Patients were classified based on age at surgery into the following groups: <50 years of age, 50–59 years, 60–69 years and ≥70 years. Race was categorized as white, black, other or unknown. Body mass index was calculated as the weight (kg) divided by height (m^2) and recorded as: normal (<25 kg/m^2), overweight (25–29.9 kg/m^2), obese (≥30 kg/m^2), and unknown.

Covariates potentially associated with performance status including American Society of Anesthesiology (ASA) classification score (1, 2, 3, 4, 5, or unknown), preoperative functional status (independent, partially dependent, totally dependent, and unknown) and preoperative albumin (<3.5 g/dL, 3.5–4 g/dL, and >4 g/dL), were recorded for each patient [17]. The presence of a number of preoperative medical comorbidities including diabetes mellitus (insulin dependent or non-insulin dependent), tobacco use, chronic obstructive pulmonary disease, congestive heart failure, hypertension, corticosteroid use, and the presence of ascites were noted for each patient [19].

2.3. Outcome variables

The primary outcomes of the study were perioperative morbidity and mortality. Any complication was defined as a composite measure if the patient was noted to have any of the following postoperative complications: pneumonia, acute renal failure, urinary tract infection, cerebrovascular accident, coma, sepsis, shock, cardiac arrest, myocardial infarction, pulmonary embolism, deep venous thrombosis, prolonged mechanical ventilation, unplanned re-intubation, or progressive renal insufficiency [19]. Severe complications were analyzed based on Clavian class IV complications and included shock, cardiac arrest, myocardial infarction, pulmonary embolism, prolonged intubation or unplanned re-intubation [20–22]. Wound complications included superficial or deep surgical site infections or an organ space surgical site infection [19].

Prolonged length of stay was defined as hospitalization after surgery of >8 days while non-routine discharge was defined as discharge to a rehabilitation or skilled nursing facility. Intraoperative or postoperative transfusion of blood products and readmission within 30-days of the intervention were noted for each patient. Return to the operating room after the primary procedure was defined as reoperation. Perioperative mortality was defined as death within 30-days of the index surgical procedure [19].

2.4. Statistical analysis

Frequency distributions between categorical variables were compared using χ^2 tests. Clinical and demographic data are reported descriptively stratified by age while outcomes are reported stratified by age and procedure score. Multivariable logistic regression models were developed to examine the association between the clinical and demographic characteristics and the number of extended procedures performed and outcomes. Results are reported with risk ratios and 95% confidence intervals.

A number of model fit statistics were estimated to examine the strength of the model to predict the outcome based on clinical characteristics (age, functional status, preoperative albumin, and procedure score) and outcomes. The area under the receiver operating characteristics (ROC) curve of a plot of the true positive rate (sensitivity) versus the false positive rate was estimated with the c-statistic. The c-statistic represents the ability of a model to accurately predict the outcome. Values for the c-statistic range from 0.5 (model no better than chance in discriminating outcome) to 1 (perfect prediction of the outcome).

The pseudo-R^2 is an indicator of the variability in outcome that is explained by the model and is analogous to R^2 derived from least squares linear regression. Likelihood ratio tests (LRT) compare the fit of a model with the covariates of interest to a null model (no covariates included). A higher LRT suggests a greater importance of the variable or variables. The Akaike information criterion (AIC) measures the goodness of fit of a model in the context of the overall complexity of the model. A lower AIC suggests greater importance for a variable.

We estimated the ability of a given covariate or set of covariates to distinguish the outcomes of interest. We first assumed that the c-statistic of a null model was 0.5 and the calculated the predictive ability of covariates as: (c-statistic of model with one or more variables) / (c-statistic of null model) [23]. Data analysis was performed using SAS version 9.4 (SAS Institute Inc, Cary, North Carolina). All statistical tests were two-sided. A P-value of <0.05 was considered to be statistically significant