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Risk-scoring models for individualized prediction of overall survival in low-grade and high-grade endometrial cancer

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HIGHLIGHTS

- Endometrial cancer consists of two disparate patient populations.
- Risk scoring models were developed to predict overall survival in endometrial cancer.
- Enhanced discrimination of risk scoring models enables personalized counseling and treatment.

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ABSTRACT

Objective. Overall survival (OS) in endometrial cancer (EC) is dependent on patient-, disease-, and treatment-specific risk factors. Comprehensive risk-scoring models were developed to estimate OS in low-grade and high-grade EC.

Methods. Patients undergoing primary surgery for EC from 1999 through 2008 were stratified histologically according to the International Federation of Gynecology and Obstetrics (FIGO) as either (i) low grade: grades 1 and 2 endometrioid EC or (ii) high grade: grade 3, including non-endometrioid EC. Associations between patient-, pathological-, and treatment-specific risk factors and OS starting on postoperative day 30 were assessed using multivariable Cox regression models. Factors independently associated with OS were used to construct nomograms and risk-scoring models.

Results. Eligible patients (N = 1281) included 925 low-grade and 356 high-grade patients; estimated 5-year OSs were 87.0% and 51.5%, respectively. Among patients alive at last follow-up, median follow-up was 5.0 (low grade) and 4.6 years (high grade), respectively. In low-grade patients, independent factors predictive of compromised OS included age, cardiovascular disease, pulmonary dysfunction, stage, tumor diameter, pelvic lymph node status, and grade 2 or higher 30-day postoperative complications. Among high-grade patients, age, American Society of Anesthesiologists score, stage, lymphovascular space invasion, adjuvant therapy, para-aortic nodal status, and cervical stromal invasion were independent predictors of compromised OS. The two risk-scoring models/nomograms had excellent calibration and discrimination (unbiased c-indices = 0.803 and 0.759).

Conclusion. Patients with low-grade and high-grade EC can be counseled regarding their predicted OS using the proposed risk-scoring models. This may facilitate institution of personalized treatment algorithms, surveillance strategies, and lifestyle interventions.

Introduction

Although endometrial cancer is the most common gynecologic malignancy diagnosed in the United States, it is considered the most amenable to early diagnosis and definitive treatment, thus presupposing extended longevity [1]. Nevertheless, endometrial cancer consists of two patient populations differentiated by disparate risk factors and dissimilar long-term prognoses [2,3]. Uterine grades 1 and 2 endometrioid histologies encompass the majority of endometrial cancers, have excellent disease-free survival, and are associated with acquired risk factors [4]. These acquired risk factors, including obesity, diabetes, and metabolic syndrome, not only facilitate the pathogenesis of this disease but also, either directly or indirectly, impact overall survival [5–8]. On

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the contrary, grade 3 endometrioid, serous, and clear cell carcinomas are considered high risk and, while representing a minority of corpus cancers, they lack acquired risk factors and account for the majority of deaths from this disease [9]. Therefore, preoperative and postoperative counseling for these two disparate high-risk and low-risk populations must be sufficiently personalized to maximize treatment, surveillance, and lifestyle modifications.

Examination of overall survival as a function of time demonstrates dramatic differences between high-risk and low-risk endometrial cancer cohorts [10]. The former is characterized by marked attrition during the initial 2 to 3 years, while the latter exhibits a very gradual annual decline. Optimizing outcomes in these diverse cohorts will require individualized tailoring of care based on multiple clinical risk factors [11]. International Federation of Gynecology and Obstetrics (FIGO) staging incorporates disease-based stratification that estimates prognosis, thereby providing a standard for comparative evaluation of treatment outcomes [3]. However, for more effective counseling and tailoring of clinical decisions, patient- and treatment-specific parameters ideally should also be considered [12]. Statistical predictive outcome models and nomograms are clinically utilized in counseling and clinical decision-making in breast and other cancers [13–16]. In 2010, Abu-Rustum et al. [17] developed a nomogram to predict overall survival (OS) in endometrial cancer by combining five factors including age, number of negative nodes, 1988 FIGO stage, grade, and histology. Post-surgical treatment was not included in the modeling [12,17]. Considering the recognized demographic, pathological, and treatment differences between high-risk and low-risk endometrial cancer, models specifically targeting these two diverse populations would provide more patient-specific information, enabling personalized counseling and treatment. Thus, comprehensive risk-scoring models with enhanced discrimination were developed for the prediction of OS after 30 days post-surgery for both high-risk and low-risk endometrial cancer patients.

Methods

Study patients

This retrospective risk-adjusted outcome assessment was approved by the Mayo Clinic Institutional Review Board. Between January 1, 1999, and December 31, 2008, 1415 patients presenting with EC were counseled and elected to pursue primary surgical intervention. In compliance with the Minnesota Statue for Use of Medical Information in Research, 22 women who declined the use of their recorded medical information were excluded from the study. An additional 112 patients were excluded predominantly due to the presence of synchronous invasive cancers ($n = 79$) and neoadjuvant chemotherapy ($n = 11$), with the remaining exclusions distributed among non-epithelial carcinoma, death within 30 days of surgery, loss to follow-up within 30 days, or unknown date of death. Therefore, the eligible study population consisted of 1281 patients.

Treatment

The standardization of the Mayo Clinic surgical algorithm for EC evolved during the early phases of this study period, being formally implemented with prospective quality assessment in January 2004. Following hysterectomy and removal of the adnexal structures, prompt frozen section assessment was performed as previously described [18]. In the absence of extra-uterine disease and favorable intrauterine pathology (endometrioid, FIGO grade 1/2, primary tumor diameter ≤ 2 cm, myometrial invasion [MI] $\leq 50\%$, or noninvasive endometrioid regardless of grade or size), hysterectomy alone was deemed sufficient [19]. For specimens failing to meet these criteria, definitive surgical staging including lymphadenectomy up to the renal vessels was recommended, as well as cytoreduction in the presence of intra-abdominal disease [20].

Stage and architectural grade assignments were in accord with the 2009 FIGO classification system [21]. The World Health Organization's taxonomy principles were used to designate histologic subtypes [22]. Primary tumor diameter was defined as the largest of the three dimensions of the tumor. To ensure the accuracy of assigned diagnoses, pathology slides were reviewed by a single gynecologic oncology pathologist (G.L.K.).

In the presence of lymph node metastases, irradiation was delivered in standard doses of 45.0 to 50.4 Gy to the pelvis, and 45.0 Gy to the paraaortic fields when indicated. Systemic therapy with or without radiotherapy was administered when patients harbored advanced disease or were perceived to be at high risk for occult dissemination. Platinum-based combination chemotherapy, predominantly using paclitaxel or doxorubicin or both, was the adjuvant systemic treatment of choice. In the presence of grade 3 histology or lymph-vascular space involvement, adjuvant brachytherapy was generally administered alone or in combination with other regional or systemic therapies.

Data collection

More than 130 patient-, disease-, and treatment-specific variables were abstracted from medical records by a dedicated registered nurse using a modification of the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) platform [23,24]. Patient and tumor registry records were periodically reviewed to ascertain current information regarding complications, disease progression, and vital status. When information detailing disease status was insufficient, death certificates were reviewed, letters were sent to patients and/or personal physicians, and telephone interviews were conducted to garner additional information.

Patient-specific risk factors including demographic variables, patient comorbidities, and American Society of Anesthesiologist (ASA) scores were recorded. Pulmonary disease was defined by the presence of at least one of the following: dyspnea, history of severe chronic obstructive pulmonary disease (COPD), current pneumonia, history of sleep apnea, or past/current continuous use of positive airway pressure (CPAP). Cardiovascular disease included a history of congestive heart failure (CHF) within 30 days of surgery, angina within 30 days of surgery, myocardial infarction within 6 months of surgery, cardiac stenting, cardiac surgery, revascularization, or amputation for peripheral vascular disease and/or rest pain/gangrene.

Clinical and surgical variables pertinent to this study included surgical approach (laparotomy vs minimally invasive surgery), type and extent of lymphadenectomy, number of lymph nodes harvested, and adjuvant therapy. An adequate systematic lymphadenectomy was defined as removal of at least 10 pelvic and 5 para-aortic lymph nodes. Postoperative complications within the first 30 days of surgery were abstracted and graded using the modified Accordion Severity Grading System [25]. The grades were collapsed for analysis purposes as none or grade 1, grade 2 or 3, and grade 4, 5, or, 6.

Pathology variables included FIGO grade, peritoneal cytology, presence of macroscopic extrauterine disease, cervical stromal invasion, lymphovascular space invasion, primary tumor diameter, and depth of myometrial invasion as a percentage of myometrial thickness. Patients were ultimately stratified histologically for the purpose of this study according to: (i) FIGO grades 1 and 2 endometrioid endometrial cancer (low-risk) and (ii) grade 3, including non-endometrioid endometrial cancer (high-risk).

Statistical analysis

The demographic, clinical, and pathologic characteristics of patients classified as low-risk versus high-risk were contrasted and compared using the two-sample t test for age and BMI (body mass index), the Wilcoxon rank sum test for the extent of myometrial invasion and number of nodes removed, and the χ^2 test for all other variables. The primary