Gynecologic Oncology 131 (2013) 103–108

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Risk-scoring system for the individualized prediction of lymphatic dissemination in patients with endometrioid endometrial cancer

M.M. AlHilli [a], K.C. Podratz [a], S.C. Dowdy [a], J.N. Bakkum-Gamez [a], A.L. Weaver [b], M.E. McGree [b], G.L. Keeney [c], W.A. Cliby [a], A. Mariani [a,*]

[a] Department of Obstetrics and Gynecology, Division of Gynecologic Surgery, Mayo Clinic, Rochester, MN, USA
[b] Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA
[c] Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, MN, USA

HIGHLIGHTS

- Individualized predictions of the risk of lymphatic dissemination after the diagnosis of occult endometrioid endometrial carcinoma can aid patient counseling
- A validated risk-scoring system can facilitate decisions regarding secondary lymphadenectomy
- Tumor diameter is an important component of the risk-scoring system and should be routinely measured in uterine pathology specimens

ARTICLE INFO

Article history:
Received 9 May 2013
Accepted 25 June 2013
Available online 9 July 2013

Keywords:
Risk-Scoring Model
Endometrial Cancer
Nomogram

ABSTRACT

Objective. To develop a risk-scoring system (RSS) for the prediction of lymphatic dissemination after hysterectomy in endometrioid endometrial carcinoma (EC).

Methods. Patients who underwent surgery from 1/1/1999-12/31/2008 were evaluated. Patients with non-endometrioid histology, stage IV with macroscopic extrauterine disease, or receiving adjuvant therapy (excluding brachytherapy) without pelvic and/or paraaortic (P/PA) lymphadenectomy (LND) were excluded. Lymph node dissemination was defined as nodal metastasis when P/PA LND was performed or P/PA lymph node recurrence after negative LND or when LND was not performed. Logistic regression analysis was used to identify predictors for lymphatic dissemination and develop a RSS and nomogram. The RSS was assessed for calibration and verified for discrimination.

Results. Overall, 883 patients were assessed of which 521 (59.0%) underwent P/PA LND and 57 (10.9%) had positive lymph nodes. Of patients who did not undergo P/PA LND (N = 362) or had negative nodes (N = 464), 10 (1.2%) patients had P/PA lymph node recurrence. Myometrial invasion, tumor diameter (TD), FIGO grade, cervical stromal invasion and lymphovascular space invasion were significant on univariable analysis. All preceding variables were included in a multivariable logistic model. A parsimonious model and an alternative full model not including TD were considered. The full model with TD (illustrated in nomogram) had the highest predictive ability (concordance index 0.88).

Conclusion. Our RSS allows accurate quantification of the probability of lymphatic dissemination and can be used as an adjunct to clinical decision-making after hysterectomy in the absence of staging. TD is an important component of the RSS and should be routinely assessed.

Introduction

The global burden of endometrial cancer (EC) is rapidly increasing; approximately 300,000 new cases of EC are diagnosed annually. In the United States, EC is the fourth most common malignancy in women after breast, colorectal and lung cancers [1–3]. The estimated 5-year overall survival for early-stage EC is 81.8%, decreasing remarkably to 67.0% and 15.9% for regional and distant disease, respectively [1]. While the majority of patients are diagnosed with stage I and II disease (approximately 83%), those with advanced-stage EC or unfavorable pathologic characteristics have a guarded prognosis [4].

The International Federation of Gynecology and Obstetrics (FIGO) has played a pivotal role in providing estimates of prognosis and survivorship in EC [5]. Yet, in an era where "personalized medicine" prevails, these estimates are seemingly insufficient [6–8]. "Personalized medicine" refers to the application of pharmacogenomics information to individuals in order to enhance diagnosis and treatment. This definition can be expanded to include methods of tailoring treatment decisions to individual patients [9]. One such method of treatment

* Corresponding author at: Eisenberg Lobby 71, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA. Fax: +1 507 266 9300.

0090-8258/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.ygyno.2013.06.037

individualization is the use of statistical prediction models whereby a numerical probability of a clinical event can be generated [10]. Risk-scoring models have not been fully adopted in gynecologic malignancies [11,8]. In other solid cancers such as breast cancer and prostate cancer, however, risk-scoring models are frequently utilized [7,12,13]. It has been shown that nomograms, graphical tools that illustrate the probability of a clinical event based on a combination of prognostic factors, have better individual discrimination than current staging systems [7,11,14,15]. Furthermore, risk-scoring models may prove to be instrumental in situations where information on surgical stage is not available.

The incidental diagnosis of EC after hysterectomy for benign indications often creates a clinical conundrum, particularly since the indications for surgical staging through pelvic and paraaortic (P/PA) lymphadenectomy have not been clearly defined among gynecologic oncologists [16,17]. In many instances, patient factors such as age and underlying comorbidities may influence the decision to undergo a secondary surgery. The precise quantification of the risk of lymphatic dissemination, as either the risk of undiagnosed positive lymph nodes or the risk of lymphatic recurrence, may assist in guiding treatment decisions in such circumstances. Previously developed nomograms and risk-scoring models estimating the risk of locoregional and distant recurrence in EC have included all incoming EC patients regardless of histologic subtype [8,18]. However, it is the management of type I EC that requires complex decision-making processes in the event of an occult malignancy [19]. In this study, we sought to construct a risk-scoring model for the prediction of lymphatic dissemination in patients with endometrioid EC with no macroscopic extrauterine disease.

Methods

Patients who underwent primary surgical management for endometrioid EC at Mayo Clinic, Rochester between January 1, 1999 and December 31, 2008 were considered in this study. All patients submitted to treatment with hysterectomy with or without bilateral salpingo-oophorectomy, while surgical staging was based on surgeons' discretion from 1999–2003. In January 2004, a prospective treatment algorithm was developed whereby lymphadenectomy was omitted in patients at low risk for lymphatic dissemination (patients with FIGO grade 1 or 2 endometrioid carcinoma, ≤50% myometrial invasion (MI), and primary tumor diameter (TD) of ≤2 cm) [19].

Our cohort was restricted to patients where a choice between performing a separate surgical staging procedure versus no additional treatment was needed. Thus, patients with highest risk factors where lymphadenectomy is generally indicated were excluded from the analysis. These risk factors included stage IV tumors with gross extrauterine disease, uterine serosal and/or adnexal involvement, non-endometrioid histology, and synchronous invasive cancers. Furthermore, patients who had preoperative therapy and patients without lymphatic recurrences who had any adjuvant therapy aside from vaginal brachytherapy when P/PA lymphadenectomy was not performed were excluded. Among the patients without documented lymphatic dissemination, the following exclusions were applied in order to ensure complete recognition of disease outcomes: (i) patients who died within the first 2 years whose date of last clinical follow-up was greater than 3 months prior to their death, and (ii) patients who were last known to be alive but lacked 2 years of clinical follow-up. Mayo Clinic Institutional Review Board approval was obtained and all patients were screened for research consent.

Data were obtained from our comprehensive EC database, which has been previously described [20–23]. An adequate lymphadenectomy was defined as a systematic P/PA lymphadenectomy where at least 10 pelvic and 5 paraaortic lymph nodes were resected [19,24]. On all patients, pathologic variables including FIGO grade, cervical stromal invasion, LVSI, primary TD, and MI were examined. Stage and grade assignment was according to FIGO guidelines. Primary TD was defined as the largest of the three dimensions of the tumor measured on fresh tissue. If more than one lesion was present, the lesion with the largest diameter was considered. Intraoperative frozen section was used for initial evaluation and risk determination. The technique for intraoperative frozen section analysis at Mayo Clinic was previously described [25]. All final pathology slides were reviewed by one gynecologic pathologist (GLK) to ensure accurate diagnoses.

The primary outcome evaluated was the presence of P/PA lymphatic dissemination. This was defined as (1) positive P/PA lymph nodes where P/PA lymphadenectomy was performed or (2) P/PA lymph node recurrence after negative lymphadenectomy or where P/PA lymphadenectomy was not performed. Of note, lymph node recurrences were classified as any P/PA lymphatic recurrence identified after the primary cancer surgery, where a new mass was detected in the P/PA lymph node basins either by clinical examination or with imaging. Diagnostic biopsies were performed for histologic confirmation of the recurrence per the treating clinician's discretion. All clinical and pathologic variables were assessed for an association with P/PA lymph node dissemination using univariable logistic regression models. Multivariable logistic regression analysis was used to identify a set of predictors for P/PA lymph node dissemination. Associations were summarized using the odds ratio (OR) and corresponding 95% confidence interval (CI) estimated from the models. Continuous variables were evaluated univariately as non-transformed, log-transformed, or using restricted cubic splines to identify the best fit. All calculated p-values were two-sided and p-values less than 0.05 were considered statistically significant.

Three final models were considered: a full model including all of the variables that were significant on univariate analysis, a parsimonious model identified using stepwise and backward variable selection methods, and an alternative full model not considering TD that would be useful for patients with unknown TD. Receiver operating characteristic (ROC) curves were generated to graphically compare each model's overall predictive ability. Risk-scoring systems (RSS) and nomograms were created using R software (version 2.14.0) for the two full models (with and without TD). In addition, the two full models were assessed for discrimination and calibration [9]. Discrimination was assessed with 300 bootstrap resamples. For each bootstrap sample, a logistic regression model was fit using the variables identified in the final model and the concordance index (c-index) was calculated. The c-index is a measure of a model's predictive accuracy (discrimination). An unbiased estimate of the c-index was obtained based on averaging the 300 c-indices. Calibration was assessed graphically by examining how far the predicted probabilities are from the actual observed proportion with lymphatic dissemination. Statistical analyses were performed using SAS (version 9.2) and R.

Results

Of the 1393 consenting patients within in our database, 883 patients fulfilled our inclusion criteria. Among these patients, 521 (59.0%) underwent P/PA lymphadenectomy and 57 (10.9%) had positive lymph nodes. Of patients who did not undergo P/PA lymphadenectomy (N = 362) or had negative nodes (N = 464), 10 (1.2%) patients (2 and 8 from each of the respective groups) had P/PA lymph node recurrence. Of the 10 patients determined to have a P/PA lymph node recurrence, the median time to recurrence was 2 years (range, 0.1–5.7 years). Among the 8 patients who developed subsequent P/PA lymph node recurrences, 5 patients had an isolated pelvic lymph node recurrence and 1 patient developed a recurrence in both the pelvic and inguinal nodes. The remaining 2 patients had a paraaortic lymph node recurrence in addition to positive mediastinal and supraclavicular lymph nodes, respectively. In 4 out of 8 patients with recurrent disease, confirmation of diagnosis was made with a diagnostic biopsy or at the time of secondary debulking surgery. Overall, 67 patients (7.6%) were confirmed to have evidence