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Prediction of lymphatic dissemination in endometrioid endometrial cancer: Comparison of three risk-stratification models in a single-institution cohort

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HIGHLIGHTS

- The models were similarly accurate in predicting lymphatic dissemination in endometrial cancer.
- The proportions of patients at low risk for lymphatic dissemination differed.
- The models also predicted disease specific survival in patients with stage I disease.

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ABSTRACT

Objectives. To compare the performance characteristics of 3 risk-stratification models, referred to as Mayo, Helsinki and Milwaukee models, in predicting lymphatic dissemination in endometrial cancer.

Methods. A total of 1052 patients with stage I–III endometrioid endometrial cancer were included in the study. The areas under curve were compared with the receiver operating characteristic curve area comparison test. Chi-square and Fisher exact test were used for comparing categorical variables. The Kaplan-Meier method and multivariable Cox regression models were used for survival analyses. The median follow-up time was 55 months (range 1–108).

Results. Areas under curve were 0.781, 0.830 and 0.829 for the Mayo, Helsinki ($P = 0.285$ vs. Mayo) and Milwaukee ($P = 0.292$ vs. Mayo) models, respectively, in predicting lymphatic dissemination. The rates of false negatives and false positives were similar for all models. The lymphadenectomy rate decreased in the order of Mayo model (71.5%) > Helsinki model (62.4%) > Milwaukee model (48.8%). In patients with stage I cancer, disease specific survival was better for those who satisfied low-risk criteria according to any of the models. In patients with stage II–III cancer, this difference in survival was significant only for the Milwaukee model. Both lymphatic dissemination and high-risk tumor features as per the risk models were independent predictors of survival.

Conclusions. The studied models had a similar accuracy in predicting lymphatic dissemination in endometrial cancer. Lymphadenectomy rate was lowest for the Milwaukee model. Survival analyses suggest that variables included in the models predict patient outcome independently of tumor stage.

1. Introduction

The surgical treatment of patients with apparent early low-risk endometrial cancer consists of total hysterectomy with bilateral salpingo-oophorectomy. Pelvic-aortic lymphadenectomy is undertaken in high-risk patients for accurate staging, which improves prognostication and allows triage for tailored adjuvant treatment [1].

The recognition of true low-risk endometrial cancers remains a challenge. In clinical practice, risk-stratification is mainly based on preoperative or intraoperative identification of the features of the primary tumor ("uterine risk factors"), sometimes combined with tumor markers in serum. A proper risk-stratification method is accurate, and concurrently associated with an acceptable lymphadenectomy rate. Ideally, it should also facilitate the prediction of patient survival.

In 2000, Mariani et al. introduced a risk-stratification schema that is now vastly utilized to define low-risk endometrial cancers [2]. According to these Mayo criteria, named after the Mayo Clinic, Rochester, MN, the low-risk group is comprised of tumors with grade 1–2

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endometrioid histology, myometrial invasion ≤50%, and diameter ≤2 cm. Subsequently, Bogani et al. developed a 5-category risk-stratification system based on frozen section analysis where also noninvasive endometrioid carcinomas are included as low-risk cases, regardless of grade and size [3]. Recently, Cox Bauer et al. at the Aurora Sinai Medical Center and St. Luke's Medical Center, Milwaukee, WI, introduced a schema for endometrioid carcinomas that contains depth of myometrial invasion and tumor size as parameters for identifying patients at low risk for lymph node involvement, with low-risk criteria being satisfied when the depth of invasion is ≤33% and diameter ≤50 mm, regardless of grade [4]. This schema was based on findings on final pathology but the variables were considered potential intraoperative predictors of lymphatic dissemination. Notably, the authors reported that these novel low-risk criteria allow for an additional 20% of patients to be spared surgical lymph node assessment, compared with the Mayo criteria. We have earlier demonstrated a combined preoperative and intraoperative scoring system for a prediction of stage IIIC–IV endometrial cancer [5]. Patients at low risk for an advanced disease were those with a normal platelet count and CA125 value, and grade 1–2 endometrioid carcinoma of <3 cm in size according to preoperative histology and gross visual inspection.

To test the universal applicability of the risk models by Bogani et al. [3] and Cox Bauer et al. [4], we validated the findings of the original studies in our own cohort of endometrial cancer patients. The performance characteristics of the 2 models were compared with our own published model [5]. Further, we assessed the value of each model as a prognostic tool in endometrial cancer.

2. Materials and methods

Patients who underwent primary surgical treatment for stage I-IIIC endometrioid endometrial cancer at the Department of Obstetrics and Gynecology, Helsinki University Hospital, between January 1, 2007 and December 31, 2013 were included in this study ($n = 1052$). Carcinosarcomas ($n = 16$) were included as high grade endometrioid carcinomas [6]. Indications for lymphadenectomy in our cohort have been reported earlier [7]. Briefly, the initial strategy was to perform pelvic lymphadenectomy routinely in all patients, and para-aortic lymphadenectomy selectively in patients considered to be at highest risk for lymph node metastasis. As of January 2012, routine pelvic lymphadenectomy was abandoned and the decision on lymphadenectomy was based on preoperative histology and assessment of local disease spread by magnetic resonance imaging. Pertinent patient characteristics and surgical and pathology data are shown in Table 1. Stage was determined according to the International Federation of Gynecology and Obstetrics (FIGO) guidelines revised in 2009 [8].

We compared 3 risk-stratification models for endometrioid endometrial cancer, referred to in the following as Mayo [3], Helsinki [5] and Milwaukee [4] models. For each model, the area under the receiver operating characteristic curve was built. Unlike the previously reported Mayo criteria [3,9], frozen section analysis was not available to us for review. Thus, women were identified as being at low risk for nodal metastasis based on modified Mayo criteria: grade 1–2 endometrioid histology, myometrial invasion <50% and diameter <2 cm on final pathology reports [10], and noninvasive cancers of any grade and size [3]. Findings on final pathology were also used for validation of the Helsinki and Milwaukee models. Similar to the Cox Bauer study [4], we restricted our analysis to stage I–IIIC cancers of the endometrioid type, although the original Helsinki model also considered stage IV and nonendometrioid carcinomas [5]. Risk schemas for the different models are detailed in Table 2. Patients with available data for all risk parameters considered in each model were included in the calculations ($n = 1045$ for the Mayo model, $n = 881$ for the Helsinki model, $n = 987$ for the Milwaukee model).

For the Helsinki model, pretreatment serum CA125 concentration was quantitated with the chemiluminescent microparticle immunoassay on the Abbott Architect 2000i Analyzer (Abbott Diagnostics, Abbott Park, IL). The concentration was considered increased when >35 U/mL [11]. Last pretreatment platelet count was analyzed by electrical impedance technology and flow cytometry. Thrombocytosis was defined as a platelet count $>360 \times 10^9$/L [12].

The areas under curve were compared with the 2-tailed receiver operating characteristic curve area comparison test. Chi-square and Fisher

Table 1
Clinicopathologic data ($n = 1052$).

Age (years) (mean ± SD)	67.2 ± 10.4
Body mass index (kg/m^2) (mean ± SD)[a]	28.7 ± 6.3
Pelvic lymphadenectomy (number of cases, percent)	550 (52.3%)
Pelvic-aortic lymphadenectomy (number of cases, percent)	134 (12.7%)
Lymph node yield, pelvic lymphadenectomy (mean ± SD)[b]	15.3 ± 8.0
Lymph node yield, pelvic-aortic lymphadenectomy (mean ± SD)[c]	26.1 ± 9.9
Laparoscopic hysterectomies (number of cases, percent)[d]	859 (81.7%)
Adjuvant therapy (number of cases, percent)	
Vaginal brachytherapy	497 (47.2%)
Whole pelvic radiotherapy	144 (13.7%)
Chemotherapy	20 (1.9%)
Chemotherapy and vaginal brachytherapy	27 (2.6%)
Chemotherapy and whole pelvic radiotherapy	107 (10.2%)
Grade (number of cases, percent)	
Grade 1	642 (61.0%)
Grade 2	264 (25.1%)
Grade 3[e]	146 (13.9%)
FIGO 2009 stage (number of cases, percent)	
IA	653 (62.1%)
IB	216 (20.5%)
II	60 (5.7%)
IIIA	43 (4.1%)
IIIB	7 (0.7%)
IIIC1	51 (4.8%)
IIIC2	22 (2.1%)

[a] Number of cases 1051 (body mass index missing for 1 patient).
[b] Number of cases 542 (lymph node yield missing for 8 patients).
[c] Number of cases 132 (lymph node yield missing for 2 patient).
[d] Traditional laparoscopic hysterectomies, $n = 789$; robotic hysterectomies, $n = 70$.
[e] Including 16 carcinosarcomas.

Table 2
Risk-stratification schemas.

Mayo	Low risk
	TD <2 cm, grade 1 or 2, MI <50%
	MI 0%, any TD or grade
	Low-intermediate risk
	TD ≥2 cm or unknown, grade 1 or 2, MI <50%
	High-intermediate risk
	Grade 1 or 2, 50% < MI ≤ 66%
	Grade 3, MI <50%
	High risk
	Grade 1 or 2, MI >66%
	Grade 3, MI ≥50%
	Adnexal metastasis
Helsinki	Low risk
	0 risk score points[a]
	Low-intermediate to high risk
	1–8 risk score points
Milwaukee	Low risk
	TD ≤50 mm, any grade, MI ≤33%
	Low-intermediate risk
	TD >50 mm, any grade, MI ≤33%
	TD ≤50 mm, any grade, 33% < MI ≤ 66%
	TD ≤50 mm, grade 1, MI >66%
	High-intermediate risk
	TD >50 mm, grade 1, 33% < MI ≤ 66%
	TD ≤50 mm, grade 2 or 3, MI >66%
	High risk
	TD >50 mm, any grade, MI >66%
	TD >50 mm, grade 2 or 3, 33% < MI ≤ 66%

MI, myometrial invasion; TD, tumor diameter.
[a] 1 point for thrombocytosis, 2 points for poor differentiation (grade 3), 2 points for TD ≥3 cm, 3 points for CA125 >35 U/mL.

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