

How low is low enough? Evaluation of various risk-assessment models for lymph node metastasis in endometrial cancer: a Korean multicenter study

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Objective: The aim of this study was to identify a standard for the evaluation of future models for prediction of lymph node metastasis in endometrial cancer through estimation of performance of well-known surgicopathological models.

Methods: Using the medical records of 947 patients with endometrial cancer who underwent surgical management with lymphadenectomy, we retrospectively assessed the predictive performances of nodal metastasis of currently available models.

Results: We evaluated three models included: 1) a model modified from the Gynecologic Oncology Group (GOG) pilot study; 2) one from the GOG-33 data; and 3) one from Mayo Clinic data. The three models showed similar negative predictive values ranging from 97.1% to 97.4%. Using Bayes' theorem, this can be translated into 2% of negative post-test probability when 10% of prevalence of lymph node metastasis was assumed. In addition, although the negative predictive value was similar among these models, the proportion that was classified as low-risk was significantly different between the studies (56.4%, 44.8%, and 30.5%, respectively; $p < 0.001$).

Conclusion: The current study suggests that a false negativity of 2% or less should be a goal for determining clinical usefulness of preoperative or intraoperative prediction models for low-risk of nodal metastasis.

Keywords: Endometrial cancer, Low-risk group, Lymph node dissection, Lymphadenectomy, Prediction, Sensitivity and specificity

INTRODUCTION

Despite recently published randomized trials suggesting no survival benefit for routine lymphadenectomy in endometrial

cancer [1,2], full pelvic and paraaortic lymphadenectomy is still recommended by many gynecologic oncologic societies and guideline committees [3-5]. However, although there is ongoing controversy concerning the benefit of routine lymphadenectomy [6-8], the general consensus is that there is a certain subset of patients in which the omission of routine lymphadenectomy may be justified [9-11].

For several decades, researchers have proposed several models to predict patients at low-risk for nodal metastasis [12-15]. Most of these prediction models were designed using surgicopathological parameters, such as depth of myometrial

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Table 1. Description of three surgicopathological prediction models for the low-risk group of lymph node metastasis in endometrial cancer

Model	Description
Model A [11,12]	Endometrium only, any grades
	No myometrial invasion or invasion $\leq 50\%$, grades 1 and 2 or invasion $\geq 50\%$, grade 1
	No lymphovascular space invasion/ no cervix or adnexa invasion
Model B [13]	Endometrioid histology
	No myometrial invasion, any grades or invasion $\leq 50\%$, grade 1
	No intraperitoneal disease
Model C [14]	Endometrioid histology
	Myometrial invasion $\leq 50\%$, histologic grades 1-2
	Primary tumor diameter ≤ 2 cm
	Endometrioid histology

invasion or pathological grade [13,14,16,17]. Therefore, it has been frequently challenged whether we can apply frozen section results in these models due to the inaccuracy of frozen section examination [18,19], and many have claimed that routine lymphadenectomy is unavoidable [20].

Although many researchers have suggested several methods to identify the low-risk group of nodal metastasis before lymphadenectomy [21-25], many gynecologic oncologists are still skeptical about these results [26]. Moreover, there has been no consensus about the desirable performance of a prediction method. The American Society of Breast Surgeons recommended a false-negative rate of 5% or less in order to abandon axillary dissection [27]. Then, how should an acceptable false-negative rate of lymph node metastasis be determined in endometrial cancer?

To answer these questions, we began a multi-institutional, retrospective study. If we are able to estimate the innate false-negative rate of the final pathology-based models, we may also use that as a tool for determining clinical usefulness of pre- or intra-operative prediction models which are in development.

MATERIALS AND METHODS

1. Patient selection

Using data from eight independent institutions, we retrospectively reviewed the medical records and pathological findings of patients surgically treated for endometrial cancer between 2000 and 2006. A total of 1,298 patients were identified after approval from the institutional review board. A part of the dataset has been used in previous reports; eligibility for the study and treatment strategy have been described previously [28]. Briefly, patients with histologically confirmed

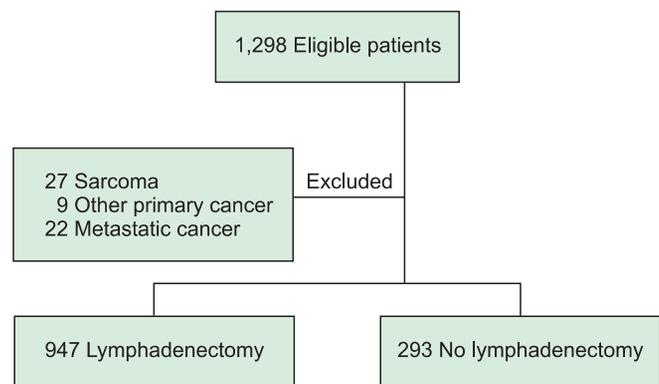


Fig. 1. Flowchart of patient selection process.

endometrial cancer who underwent surgical management, including hysterectomy, were enrolled in the study. At all institutions, patients were consecutively enrolled and defined using the selection criteria. Exclusion criteria were as follows: histologic diagnosis of sarcoma including carcinosarcoma, double primary tumor, or other metastatic cancer. Our study was designed and analyzed as recommended by the Standards for Reporting Diagnostic Accuracy Steering Group [29].

As an index test, three models predicting low-risk groups based on pathologic data were used. These included the following: 1) criteria modified from the GOG pilot study suggested by Boronow et al. [12,13] (Model A) ; 2) criteria modified from the GOG-33 data suggested by Creasman et al. [14] (Model B) ; and 3) the Mayo clinic criteria suggested by Mariani et al. [15,21] (Model C) . Detailed descriptions of these models are summarized in Table 1.

The reference standard was defined as the final pathologic diagnosis of the harvested lymph nodes. Central pathologic review was not performed, as pathologists from each participating center assessed lymph node status. No restriction of harvested lymph nodes was applied if one or more lymph

Table 2. Characteristics of the 1,240 patients included in the analysis

Characteristic	Lymphadenectomy (n=947, 76.4%)	No lymphadenectomy (n=293, 23.6%)	p-value
Age (yr)	53 (22-93)	51 (28-84)	0.287
Body mass index	24.5 (14.0-67.9)	24.2 (17.1-43.1)	0.478
Menopause			0.260
No	344 (36.3)	122 (41.6)	
Yes	530 (56.0)	150 (51.2)	
Unknown	73 (7.7)	21 (7.2)	
Stage			<0.001
I	660 (69.7)	229 (78.2)	
II	74 (7.8)	17 (5.8)	
III	180 (19.0)	15 (5.1)	
IV	16 (1.7)	9 (3.1)	
Unknown	17 (1.8)	23 (7.8)	
Histologic type			0.674
Endometrioid	846 (89.3)	250 (85.3)	
Non-endometrioid	97 (10.2)	26 (8.9)	
Unknown	4 (0.4)	4 (0.4)	
Grade			0.001
I	476 (50.3)	165 (56.3)	
II	240 (25.3)	59 (20.1)	
III	112 (11.8)	14 (4.8)	
Unknown	119 (12.6)	55 (18.8)	
Myometrial invasion			<0.001
No invasion	231 (24.4)	133 (45.4)	
Superficial (<50%)	401 (42.3)	89 (30.4)	
Deep (>50%)	289 (30.5)	37 (12.6)	
Unknown	26 (2.8)	34 (11.6)	
Lymphovascular space invasion			0.001
No	714 (75.4)	225 (76.8)	
Yes	211 (22.3)	35 (12.0)	
Unknown	22 (2.3)	33 (11.2)	
Extrauterine involvement			<0.001
No	750 (79.2)	264 (90.1)	
Yes	197 (20.8)	29 (9.9)	
No. of harvested lymph nodes	25 (1-137)	NA	
Lymph node metastasis			
No	819 (86.5)	NA	
Yes	128 (13.5)		
Paraaortic node dissection			
No	566 (59.8)	NA	
Yes	381 (40.2)		
No. of harvested paraaortic nodes	8 (1-51)	NA	
Paraaortic node metastasis			
No	329 (86.4)	NA	
Yes	52 (13.6)		

Values are presented as number (%) or median (range).
NA, not available.

nodes were harvested. Instead, we categorized optimal and suboptimal lymphadenectomy based on the number of harvested lymph nodes. Optimal lymphadenectomy was arbitrarily defined as more than ten harvested nodes and four or more harvested paraaortic nodes [30,31].

2. Statistical analysis

All statistical analyses were performed using STATA ver. 11.0 (STATA, College Station, TX, USA). To estimate continuous variables, Student’s t-test and the Wilcoxon rank-sum test were used. For categorical variables, chi-square and Fisher exact tests were used. All p-values presented are two-sided, and associations are considered significant if the p-value is <0.05.

To assess the performance of models predicting low-risk groups for lymph node metastasis, we selected the negative likelihood ratio (LR) as a primary endpoint [32,33]. We concluded that the negative predictive value was not an adequate endpoint, as negative predictive value is vulnerable to the prevalence of events. Using Bayes’ theorem, the negative post-test probability (PTP) was derived from the negative LR based on the assumed pre-test probability of lymph node metastasis as 10%. PTP was calculated as: post-test odds/(post-test odds+1), where post-test odds is calculated as: prevalence/(1-prevalence) × sensitivity/(1-specificity).

RESULTS

The records of 1,298 patients who received surgical management for uterine cancer were reviewed (Fig. 1). Of the 1,298 patients, 58 patients were excluded because of a diagnosis of non-epithelial cancer including carcinosarcoma, double primary tumor, or other metastatic cancer. Furthermore, 293 patients who did not undergo lymph node dissection were excluded. The characteristics of the remaining 947 patients are summarized in Table 2. As expected, the distribution of

stage, tumor grade, myometrial invasion, lymphovascular space invasion (LVSI), and extra-uterine involvement were significantly different between the lymphadenectomy versus non-lymphadenectomy groups, representing the tendency to avoid lymphadenectomy in cases with fewer risk factors.

The negative predictive values (NPVs) and negative LRs were not statistically different among the three models (Table 3). However, the proportion of patients classified as low-risk group was significantly different among the models. Model A, which included LVSI information, identified the largest number of patients as a low-risk group (56.4%) without hampering the negative predictive value. Model C identified the smallest low-risk group (30.5%), although its predictive performance was similar to that of other models. In addition, using Bayes’ theorem, the negative PTP could be calculated at the 10% of assumed prevalence of lymph node metastasis (Table 3). All models indicated that false negative rate might be 2% when the prevalence of lymph node metastasis was 10%.

DISCUSSION

In the current study, we compared the predictive performance of various prediction models to identify a low-risk group in a large cohort of patients with endometrial cancer. Several clinical implications suggested by our data are as follows.

First, our study revealed that three models based on surgical pathology showed similar negative predictive powers. Our data suggest that the low-risk group can be identified with a false negativity rate of 2% by final pathologic data (Table 3), regardless of the choice of prediction model. Second, although the false negativity of these models was similar, the model from the Gynecologic Oncology Group (GOG) pilot study [12,13], which included LVSI as a predictor, was able to identify the largest number of patients (56%) as a low-risk

Table 3. Comparison of model performance in predicting a low-risk group of nodal metastasis

Model	Total		Lymphadenectomy group		
	Proportion of low-risk group	Proportion of low-risk group	Negative predictive value	Negative likelihood ratio	Negative post-test probability
Model A	55.8* (52.6-60.1)	56.4 (52.6-60.1)	97.4 (95.3-98.7)	0.20 (0.11-0.35)	2 (1-4)
Model B	44.8 (42.1-47.6)	44.8 (41.1-48.5)	97.4 (94.9-98.9)	0.20 (0.10-0.38)	2 (1-4)
Model C	33.2 (30.7-35.9)	30.5 (27.2-34.1)	97.1 (93.8-98.9)	0.22 (0.10-0.47)	2 (1-5)

Values are presented as percentage (95% confidence interval).

*Comparison with model B and C yielded p<0.001 for both comparisons (chi-square test).

group. The proportions of patients in the low-risk group identified using those two models (A and C) were significantly different.

In summary, even with final pathologic data, the currently available prediction identifying the low-risk group of lymph node metastasis in endometrial cancer has a false negative rate about 2% at 10% of the assumed prevalence. Therefore, future pre-/intra-operative prediction models may be regarded as clinically useful if the model shows a false negative rate less than 2%, when the prevalence of nodal metastasis was assumed as 10%.

CONFLICT OF INTEREST

No potential conflict of interests relevant to this article was reported.

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