Preoperative Prediction Model of Lymph Node Metastasis in Endometrial Cancer

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Background: We aimed to develop a preoperative prediction model identifying the low-risk group for lymph node metastasis in endometrial cancer.

Methods: In 110 patients who underwent preoperative magnetic resonance imaging and serum CA-125 test, logistic analysis was performed to identify predictors. The coefficients obtained from logistic regression were used to construct a scoring system, and a receiver operator characteristic curve was created.

Results: Lymph node metastases were found in 14 (12.7%) of 110 patients. After multivariate logistic regression analysis, histologic grade, preoperative CA-125 levels, disease extent, and myometrial invasion assessed by magnetic resonance imaging were selected as viable predictors. The scoring system was internally validated using bootstrapping ($P < 0.001$), and receiver operator characteristic curve yielded the area under the curve of 0.902. The patients with the score of 0 or 1 (57.3%) were identified as a low-risk group, and no nodal metastasis was observed among them (negative predictive value, 100%: 95% confidence interval, 94.3%–100%).

Conclusion: The current study suggests that preoperative prediction system to identify the risk of lymph node metastasis is feasible. This model may be useful in preoperative counseling about cost and benefit of systemic lymph node dissection.

Key Words: Endometrial cancer, Risk factor, Lymph node metastasis, Surgical staging, Magnetic resonance image

Received March 1, 2010, and in revised form July 12, 2010.
Accepted for publication July 28, 2010.

(*Int J Gynecol Cancer* 2010;20: 1350–1355)

Lymph node metastasis is found in 9% of patients with early-stage endometrial cancer[1] and is the most important prognostic factor.[2–4] However, whether to perform routine lymph node dissection has been debated. Because of a number of evidences negating its contribution to improvement of survival,[5,6] some have denied the usefulness of the routine systematic lymph node dissection. Indeed, 2 randomized trials indicated that the routine lymph node dissection did not improve disease-free survival and overall survival in endometrial cancer.[7,8] Moreover, there have been no prospective data to claim the therapeutic benefit of routine lymph node dissection.

In contrast, many gynecologic oncologists still advocate the routine lymph node dissection because it may be important in determining prognosis and tailoring adjuvant therapy.[7,9] Nevertheless, it is evident that the procedure does not only have the benefit. The procedure is associated with statistically longer operating time and more late postoperative complications such as lymphedema.[7–9] Thus, several

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This study was funded by National Cancer Center, Korea (Grant No. 0910260-2).
The authors declare that they have no conflict of interest.

ISSN: 1048-891X
DOI: 10.1111/IGC.0b013e3181f44f5a

investigators explored a way to predict a risk of lymph node metastasis before deciding whether to perform lymph node dissection. Based on data from GOG 33, it is well-known that a risk of lymph node metastasis is low in the disease with grade 1 histology and/or no myometrial invasion.[1] Furthermore, Mariani et al[10] have suggested the criteria determining a low-risk patient that lymph node dissection can be safely omitted in. They claimed that patients who have International Federation of Gynecology and Obstetrics grade 1 or 2 endometrioid corpus cancer with greatest surface dimension of 2 cm or less, myometrial invasion of 50% or less, and no intraoperative evidence of macroscopic disease can be treated optimally with hysterectomy only. In addition, the authors prospectively observed that the 22 patients classified into the low-risk group had no metastasis.[11] However, the prediction model has a limitation. Because the model requires an intraoperative assessment of the uterus, physicians cannot share the information with the patient in their counseling.

Therefore, we wanted to construct a preoperative prediction model for lymph node metastasis to identify the low-risk group. Instead of using the data from intraoperative assessment of the uterus, we used those that can be obtained before operation, such as image parameters from magnetic resonance imaging (MRI) and serum concentration of CA-125. By doing so, our prediction model enables physicians to counsel their patients with the estimated risk of lymph node metastasis preoperatively.

MATERIALS AND METHODS

We retrospectively reviewed the medical records of patients treated for endometrial carcinoma between July 1, 2001, and December 31, 2008. After excluding nonepithelial tumors, a total of 110 patients were selected for the analysis subsequently. All the patients had primary, previously untreated, and histologically confirmed endometrial cancer. The inclusion criteria for analysis were as follows: (1) patients who underwent adequate surgical staging and systematic pelvic and para-aortic lymph node dissection, (2) available preoperative MR image and serum CA-125 within 4 weeks' interval from the operation, and (3) preoperative assessment of histologic type and grade using endometrial biopsy.

Surgical staging and systematic lymph node dissection were performed according to institutional practice guidelines—in brief, type 1 hysterectomy, bilateral salpingo-oophorectomy, and systematic pelvic and para-aortic lymph node dissections. All lymphatic tissue and fat tissue around the vessel were removed for biopsy. Pelvic lymph node dissection was performed along common, external iliac, internal iliac, and obturator vessels. The minimum extent of para-aortic lymph node dissection was at the level of inframesenteric artery. Para-aortic lymph node dissection was allowed to be omitted if the patient has grade 1 endometrial cancer, and myometrial invasion was not observed. Methods of surgical procedure in laparotomy or laparoscopy were selected according to the surgeon's preference and the patient's condition. Type 2 or 3 hysterectomy was performed on clinical stage II endometrial cancer. All surgeries were performed under the charge of gynecologic oncologists.

In endometrial cancer, preoperative MRI was routinely performed according to the policy of institution. Magnetic resonance imaging was performed using a 1.5-T system with a pelvic array coil for pelvic scans and a torso phase-array coil for para-aortic scans. Scans were obtained by using the following parameters: extent of myometrial invasion, tumor metastasis in pelvic and para-aortic lymph nodes, and evidence of extrauterine extension of tumor. Myometrial invasion was categorized into 3 levels: (1) no invasion, (2) invasion of less than one half of the myometrium, and (3) invasion of more than one half of the myometrium. The nodal status was categorized into 2 levels: (1) no evidence of lymph node metastasis and (2) suspicious lymph node metastasis with a short-axis dimension of 1 cm or greater. All the image data were interpreted by 2 experienced

TABLE 1. Clinical characteristics of the study population

	N = 110 (%)
Age (median, range)	52 (23–76)
FIGO surgical stage	
IA	36 (32.7)
IB	37 (33.6)
IC	5 (4.6)
II-III	32 (29.0)
Grade	
1	57 (51.8)
2	38 (34.6)
3	15 (13.6)
Histology	
Endometrioid	102 (92.7)
Nonendometrioid	8 (7.3)
Myometrial invasion	
No myometrial invasion	37 (33.6)
Less than half of myometrium	49 (44.6)
More than half or myometrium	24 (21.8)
Tumor size	
<2 cm	40 (39.2)
2 cm or more	62 (60.8)
Preoperative serum CA125 (median, range)	18.3 (5.0–788.0)
Lymph node metastasis	
Absent	96 (87.3)
Present	14 (12.7)
Number of harvested nodes (mean, range)	
Pelvic nodes	20.5 (2–48)
Para-aortic nodes	8.2 (0–23)
Pelvic and para-aortic nodes	28.7 (4–65)

All the parameters listed above were determined after surgery based on final pathologic assessment.

radiologists blinded to the results of surgery. Histopathologic evaluation of endometrial biopsy was performed by 2 experienced pathologists. Thin sections were stained with hematoxylin and eosin and were examined microscopically. Each lymph node was sliced at maximum of 3-mm intervals perpendicular to the greatest dimension.

All statistical analyses were performed using STATA software (Version 10.0, College Station, Tex). The χ^2 or the Fisher exact test was used to analyze the frequency distribution. To estimate continuous variables, the Student *t* test and the Wilcoxon rank-sum test were used. To obtain an odds ratio and a regression coefficient of each parameter, univariate and multivariate logistic regression analyses were used. To convert continuous parameter into a dichotomizing categorical parameter, receiver operator characteristic (ROC) curve was constructed, and the cutoff value providing the best accuracy was selected. After obtaining the regression coefficient of each parameter, the score weighted according to the coefficient was assigned to each parameter. The association of summarized score with the risk of lymph node metastasis was tested with logistic regression analysis. To validate this internally, bootstrapping method was applied with 200 repetitions. The bootstrapping method is a validating method that repeatedly analyzes subsamples of the data, and each subsample is a randomly selected sample with replacement from the full sample. The predictive performance of summarized score was tested by ROC curve, and performance indicators such as sensitivity and specificity were described. Because we wanted to identify the low-risk group, negative likelihood ratio (LR) was used to determine the cutoff of summarized score. The formula for a negative LR is (1 − sensitivity)/specificity. In general, it was believed that LRs of more than 10 or less than 0.1 generate large conclusive changes and LRs between 5 to 10 and 0.1 to 0.2 are associated with moderate changes in probability.[12] In the current study, a positive LR of more than 5 and a negative LR of less than 0.2 were defined as a clinically useful test.

RESULTS

The characteristics of 110 patients selected for the model analysis are summarized in Table 1. The median age was 52 years, and 92.7% of the patients had endometrial histology. The average numbers of harvested pelvic lymph nodes and of para-aortic nodes were 20.5 and 8.2 (Table 1). Lymph node metastases were found in 12.7% of the patients. Metastases to pelvic nodes and para-aortic nodes were found in 12 (10.9%) of 110 and 5 (5.3%) of 95 patients. Systematic para-aortic lymph node dissection was omitted in 15 cases (13.6%) that had no myometrial invasion. After an average follow-up of 49 months, no recurrence was found among them, and these cases were regarded as having no para-aortic nodal metastasis in the current analysis. When we compared the MRI-based assessment of myometrial invasion with pathologic assessment after surgery, 22.7% of the cases were upstaged and 20.0% of the cases were downstaged after pathologic evaluation. In tumor grade, 10.9% were upgraded and 7.2% were downgraded after pathologic evaluation.

Among the diagnostic parameters obtained by MRI, disease extent and myometrial invasion depth were selected as candidate predictors. In addition, histologic grade and subtype assessed by preoperative endometrial biopsy and initial level of CA-125 were also selected. Univariate and multivariate logistic regression analyses were performed (Table 2). In univariate analysis, the predictors correlated with the lymph node metastasis were as follows: disease extension beyond uterine corpus at MR image including lymph node metastasis, half or more myometrial invasion at MRI, grade 3 histology, nonendometrioid histology, and preoperative serum CA-125. After a multivariate stepwise backward logistic regression,

TABLE 2. Logistic regression model predicting lymph node metastasis using the preoperative information

	Univariate		Multivariate	
	Odds Ratio (95% CI)	***P***	**Odds Ratio (95% CI)**	***P***
Extent of disease (MRI)				
Extension beyond corpus	1.8 (1.1–2.8)	0.015	7.4 (1.3–41.0)	0.022
Myometrial invasion depth (MRI)				
Less than half	5.3 (0.6–50.0)	0.143	9.0 (0.6–143.2)	0.119
Half or more	20.8 (2.5–176.2)	0.005	22.6 (1.7–298.3)	0.018
Histologic grade				
Grade 2	3.9 (0.9–16.1)	0.061	3.7 (0.6–24.5)	0.170
Grade 3	9.2 (1.7–48.7)	0.009	24.0 (2.2–262.0)	0.009
Histologic type				
Nonendometrioid	5.0 (1.04–23.7)	0.044	NA*	NA
Preoperative CA-125	7.8 (2.4–26.0)	0.001	11.1 (2.60–59.60)	0.006

*Not available because it was dropped out during stepwise analysis (cutoff α-error, 0.25).
NA, not available.

TABLE 3. Multivariate logistic model for prediction of lymph node metastasis and coefficient-based prediction score

	Regression Coefficient (95% CI)	*P*	Prediction Score
Preoperative CA125			
>70 U/mL	2.2 (0.7–3.7)	0.005	1
Myometrial invasion depth (MRI)			
Any depth of invasion	2.5 (0.1–4.8)	0.038	1
Preoperative histologic grade			
Grades 2–3	1.8 (0.1–3.5)	0.035	1
Extent of disease (MRI)			
Extension beyond corpus	1.5 (0.1–2.91)	0.047	1

the parameters that showed significant correlation were extension of disease, myometrial invasion depth of 1/2 or greater, histologic grade 3 disease, and preoperative CA-125 levels.

With these parameters, coefficients of logistic regression were obtained (Table 3). To convert CA-125 into a categorical parameter, the ROC curve was used. The area under the curve was 0.734, and the maximum accuracy was observed at the cutoff of approximately 70 U/mL, which is 2 times the upper normal level of CA-125. Although the 2 parameters, grade 2 histology and myometrial invasion of less than ½, were not significantly correlated, we integrated these into grade 3 histology and myometrial invasion of ½ or greater. The reasons were as follows: first, we wanted to create a model to allow an inaccuracy of preoperative evaluation tools such as MRI or endometrial biopsy; second,

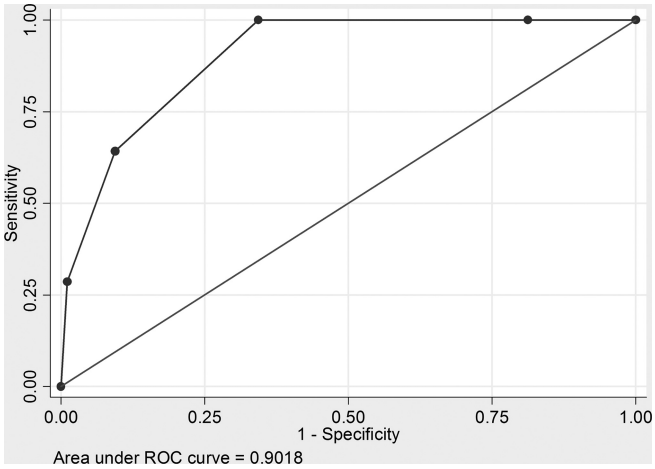

FIGURE 1. Receiver operator characteristics curve of scoring system for preoperative assessment of lymph node metastasis.

TABLE 4. Diagnostic performance of the scoring system in prediction of lymph node metastasis

Cutoff Score	Sensitivity (%)	Specificity (%)	Positive LR	Negative LR
1	100.0	18.75	1.23	0
2	100.0	65.6	2.91	0
3	64.3	90.6	6.86	0.39
4	28.6	99.0	27.4	0.72

because our sample size was limited, we wanted to use a wider α-error to pick up risk factors. Because all the confidence intervals (CIs) of the coefficients were not significantly different across the parameters (1.5–2.5 with overlapped CI), we allocated a prediction score of 1 to each parameter instead of using the individual coefficient. The calculated score was significantly associated with the nodal metastasis ($P < 0.001$), and it was internally validated using rigorous bootstrapping method with 200 repetitions.

The predictive performance of the model was investigated. Using the score system, the ROC curve was constructed (Fig. 1), and the calculated area under the curve was 0.902. The diagnostic performance at each cutoff score is summarized in Table 4. At the cutoff score under 2, the negative LR was 0 for prediction of nodal metastasis. The negative predictive value (NPV) was 100% (95% CI, 94.3%–100%). Thus, the cases with the score of 0 or 1 were classified into the low-risk group. Meanwhile, at the cutoff of 3, the positive LR was over 5.0 and the specificity was 90.6%. Therefore, the cases with a score of 3 or 4 were classified into the high-risk group. The remaining cases, with score of 2, comprised the intermediate-risk group. The number of patients of each risk category and the frequency of nodal metastasis are summarized in Table 5. The cases classified as low-risk group had no pelvic node metastasis, whereas the cases classified as intermediate group showed 17.2% of pelvic nodal metastasis. In high-risk group, the frequency of pelvic nodal metastasis was 50.0%. In para-aortic metastasis, the cases classified as low-risk group had no para-aortic metastasis, whereas the cases classified as

TABLE 5. Frequency of lymph node metastasis among the classified risk groups

	No. Patients (%)	Lymph Node Metastasis (%)	Para-Aortic Node Metastasis (%)
Low-risk group (score 0 or 1)	63 (57.3)	0/63 (0)	0/50 (0)
Intermediate-risk group (score 2)	29 (26.4)	5/29 (17.2)	2/29 (6.9)
High-risk group (score 3 or 4)	18 (16.3)	9/18 (50.0)	3/16 (18.8)

intermediate group showed 6.9% of para-aortic nodal metastasis. In high-risk group, the frequency of para-aortic nodal metastasis was as much as 18.8%.

DISCUSSION

In the current analysis, we proposed a new prediction model using several preoperative variables. With the current data as our basis, we propose 4 prediction criteria for the prediction of nodal metastasis in endometrial cancer (Table 3). If a patient has 0 or 1 predictor suggested above, she can be classified in the low-risk group. Thus, systematic lymph node dissection is not recommended in this group. However, in the cases with score of more than 1, the systematic lymph node dissection, including para-aortic lymph node dissection, may be considered for accurate staging or planning further treatment.

Our prediction model has several strengths. First, using the model, we identified 57.3% of the analyzed patients as belonging to the low-risk group, and no one experienced any metastasis in either of pelvic and para-aortic lymph nodes. For comparison, the prediction criteria of Mariani et al identified 33% of the patients as belonging to the low-risk group.[11] Second, all predictors could be obtained preoperatively. So the results can be used in counseling with the patients about risk and benefit of lymphadenectomy or referring high-risk patients to specialized gynecologic oncologists for comprehensive surgical staging including systematic lymphadenectomy.

In endometrial cancer, the prediction system using preoperative factors such as diagnostic image or serum biomarker is not that new,[13,14] although the clinical usefulness of such tools has not been elucidated. However, as a single diagnostic tool, most of the predictors were not proven to be useful in a clinical setting because even a small false-negative rate may not be acceptable in the physician's view. Thus, the prediction model using MRI, histologic assessment, and CA-125 level has been suggested. Todo et al[15] identified 51.4% of patients as belonging to a low-risk group using MRI and serum CA-125 levels as predictors. However, in the model, 3.6% of patients classified as low risk were found to have pelvic lymph node metastasis. Our model was not much different from the previous model except for a several points. First, we actively included many diagnostic information provided by MRI and integrated them into a single parameter. By doing so, we could include many important parameters such as spread of tumor to cervix, adnexa, and/or extrauterine organ. Second, instead of tumor volume, we used myometrial invasion as a parameter. Third, we allowed more α-error for the selection of predictors. However, it should not be concluded that the performance of our prediction model is superior to that of the previous model. The 95% CI of the NPV in the previous model was from 90.4% to 98.8%, whereas in our model, it ranged from 94.3% to 100%.

The current analysis had several limitations. First, as we mentioned, the limited sample size resulted in wide 95% CI of the NPV. Although it can be safely translated into maximal false-negative rate of 5.7%, this is not enough to convince many physicians to use the model in clinical practice. Unfortunately, in endometrial cancer, there is no consensus about an acceptable rate of nodal metastasis for abandoning lymph node dissection. Considering that lymph node dissection is required for the International Federation of Gynecology and Obstetrics stage IA2 cervical cancer, which has a nodal metastasis rate of 3% to 5%,[16] it can be proposed that a less than 3% nodal metastasis rate may be regarded as the required maximal acceptable rate. Thus, the promising results should be validated in larger cohort to produce reliable and narrow CI of diagnostic performance. Second, the current study has a retrospective design and may suffer from underlying biases. Third, we did not include several important predictors, such as histologic subtype, tumor size, lower uterine segment involvement, and lymphovascular invasion, into our model. Several predictors were not considered because they can be evaluated only during or after surgery. Some histologic subtypes such as papillary serous or clear cell histology may provide important information to predict nodal metastasis. Although it was not proven to be an independent predictor in our model, the inclusion of the non-endometrial histology in prediction criteria did not hamper the prognostic performance of our model. Thus, further testing is needed to verify whether the histologic subtype should be accepted in the prediction model. Fourth, because our model used diagnostic information provided by the MR image, it cannot be applied in the low-resource setting. Fifth, we did not test cutting-edge diagnostic tools such as positron emission tomography/computed tomography or MRI using novel contrast media. It may be another interesting subject to test whether these tools can improve the prediction model.

In summary, using only the preoperative diagnostic information, we propose a prediction model composed of 4 predictors (Table 3). If a patient has none or only 1 of these 4 predictors, systematic lymph node dissection may not be necessary because nodal metastasis is unlikely. The model is very simple and intuitive and can rule out the possibility of nodal metastasis with high diagnostic performance. Although it needs further validation, the model may be useful for discussing the risks and benefits of systematic lymph node dissection with the patients before surgery and referring the patients to specialized clinics.

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