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Original Article

A predictive model for lymph node metastasis using tumor location in presumed early-stage endometrioid endometrial cancer patients

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ABSTRACT

Objective: The aim of this study was to identify high- and low-risk subgroups of patients with lymph node (LN) metastasis in presumed early-stage endometrioid endometrial cancer (EC) patients.
Methods: Clinicopathologic data of presumed early-stage endometrioid EC patients (n=361) treated with lymphadenectomy between March 2000 and July 2022 were analyzed. None of the patient had definite evidence of LN metastasis in a preoperative magnetic resonance imaging (MRI). A received operating characteristic curve analysis was conducted to define the sensitivity and specificity for the combined preoperative risk factors for LN metastasis, which was determined by multivariate analysis.
Results: Nineteen patients (5.3%) had LN metastasis. Multivariate analysis identified cervical stromal invasion on MRI (odds ratio [OR]=4.386; 95% confidence interval [CI]=1.020–18.852; p=0.047), cornual location of tumor on MRI (OR=36.208; 95% CI=7.902–165.913; p<0.001), and lower uterine segment/isthmic location of tumor on MRI (OR=8.454; 95% CI=1.567–45.610; p=0.013) as independent prognostic factors associated with LN metastasis. Patients were categorized into low- and high-risk groups according to risk criteria. Significant differences in the rates of LN metastasis were observed between the two groups (0.4% vs. 22.2%, p<0.001).
Conclusion: Approximately 95% of presumed early-stage endometrioid EC patients did not have LN metastasis. A model using tumor location was significantly correlated with the risk of LN metastasis. Even in presumed early-stage endometrioid EC patients, therefore, tumor location should be investigated to determine whether to perform LN assessment.

Keywords: Endometrial Neoplasms; Lymph Nodes; Lymphatic Metastasis

Synopsis

A majority of early-stage endometrioid endometrial cancer patients did not have lymph node (LN) metastasis. Patients with LN metastasis were more likely to have tumors located in the cornua and lower uterine segment/isthmus. A careful investigation of tumor location on the magnetic resonance imaging may provide valuable guidance on LN assessment.

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

Author Contributions
Conceptualization: K.T.W., C.S.J.; Data curation: K.T.W., K.J., L.J., K.J., S.J.H.; Formal analysis: K.T.W., K.J.; Supervision: C.S.J.; Visualization: S.J.H.; Writing - original draft: K.T.W., L.J., K.J.; Writing - review & editing: S.J.H., C.S.J.

INTRODUCTION

Endometrial cancer (EC) is the most common cancer in females of developed countries and the second most common gynecological cancer in the world [1]. Type 2 ECs including uterine papillary serous carcinoma, clear cell carcinoma, and carcinosarcoma have a risk for extrauterine spread such as lymph node (LN), lung, liver, and peritoneum with a poor prognosis [2]. On the contrary, most type 1 endometrioid ECs are early-stage diseases with a good prognosis. A preoperative model for LN metastasis using data from the Surveillance, Epidemiology, and End Results database provided a more individualized and accurate estimation of LN metastasis for presumed stage I and II EC [3]. However, it had no clear definition for presumed stage I and stage II EC, and type 2 EC patients known to have a propensity for extra-uterine spread were included. Moreover, variables including tumor grade, myometrial invasion (MI), and cervical stromal invasion (CSI) were pathological hysterectomy characteristics, not preoperative variables. The Korean Gynecologic Oncology Group proposed preoperative criteria for LN metastasis using a combination of preoperative serum cancer antigen 125 (CA-125) value, preoperative tumor grade, MI on magnetic resonance imaging (MRI), and LN enlargement and extrauterine spread on MRI [4]. However, this predictive model included patients with microscopic LN metastasis as well as patients with macroscopic LN metastasis. In addition, the rate of para-aortic lymphadenectomy was 50% to 60%, and not all patients with LN metastasis were evaluated.

So far, MRI is considered the most accurate imaging technique for preoperative evaluation of LN metastases in EC. The presence of central necrosis on T2-weighted images of MRI has a 100% positive predictive value in the diagnosis of LN metastasis, although central necrosis is frequently found when the maximal transverse diameter of the LN is 2 cm or greater [5]. However, MRI has a limitation in the assessment of LN status because central necrosis is absent when the size criterion for differentiating metastatic from normal LNs in cancer patients is 1 cm, leading to false-positive or negative results. In addition to the fact that more than 50% of MI is associated with LN metastasis, the location of the tumor within the uterus is also important. In particular, the lower uterine segment (LUS) and cornual region of the uterus have been known to be an increased risk factor for LN metastasis because of their thin myometrium and abundant blood supply to the pelvis or aorta [6-8]. Thus, a more accurate predictive model for LN metastasis based on tumor location might be necessary for patients with presumed early-stage endometrioid EC whose MRI does not show any evidence of LN metastasis.

The aim of this study was to preoperatively identify high- and low-risk subgroups of patients with LN metastasis in presumed early-stage endometrioid EC patients treated with systematic pelvic and para-aortic lymphadenectomy.

MATERIALS AND METHODS

1. Data acquisition and treatments

A total of 529 International Federation of Gynecology and Obstetrics (FIGO) stage I-IIIC EC patients between March 2000 and July 2022 were screened in this study. Inclusion criteria were as follows: patients who were diagnosed with endometrioid EC, presumed stage I and II EC patients without definite evidence of LN metastasis during preoperative MRI, patients who underwent systematic pelvic and para-aortic lymphadenectomy, and those without underlying disease or co-existing malignancy that might influence their survival. Seventy-nine patients with serous

carcinoma (n=15), carcinosarcoma (n=19), mixed carcinoma (n=23), mucinous carcinoma (n=1), clear cell carcinoma (n=3), large cell neuroendocrine cell carcinoma (n=1), undifferentiated carcinoma (n=1), endometrial stromal sarcoma (n=6), adenosarcoma (n=3), co-existing ovarian malignancy (n=3), or no lymphadenectomy (n=4) were excluded. Twenty-seven patients with macroscopic nodal disease, which was defined when the short axis of the LN on preoperative MRI was greater than 1 cm with central necrosis, soft tissue with the same signal intensity of the tumor within the node, and extracapsular extension of the tumor beyond the nodal capsule, were excluded [9]. In addition, 62 patients with tumors confined to the endometrium and no clear mass were excluded. A total of 361 patients with endometrioid histology received complete staging procedures including total hysterectomy with or without salpingo-oophorectomy and pelvic/para-aortic lymphadenectomy. They were surgically staged according to the 2009 FIGO staging system. Their clinicopathological data were obtained from their medical records following the approval of this study by the center's Institutional Review Board (AJIRB-MED-MDB-21-144).

2. Definition of parameters

All MRI studies were performed with a 1.5T or a 3.0T magnet (Achieva; Philips Medical Systems, Best, The Netherlands) after gadolinium enhancement. Based on MRI findings, nodal metastasis was defined when the short axis of the LN on preoperative MRI was equal to or larger than 1 cm. LN metastases were pathologically confirmed [10]. On T2-weighted imaging, CSI was defined as a disruption of the normal signal intensity of the cervical stroma by the intermediate signal intensity of the tumor [11]. When the intermediate signal of the tumor disrupted the junctional zone and extending more than 50% into the deep myometrium on T2-weighted and post-contrast images, it was classed as clinically stage IB disease [6]. Serum CA-125 level was determined by a radioimmunoassay. LNs were examined by gynecologic pathologists. Conventional microscopic evaluation was performed with hematoxylin-eosin staining. The tumor location was classified into 3 types according to whether it was associated with LN metastasis in previous studies [7,8,12,13]: 1) focal or symmetrical lesions in body or fundus (**Fig. S1**); 2) uterine cornua (**Fig. S2**); and 3) LUS/isthmus (**Fig. S3**).

3. Statistical analysis

A normality test (Kolmogorov-Smimov test) was performed to determine whether the data were Gaussian in distribution. Comparing continuous parametric and nonparametric variables was done with the t-test and Mann-Whitney U test, respectively. Categorical data were analyzed using the Pearson χ^2 test and Fisher exact test. Preoperative risk factors including age, CA-125, preoperative tumor grade, tumor size on MRI, CSI on MRI, and deep MI on MRI for LN metastasis were used to identify independent variables associated with LN metastasis. Independent variables for LN metastasis were determined based on multivariate logistic regression analysis with a backward elimination method. Using these risk factors for LN metastasis, patients were categorized into low- and high-risk groups for LN metastasis. A receiver operating characteristic (ROC) curve analysis was conducted to define the sensitivity and specificity for the combined preoperative risk factors for LN metastasis. Data were analyzed using SPSS ver. 20.0 (IBM Co., Armonk, NY, USA). All tests except the univariate analysis were 2-sided and p-value <0.05 was considered statistically significant.

RESULTS

Clinicopathologic characteristics of FIGO stage I-IIIC endometrioid EC patients who underwent systematic lymphadenectomy are summarized in **Table 1**. Of 250 patients whose

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biopsies were read as grade 1 (G1), 15 (6.0%) were upgraded to grade 2 (G2) and 1 (0.4%) was upgraded to grade 3 (G3) on final pathology. Among 81 patients whose biopsies were read as G2, 2 (2.5%) were upgraded to G3 on final pathology. Tumor grade was downgraded for 29 (26.1%) out of 111 patients with G2 and G3 (G3 to G2, n=3; G3 to G1, n=3; and G2 to G1, n=23). Fifty-two (14.4%) patients had lymphovascular space invasion. Median numbers of dissected pelvic and para-aortic LNs were 17.0 (range, 5.0–55.0) and 8.0 (range, 4.0–52.0), respectively. Of 361 patients, 19 (5.3%) had LN metastases, 10 (2.8%) had positive pelvic LNs only, 7 (1.9%) had both pelvic and para-aortic LN metastases, and 2 (0.6%) had positive para-aortic LNs without pelvic LN metastasis.

Table 1. Clinicopathologic characteristics of FIGO stage I-IIIC endometrioid endometrial cancer patients who underwent systematic pelvic and para-aortic lymphadenectomy (n=361)

Variables	Values
Age (yr)	51.0 (27.0–81.0)
Surgical approach	
Laparotomy	114 (31.6)
Laparoscopy	201 (55.7)
Robot	46 (12.7)
CA-125 (IU/mL)	12.7 (0.1–287.0)
<35	320 (88.6)
≥35	41 (11.4)
Tumor size on MRI (cm)	1.9 (0.5–10.2)
Preoperative tumor grade	
1	250 (69.3)
2	81 (22.4)
3	30 (8.3)
Cervical stroma invasion on MRI	
No	306 (84.8)
Yes	55 (15.2)
Myometrial invasion on MRI	
<50%	297 (82.3)
≥50%	64 (17.7)
Tumor location on MRI	
Focally or diffusely endometrial enlargement or polypoid	305 (84.5)
Uterine cornua	22 (6.1)
Lower uterine segment/isthmus	34 (9.4)
FIGO stage	
IA	266 (73.7)
IB	34 (9.4)
II	40 (11.1)
IIIA/IIIB	2 (0.6)
IIIC1	10 (2.8)
IIIC2	9 (2.5)
Postoperative tumor grade	
1	260 (72.0)
2	74 (20.5)
3	27 (7.5)
Pathological tumor size	2.0 (0.0–11.0)
Lymphovascular space invasion (+)	52 (14.4)
Number of pelvic LNs harvested	17.0 (5.0–55.0)
Number of para-aortic LNs harvested	8.0 (4.0–52.0)
Pelvic LN metastasis only	10 (2.8)
Number of positive pelvic LNs	1.0 (1.0–6.0)
Isolated para-aortic LN metastasis	2 (0.6)
Number of positive para-aortic LNs	3.0 (1.0–6.0)
Pelvic and para-aortic LN metastases	7 (1.9)

Values are presented as number (%) or median (range).
FIGO, International Federation of Gynecology and Obstetrics; CA-125, cancer antigen 125; MRI, magnetic resonance imaging; LN, lymph node.

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Multivariate analysis of preoperative clinicopathologic factors for predicting LN metastasis identified CSI on MRI (odds ratio [OR]=4.386; 95% confidence interval [CI]=1.020–18.852; p=0.047), cornual location of tumor on MRI (OR=36.208; 95% CI=7.902–165.913; p<0.001), and LUS/isthmic location of tumor on MRI (OR=8.454; 95% CI=1.567–45.610; p=0.013) as independent prognostic factors (**Table 2**).

Based on these results, we developed risk criteria combining the preoperative risk factors of CSI and tumor location on MRI. We identified 280 low-risk patients (negative CSI on MRI and tumor location in body and fundus) and 81 high-risk patients (positive CSI on MRI and/or LUS/isthmic/cornual location on MRI), respectively (**Table 3**). Significant differences in the rates of LN metastasis were observed between the two groups (0.4% vs. 22.2%, p<0.001).

Fig. 1 shows the ROC curves using CSI and tumor location on MRI for discriminating between high- and low-risk patients for LN metastasis. The areas under the cure for this criterion were 0.882 (95% CI=0.816–0.947; p<0.001).

DISCUSSION

This study included only endometrioid EC patients with no LN metastases and clearly visible tumor in the uterus on preoperative MRI. The MI, CSI, tumor diameter, and tumor location, which were pathologically known to be related to LN metastasis, were evaluated to determine whether they were independently associated with the actual LN metastases. Our study showed that positive CSI on MRI and cornual or LUS/isthmic locations of tumor were independent risk factors for LN metastasis.

According to radiological examination and pathological findings, ≥50% MI has been invariably known as a risk factor for LN metastasis [3,4,14]. In particular, the myometrial thickness was

Table 2. Univariate and multivariate analysis of preoperative clinicopathologic factors for predicting microscopic LN metastasis

Variables	Parameter	Number of patients	LN metastasis (%)	Univariate analysis		Multivariate analysis	
				OR (95% CI)	p-value	OR (95% CI)	p-value
CA-125 (IU/mL)	<35	320	15 (4.7)	2.198 (0.693–2.198)	0.181	2.075 (0.482–8.934)	0.327
	≥35	41	4 (9.8)				
Myometrial invasion on MRI	<50%	297	7 (2.4)	9.560 (3.956–25.416)	<0.001	2.763 (0.885–8.624)	0.080
	≥50%	64	12 (18.8)				
Cervical stroma invasion on MRI	No	306	8 (2.6)	9.312 (3.551–24.423)	<0.001	4.386 (1.020–18.852)	0.047
	Yes	55	11 (20.0)				
Tumor location on MRI	Focal or symmetrical lesion in uterine body or fundus	305	3 (1.0)	-	-	-	-
	Uterine cornua	22	7 (31.8)	46.978 (11.036–199.967)	<0.001	36.208 (7.902–165.913)	<0.001
	Lower uterine segment/isthmus	34	9 (26.5)	36.240 (9.220–142.450)	<0.001	8.454 (1.567–45.610)	0.013

LN, lymph node; OR, odds ratio; CI, confidence interval; CA-125, cancer antigen-125; MRI, magnetic resonance imaging.

Table 3. Rate of lymph node metastasis in presumed early-stage endometrioid endometrial cancer patients treated with systematic pelvic and para-aortic lymphadenectomy

Risk group	No.	Lymph node metastasis	
		Negative (%)	Positive (%)
Low risk			
Cervical stroma invasion (–): Focal or symmetrical lesion in uterine body or fundus	280	279 (99.6)	1 (0.4)
High risk	81	63 (77.8)	18 (22.2)
Cervical stroma invasion (+): Focal or symmetrical lesion in uterine body or fundus	25	23 (92.0)	2 (8.0)
Cervical stroma invasion (–): Uterine cornua or lower uterine segment/isthmus	26	19 (73.1)	7 (26.9)
Cervical stroma invasion (+): Uterine cornua or lower uterine segment/isthmus	30	21 (70.0)	9 (30.0)

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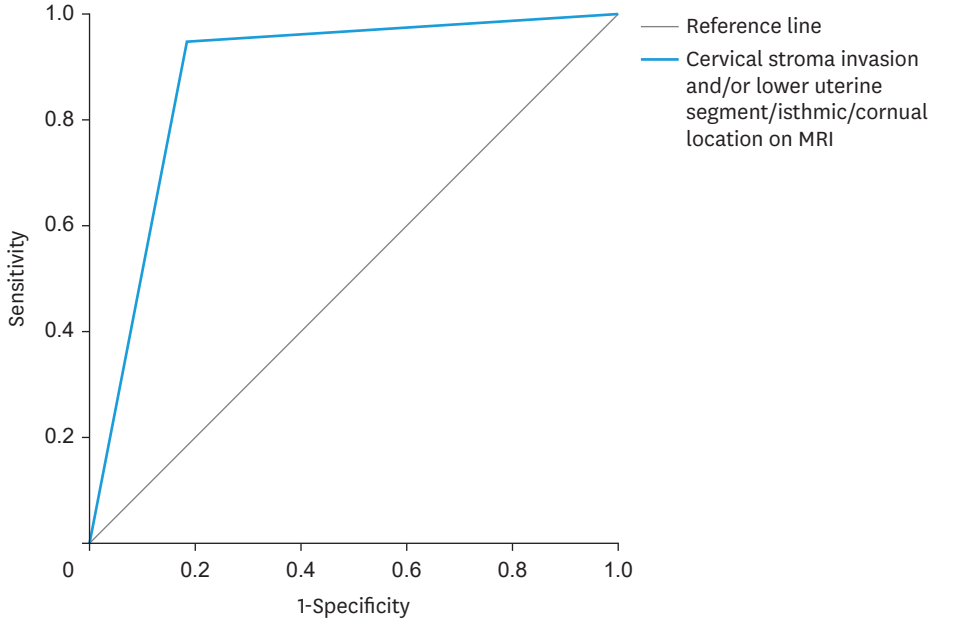

Fig. 1. Receiver operating characteristic curve using cervical stroma invasion and lower uterine segment/isthmic/cornual location of tumor on MRI to discriminate between low- and high-risk patients for microscopic lymph node metastasis.
MRI, magnetic resonance imaging.

estimated with higher accuracy by MRI than transvaginal ultrasonography [15,16]. However, for thin myometrium in cornual region and LUS, the myometrial thickness is difficult to measure, especially in elderly women with atrophy of the uterus and poorly discerned junctional zone [11]. LN metastasis may be affected by the location and blood supply of the tumor in the uterus. The LUS drains into the parametrium, paracervical, and obturator nodes, while the upper part of the uterus including cornual region drains into the common iliac and para-aortic LNs [6]. In addition, there was an increased risk for extrauterine disease and LN metastasis as well as recurrence if the uterine isthmus or cervix was involved with tumor [17]. Patients with intermediate-risk EC with nodal metastasis were more likely to have tumors located in the cornua and LUS involvement was also a predictor of LN metastasis, particularly for those patients with endometroid tumors [7,8]. Similarly, our study showed that only 1 patient (0.4%) out of 280 in the low-risk group showed LN metastasis, while 18 (22.2%) out of 81 in the high-risk group had LN metastasis. A detailed analysis of the tumor location in 81 high-risk group patients showed that tumors were located in the cornua (n=7) and the LUS/isthmus (n=9). Thus, a careful investigation of tumor location on the MRI before surgery is necessary.

The correlation between CSI and LN metastasis according to the pathological findings has already been demonstrated and MRI was excellent for predicting stromal invasion in EC, showing the highest positive predictive value (75%) and the highest likelihood ratio (12.5) [3,12,18-21]. In addition, the diagnostic accuracy of contrast-enhanced MRI was 94.6%, indicating that most patients diagnosed without CSI on MRI could be excluded pathologically as no CSI [22]. Therefore, preoperative identification of CSI is important as a significant proportion of EC patients with CSI have LN metastasis or extrauterine disease.

This study had several limitations inherent to its retrospective design and selection bias. First, compared with final pathological specimens of endometrioid EC patients, preoperative

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biopsy has limitations in predicting tumor grade [23]. In addition, discrepancies between preoperative biopsy and hysterectomy specimens were more likely to occur for preoperative grade 1 or 2 tumors (15 patients upgraded from G1 to G2; 1 patient upgraded from G1 to G3; 2 patients upgraded from G2 to G3; and 23 patients downgraded from G2 to G1) but less likely to occur for grade 3 tumors (6 patients downgraded from G3 to G1 or G2). Therefore, it seemed that tumor grade was not included as a risk factor for LN metastasis because of the discrepancy in tumor grade between preoperative biopsy and final pathologic results. Second, this model did not completely predict LN metastasis. Since there was only one patient with LN metastasis in the low-risk group, however, this model could be an important guideline for omitting lymphadenectomy. This patient showed deep myometrial invasion with a tumor size of 6.5 cm on MRI. Therefore, the presence of LN metastasis should be closely investigated in patients with deep MI, which showed statistical significance in univariate analysis (2.4% vs. 18.8%, $p<0.001$) but no statistical significance in multivariate analysis. Third, a certain proportion of presumed early-stage endometrioid EC patients may receive unnecessary lymphadenectomy since only 22.2% of the patients in the high-risk group had LN metastases. In addition, this study has the obvious limitation of not analyzing LN metastases and patient outcomes according to the molecular classification included in the revised 2023 FIGO staging system [24]. In other words, different prognosis can be shown depending on the molecular classification of the tumor (e.g., good prognosis, pathogenic POLE mutation; poor prognosis, p53 abnormal) regardless of whether there is pathological LN metastasis following surgery. However, the purpose of this study is to further identify risk factors (e.g., tumor location) for LN metastasis, which are known to be important prognostic factors in EC patients, and to carefully perform sentinel lymph node (SLN) biopsy and lymphadenectomy. In the future, therefore, it will be necessary to analyze the presence or absence of LN metastasis, tumor grade, molecular classification, and prognosis according to tumor location in a larger number of patients.

In conclusion, approximately 99% of presumed early-stage endometrioid EC patients who showed a focal or symmetrical lesion in the uterine body or fundus and did not have enlarged lymph nodes on MRI (302/305, 99.0%) might not require lymphadenectomy. Therefore, this predictive model using tumor location may provide valuable guidance for physicians on SLN biopsy or further lymphadenectomy. In addition, further studies may be conducted to determine the presence or absence of pathological LN metastases by performing SLN biopsy in patients with tumors in the uterine cornua or LUS/isthmus.

SUPPLEMENTARY MATERIALS

Fig. S1
Focal or symmetrical endometrial lesions in the uterine body or fundus on magnetic resonance imaging (A, C) and hysterectomy specimen (B).

Fig. S2
Asymmetrical endometrial lesions in the uterine cornua on magnetic resonance imaging (A, C) and hysterectomy specimen (B).

Fig. S3
Endometrial lesions in the lower uterine segments/isthmus on magnetic resonance imaging (A, C) and hysterectomy specimen (B).

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