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Feasibility of routine lymphadenectomy in clinical stage-I endometrial cancer

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A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

Summary

Background: To determine the accuracy of several preoperative tests in predicting lymph node (LN) metastases and the feasibility of doing a routine lymphadenectomy in clinical stage-I endometrial cancer.

Material/Methods: We reviewed 132 patients with clinical stage-I endometrial cancer. The preoperative tests used to predict LN metastases were serum CA-125 level, histologic type and grade, LN status assessed by pelvic magnetic resonance image (MRI) or computed tomography (CT), and depth of myometrial invasion assessed only by pelvic MRI. The cutoff value of the serum CA-125 level was determined using receiver operating characteristic curves. Multivariate logistic regression analyses were used to determine which tests are good predictors of LN metastases.

Results: Of 132 patients, 13 (9.8%) had LN metastases. On univariate logistic regression analysis, a high CA-125 level and preoperative LN evaluation by pelvic MRI or CT were significant predictors for LN metastases (OR=17.41, 95% CI: 4.36–69.56 and OR=14.30, 95% CI: 4.02–50.63, respectively). However, on multivariate logistic regression analysis adjusted for age and all preoperative tests, a high CA-125 level was the most significant predictor (OR=13.73, 95% CI: 2.03–92.73). Among the 97 patients with no significant predictor of LN metastases, pelvic LN metastases were observed in 3 patients (3.1%) and para-aortic LN metastases were observed in 1 patient (1.1%). Surgical complications were mild (lymphocele, n=9; lymphedema, n=2; wound problem, n=2).

Conclusions: Considering the importance of LN metastases as an indicator of prognosis, and the relatively low surgical risk of lymphadenectomy, clinicians should cautiously consider routine lymphadenectomy in patients with clinical stage-I endometrial cancer.

key words: endometrial cancer • lymphatic metastases • lymphadenectomy

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BACKGROUND

Endometrial cancer is the most common gynecologic malignancy, with 41 200 new cases and 7350 deaths estimated in the United States in 2006 [1]. Because of Western influences on South Korean lifestyles, the incidence of endometrial cancer in South Korea has increased. A lymph node (LN) metastasis is the most important prognostic factor in clinical early-stage endometrial cancer [2]. The incidence of pelvic LN metastases varies from 5% to 16% in clinical stage-I endometrial cancer. In women with clinical stage-I endometrial cancer, the 5-year disease-free survival rate for patients with LN metastases was 54% compared with 90% for patients without LN metastases [2–4].

In 1988, the International Federation of Gynecology and Obstetrics established the surgical staging system and included retroperitoneal lymphadenectomy for managing endometrial cancer; however, it did not specify the type and extent of LN dissection. Since then, numerous studies have suggested the importance of pelvic and para-aortic lymphadenectomy for defining the prognosis and providing important information about the need for adjuvant therapy [5]. However, doing a pelvic or para-aortic lymphadenectomy is controversial in clinical stage-I endometrial cancer. Some researchers consider complete evaluation of nodal status as mandatory [6,7]. Others have questioned the clinical utility of this procedure, especially for patients with a low risk of nodal involvement [8,9]. The known low-risk factors for LN metastases include a superficial myometrial invasion (less than half), small tumor size (<2 cm), and a low tumor grade (grades 1 and 2) [10–12].

Identifying an accurate test to predict LN metastases in clinical stage-I endometrial cancer could have clinical benefits. Surgical morbidity and time for lymphadenectomy could be decreased. Preoperatively predicting LN metastases can be done by examining the results of pelvic magnetic resonance image (MRI) or computed tomography (CT) scanning, or by determining the histologic type and grade of curettage or the preoperative serum CA-125 level [13,14]. We sought to determine the accurate predictor(s) of pelvic or para-aortic LN metastases among the above-mentioned preoperative tests and whether lymphadenectomy should be performed in selected or all patients with clinical stage-I endometrial cancer.

MATERIAL AND METHODS

Patients

The Seoul National University Hospital Tumor Registry was thoroughly reviewed to identify all of the patients with endometrial cancer who received surgical treatment from January 2000 to April 2006. Institutional review board approval was obtained in advance for this study. Within this hospital, 4 or 5 gynecologists are responsible for managing patients with gynecologic cancer. The type and extent of lymphadenectomy depends on the surgeon's preference. One hundred thirty-two patients met the following inclusion criteria: (1) clinical stage-I endometrial cancer, (2) pelvic surgery lymphadenectomy with or without para-aortic lymphadenectomy including hysterectomy, and (3) preoperative pelvic MRI or CT scanning done. The clinical extent of the tumor was evaluated in all patients and included a chest radiograph. Serum CA-125 levels were measured preoperatively in all 132 patients except 7 (the medical records of these 7 were incomplete). The initial diagnosis of endometrial cancer was based on the results of endometrial biopsies obtained by hysteroscopy, curettage, or both. Preoperative curettage was done in all the patients except 22; these 2 patients were operated on without curettage for suspected adenomyosis and leiomyoma. T. They were reoperated on after a diagnosis of endometrial cancer from the final report had been made.

Preoperative tests used to predict LN metastases

We used histologic grade (grades 1 and 2 vs 3) and type (endometrioid type vs nonendometrioid type) of the preoperative curettage, serum CA-125 level, pelvic or para-aortic LN status, and depth of myometrial invasion by pelvic imaging study as predictors of LN metastases. Because serum CA-125 levels are affected by the estrogen status [15], 132 patients were divided into 2 groups: those aged younger than 50 years and those aged 50 years and older. Cutoff levels of CA-125 were obtained using receiver operating characteristic (ROC) curves. The preoperative LN status was evaluated by pelvic MRI or CT scanning. The depth of preoperative myometrial invasion was evaluated by pelvic MRI only. All pelvic MRI examinations were done with a Magnetom 1.5 T scanner (Siemens, Erlangen, Germany) or a Signa 1.5 T scanner (General Electric Medical Systems, Milwaukee, WI, USA). All patients had spin-echo T1-weighted images and T2-weighted fast-spin-echo images done. Gadolinium-enhanced T1-weighted fat saturation sequences were taken before and after intravenous injection of contrast media. A Somatom plus-4 scanner (Siemens Medical System, Erlangen, Germany) was used for CT scanning. Nonenhanced and contrast-enhanced scans were obtained in all patients. In all cases, scanning was initiated 60 seconds after an intravenous injection of 120 mL contrast material containing 300 mgI/mL (Ultravist 370, Schering, Berlin, Germany) at a rate of 3 mL/second. The scanning parameters included 7 mm/second table speed, 1:1 pitch, and 7 to 8 mm thickness.

Surgical procedure

A median laparotomy was performed. After obtaining a peritoneal cytology specimen, all the intra-abdominal organs and peritoneal surfaces were examined, and suspicious areas were biopsied. A total hysterectomy, bilateral salpingo-oophorectomy, and retroperitoneal lymphadenectomy were then done. Pelvic lymphadenectomy included mobilizing the external iliac artery and vein from the psoas muscle with en bloc removal of the lymphatic tissue overlying the external iliac vessels, the internal iliac artery, and the obturator fossa above the obturator nerve. Para-aortic lymphadenectomy usually consists of removing the precaval and lower right and left aortic lymphatic tissue to the level of the inferior mesenteric artery.

Statistics

The *t* test was used to compare the mean values of age and parity between LN-positive and LN-negative groups. Univariate and multivariate logistic regression analyses were

used to discriminate the significant risk factors for LN metastases. The Kappa index and chi-square test (by linear association) were used to analyze the association between variables. Statistical analyses were done with SPSS software (Statistical Product and Services Solutions, version 12.0, SPSS Inc, Chicago, IL, USA).

Results

The mean age and parity of 132 patients were 53.8 years and 2.1. There were 113 patients with stage-I (78%), 9 patients with stage-II (6.8%), 19 patients with stage-III (14.4%), and 1 patient with stage-IV (0.8%) cancers. The endometrioid type was most common (n=126, 95.4%). We found papillary serous type in 3 patients (2.3%), clear cell type in 2 patients (1.5%), and poorly differentiated type in 1 patient (0.8%). Table 1 shows the postoperative characteristics of patients in the LN-negative and LN-positive groups.

Of 132 patients, 119 patients (90.2%) had no LN metastases and 13 patients (9.8%) had a LN metastasis. Among those 13 patients, 5 patients (38.5%) had para-aortic LN metastases along with pelvic LN metastases. None of the patients had a para-aortic LN metastasis without a pelvic LN metastasis. A para-aortic lymphadenectomy was done in 19 (15.8%) of the 119 patients with no LN metastases and in 7 (53.8%) of the 13 patients with a LN metastasis. Two cutoff values for CA-125 levels using ROC curves divided the patients into low- and high-risk groups for pelvic LN metastases (20 U/mL for patients aged <50 years [AUC=0.734, sensitivity=0.667, specificity=0.216] and 28 U/mL for patients aged ≥50 years [AUC=0.833, sensitivity=0.800, specificity=0.133]) (Figure 1).

The relations of the preoperative tests with LN metastases are shown in Table 2. Regarding age, no significant difference was found for patients with LN metastases when compared with patients without LN metastases (P=0.095). On univariate logistic regression analyses, a high CA-125 level and preoperative LN evaluation by pelvic MRI or CT were found to be significant predictors for LN metastases, with OR=17.41 (95% CI: 4.36–69.56) and OR=14.30 (95% CI: 4.02–50.63), respectively. On multivariate logistic regression analyses adjusted for age and all the preoperative tests, a high CA-125 level was found to be the most significant predictor of LN metastases (OR=13.73, 95% CI: 2.03–92.73). There was a significant association between a high CA-125 level and preoperative LN evaluation by pelvic MRI or CT (PP<0.001). A high preoperative CA-125 level was not associated with the depth of myometrial invasion (PP=0.315). Among the 97 patients with no significant predictor of LN metastases, pelvic LN metastases were observed in 3 patients (3.1%) and para-aortic LN metastases were observed in 1 patient (1.1%). Among the 13 patients with LN metastases, 3 patients (23.1%) had no significant predictor for LN metastases.

Postoperative clinicopathologic characteristics according to LN metastases are shown in Table 3. The numbers of dissected lymph nodes were not different between the groups. On multivariate logistic regression analyses, myometrial invasion more than half was the only risk factor for LN metastases (OR=5.38, 95% CI: 1.44–20.09).

A disagreement rate between preoperative grade and postoperative grade was 9.2% (kappa=0.455, P<0.001). A disagreement rate between preoperative myometrial evaluation by pelvic MRI and postoperative myometrial invasion was 19.6% (kappa=0.663, P<0.001). The sensitivity, specificity, and false-positive and false-negative rates of the preoperative predictors for LN metastases are summarized in Table 4.

Table 1. Characteristics of 132 patients.

Characteristics	LN negative group (%)	LN positive group (%)
Patients	119	13
FIGO stage		
I	103 86.6%)	
II	9 7.6%)	
III	7 5.9%)	12 92.3%)
IV		1 7.7%)
Postoperative grade		
1	74 62.2%)	3 23.1%)
2	28 23.5%)	6 46.2%)
3	15 12.6%)	4 30.8%)
Histologic type		
Endometrioid type	114 95.8%)	12 92.3%)
Papillary serous type	2 1.7%)	1 7.7%)
Clear cell type	2 1.7%)	
Poorly differentiated type	1 0.8%)	

LN – lymph node.

Discussion

The aim of this study was to determine the accuracy of several preoperative tests that predict LN metastases and determine the feasibility of doing routine lymphadenectomy in patients with clinical stage-I endometrial cancer. A high CA-125 level and preoperative LN evaluation by pelvic MRI or CT scanning were found to be significant predictors of LN metastases. However, on multivariate logistic regression analyses adjusted for age and all the preoperative tests, a high CA-125 level was the most significant predictor.

A previous study at our institution also showed that LN metastases have the most significant effect on elevating preoperative serum CA-125 levels (P=0.004) [16]. Higher CA-125 levels correlated with deep myometrial invasion (P=0.001). The cutoff value of preoperative serum CA-125 levels for LN metastases was 28.5 U/mL. Serum CA-125 levels are known to be affected by ovarian hormones and age. Therefore, we divided the patient population into 2 groups, by age, using 50 years as the dividing point. For preoperative serum CA-125 levels, the cutoff values for LN metastases were 20 U/mL for patients aged <50 years and 28 U/mL for patients aged ≥50 years.

Todo and associates used cutoff values of preoperative serum CA-125 levels of 28 U/mL for patients aged <50 years

Table 2. Relationships between preoperative tests and postoperative LN metastasis.

Preoperative test	LN metastasis		P	OR (95% CI)*	OR (95% CI)**
	Negative (%)	Positive (%)			
Age, y (mean ±SD)	53.3±10.0	58.5±13.8	0.095		
Parity (mean ±SD)	2.0±1.4	2.5±2.7	0.234		
CA-125					
Low***	94 (83.9)	3 (23.1)		1.0	1.0
High#	18 (16.1)	10 (76.9)		17.41 (4.36–69.56)	13.73 (2.03–92.73)
LN status by pelvic MRI or CT					
Negative	107 (89.9)	5 (38.5)		1.0	1.0
Positive	12 (10.1)	8 (61.5)		14.30 (4.02–50.63)	3.68 (0.52–26.01)
MM invasion by pelvic MRI					
Less than half	74 (79.6)	5 (55.6)		1.0	1.0
More than half	19 (20.4)	4 (44.4)		3.12 (0.76–12.74)	1.18 (0.17–8.2)
Histologic type					
Endometrioid	112 (95.7)	12 (92.3)		1.0	1.0
Non-endometrioid##	5 (4.3)	1 (7.7)		1.87 (0.20–17.33)	0.87 (0.02–42.3)
Histologic grade					
1,2	91 (83.5)	10 (76.9)		1.0	1.0
3	18 (16.5)	3 (23.1)		1.52 (0.38–6.06)	2.69 (0.24–29.9)

LN – lymph node; MM – myometrium. * By univariate logistic regression analysis; ** By multivariate logistic regression analysis adjusted for age, CA-125, histologic grade and type, LN status by pelvic MRI or CT, MM invasion by pelvic MRI; *** Low: Level <20 (if age <50 yrs), level <28 (if age ≥ 50yrs); # High: Level ≥20 (if age <50 yrs), level ≥28 (if age ≥5 0yrs). ## Non-endometrioid: Clear cell, serous papillary, poorly differentiated.

and 70U/mL for patients aged ⩾50 years [13]. The difference between our study and the one by Todo and associates is the enrollment criteria. Because we included the only patients with clinical stage-I endometrial cancer, the proportion of patients with advanced surgical stage (III or IV) in our study (15.2%) was lower than that of Todo and associates (26.6%). Therefore, the cutoff level of CA125 in our study is lower. Sood and associates also demonstrated that patients with positive pelvic or para-aortic LN metastases had significantly higher preoperative CA-125 levels [17]. In another study, preoperative serum CA-125 levels offered no information with which to predict LN metastases in patients with endometrial cancer [19]. In our study, although a cutoff value of a high CA-125 level was not useful in predicting the depth of myometrial invasion; higher CA-125 levels were correlated with deeper myometrial invasion (P<0.001).

MRI and CT scanning may be used to predict LN metastases. Nodal size is the current standard criteria for predicting LN metastases on imaging study. Although a 1 cm diameter is the preferred criterion, there is some variability with regard to size threshold [20,21]. However, it is not possible to differentiate metastatic nodes from hyperplastic nodes of a similar size. In 1993, Girardi and associates reported that 37% of metastatic LNs were 2 mm or less in diameter [22]. This explains the inaccuracy of MRI and CT scanning for predicting LN metastases. Sensitivities for LN metastases in gynecologic cancers range from 43% to 73% [23]. The sensitivity of MRI and CT for LN staging in our study was 61.5%.

The role of CT and MRI in evaluating LN status is controversial [24]. On multivariate logistic regression analyses, preoperative pelvic MRI or CT was not found to be a significant predictor of LN metastases. The chi-square test showed a significant correlation between a high CA-125 level and preoperative LN evaluation by pelvic MRI or CT (P<0.001), suggesting a confounding effect of preoperative LN evaluation by pelvic MRI or CT and a high CA-125 level. Consequently, we should realize that CT and MRI are only moderately sensitive for detecting LN metastases, and applying their results clinically is limited.

The junctional zone just beneath the endometrium on a T2-weighted image is an excellent indicator for determining myometrial invasion. In our study, preoperative evaluation by pelvic MRI of the depth of myometrial invasion was not a significant predictor for LN metastases. However, the depth of postoperative myometrial invasion was a significant risk factor for LN metastases (P=0.008), suggesting that evaluating myometrial invasion by pelvic MRI is not an accurate method for predicting LN metastases. A meta-analysis showed the sensitivity for deep myometrial invasion using contrast-enhanced imaging to be 78.6% to 100% with

Table 3. Postoperative clinicopathologic characteristics and LN metastasis.

Characteristics	LN metastasis				OR (95% CI)*		OR (95% CI)**	
	Negative (%)		Positive (%)					
Patients	119	(90.2)	13	(9.8)				
Number of dissected LNs (mean ±SD)	24.6±12.0		29.5±8.4		1.04	(0.99–1.09)	1.01	(0.96–1.08)
Histology	119		13		0.91	(0.07–12.32)	0.95	(0.07–12.80)
Endometrioid	114	(95.1)	12	(92.3)				
Non-endometrioid***	5	(4.9)	1	(7.7)				
Grade	117		13		1.56	(0.33–7.26)	1.40	(0.28–7.10)
1,2	102	(87.2)	9	(69.2)				
3	15	(12.8)	4	(30.8)				
MM involvement	119		13		5.82	(1.62–20.87)	5.38	(1.44–20.09)
Less than half	96	(80.7)	5	(38.5)				
More than half	23	(19.3)	8	(61.5)				

LN – lymph node; LNs – lymph nodes; MM, myometrium; * By univariate logistic regression analysis; ** By multivariate logistic regression analysis adjusted for number of dissected LNs, histology, grade, MM involvement; *** Non-endometrioid: Clear cell, serous papillary, poorly differentiated.

Table 4. Sensitivity, specificity, and false positive/negative rate of preoperative predicors for LN metastasis.

Predictor	No.	Sensitivity	Specificity	False positive rate	False negative rate
High CA-125 level*	125	76.9%	83.9%	64.3%	3.1%
LN status by pelvic MRI or CT	132	61.5%	90.0%	60.0%	4.4%
Histologic grade 3	122	23.1%	83.5%	85.7%	9.9%
MM invasion by pelvic MRI**	102	44.4%	79.6%	82.6%	6.3%
Histologic type***	130	7.7%	95.7%	83.3%	9.7%

LN – lymph node; No – the number of patients; MM – myometrium; * High: Level ≥20 (if age <50 yrs), level ≥28 (if age ≥50 yrs); ** MM invasion by pelvic MRI: more than half; *** Histologic type: Clear cell, papillary serous, undifferentiated type.

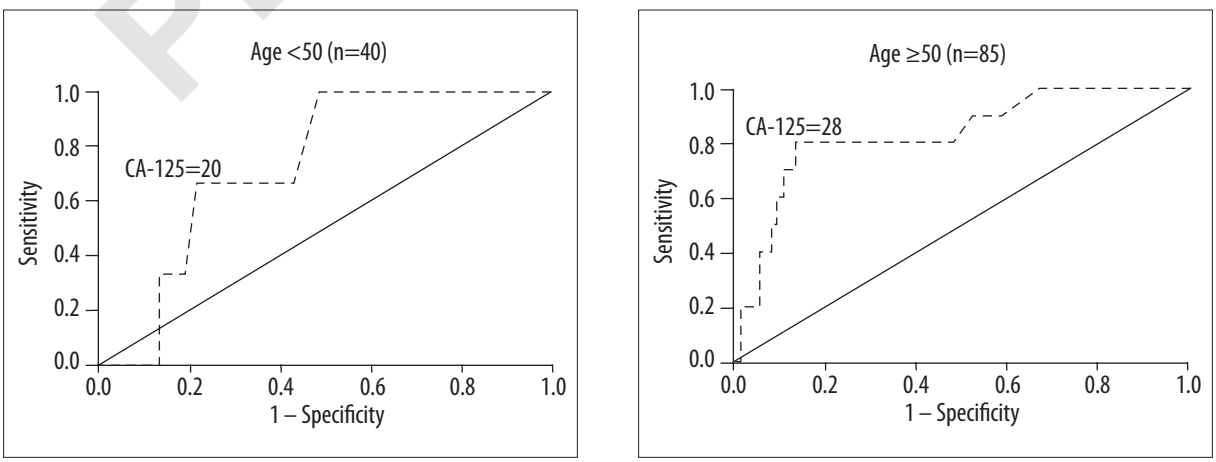

Figure 1. Receiver operating characteristic curves obtained from relationship between serum CA 125 level and LN metastasis.

a specificity of 83.3% to 100% [25]. In our study,, the sensitivity for deep myometrial invasion was 44.4% and the specificity was 79.6%. Another study at our institution suggested that polypoid tumor and junctional zone isointense to myometrium are factors associated with false-negative results of myometrial invasion on pelvic MRI [26].

Histologic grade is strongly correlated with LN metastases in endometrial cancer. However, this result is based on the histologic grade assigned at final pathology [27]. Most studies report an upgrade of the grade of preoperative curettage in at least 20% of cases [28]. In our study, we found that 26.3% of the patients that were classified as high risk (grade 3) after evaluation of the hysterectomy specimen previously had been classified as low risk (grade 1 and 2). Furthermore, attempts to improve these results by examining frozen sections during the operation also were unsuccessful; the specificity was 98% and the accuracy was 87%, but the sensitivity was as low as 40% [29]. Serous, poorly differentiated, and clear cell adenocarcinomas of the endometrium have been shown to be associated with poor survival [30]. Although our study shows poor predictability of LN metastases by histologic type, this result may be associated with the small number of cases (n=6).

Although a high CA-125 level was the most significant predictor of LN metastases, the sensitivity (76.9%) was relatively low to predict LN metastases and the false-negative rate was 3.1%. Developing new tests is necessary to predict accurate LN evaluation.

The additional surgical morbidity and time for pelvic lymphadenectomy are minimal [3]. In our study, surgical complications were mild (lymphocele [n=9], lymphedema [n=2], and wound problems [n=2, umbilical hernia and wound dehiscence]). Approximately 10% to 20% of endometrial cancer patients have severe medical conditions that preclude surgery [31]; these patients tend to be morbidly obese [32]. The body mass index cutoff for assessing obesity for the Asians, such as the Koreans, is lower than that in Western populations (25.0 kg/m^2 vs 30.0 kg/m^2, respectively) [33]. The prevalence of Korean women with body mass indexes >30.0 kg/m^2 is 0.7% [34], compared with 31% of women in the United States. In fact, few patients in this study were inoperable because of severe obesity. Inoperability because of obesity is rare in Korean women with endometrial cancer.

Conclusions

Because of its low sensitivity to preoperative tests, the clinical significance of LN metastases, the discrepancy between clinical and surgical staging, and the low surgical morbidity from lymphadenectomy, clinicians should cautiously consider routine lymphadenectomy in patients with clinical stage-I endometrial cancer.

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