

# Predicting Factors for Pelvic Lymph Node Metastasis in Patients with Apparently Early-Stage Endometrial Cancer

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## Abstract

**Background:** Performing lymphadenectomy in all patients with early-stage endometrial cancer (EC) is debatable because the procedure may expose patients to unnecessary risks of postoperative complications. Aim of this study was to evaluate the prevalence and risk factors of pelvic lymph node metastasis (PLNM) in patients with apparently early-stage EC. **Materials and methods:** Two hundred and two patients with apparently early-stage EC who underwent surgical staging at Thammasat University Hospital between the years 2013 and 2020 were included in this retrospective study. Clinicopathological data and preoperative laboratory results were obtained from computer-based medical records. All data were statistically analyzed to determine the prevalence of PLNM and risk factors for developing PLNM. **Results:** PLNM was detected in 22 (10.9%) patients. Univariate analysis demonstrated that having grade 3 tumor, myometrial invasion of 50% or greater, vaginal involvement, cervical involvement, adnexal involvement, lower uterine segment involvement, lymphovascular space invasion (LVSI), and positive peritoneal cytology were associated with higher risk for developing PLNM. In addition, lower preoperative hemoglobin level and higher preoperative white blood cell count were significantly associated with PLNM. Multivariate analysis demonstrated that myometrial invasion of 50% or greater and LVSI were independent risk factors for developing PLNM (odds ratio (OR) 9.31, 95% confidence interval (CI) 2.58-33.55,  $p=0.001$ , and OR 3.73, 95%CI 1.39-10.02,  $p=0.009$ , respectively). **Conclusions:** Myometrial invasion of 50% or greater and LVSI were independent risk factors for developing PLNM in patients with apparently early-stage EC and thus lymphadenectomy in these patients should be provided.

**Keywords:** Endometrial cancer- risk factors- pelvic lymph node metastasis- lymphadenectomy

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## Introduction

Endometrial cancer (EC) is the most prevalent gynecologic malignancy in the developed countries with the incidence of approximately 12.9 patients per 100,000 women (Jemal et al., 2011). In Thailand, EC is the third most common gynecologic malignancy with the age-standardized incidence rate of 4.3 cases per 100,000 women (Khuhaprema et al., 2007). Women with prolonged unopposed estrogen stimulation, late menopause, infertility, diabetes mellitus and hypertension, and overweight women are at increased risk for developing EC.

Approximately 70% of patients with EC are diagnosed with stage I disease. In early-stage EC, surgery is often curative, with a 5-year-survival rate of greater than 90%. The occurrence of pelvic lymph node metastasis ranges from 10.5% to 14.9% (Lee et al., 2016; Karalok et al., 2017; Sari et al., 2017). Intraabdominal lymph node metastasis are often associated with poor prognosis and

thus require adjuvant chemotherapy and radiotherapy (Shah et al., 2011).

Concerning the recommendations of the current National Comprehensive Cancer Network (NCCN) guidelines 2021, a combination of hysterectomy with bilateral salpingo-oophorectomy, along with lymph node assessment is the mainstay treatment of EC (NCCN, 2021). However, the therapeutic benefits of pelvic and para-aortic lymphadenectomy are still debatable. Data from the two randomized controlled trials (Benedetti Panici et al., 2008; Kitchener et al., 2009) did not support the therapeutic benefit of lymphadenectomy in early-stage EC. In contrast, data from the retrospective study suggested that patients who underwent systematic lymphadenectomy had improved survival rate as compared with those who had no sampling performed (Kilgore et al., 1995). According to the two previously-mentioned randomized controlled trials (Benedetti Panici et al., 2008; Kitchener et al., 2009), the overall survival and recurrence-free survival rates were not increased among patients with early-stage EC who

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underwent pelvic lymphadenectomy, while neurovascular injury, pelvic infection, lymphocyst and lymphedema formation rates were increased. Regarding those complications, some of them were potentially irreversible and might have a negative impact on long-term quality of life of the patients (Achouri et al., 2013; Hareyama et al., 2015). The European Society of Gynaecological Oncology (ESGO), the European Society for Radiotherapy and Oncology (ESTRO), and the European Society of Pathology (ESP) guidelines (Concin et al., 2021) recommend against lymphadenectomy in patients with low and intermediate risk, early-stage EC owing to low rate of lymph node invasion in these groups of patients and high risk for developing morbidity following the surgical procedure. Therefore, performing lymphadenectomy in all patients with early-stage EC is debatable because the procedure may expose patients to unnecessary risks of postoperative complications.

The aim of this study was to evaluate the prevalence of pelvic lymph node metastasis (PLNM) in patients with early-stage EC and the possible risk factors for developing PLNM in these patients. Determining the risk factors would help in identifying patients who might benefit from undergoing lymphadenectomy and avoid unnecessary procedure and thus postoperative complications.

## Materials and Methods

This retrospective study was conducted at Thammasat University Hospital, a tertiary care, teaching hospital in Pathumthani, Thailand. The study protocol was approved by the ethics committee of Thammasat University.

Patients with apparently early-stage EC who underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymphadenectomy with or without para-aortic lymphadenectomy at Thammasat Hospital between the years 2013 and 2020 were enrolled. Apparently early-stage EC (clinical stages I and II) was defined as the disease which was confined to the uterus without evidence of metastasis. Patients who had preoperative evidence of extrauterine metastasis and no histological data were excluded. Their computer-based medical records were reviewed. Clinical characteristics, including age, parity, and body mass index (BMI) were collected. Serum carbohydrate antigen 125 (CA-125), human epididymis protein 4 (HE4), complete blood count (CBC) and routine preoperative blood tests were also collected.

Pathological characteristics including histological type, tumor grade, tumor size, lymph node status, myometrial invasion, lower uterine segment involvement (LUSI), vaginal involvement, cervical involvement, adnexal involvement, uterine serosa involvement, lymphovascular space invasion (LVSI), and peritoneal cytology were obtained. EC staging was determined according to the International Federation of Gynecology and Obstetrics (FIGO) 2009 staging for EC.

Continuous variables were non-normally distributed, so they were expressed as median (range) and compared using Mann-Whitney U test. For categorical variables, chi-squared test or Fisher's exact test was used to evaluate

the associations between variables. Multivariate logistic regression analysis was used to identify independent risk factors for having PLNM. A p-value of less than 0.05 was considered statistically significant. Statistical Package for the Social Sciences, version 25.0 Software (SPSS Inc, Chicago, IL, USA) was used for statistical analysis.

## Results

There were 365 women with EC who underwent surgery during the period of the study. Two hundred and two of them met the inclusion criteria and were included in the study. The clinicopathological characteristics of the enrolled patients are shown in Table 1. Their median (range) age was 60 (31-85) years and the median (range) BMI was 25.8 (15.0-54.7) kg/m<sup>2</sup>. Most patients had endometrioid histology (80.7%). Grade I, II, and III tumors were found in 38 (18.8%), 86 (42.6%), and 78 (38.6%) women, respectively. Myometrial invasion of 50% or greater and LVSI were detected in 80 (39.6%) and 56 (27.7%) patients, respectively. PLNM was detected in 22 (10.9%) patients.

Univariate analysis demonstrated that the risk of PLNM was significantly increased in patients with grade 3 tumor (p = 0.037), myometrial invasion of 50 % or greater (p < 0.001), vaginal involvement (p < 0.001), cervical involvement (p < 0.001), adnexal involvement (p < 0.001), LUSI (p = 0.03), LVSI (p < 0.001), positive peritoneal cytology (p = 0.005), and preoperative serum CA-125 level of greater than 35 U/mL (p = 0.015). In addition, the pelvic lymph node-positive group had lower preoperative hemoglobin (Hb) level than the pelvic lymph node-negative group (11.9 vs 12.5 g/dL, respectively, p = 0.017). Preoperative white blood cell count (WBC) count was significantly higher in the pelvic lymph node-positive group as compared with the pelvic lymph node-negative group (8.4 x 10<sup>3</sup> vs 7.3 x 10<sup>3</sup> /μL, respectively, p = 0.043). In contrast, platelet count, absolute neutrophil count (ANC), absolute monocyte count (AMC), absolute lymphocyte count (ALC), neutrophil-lymphocyte ratio (NLR), monocyte-lymphocyte ratio (MLR), and platelet-lymphocyte ratio (PLR) had no significant correlations with PLNM (Table 2).

Multivariate analysis revealed that myometrial invasion of 50% or greater and LVSI were independent risk factors for developing PLNM in patients with apparently early-stage EC (odds ratio (OR) 9.31, 95% confidence interval (CI) 2.58-33.55, p = 0.001, and OR 3.73, 95% CI 1.39-10.02, p = 0.009, respectively) (Table 3).

## Discussion

This study demonstrated the prevalence of PLNM at 10.9% (22 out of 202 patients) which is comparable to those of the previous studies (10.5-14.9%) (Lee et al., 2016; Karalok et al., 2017; Sari et al., 2017).

Currently, several models have been proposed to predict lymph node metastasis in patients with EC. However, no definite consensus regarding the optimal model for using in clinical practice (Keys et al., 2004; Vargas et al., 2014; Bendifallah et al., 2014). Those

Table 1. Clinicopathological Characteristics of Apparently Early-Stage Endometrial Cancer Patients (N = 202)

Characteristics	N (%)
Age (years), median (range)	60 (31-85)
Parity	
Nulliparous	69 (34.2)
Multiparous	133 (65.8)
BMI (kg/m <sup>2</sup> ), median (range)	25.8 (15.0-54.7)
Stage	
I	147 (72.8)
II	22 (10.9)
III	27 (13.3)
IV	6 (3)
Histology	
Endometrioid	163 (80.7)
Non-endometrioid	39 (19.3)
Tumor grade	
I	38 (18.8)
II	86 (42.6)
III	78 (38.6)
Tumor size	
<2 cm	25 (12.4)
2-4 cm	80 (39.6)
>4 cm	97 (48)
Myometrial invasion	
<50%	122 (60.4)
≥50%	80 (39.6)
Vaginal involvement	
Yes	2 (1)
No	200 (99)
Cervical involvement	
Yes	39 (19.3)
No	163 (80.7)
Adnexal involvement	
Yes	13 (6.4)
No	189 (93.6)
LUSI	
Yes	85 (42.1)
No	117 (57.9)
LVSI	
Yes	56 (27.7)
No	146 (72.3)
Peritoneal cytology	
Positive	32 (15.8)
Negative	170 (84.2)
Pelvic lymph node metastasis	
Yes	22 (10.9)
No	180 (89.1)

BMI, body mass index; LUSI, lower uterine segment involvement; LVSI, lymphovascular space invasion

Table 2. Univariate Analysis of Risk Factors for Pelvic Lymph Node Metastasis

Variables	Pelvic lymph node		P-value
	Positive (N = 22)	Negative (N = 180)	
BMI (kg/m <sup>2</sup> ), N (%)			0.859
<30	17 (77.3)	136 (75.6)	
≥30	5 (22.7)	44 (24.4)	
Pathology, N (%)			0.32
Endometrioid	16 (72.7)	147 (81.7)	
Non-endometrioid	6 (27.3)	33 (18.3)	
Tumor grade, N (%)			0.037
Low (grade I-II)	9 (40.9)	115 (63.9)	
High (grade III)	13 (59.1)	65 (36.1)	
Tumor size, mean (SD), N (%)	6.1 (3.4)	4.5 (2.5)	0.009
Myometrial invasion, N (%)			< 0.001
<50%	3 (13.6)	119 (66.1)	
≥50%	19 (86.4)	61 (33.9)	
Vaginal involvement, N (%)			< 0.001
Yes	2 (9.1)	0 (0)	
No	20 (90.9)	180 (100)	
Cervical involvement, N (%)			< 0.001
Yes	14 (63.6)	25 (13.9)	
No	8 (36.4)	155 (86.1)	
Adnexal involvement, N (%)			< 0.001
Yes	7 (31.8)	6 (3.3)	
No	15 (68.2)	174 (96.7)	
LUSI, N (%)			0.03
Yes	14 (63.6)	71 (39.4)	
No	8 (36.4)	109 (60.6)	
LVSI, N (%)			< 0.001
Yes	14 (63.6)	42 (23.3)	
No	8 (36.4)	138 (76.7)	
Peritoneal cytology, N (%)			0.005
Positive	8 (36.4)	24 (13.3)	
Negative	14 (63.6)	156 (86.7)	
CA 125 level (U/mL), N (%)			0.015
≤35	2 (25)	52 (68)	
>35	6 (75)	24 (32)	
Hb (g/dL), median (range)	11.9 (10.2-12.6)	12.5 (11.4-13.4)	0.017
WBC (x 10 <sup>3</sup> /μL), median (range)	8.4 (7.1-9.2)	7.3 (6.1-8.8)	0.043
Platelets (x 10 <sup>3</sup> /μL), median (range)	307.5 (270-364)	290.5 (244.5-341)	0.27
ANC (x 10 <sup>3</sup> /μL), median (range)	63.9 (53.7-71.4)	61.1 (54.9-67.3)	0.21
AMC (x 10 <sup>3</sup> /μL), median (range)	7.1 (6.0-8.2)	6.9 (5.8-8.1)	0.7

Table 2. Continued

Variables	Pelvic lymph node		P-value
	Positive (N = 22)	Negative (N = 180)	
ALC (x 10 <sup>3</sup> /μL), median (range)	24.4 (19.1-27.8)	27.5 (22.0-33.8)	0.092
NLR, median (range)	2.6 (2.0-3.7)	2.2 (1.6-3.0)	0.13
MLR, median (range)	0.3 (0.2-0.4)	0.2 (0.2-0.3)	0.19
PLR, median (range)	151.1 (113.7-210.1)	139.1 (111.0-180.1)	0.5

BMI, body mass index; LUSI, lower uterine segment involvement; LVSI, lymphovascular space invasion; CA-125, carbohydrate antigen 125; Hb, hemoglobin, WBC, white blood cell; ANC, absolute neutrophil count; AMC, absolute monocyte count; ALC, absolute lymphocyte count; NLR, neutrophil-lymphocyte ratio; MLR, monocyte-lymphocyte ratio; PLR, platelet-lymphocyte ratio; SD, standard deviation

models suggested that lymphadenectomy could be omitted in patients who were classified as having low risk EC. In contrast, lymphadenectomy was recommended for patients classified as having high risk EC. Li (2019) proposed the model comprising additional biomarker including preoperative serum CA-125 and HE4 to predict lymph node metastasis. They showed that serum CA-125 of 27.6 U/mL or greater, serum HE4 of 132 pmol/L or greater, and having non-endometrioid histology, myometrial invasion of 50% or greater, positive peritoneal cytology, and LVSI were independent predictors of PLNM. Stalberg (2017) concluded that non-endometrioid histology, tumor grade 3, and deep myometrial invasion were significantly correlated with PLNM. Kadan (2017) established lower BMI as a significant preoperative risk factor for PLNM in low risk EC patients. Our study demonstrated that myometrial invasion of 50% or greater and LVSI were independent risk factors for developing PLNM, and EC patients with deep myometrial invasion and LVSI were approximately 9 times and 4 times, respectively more likely to have PLNM. Our study and previous studies (Stalberg et al., 2017; Li et al., 2019) agreed that deep myometrial invasion was a significant co-risk factor for developing PLNM in EC patients. The diagnostic accuracies of magnetic resonance imaging (MRI), ultrasonography, and intraoperative gross examination for assessing the depth of myometrial invasion were 73-83%, 68-77%, and 74-87%, respectively (Akabayir et al., 2011; Mavromatis et al., 2012; Christensen et al., 2016; Usta et al., 2017; Jonsdottir et al., 2021). Therefore, we would suggest to utilize both preoperative assessment of myometrial invasion using ultrasonography or MRI, and intraoperative gross myometrial invasion evaluation for selecting patients who would benefit from lymphadenectomy.

Furthermore, blood cell findings including neutrophilia, thrombocytosis and relative lymphopenia have been proposed as noninvasive, inexpensive, and readily accessible tools to predict lymph node

Table 3. Multivariate Analysis of Risk Factors for Pelvic Lymph Node Metastasis

Variables	Odds ratio (95% Confidence interval)	P-value
Myometrial invasion		
<50%	1	-
≥50%	9.31 (2.58-33.55)	0.001
LVSI		
No	1	-
Yes	3.73 (1.39-10.02)	0.009

LVSI, lymphovascular space invasion

involvement in EC patients (Grivennikov et al., 2010; Suh et al., 2012; McMillan, 2013; Li et al., 2019; Aoyama et al., 2019; Gao and Gao, 2021). Systemic inflammatory response accounts for those changes and represents the development and progression of malignancy (Hanahan and Weinberg, 2011).

Previous studies showed conflicting data regarding NLR and PLR changes in EC patients. Some studies reported that NLR and PLR were higher in lymph node-positive EC patients as compared with those of lymph node-negative patients (Suh et al., 2012; Gao and Gao, 2021). Kadan (2017) demonstrated that NLR had no significant correlation with nodal metastasis. Univariate analysis of our study did not show the associations of PLNM with ANC, AMC, ALC, NLR, MLR and PLR. However, the pelvic lymph node-positive group had lower Hb level and higher WBC count than the pelvic lymph node-negative group. Therefore, NLR and PLR might not be a reliable predictor of lymph node metastasis in EC patients.

The strengths of our study are the standard staging surgeries were performed by experienced gynecologic oncologists and the detailed analyses of several clinicopathologic factors that might affect lymph node metastasis were included. However, we acknowledge the limitation of this study which was a single-center retrospective study, potential practice bias could not be excluded.

In conclusion, myometrial invasion of 50% or greater and LVSI were independent risk factors of PLNM in patients with apparently early-stage EC. Therefore, preoperative assessment of myometrial invasion by using imaging modalities and intraoperative gross myometrial invasion evaluation should be performed to select the EC patients who would benefit from lymphadenectomy.

### Author Contribution Statement

PG, YP and CT designed the research study, acquisition of the data, analysis and interpretation of the data. PG and YP wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

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#### Study Approval

This manuscript is a part of an approved resident thesis by Department of Obstetrics and Gynecology, Faculty of Medicine, Thammasat University Hospital.

#### Ethical Approval

The study was approved by the ethical approval from Human Research Ethics Committee of Thammasat University.

#### Availability of Data

The datasets used in this study are available from the corresponding author upon reasonable request.

#### Conflict of Interest

Authors have no conflict of interest to declare.

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