

# Factors associated with lymph node metastasis in endometrial cancer

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**Submission date:** 27-Sep-2022 12:48PM (UTC+0700)

**Submission ID:** 1910194941

**File name:** 057\_-\_3642\_-\_Very\_Great\_Eka\_Putra\_-\_Galley.pdf (324.09K)

**Word count:** 3973

**Character count:** 21275

## Factors associated with lymph node metastasis in endometrial cancer



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Received: 2022-06-02  
Accepted: 2022-07-31  
Published: 2022-08-12

### ABSTRACT

**Introduction:** Lymph node metastasis is considered one of the most significant prognostic markers in endometrial cancer, particularly in the initial stages. As the incidence rate of endometrial cancer increases, appropriate treatment is needed to increase the survival rate, including lymphadenectomy. This study aims to compare the characteristics of endometrial cancer with or without lymph node metastasis.

**Methods:** A retrospective analytical study of 155 women with a history of endometrial cancer following complete surgical staging treatment from January 2017 to December 2021 at Dr. Kariadi General Hospital Semarang. All data were obtained using medical records.

**Results:** All 155 patients were divided into two groups, with and without lymph node metastasis. These, 19 patients have lymph node metastasis (12.25%). The body mass index is the only subject characteristic that is statistically significant between the two groups ( $p=0.024$ ). In our multivariable risk analysis, three clinical variables were identified that might predict the probability of lymph node metastasis, including ovarian metastasis ( $OR=2.98$ ,  $p<0.01$ ) and cervical metastasis ( $OR=8.27$ ,  $p=0.002$ ), and tumor differentiation grading ( $OR=6.77$ ,  $p<0.01$ ).

**Conclusion:** The study results indicated ovarian metastasis, cervical metastasis, and tumor differentiation grading were independent prognostic factors for lymph node metastasis.

**Keywords:** endometrial cancer, lymph node metastasis, prognosis.

**Cite This Article:** Iskandar, T.M., V.G.E., Ambari, E., Cahyono, E., Lubena. 2022. Factors associated with lymph node metastasis in endometrial cancer. *Bali Medical Journal* 11(2): 784-788. DOI: 10.15562/bmj.v11i2.3642

### INTRODUCTION

Endometrial cancer is becoming more common, and the incidence is increasing. The most frequent gynecological cancer in high and middle-income countries is endometrial cancer.<sup>1</sup> In 2018, there were 382,069 new cases, according to GLOBOCAN cancer data. Furthermore, gynecologic cancer deaths from endometrial cancer were the fourth most prevalent cause of death for women worldwide.<sup>2</sup> Endometrial cancer has a good prognosis when diagnosed early, while high-grade cancer frequently tends to recur. Patients with advanced disease have a very poor prognosis, with metastasis being the primary cause of mortality.<sup>3</sup>

Type 1 and type 2 endometrial carcinoma are the two subtypes of endometrial cancer. Type 1 endometrial carcinomas are low-grade, diploid, and have either well-differentiated or moderately-differentiated hormone receptors (hormone-receptor positive). Women who are obese are

more likely to develop this malignancy. However, type 2 endometrial cancer, which is high-grade and histologically non-endometrioid, is significantly more common in non-obese women.<sup>4</sup> The most common subtype of endometrial cancer is endometrial adenocarcinoma, also known as endometrioid carcinoma. Unopposed estrogen exposure, both exogenous and endogenous in the absence of progestin, leads to the growth of endometrial cancer.<sup>5</sup> Other risk factors for endometrial carcinoma include obesity, nulliparous, and the usage of tamoxifen.<sup>6</sup>

Lymph node metastasis is a significant predictive factor for predicting mortality in endometrial cancer patients. As a result, some studies show that lymphadenectomy should be performed in association with other endometrial cancer treatments. There are concerns regarding the therapeutic advantages of systemic lymphadenectomy of endometrial cancer. Lymphedema, whose incidence will increase with

advanced age, is one of the long-term consequences of lymphadenectomy.<sup>7</sup>

Over this, specific predictor criteria are required to identify the probability of lymph node metastasis in endometrial carcinoma, allowing for more specific targeting of lymphadenectomy and preventing it from becoming a standard treatment for all patients with endometrial carcinoma. Tumor histology, tumor grade, DNA ploidy, and myometrial invasion are a few prognostic factors that have been found in earlier studies.<sup>7,8</sup>

While many studies have been conducted on several different predictor factors for lymph node metastasis in endometrial carcinoma cases, few have published conclusive findings. For this reason, this study was done to compare the characteristics and risk factors of lymph node metastasis and endometrial carcinoma. This study aims to compare the characteristics of endometrial cancer with or without lymph node metastasis.

## METHODS

This study design is a retrospective analytic study using data from the medical records of patients diagnosed with endometrial cancer following complete surgical staging treatment from January 2017 to December 2021 at Dr. Kariadi General Hospital Semarang, which serves as a gynecologic oncology referral center for the Central Java region.

The inclusion criteria were all newly diagnosed cases of primary endometrial cancer proven by official histopathology reports at Dr. Kariadi General Hospital Semarang and recorded within the study period. The exclusion criteria were cases with incomplete data and cancer other than endometrial cancer.

Data regarding the demographics, hormonal factors (age, body mass index, number of parity), and clinicopathology (carcinoma subtypes, tumor differentiation grading, myometrial invasion, lymph node, ovaries, cervical, and peritoneal metastasis) were all extracted from the medical records. The 155 patients who met the inclusion criteria were subsequently divided into two groups, with and without lymph node metastasis.

The data were analyzed with SPSS 24.0. The statistical analysis from subject characteristics is presented descriptively before applying an unpaired T-test for the numerical variable or chi-square for the nominal variable to see mean differences and the proportional difference between the two groups. We conducted a bivariate analysis to compare lymph node metastasis and clinicopathology characteristics. If more than one bivariate analysis significantly correlated ( $P < 0.25$ ), the study was continued with multivariate analysis. To get the final results, which contain variables with a P-value under 0.05, we used logistic regression of prognostic models for multivariate analysis. After showing the coefficient value, the quality of the logistic regression equation's calibration and discrimination abilities were evaluated. The Homer and Lemeshow test tested calibration ability, while the amount of area under the curve (AUC) obtained by the receiver operating characteristic assessed discrimination ability.

## RESULTS

This study consisted of 155 endometrial cancer patients. Of these, 19 patients have lymph node metastasis (12.25%), while the others did not. Subject characteristics data are shown in Table 1. Although the lymph node metastasis group's patients were older on average than those in the non-lymphatic metastasis group, the difference was not statistically significant ( $p = 0.254$ ). The average of the non-lymphatic

metastatic group's body mass index (BMI) was considerably greater than that of the metastatic group ( $p = 0.024$ ). The number of parity between the two groups did not differ significantly ( $p = 0.171$ ), and most patients had multiple pregnancies. The clinical characteristics of endometrial cancer patients showed no significant differences in the carcinoma type between groups with and without lymph node metastasis ( $p = 0.256$ ). As the degree of tumor differentiation worsened,

**Table 1. Characteristics of Subject**

Characteristics	Lymph Node Metastasis		P-value
	With N = 19	Without N = 136	
Age (yr), average (SD)	54.47 (10.68)	51.43 (9.97)	0.254 <sup>a</sup>
BMI (kg/m <sup>2</sup> ), average (SD)	22.17 (4.49)	24.82 (4.66)	0.024 <sup>a</sup>
Parity			0.171 <sup>b</sup>
P0, n (%)	4 (8.2)	45 (91.8)	
P1, n (%)	2 (6.5)	29 (93.5)	
>P1, n (%)	13 (17.3)	62 (82.7)	

<sup>a</sup>BMI: body mass index, a: test with unpaired T-test, b: test with Chi-Square

**Table 2. Association of Clinical Characteristics and Lymph Node Metastasis in Patients with Endometrial Carcinoma**

Variables	Lymph Node Metastasis		P-value	OR	95% CI
	With N = 19	Without N = 136			
Subtypes of carcinoma, n (%)			0.256 <sup>a</sup>	0.47	0.14-1.59
Endometrioid	15 (11)	121 (89)			
Non-endometrioid	4 (21.1)	15 (7.89)			
Tumor differentiation grading, n (%)			<0.001 <sup>b</sup>		
G1	0 (0)	44 (100)			
G2	6 (9)	61 (91)			
G3	13 (29.5)	31 (70.5)			
Myometrial invasion, n (%)			0.022 <sup>b</sup>	0.13	0.02-0.1
<50%	1 (2.4)	41 (97.6)			
>50%	18 (15.9)	95 (84.1)			
Ovarian metastasis, n (%)			0.001 <sup>b</sup>	4.86	1.79-13.17
Yes	11 (26.8)	30 (73.2)			
No	8 (7)	106 (93)			
Cervical metastasis, n (%)			<0.001 <sup>a</sup>	6.92	2.49-19.25
Yes	12 (30.8)	27 (69.2)			
No	7 (6)	109 (94)			
Peritoneal metastasis, n (%)			0.041 <sup>a</sup>	3.23	1.08-9.64
Yes	6 (26.1)	17 (73.9)			
No	13 (9.8)	119 (90.2)			
Metastasis other than the ovaries, uterine, and lymph nodes, n (%)			0.201 <sup>a</sup>	2.36	0.59-9.5
Yes	3 (23.1)	10 (76.9)			
No	16 (11.3)	126 (88.7)			

a: test with unpaired T-test, b: test with Chi-Square

**Table 3. Multivariate analysis of logistic regression**

	Coefficient	S.E	Wald	df	p-Value	OR	95% CI	
							Max	Min
Ovarian metastasis	1.094	0.582	3.537	1	0.060	2.986	0.955	9.334
Cervical metastasis	2.113	0.597	12.539	1	0.000	8.274	2.569	26.648
G3 tumor differentiation	1.913	0.607	9.933	1	0.002	6.771	2.061	22.243
Constanta	-4.143	0.664	38.954	1	0.000	0.016		

the incidence of lymph node metastasis increased significantly ( $p = 0.001$ ), with the G3 group showing the highest percentage and the G1 group showing the lowest percentage. Moreover, patients with endometrial cancer showed a significant difference in myometrial invasion ( $p = 0.022$ ), ovarian metastases ( $p = 0.001$ ), cervical metastases ( $p < 0.001$ ), and peritoneal metastases ( $p = 0.041$ ) between groups with and without lymph node metastasis. On the contrary, there was no significant difference between the groups with and without lymph node metastasis in the frequency of metastases other than those to the ovaries, uterus, and lymph nodes ( $p = 0.201$ ) [Table 2].

Seven categorical variables from the bivariate analysis with  $p$  values  $< 0.25$  were included in the multivariate analysis. The seven factors were parity, tumor differentiation grading, myometrial invasion, ovarian metastasis, cervical metastasis, and metastases other than uterine, ovaries, and lymph nodes. Table 3 shows the results of multivariate logistic regression analysis to evaluate predictors of lymph nodes metastasis in endometrial cancer patients.

The results of logistic regression showed that significantly correlated ( $P < 0.05$ ) variables with lymph nodes metastasis are ovarian metastasis, cervical metastasis, and G3 tumor grading (poorly-differentiated tumor). The strength of the correlation from the strongest to the weakest are cervical metastasis (OR: 8.27; 95% CI: 2.569–26.648), G3 tumor grading (OR: 6.77; 95% CI: 2.061–22.243), and ovarian metastasis (OR: 2.98; 95% CI: 0.955–9.334) (Table 3). Using equation  $y = \text{constant} + a_1x_1 + a_2x_2 + a_3x_3$  and with the value of constant  $-4.143$ , a stands for value of coefficient for each variable, and  $x$  stands for risk factor, therefore the logistic regression equation was revealed as  $y = -4.143 + 1.094$  (ovarian metastasis)

+ 2.113 (cervical metastasis) + 1.913 (G3 tumor grading). The  $P$ -value of the Hosmer and Lemeshow test was 0.435 showing that the equation has a relatively good ability of calibration. Furthermore, the quality of discrimination was assessed by the ROC curve, the AUC value is 85.3%, which means there is strong discrimination [Figure 1].

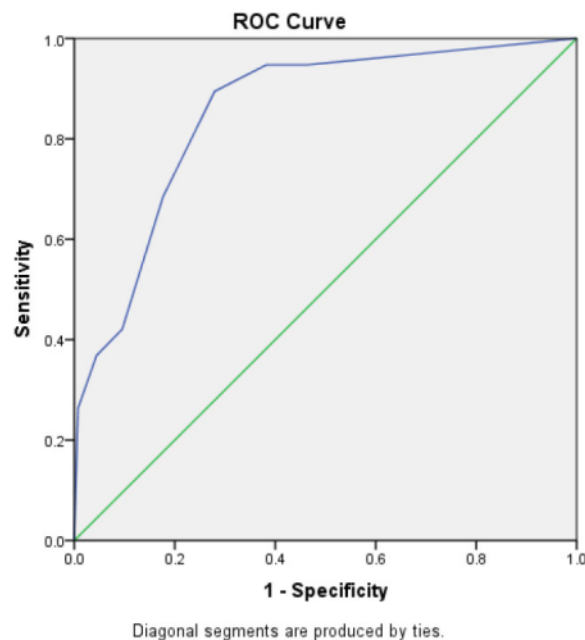
## DISCUSSION

In early-stage endometrial cancer, lymphadenectomy is a challenging procedure because the incidence of lymphatic dissemination is difficult to estimate accurately. Furthermore, it is yet unclear the significance of lymphadenectomy contributes to patients with stage I and stage II endometrial cancer's long-term survival. According to

several studies, lymphadenectomy can be done to determine the lesion's grade, direct adjuvant therapy, and increase prognosis.<sup>9</sup> However, contradictory findings were reported in two RCT investigations by ASTEC (2009) and Uccella et al. (2009). Patients with endometrial cancer who experienced lymphadenectomy do not receive an improvement in disease-free survival or overall survival, and as the surgical impact is increased, it is more common for complications like intestinal obstruction, lymphocytes, deep vein thrombosis, and other issues to occur.<sup>10,11</sup>

## Characteristics of Subject

The average age of endometrial cancer diagnosis ranged from 55 to 64 years old, with the median at 62 years old.<sup>3</sup> The average (SD) ages of the two groups in this study were 54.47 (10.68) and 51,

**Figure 1. ROC curve**



respectively. Both of them fit into the category of individuals at the peak age for endometrial cancer. According to the bivariate analysis results, there was no significant difference in age between the patient groups with and without lymph node metastasis ( $p = 0.254$ ). These findings are in accordance with the study by Milam et al. (2012). They found no significant difference in age between groups of patients with and without lymph node metastases in endometrioid subtype endometrial cancer.<sup>12</sup> In this study, it can be concluded that age is not a confounding factor.

Endometrial cancer risk is known to be influenced by parity through progesterone and estrogen levels. The patient continues to produce sex steroid hormones in chronic anovulation, although not cyclically. This results in no regular endometrial turnover. The endometrium can continue to proliferate because chronic estrogen production is not adequately countered by progesterone production. In the end, the disease may result in endometrial cancer and endometrial hyperplasia. Although they are not independent risk factors, nulliparity and infertility are known to be linked to endometrial cancer.<sup>13</sup> In this study, there was no significant difference in parity between groups with and without lymph node metastasis ( $p = 0.171$ ). Parity was not a confounding factor in this investigation similar to age.

Several studies have examined the association between BMI and endometrial cancer patient outcomes. However, the findings are still unclear. While Milam et al. (2012) showed no association between body weight and lymph node metastases, Reeves et al. (2011) reported that obesity was associated with a better prognosis.<sup>12,14</sup> The BMI value in the group with lymph node metastasis in this study was considerably lower than in the group without metastases ( $p = 0.024$ ). The results of studies associating BMI with lymph node metastasis in endometrial cancer patients were still unclear. Therefore, the researchers concluded that even if there were statistically significant differences, this value was not clinically important. It is therefore unclear if BMI serves as a confounding factor in this study.

### Association of Clinical Characteristics and Lymph Node Metastasis in Patients with Endometrial Carcinoma

No significant differences in subtypes of carcinoma were found between the groups with and without lymph node metastasis. This is likely because there are significantly fewer participants in the non-endometrioid group than in the endometrioid group, which makes it difficult to determine the true prevalence of lymph node metastasis in the general population. Another explanation is that lymph node metastasis varies depending on the degree of differentiation in each carcinoma subtype.

Based on the tumor differentiation grading, 31.3% of patients in the G2 group and 68.4% in the G3 group had lymph node metastasis. Patients in the G1 group showed no incidence of metastases. This difference was statistically significant ( $p = 0.001$ ). This study's findings align with a study by Muallem et al. (2016) which found that patients with a poorly-differentiated tumor had a five times higher risk of developing lymph node metastasis.<sup>15</sup>

The invasion of endometrial cancer cells into the myometrium is known as a myometrial invasion. The depth of invasion is significant in determining the clinical stage. Nearly all of the patients in this study who had lymph node metastasis also had greater than 50% of myometrial invasion.

This study showed a significant difference in the incidence of ovarian metastases with lymph node metastasis ( $p = 0.001$ ). There are two ways that endometrial cancer can spread to the ovary, either through the fallopian tubes attached to the ovary's surface or through the lymphatic system. The findings of this study are consistent with those of Zhou et al. (2005), who found that patients with lymph node metastases had a considerably higher risk of ovarian metastases ( $p < 0.01$ ).<sup>16</sup>

In this study, between the groups with and without metastases, there was a significantly different incidence of lymph node metastasis (OR 6.92, 95% CI 2.49-19.25,  $p < 0.001$ ). These findings are consistent with studies by Boren et al. (2012), which found that there was a

statistically significant difference in the incidence of cervical metastases between groups with and without lymphatic metastases ( $p < 0.01$ ).<sup>17</sup>

In early-stage endometrial cancer, peritoneal metastases are 5–10% more common and are identified by positive peritoneal cytology. Following the 2009 Federation of Gynecology and Obstetrics (FIGO) classification, endometrial cancer patients with positive peritoneal cytology were characterized as stage IIIA. According to this study, endometrial cancer patients who also have peritoneal metastases are significantly more likely to have lymph node metastasis (OR 3.23, 95% CI 1.08-9.64,  $p = 0.041$ ). The existence of peritoneal metastases should always be considered in patient treatment decisions; however, it is no longer a requirement for FIGO staging.<sup>18</sup>

### Factors that Predict Lymph Node Metastasis in Patients with Endometrial Cancer

Several studies have been conducted on the risk factors for lymph node metastasis in individuals with endometrial cancer. However the findings are still unclear. Stalberg et al. (2017) examined the relationship of myometrial invasion, DNA ploidy, FIGO stage, and tumor histology on the incidence of lymph node metastasis in endometrial cancer patients. Multivariate analysis showed that patients with >50% myometrial invasion, non-endometrioid histology, and stage 3 FIGO had a higher risk of lymph node metastasis than patients with stage 1-2.<sup>19</sup> As predictors of lymph node metastasis, Kadan et al. (2017) assessed the neutrophil-lymphocyte ratio (NLR), body mass index (BMI), and myometrial invasion. They discovered that the lymph node metastasis group had a substantially lower BMI, 31.5 vs. 34.4 kg/m<sup>2</sup> ( $p = 0.03$ ).<sup>20</sup>

In this study, ovarian metastases (OR 2.99, 95% CI 0.95-9.33), cervical metastases (OR 8.27, 95% CI 2.56-26.64), and G3 tumor stage were identified in the multivariate analysis as independent risk factors for lymph node metastasis in patients with endometrial cancer. The findings of this study are aligned with those of earlier investigations and vary from them. This

might result from variations in the study population, inclusion criteria, and variable combinations assessed among studies.

## CONCLUSIONS

There were significant differences in BMI values, tumor differentiation grading, myometrial invasion, ovarian metastases, cervical metastases, and peritoneal metastases between endometrial cancer patients with or without lymph node metastasis.

The study results indicated ovarian metastasis, cervical metastasis, and tumor differentiation grading were independent prognostic factors for lymph node metastasis.

## CONFLICT OF INTEREST

The author reports no conflicts of interest in this work.

## ETHICS APPROVAL

This study has been approved by the Ethics Committee of the Dr. Kariadi General Hospital Semarang, with the Ethical Clearance Certificate No. 959/EC/KEPK-RSDK/2021

## FUNDING

This study was funded by the authors

## AUTHOR CONTRIBUTION

All authors contributed equally to the writing of this article

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