

# Clinicopathological characteristics and possible risk factors for extrauterine metastases in endometrial carcinoma



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## ABSTRACT

**Introduction:** Extrauterine metastases often occur in patients with advanced stages of endometrial carcinoma. Retroperitoneal lymph nodes and pelvic lymph nodes are the most common metastatic sites for endometrial carcinoma, while distant metastases, including those to the lung, liver, and brain, are uncommon. This study compares the characteristics of endometrial carcinoma with or without extrauterine metastases and evaluates risk factors associated with extrauterine metastases.

**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. The clinical and pathological characteristics were compared using the Unpaired T-test and Chi-Square test. Multivariate logistic models were performed to estimate the odds ratio (OR) and 95% CI to analyze independent risk factors for extrauterine metastases.

**Results:** A total of 155 endometrial cancer patients were included in this study. Of these, 77 patients have extrauterine metastases (49.67%). The most common site for extrauterine metastases is ovarian metastases (26.5%). Using univariable and bivariate analysis, tumor differentiation grading (OR=3.69, p=0.027) and myometrial invasion (OR=2.84, p=0.027) were the two risk factors associated with extrauterine metastases.

**Conclusion:** There were significant differences in clinicopathological characteristics between the two groups with and without extrauterine metastases. Tumor differentiation grading and myometrial invasion were two independent risk factors.

**Keywords:** endometrial cancer, extrauterine metastases, risk factors.

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## INTRODUCTION

The most prevalent malignancy among women in developed countries is endometrial carcinoma. According to the latest data in 2018, there were 382,069 new cases.<sup>1</sup> Patients with advanced disease of endometrial cancer have a very poor prognosis, with metastasis being the primary cause of mortality.<sup>2</sup>

Patients with advanced stages of endometrial cancer may develop extrauterine metastases. Retroperitoneal lymph nodes and pelvic lymph nodes are the most common metastatic sites for endometrial carcinoma, while distant metastases, including those to the lung, liver, and brain, are uncommon.<sup>3</sup> Haematogenous, lymphatic, and transcoelomic are the main routes in

which distant tumor metastasis originates. Furthermore, tumor dissemination can also occur locally inside the gynecological tract.<sup>4</sup>

Endometrial carcinoma is divided into two different subtypes. Type 1 endometrial carcinomas are low-grade, diploid, and have either well-differentiated or moderately-differentiated hormone receptors (hormone-receptor positive). Type 2 endometrial cancer is high-grade and histologically non-endometrioid.<sup>5</sup> The most common subtype of endometrial cancer is endometrioid carcinoma. Risk factors for endometrial carcinoma include unopposed estrogen exposure, obesity, nulliparous, and the usage of tamoxifen.<sup>6</sup>

This study compares the characteristics of endometrial carcinoma with or without extrauterine metastases and evaluates

risk factors associated with extrauterine metastases. The outcomes of this study are expected to improve the optimal treatment of endometrial cancer.

## METHODS

A retrospective analytic study design was used in this research. Data were obtained 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.

Among eligible cases, patient demographics and hormonal factors (age, body mass index, number of parity) were abstracted from medical records. For pathology results, carcinoma subtypes, tumor differentiation grading, depth of myometrial tumor invasion, peritoneal metastasis, ovarian metastasis, and cervical metastasis were collected based on histopathological examination after complete surgical staging. Liver metastasis and pulmonary metastasis early detection were obtained from ultrasound examination and chest x-ray, respectively. The 155 patients who met the inclusion criteria were subsequently divided into two groups, with and without extrauterine metastases.

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. We used logistic regression of predictive models for multivariate analysis to get the final results, which contain variables with a P-value under 0.05. After showing the coefficient value, the quality of the logistic regression equation's calibration was evaluated using The Hosmer and Lemeshow test.

## RESULTS

A total of 155 endometrial cancer patients were included in this study. Of these, 77 patients have extrauterine metastases (49.67%), while the rest have not. Subject characteristics data are shown in Table 1. The average age of patients with extrauterine metastases was older than those without metastases, but the difference was not statistically significant ( $p = 0.143$ ).

**Table 1. Characteristics of Research Subjects.**

Characteristics	Extrauterine Metastases		P-value
	With N = 77	Without N = 78	
Age (yr), average (SD)	53 (10.77)	50.62 (9.24)	0.143 <sup>a</sup>
BMI (kg/m <sup>2</sup> ), average (SD)	24.12 (4.83)	24.85 (4.56)	0.333 <sup>a</sup>
Parity			0.629 <sup>b</sup>
P0, n (%)	25 (16.1)	24 (15.5)	
P1, n (%)	13 (8.4)	18 (11.6)	
>P1, n (%)	39 (25.2)	36 (48)	

\*BMI : body mass index, a: test with unpaired T-test, b: test with Chi-Square

**Table 2. Locations of extrauterine metastases.**

Sites of Metastasis	Value (n,%)
Peritoneal metastasis	23 (14,8)
Ovarian metastasis	41 (26,5)
Lymph node metastasis	19 (12,3)
Hepatic metastasis	4 (2,6)
Pulmonary metastasis	13 (8,4)

**Table 3. Pathological characteristics of extrauterine metastases in 155 patients with endometrial carcinoma.**

Features	Value
<i>Peritoneal Metastasis</i>	
<b>Subtypes of Carcinoma</b>	
Endometrioid	21 (91.3)
Non-endometrioid	2 (8.7)
<b>Tumor Differentiation Grading</b>	
G1	2 (8.7)
G2	8 (34.8)
G3	13 (56.5)
<b>Myometrial Invasion</b>	
<50%	22 (95.7)
>50%	1 (4.3)
<i>Ovarian Metastasis</i>	
<b>Subtypes of Carcinoma</b>	
Endometrioid	34 (82.9)
Non-endometrioid	7 (17.1)
<b>Tumor Differentiation Grading</b>	
G1	2 (4.9)
G2	17 (41.5)
G3	22 (53.7)
<b>Myometrial Invasion</b>	
<50%	3 (7.3)
>50%	38 (92.7)
<i>Lymph Node Metastasis</i>	
<b>Subtypes of Carcinoma</b>	
Endometrioid	15 (78.9)
Non-endometrioid	4 (21.1)

The non-metastatic group's body mass index (BMI) average was discovered to be greater than the metastatic group's, but the statistical test reveals insignificance ( $p = 0.333$ ). The number of parities between the two groups did not differ significantly ( $p = 0.629$ ), and most patients had multiple pregnancies.

According to the data shown in [Table 2](#), the most common site for extrauterine metastases in this study is ovarian metastases, with a total of 41 patients (26.5%), peritoneum (14.8%), and lymph node (12.3%). Metastases to the lungs and liver are uncommon, occurring in only 8.4% and 2.6% of cases, respectively.

In [Table 3](#), extrauterine metastases were most frequently seen in the endometrioid carcinoma subtype. Endometrioid carcinoma most common found in peritoneal metastasis (91.3%), followed by ovaries (82.9%), lymph node (78.9%), lungs (76.9%) and liver (50%). The rate of extrauterine metastasis was highest in poorly-differentiated tumors (G3) in lymph node metastasis (68.4%), followed by peritoneum (56.5%), ovaries (53.7%), and liver (50%). In pulmonary metastasis, the highest rate of extrauterine metastasis was found in moderately differentiated tumors (G2), with a total of 8 patients (41%). In our study, the myometrial invasion in lymph node metastasis was more than one-half in nearly all patients (94.7%), followed by ovaries (92.7%), lungs (84.6%), and liver (50%). On the contrary, in peritoneal metastasis, the depth of myometrial invasion was less than one-half in nearly all patients (95.7%).

Analysis of the clinical characteristics of endometrial cancer patients showed no significant differences in the subtype of carcinoma between groups with and without extrauterine metastases ( $p = 0.512$ ). As the degree of tumor differentiation worsened, the incidence of extrauterine metastasis increased significantly ( $p < 0.001$ ), with the G2 group showing the highest percentage (23.8%) and the G1 group showing the lowest percentage (4%).

This may occur due to the G2 group having a larger number of samples than the G3 group. In addition, endometrial cancer patients showed a significant difference in myometrial invasion between groups

Features	Value
<b>Tumor Differentiation Grading</b>	
G1	0 (0)
G2	6 (31.6)
G3	13 (68.4)
<b>Myometrial Invasion</b>	
<50%	1 (5.3)
>50%	18 (94.7)
<b>Hepatic Metastasis</b>	
<b>Subtypes of Carcinoma</b>	
Endometrioid	2 (50)
Non-endometrioid	2 (50)
<b>Tumor Differentiation Grading</b>	
G1	1 (25)
G2	1 (25)
G3	2 (50)
<b>Myometrial Invasion</b>	
<50%	2 (50)
>50%	2 (50)
<b>Pulmonary Metastasis</b>	
<b>Subtypes of Carcinoma</b>	
Endometrioid	10 (76.9)
Non-endometrioid	3 (23.1)
<b>Tumor Differentiation Grading</b>	
G1	1 (2.3)
G2	8 (11.9)
G3	4 (9.1)
<b>Myometrial Invasion</b>	
<50%	2 (15.4)
>50%	11 (84.6)

with and without extrauterine metastases ( $p < 0.001$ ) ([Table 4](#)).

The multivariate analysis included two variables from the bivariate analysis with  $p$  values  $< 0.25$ . The variables entered in the multivariate analysis in [Table 5](#) shows the results of multivariate logistic regression analysis to evaluate the risk factors of extrauterine metastasis in patients with endometrial carcinoma. The logistic regression results showed that all variables are significantly correlated ( $P < 0.05$ ). The strength of the correlation from the strongest to the weakest is tumor differentiation grading (OR: 3.69; 95% CI: 2.103–6.504) and myometrial invasion (OR: 2.84; 95% CI: 1.127–7.205) ([Table 5](#)). Using equation  $y = \text{constant} + a_1x_1 + a_2x_2$  and with the value of constant

$-4.488$ , a stands for value of coefficient for each variable, and  $x$  stands for risk factor, therefore the logistic regression equation was revealed as  $y = -4.488 + 1.308$  (tumor differentiation grading)  $+ 1.047$  (myometrial invasion). We calculated using the equation that the probability of extrauterine metastasis was 20.4%. The P-value of the Hosmer and Lemeshow test was 0.891 showing that the equation has a relatively good ability of calibration.

According to [Table 6](#), the presence of lymph node metastasis for the prediction of ovarian metastasis was a significant indicator in comparative analysis. In the presence of lymph node metastasis, the rate of ovarian metastasis was 26.5% ( $p < 0.001$ ).

**Table 4. Association of Clinical Characteristics and Extrauterine Metastasis in Patients with Endometrial Carcinoma.**

Variables	Extrauterine Metastasis		P-value
	With N = 77	Without N = 78	
Subtypes of carcinoma, n (%)			0.512 <sup>a</sup>
Endometrioid	68 (43.9)	68 (43.9)	
Non-endometrioid	9 (5.8)	10 (6.5)	
Tumor differentiation grading, n (%)			<0.001 <sup>a</sup>
G1	6 (3.9)	38 (24.5)	
G2	37 (23.9)	30 (19.4)	
G3	34 (21.9)	10 (6.5)	
Myometrial invasion, n (%)			<0.001 <sup>a</sup>
<50%	9 (5.8)	33 (21.3)	
>50%	68 (43.9)	45 (29)	

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

**Table 5. Multivariate analysis of logistic regression.**

	Coefficient	S.E.	Wald	df	p-Value	OR	95% CI	
							Max	Min
Tumor differentiation grading	1.308	0.473	4.892	1	0.027	3.699	2.103	6.504
Myometrial invasion	1.047	0.473	4.892	1	0.027	2.849	1.127	7.205
Constanta	-4.488	0.946	22.528	1	0.000	0.011		

**Table 6. Risk of lymph node metastasis in patients according to presence of ovarian metastasis.**

Lymph Node Metastasis	Ovarian Metastasis		P-value
	Yes	No	
Present metastasis (n%)	41 (26.5%)	36 (23.2%)	<0.001 <sup>a</sup>
No metastasis (n%)	0 (0%)	78 (50.3%)	

## DISCUSSION

This study analyzed the clinicopathological characteristics and risk factors of endometrial carcinoma with extrauterine metastases, including the ovaries, peritoneum, lymph node, liver, and lung. Earlier studies have shown that patients with endometrial cancer in an advanced stage, such as stage IVB endometrial carcinoma, have intra-abdominal metastases, including the liver and omentum. The prognosis of patients with advanced stage is generally poor. The importance of surgery is still unclear for patients with advanced endometrial cancer and distant metastases.<sup>7</sup>

### Characteristics of Subject

In this study, the average age of the two groups, with and without extrauterine metastases, were 53 and 50.62, respectively. Both belong to the group of people whose risk for endometrial cancer is highest at their age.

There was no significant difference

between the two groups ( $p = 0.143$ ). In this study, it can be concluded that age is not a confounding factor. Compared to patients older than 45, individuals under age 45 had a lower frequency of advanced-stage disease, a higher degree of tumor differentiation, and a better prognosis.<sup>8</sup>

Endometrial cancer has been associated with nulliparity and infertility.<sup>9</sup> In this study, there was no significant difference between groups with and without extrauterine metastasis ( $p = 0.629$ ). Parity was not a confounding factor in this study, similar to age.

This study discovered that the BMI value in the group with extrauterine metastases was lower than in those without metastases, but it was not statistically significant ( $p=0.333$ ). A previous study by Secord et al. showed women with advanced endometrial cancer (stage III and IV) who had a BMI more than 40 had a significantly higher mortality rate than those with a BMI less than 25 (HR=1.86; CI 1.16-2.99;  $p=0.01$ ).<sup>10</sup>

### Clinicopathological Characteristics of Extrauterine Metastases with Endometrial Carcinoma

For both groups with and without extrauterine metastases, there were no significant differences in the carcinoma subtypes ( $p=0.512$ ). This is most likely because the non-endometrioid group had much fewer participants than the endometrioid group, making it difficult to determine the actual frequency of extrauterine metastasis in the general population.

In terms of tumor differentiation grading, the majority of patients (23.9%) classified into the G2 group (moderately-differentiated tumor), followed by the G3 group with 21.9% of patients, and the G1 group with only 6% of patients having extrauterine metastases. ( $p = 0.001$ ) The difference was statistically significant. The degree of cellular differentiation plays an important role in how endometrial cancer spreads. Well-differentiated tumors usually limit their spread to the endometrial surface, while the myometrial invasion is less frequent. Patients with poorly differentiated tumors are considerably more likely to have a myometrial invasion, which frequently causes lymph node involvement and distant metastases.<sup>11</sup> Nearly half of the patients (43.9%) in this study who had extrauterine metastasis



also had myometrial invasion greater than 50%.

### Risk Factors Associated with Extrauterine Metastasis in Patients with Endometrial Carcinoma

There are few studies on the risk factors for extrauterine metastases in patients with endometrial cancer, and the results are still inconclusive. According to a study by Gua J (2020), invasion into the cervical stroma, poorly differentiated tumors, and positive peritoneal washings cytology findings were all independent predictors of high-risk endometrial carcinoma.<sup>7</sup>

In this study, tumor differentiation grading (OR 3.69, 95% CI 2.10-6.50) and myometrial invasion (OR 2.84, 95% CI 1.12-7.25) were identified in the multivariate analysis as independent risk factors for extrauterine metastases in patients with endometrial cancer. The findings of this study are aligned with those of earlier investigations and different from those earlier studies, which could result from variations in the study population and inclusion criteria.

### Association of lymph node metastasis in patients according to the presence of ovarian metastasis

The presence of lymph node metastasis for predicting ovarian metastasis was a significant indicator in comparative analysis ( $p < 0.001$ ). Table 6 shows that all 41 patients from the group with ovarian metastases also had lymph node metastases. In endometrial cancer, there are two possible ovarian metastatic pathways. First, cancer cells infiltrate the ovary directly through the fallopian tube. The second method uses the lymphatic system. In endometrial cancer, the lymphatic pathway is thought to be the primary pathway for ovarian metastases. This result is in line with a study by Zhou et al. (2005), which found that patients with lymph node metastases had

a significantly higher risk of developing ovarian metastases ( $p < 0.01$ ).<sup>12</sup>

## CONCLUSIONS

In conclusion, our findings showed significant differences in clinicopathological characteristics between the two groups. Tumor differentiation grading and myometrial invasion were independent risk factors for extrauterine metastases. Ovarian metastasis is the most typical site for extrauterine metastases. In a comparison analysis, the presence of lymph node metastasis was a significant indicator for predicting ovarian metastasis.

## ETHICS APPROVAL

This study has been approved by the Ethics Committee of Dr. Kariadi General Hospital Semarang, with the Ethical Clearance Certificate No. 1199/EC/KEPK-RSDK/2022

## AUTHOR CONTRIBUTIONS

**Conceptualization:** Teuku Mirza Iskandar and Very Great Eka Putra. **Writing original draft preparation:** Teuku Mirza Iskandar, Very Great Eka Putra, Ediwibowo Ambari, Endy Cahyono, Lubena. **Writing review and editing:** Ediwibowo Ambari, Endy Cahyono, Lubena. All authors have read and agreed to the published version of the manuscript.

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## CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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