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Original Article

# Risk factors for pelvic and para-aortic lymph node metastasis in endometrial cancer: A retrospective analysis of 284 patients

Serra Akar, Cetin Celik

Selcuk University, Faculty of Medicine, Department of Gynecologic Oncology, Konya, Turkey



**Abstract**

**Aim:** Hysterectomy is generally used to treat patients with endometrial cancer. Although lymphadenectomy can provide prognostic information, there are serious complications that can result from lymph node dissection. In order to avoid unnecessary surgical intervention, predictors related to both pelvic and para-aortic lymph node metastasis can be identified. In this study, we sought to define independent prognosticators for pelvic and para-aortic lymph node metastasis in women with endometrial cancer.

**Material and Methods:** In total, 284 patients who were treated surgically between December 2009 and January 2019 were included in the study. The relationships between histopathological patient characteristics and definitive lymph node status were studied.

**Results:** In multivariate analysis, lymphovascular space invasion (Adjusted Odds Ratio: 4.8, 95% Confidence Interval 2.4–17.5, p = 0.001) and deep myometrial invasion (Adjusted Odds Ratio 3.8, 95% Confidence Interval 1.1–14.3) were independent factors for pelvic lymph node metastasis. In multivariate analysis for para-aortic lymph node metastasis, lymphovascular space invasion (Adjusted Odds Ratio 5.9, 95% Confidence Interval 2.1–10.3) and pelvic lymph node metastasis (Adjusted Odds Ratio 20.8, 95% Confidence Interval 8.9–32.3) were independent prognostic factors significantly associated with the presence of para-aortic lymph node metastasis.

**Conclusion:** The two independent histopathological factors identified for predicting the presence of pelvic lymph node metastasis were lymphovascular space invasion and outer half myometrial penetration of the tumor. Lymphovascular space invasion and pelvic lymph node metastasis were independently associated with the presence of para-aortic lymph node metastasis. Consideration of lymphadenectomy in patients who have evidence of outer half myometrial invasion or pelvic lymph node metastasis on preoperative imaging may be prudent. Lymphovascular space invasion and myometrial invasion findings on frozen section can be used before proceeding with lymphadenectomy in endometrial cancer.

**Keywords:** Endometrial cancer; lymph node metastasis; prognostic factors.

## INTRODUCTION

Cancer of the endometrium is the leading female genital tract tumors in countries with effective cervical cancer prevention strategies (1). The five-year survival in patients with endometrioid endometrial cancer is favorable as the disease is generally detected at an early stage (2). More than 90% of patients with endometrial cancer are diagnosed early owing to the onset of vaginal bleeding early in the disease (2,3). Hysterectomy is generally the treatment of choice. However, there is controversy surrounding the routine performance of lymphadenectomy (4-9).

Endometrial cancer stage is assigned based on nodal status, which is an important prognostic factor guiding the administration of adjuvant therapy in the form of radio- or chemotherapy. Involvement of lymph nodes is closely associated with poor prognosis (10). Several studies have reported of a survival benefit through the elimination of potential micrometastases by routine lymphadenectomy (11,12). Specifically, greater than 10% increase in survival has been shown with the removal of more than eleven lymph nodes in one study (13).

Although lymphadenectomy can provide prognostic and possible therapeutic advantage, lymph node dissection can result in serious complications (14). In

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**Corresponding Author:** Gurkan Gunaydin, Adnan Menderes University, Faculty of Health Science, Department of Physical Therapy and Rehabilitation, Aydın, Turkey **E-mail:** gunaydingrkn@gmail.com

order to avoid unnecessary surgical intervention, certain histopathological patient characteristics that are related to both pelvic and para-aortic lymph node metastasis can be investigated. Several tumor characteristics such as size, degree of myometrial invasion, grade and presence of lymphovascular space invasion (LVSI) may be assessed on frozen sections or may be evaluated on imaging preoperatively to guide surgical approach pertaining lymphadenectomy.

In this study, we attempted to examine the association between preoperative tumor grade from endometrial biopsies, postoperative final grade, size of the tumor, LVSI status and degree of myometrial invasion with lymph node metastasis (LNM) and determine risk factors that may be used to predict pelvic and para-aortic LNM in women with endometrial cancer.

## MATERIAL and METHODS

A total of 284 patients diagnosed with endometrioid endometrial cancer following surgical treatment and were followed-up in a single institution between December 2009 through January 2019 were included in the study. There were over 400 surgeries during this time. The patients who were lost to follow-up were excluded from the study. Patients received a definitive histopathological diagnosis of endometrioid endometrial cancer following hysterectomy and comprehensive pelvic and para-aortic lymph node dissection. Patient age, definitive histopathological patient characteristics were retrieved from electronic patient records. Stage and grade of the tumors were given based on the FIGO grading and staging system (15,16). The relationships between preoperative, postoperative FIGO tumor grade, LVSI status, myometrial tumor penetration, tumor size and LNM were investigated. The preoperative tumor grade was the FIGO grade assigned to the endometrial tumor based on the histopathological examination of endometrial biopsies obtained by Pipelle sampling. The other histopathological diagnoses including postoperative tumor grade were obtained from the analysis of the hysterectomy and lymphadenectomy specimen. Deep myometrial invasion was considered to be ≥ 50% myometrial invasion. Approval of the study was obtained from the Institutional Ethics Committee (2018/243).

### Statistical analysis

The relationship of lymph node status with clinicopathological patient characteristics was analyzed using the Chi-square test with posthoc Bonferroni adjustments. Receiver operating curves were used to assess the discrimination value of specific histopathological factors. The area under the curve (AUC) was determined to quantify the potential of risk factors to predict pelvic and para-aortic LNM. Multiple logistic regression analysis included variables such as tumor grade, LVSI, myometrial invasion and tumor size, with a p value < 0.05 on univariate analysis. P-value < 0.05 was considered to be statistically significant. Statistical analyses were carried out using SPSS 25.0 statistical software package (SPSS Inc., Chicago, IL).

## RESULTS

All patients were diagnosed with endometrioid endometrial cancer. The average age of patients was 58.8 ± 10.0. 54.8% of patients were aged ≤60 while 44.5% of patients were aged over 60. Thirty percent of patients had comorbidities like hypertension, diabetes and asthma. The five-year disease-specific survival for patient population was 91%. The mean disease-specific survival was 110.4 [95% Confidence Interval (CI): 105.6-115.1] months.

The distribution of histopathological tumor characteristics for the patients in this study is given in Table 1. 14.5% and 7.8% of patients had pelvic and para-aortic lymph node involvement, respectively. 4.7% and 12.1% of patients had grade 3 tumors on preoperative biopsy and postoperative histopathology, respectively. 47.1%, 22.9%, 52.7% and 17.3% of patients displayed deep myometrial invasion, LVSI, > 2 cm tumor size and advanced stage disease, respectively.

**Table 1. Distribution of clinicopathological patient characteristics**

| | | Frequency (%) |
|---|---|---|
| Preoperative tumor grade | 1 | 209 (73.6) |
| | 2 | 62 (21.8) |
| | 3 | 13 (4.6) |
| Final Tumor grade | 1 | 189 (66.5) |
| | 2 | 60 (21.1) |
| | 3 | 35 (12.3) |
| MI | Superficial | 158 (55.6) |
| | Deep | 126 (44.4) |
| LVSI | Absent | 217 (76.4) |
| | Present | 67 (23.5) |
| Tumor size | ≤2cm | 132 (46.4) |
| | >2cm | 152 (53.5) |
| Stage | I or II | 234 (82.4) |
| | III or IV | 50 (17.6) |
| Pelvic LNM | Absent | 242 (85.2) |
| | Present | 42 (14.7) |
| Para-aortic LNM | Absent | 261 (91.9) |
| | Present | 23 (8.1) |

High tumor grade, diagnosed postoperatively, tumors with LVSI, deep myometrial penetration and size > 2 cm were significantly associated with pelvic and para-aortic LNM ($p<0.05$) as shown in Table 2 and Table 3.

High postoperative tumor grade had a sensitivity of 62.2% and a specificity of 71.8% for predicting pelvic LNM [Area under the Curve (AUC): 0.70, $p<0.001$]. Deep myometrial invasion had a sensitivity of 84.2% and specificity of 62.4% in predicting pelvic LNM. (AUC: 0.73 $p<0.001$). LVSI had a sensitivity of 100% and specificity of 90% in predicting pelvic LNM (AUC: 0.95, $p<0.001$). Tumor size > 2 cm showed

a statistically significant predictive value for diagnosing metastatic pelvic lymph nodes (AUC:0.618, p=0.02) with a sensitivity of 73.7% and a specificity of 50.0%. Preoperative grade did not have a statistically significant discriminatory potential for diagnosing the presence of metastatic pelvic lymph nodes (AUC: 0.56, p= 0.63).

**Table 2. Association of histopathological patient characteristics with pelvic lymph node metastasis**

| | | Pelvic LNM | | |
|---|---|---|---|---|
| | | Absent N(%) | Present N(%) | P |
| Preoperative Tumor grade | 1 | 181 (74.7) | 28 (66.7) | 0.17 |
| | 2 | 55 (22.7) | 7 (16.7) | |
| | 3 | 6 (2.5) | 7 (16.7) | |
| Postop Tumor Grade | 1 | 173 (71.5) | 16 (38.1) | <0.001 |
| | 2 | 50 (20.7) | 10 (23.8) | |
| | 3 | 19 (7.9) | 16 (38.1) | |
| MI | <50% | 151(62.4) | 7(16.7) | <0.001 |
| | ≥50% | 91 (37.6) | 35(83.3) | |
| LVSI | Absent | 217 (89.7) | 0 (0) | <0.001 |
| | Present | 25 (10.3) | 42 (100) | |
| Tumor size | ≤2cm | 121 (50.0) | 11 (26.2) | <0.001 |
| | >2 cm | 121 (50.0) | 31 (73.8) | |

LNM, lymph node metastasis; MI, myometrial invasion; LVSI, lymphovascular space invasion

**Table 3. Association of histopathological patient characteristics with para-aortic lymph node metastasis**

| | | Para-aortic LNM | | |
|---|---|---|---|---|
| | | Absent N (%) | Present N (%) | P |
| Preoperative Tumor grade | 1 | 194 (74.3) | 15 (65.2) | 0.012 |
| | 2 | 62 (23.7) | 0 (0) | |
| | 3 | 5 (1.9) | 8 (34.8) | |
| Postop Tumor Grade | 1 | 189(72.4) | 0 (0.0) | <0.001 |
| | 2 | 49 (18.8) | 11 (47.8) | |
| | 3 | 23 (8.8) | 12 (52.2) | |
| MI | <50% | 155 (59.4) | 3 (13.0) | <0.001 |
| | ≥50% | 106 (40.6) | 20 (87.0) | |
| LVSI | Absent | 217 (83.1) | 0 (0.0) | <0.001 |
| | Present | 44 (16.9) | 23 (100.0) | |
| Tumor size | ≤2cm | 127 (48.7) | 5 (21.7) | 0.034 |
| | >2 cm | 134 (51.3) | 18 (78.3) | |
| Pelvic LNM | Absent | 240 (92.0) | 2 (8.7) | <0.001 |
| | Present | 21 (8.0) | 21( 91.3) | |

LNM, lymph node metastasis; MI, myometrial invasion; LVSI, lymphovascular space invasion

High tumor grade had a sensitivity of 68.4% and specificity of 70.1% in predicting para-aortic LNM (AUC: 0.72, p = 0.001). Deep myometrial invasion had a sensitivity of 85.1% and 60.0% specificity in diagnosing para-aortic lymph node metastasis (AUC: 0.72 , p=0.01). LVSI had a sensitivity of 100% and specificity of 83.3% in predicting para-aortic LNM (AUC: 0.92, p<0.001). Tumor size > 2 cm did not have predictive value for diagnosing metastatic para-aortic lymph nodes (AUC=0.618, p=0.08). Preoperative grade did not have a statistically significant predictive value for diagnosing metastatic para-aortic lymph nodes (AUC= 0.58, p= 0.64).

**Table 4. Multivariate logistic regression for lymph node metastasis**

| | Pelvic LNM | | Para-aortic LNM | |
|---|---|---|---|---|
| Characteristic | AOR (95% CI) | p | AOR (95% CI) | P |
| LVSI | 4.6 (2.4-17.5) | 0.001 | 5.9(2.1-10.3) | 0.01 |
| Tumor Size > 2 cm | 0.35(0.1-12.5) | 0.33 | 3.1(0.6-7.9) | 0.8 |
| Deep myometrial invasion | 3.8(1.1-14.3) | 0.04 | 2.2(0.4-8.8) | 0.34 |
| Grade 3 | 1.6(0.77-3.1) | 0.22 | 1.5(0.76-2.9) | 0.24 |
| Pelvic LNM | | | 20.8 (8.9-32.3) | <0.001 |

LVSI; lymphovascular space invasion, LNM; lymph node metastasis, AOR; Adjusted Odds ratio, CI; Confidence Interval

In multivariate analysis of pelvic LNM, LVSI [Adjusted Odds Ratio (AOR) 4.6, 95% (CI 2.4–17.5, p = 0.001] and deep myometrial invasion (AOR 3.8, 95% CI 1.1–14.3, p = 0.04) were identified as independent risk factors for pelvic LNM (Table 4). In multivariate analysis of para-aortic LNM, LVSI (AOR 5.9, 95% CI 2.1–10.3, p = 0.01), and presence of pelvic LNM (AOR 20.8, 95% CI 8.9–32.3, p < 0.001) were seen as independent prognostic factors associated with para-aortic LNM (Table 4).

## DISCUSSION

Hysterectomy is the standard treatment for endometrial cancer. Lymph node dissection can provide valuable prognostic information and guide therapeutic decision-making but is associated with several complications (14). Lymph node involvement is part of the staging criteria in endometrial cancer (16). Lymphatic spread is a common route of dissemination in patients with endometrial tumors (17). Up to 14.9% of patients diagnosed with endometrial cancer can show evidence of LNM (9,18,19).

However, for patients who have apparent early stage and low-risk endometrial tumors, the performance of lymphadenectomy is controversial. Lymphadenectomy has been associated with an advantage in survival among patients with myometrial invasion (6). According to other studies, lymphadenectomy is thought to lack therapeutic benefit (7, 20) and is associated with major morbidity such as lymphedema (8). Some experts (21) do not recommend routine lymph node dissection for patients without significant risk factors. In order to classify patients with high probability for LNM, we investigated the potential

risk factors that may be related to LNM. We specifically examined the potential association between tumor grade from endometrial sampling and LNM.

We found that preoperative grade on endometrial biopsy could not reliably predict the presence of pelvic or para-aortic LNM. This was an expected finding as preoperative endometrial biopsy (either by dilatation & curettage or Pipelle) has poor correlation with the definitive histopathological diagnosis according to a study with 332 patients (22). The risk factors associated with pelvic and para-aortic LNM were high grade tumors, tumors with LVSI, outer half myometrial invasion and size > 2cm. LVSI and outer half myometrial invasion were the factors independently associated with pelvic LNM. While, LVSI and pelvic LNM were the independent factors related to para-aortic LNM.

These findings are similar to recent studies that have evaluated the association of adverse prognostic factors with pelvic and para-aortic LNM. Li et al. have found that higher serum Human epididymis protein 4, CA 125 were associated with pelvic LNM (23). Additionally, histology of high-grade endometrial cancer, malignant cells in peritoneal cytology, outer half myometrial involvement and LVSI were independently associated with pelvic LNM (23).

On the other hand Sarı et al. conducted a retrospective study with 641 patients diagnosed with endometrial cancer to identify histopathological factors related to para-aortic LNM (18). They reported that in univariate analysis, non-endometrioid histology, age > 60 years, LVSI, high grade tumors, tumors with outer half myometrial invasion, and size ≥2 cm, infiltration of the uterine serosa, adenexal and cervical spread, the presence of pelvic LNM, malignant peritoneal cytology were prognostic factors related to para-aortic LNM. However, in multivariate analysis, the only independent risk factors for para-aortic LNM were LVSI and pelvic LNM. Similarly, in our study, tumor grade, LVSI, tumor size bigger than 2 cm, outer half myometrial invasion and pelvic LNM were all significantly related to para-aortic LNM. However, in multivariate analysis only LVSI and pelvic LNM could be seen as independent prognostic factors for para-aortic LNM. Other factors that have been associated with LNM are tumor size > 2cm, high tumor grade and adnexal involvement in various studies (9,14,24).

Based on their study of over 19000 patients Vergas et al. reported that the probability of LNM was very low with grade 1 or 2 tumors, tumors with size <2 cm and superficial myometrial invasion (25). They also demonstrated that myometrial invasion was the strongest independent predictor of LNM followed by grade 3 and 2 histology and tumor size. However, LVSI was not included among the variables in their multivariate analysis.

Kurman et al. found that the presence of pelvic or para-aortic LNM was correlated with grade 3 tumors, tumors with outer half myometrial invasion and the presence of extra uterine disease (26). They also reported that almost 50% of patients with pelvic LNM had involvement of para-aortic nodal involvement. Although some of these findings are similar to our results, LVSI was not investigated as a potential independent variable in this study. Additionally, they reported that in case of the involvement of para-aortic nodes, involvement above the inferior mesenteric artery was mostly seen.

The limitations of this study include potential bias attributable to the retrospective design of this research. Additionally, the analyses could not be made according to a more detailed knowledge of the localization of the metastatic lymph nodes. This could have added further value to the study as to the specifics of the relationship between risk factors and routes of dissemination.

## CONCLUSION

In conclusion, LVSI and myometrial invasion were found to carry independent prognostic significance for pelvic LNM. LVSI and pelvic LNM carried independent prognostic significance for para-aortic LNM. However, owing to the discrepancy in preoperative and postoperative tumor grade, preoperative tumor grade based on endometrial biopsy specimen did not have predictive value in diagnosing LNM. Based on these results, information on LVSI and myometrial invasion can be obtained on frozen section and these findings could be used to guide surgical management.

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*Serra Akar ORCID: 0000-0002-0466-140X*
*Cetin Celik ORCID: 0000-0001-6165-5092*

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