

# Risk of nodal metastasis associated with lymphovascular space invasion in endometrial cancer

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**Objective:** We conducted this study to investigate the risk of lymphovascular space invasion (LVSI) on lymph node metastasis in endometrial cancer. **Methods:** Between August 2017 and December 2019, we enrolled 88 consecutive patients with a preoperative histologically confirmed diagnosis of clinical stage 1 endometrioid type endometrial carcinoma, who had undergone hysterectomy and 59 of these patients required staging lymphadenectomy. We used Pearson's correlation coefficient and Mc Nemar's test for comparing LVSI and myometrial invasion to predict lymph node metastasis. Logistic regression analysis used for determining predictors for lymph node (LN) metastasis. **Results:** 75% of tumors with pelvic lymph node metastasis had LVSI, whereas 80% of the patients with pelvic lymph node negative tumors did not have LVSI and there was a significant correlation between LVSI and pelvic lymph node metastasis ( $p < 0.01$ ). Sensitivity for LVSI in predicting pelvic lymph node involvement was 75%, specificity was 80.4%, positive predictive value (PPV) was 38% and negative predictive value (NPV) was 95.3% ( $p < 0.05$ ) (95% confidence interval (CI) 1.3–82, hazard ratio (HR): 10.3). Sensitivity for LVSI to predict para-aortic lymph node involvement was 85.7%, specificity 80.8%, PPV 38% and NPV 97.6% ( $p < 0.05$ ) (95% CI 1.7–205 HR: 18.8). Pathological examination results with myometrial invasion more than half of the myometrium that has 75% sensitivity, 51% specificity, 19% PPV and 93% NPV for pelvic lymph node metastasis, thus, LVSI seems to have equal sensitivity but more specificity ( $p < 0.05$ ). **Discussion:** This study demonstrates that LVSI is an independent predictor of LN metastasis for apparently Stage 1 endometrioid type endometrial carcinoma. If feasible, incorporating intraoperative frozen section analysis of LVSI may be used when deciding to perform lymphadenectomy. LVSI status is at least as important as myometrial invasion status of the tumor and LVSI may be a better indicator of lymph node metastasis.

## Keywords

Endometrial cancer; Lymphovascular space invasion; Lymph node metastasis

## 1. Introduction

Endometrial cancer (EC) is the most common gynecological tumor in developed countries, the fourth leading cause of death due to gynecological cancer among women worldwide and tends to rise [1]. Usually it is diagnosed when the disease is confined to the uterus and generally spreads in a stepwise fashion; first local invasion to myometrium, fol-

lowed by lymph node (LN) metastasis and finally distant organ metastasis. LN metastasis in EC is an independent and one of the most important prognostic factors, also determines the need of adjuvant therapy and may have a therapeutic effect as well [2]. The presence of LN metastasis significantly decreases overall survival, nearly by half [3]. EC is staged surgically, hysterectomy and bilateral salpingo-oophorectomy, with or without LN dissection is standard management, and the lymphadenectomy decision is made according to myometrial invasion depth and grade determined intraoperatively with frozen section analysis [4].

Lymphovascular space invasion (LVSI), the presence of tumor in the lymphatic and vascular channels is recognized as an important prognostic factor for EC and independent risk factor for nodal metastasis [5–9]. Based on Gynecologic Oncology Group (GOG)-99 study, LVSI is deemed one of the high-intermediate risk factors for consideration of adjuvant treatment [10].

Routine dissection of pelvic and para-aortic nodes up to the level of the left renal vein is controversial in EC, as increasing the complication rate, and the benefit in terms of survival is not clear [11–14]. In stage IA endometrioid subtype grade 1 or 2 tumors, LN involvement is about 5%, whereas tumors less than 2 cm in diameter which is identified as low risk, risk of LN metastasis is less than 1% and lymphadenectomy does not seem to increase the survival of these patients [12, 15]. Grade 3, deep myometrial invasion, serous tumors is considered high risk tumors [16, 17]. Grade 1 or 2, <50% myometrial invasion, and a tumor diameter  $\geq 2$  cm may be considered as intermediate risk that LN metastasis risk is slightly higher but the need of lymphadenectomy and the benefit of lymphadenectomy for overall and recurrence-free survival rates is questionable [17]. Nonetheless, for intermediate and high-risk, systemic pelvic and para-aortic lymphadenectomy may improve overall survival [18], whereas other large trials, with some drawbacks such as not standardized para-aortic lymphadenectomy, showed no difference in survival with routine lymph node dissection (LND) [12, 19]. As a poor prognostic factor, LVSI is not a clearly defined risk factor for LN metastasis in early-stage EC.

The objective of this study is to define risk of nodal metastasis in endometrial cancer with LVSI positive and to investigate the feasibility whether LVSI investigation should be included in intraoperative frozen section analysis as a risk factor other than Grade, myometrial invasion, and cervical stromal involvement to perform lymphadenectomy in superficial invading low-grade EC.

## 2. Materials and methods

### 2.1 Methods

In this study, 88 consecutive endometrial cancer patients between August 2017 and December 2019 operated with a preoperative histologically confirmed diagnosis of endometrioid type EC were included in this study. All of the patients were evaluated preoperatively with examination, whole abdomen and thorax CT scans with intravenous contrast that 8 patients with signs of local metastasis, distant metastasis or suspicious bulky LNs were excluded from the study. All patients undergone total abdominal or laparoscopic hysterectomy and the specimen was sent to frozen section analysis at a tertiary referral center, Health Sciences University Samsun Research and Training Hospital Gynecologic Oncology Unit by a single surgeon. According to the frozen section results, lymphadenectomy was performed for 59 patients with at least one of the following features identified with intraoperative frozen section analysis; invasion more than 50% of the myometrium, cervical stromal involvement, more than 2 cms in diameter or histologically Grade 3 tumors. The study is a retrospective design and the study protocol was approved by local University Ethical Committee and Institutional Review Board and have therefore been performed in accordance with the ethical standards described in an appropriate version of the 1964 Declaration of Helsinki, as revised in 2013. Preoperative diagnosis is made in another institution with dilatation and curettage for all patients referred.

All of the patients underwent total abdominal or laparoscopic hysterectomy with bilateral salpingo-oophorectomy and specimen is sent for intraoperative frozen section analysis. As reported by final histo-pathological results, stage is determined in respect of FIGO (International Federation of Gynecology and Obstetrics) 2009 staging criteria.

### 2.2 Statistical analysis

Statistical analysis is made by using Statistical Package for Social Sciences (SPSS) 21 software (SPSS Inc, Chicago, IL, USA). Correlation analysis is performed by using Pearson correlation coefficient and Fisher's exact test. Difference between sensitivity and specificity is calculated with McNemar's test. Logistic regression analysis used for determining predictors for LN metastasis.

## 3. Results

Patient demographics, tumor stages and grades are demonstrated on Table 1. According to abovementioned criteria, systemic pelvic and para-aortic lymphadenectomy up to the level of the left renal vein is performed for 39 pa-

**Table 1. Patient demographics and tumor histological characteristics.**

Characteristics (n = 59)	Mean ± SD or n (%)
Age (years)	59 (±9.4)
FIGO stage*	
IA	20 (34)
IB	19 (32)
II	8 (13.5)
IIIA-IIIC2	10 (17)
IVA-IVB	2 (3.4)
Tumor diameter	4 (1.8)
Tumor grade	
Grade 1	18 (30.5)
Grade 2	30 (50.5)
Grade 3	11 (19)
Lymphovascular space involvement	16 (27)
Mean pelvic lymph node count	27 (13)
Mean para-aortic lymph node count	18 (8)
Pelvic lymph node metastasis	8 (13.5)
Para-aortic lymph node metastasis	7 (12)

\* FIGO (International Federation of Gynecology and Obstetrics) 2009 staging criteria.

tients, whose tumors are more than 50% of the myometrium invaded, cervical stroma invaded, or histologically Grade 3 confirmed in intraoperative frozen section analysis. In two patients operated laparoscopically, due to morbid obesity and co-morbidities paraaortic dissection is limited to inferior mesenteric artery. For 20 patients, who have low grade (Grade 1 or 2) bulky tumors  $\geq 2$  cm but  $< 50\%$  myometrial invasion, underwent pelvic LND only. 29 patients with low risk featured tumors, for whom we did not perform lymphadenectomy, were excluded from analysis. Definitive histolo-pathological examination revealed that in 54 women tumor involved the inner half of the myometrium and in 34 women involved the outer half of the myometrium. The mean pelvic LN count is 27 (6 to 82) and para-aortic 18 (4 to 49). Mean tumor diameter was 4 cm (maximum 9 cm, minimum 1 cm, std 1.9). 16 tumors had tumor deposits in lymphatic and blood channels (LVSI) (27%). 6 of the 8 (75%) tumors with pelvic LN metastasis had LVSI, whereas 41 of the 51 (80%) patients with pelvic LN negative tumors also did not have LVSI and there is good correlation with LVSI and pelvic LN metastasis ( $p < 0.01$ ). Also 6 of the 7 (86%) tumors with para-aortic LN metastasis had LVSI whereas 42 of 52 tumors (81%) without para-aortic LN metastasis were LVSI negative ( $p < 0.01$ ) (Fisher's exact test). In a Grade 3 tumor with an isolated paraaortic metastasis without pelvic LN involvement, LVSI was also positive. Sensitivity for LVSI to predict pelvic LN involvement was 75%, specificity 80.4%, positive predictive value (PPV) 38% and negative predictive value (NPV) 95.3% ( $p < 0.05$ ) (95% CI 1.3–82 HR: 10.3) (Logistic regression). Sensitivity for LVSI to predict para-aortic LN involvement was 85.7%, specificity 80.8%, PPV 38% and NPV 97.6% ( $p < 0.05$ ) (95% CI 1.7–205 HR: 18.8) (Logistic re-

**Table 2. Association of lympho-vascular space involvement and pelvic or para-aortic metastasis.**

		Pelvic lymph node metastasis		Para-aortic lymph node metastasis	
		Positive (%)	Negative (%)	Positive (%)	Negative (%)
LVSI	Positive	6 (75)	10 (19.6)	6 (85.7)	10 (19.2)
	Negative	2 (25)	41 (80.4)	1 (14.3)	42 (80.8)
Total		8 (100)	51 (100)	7 (100)	52 (100)

For both comparisons  $p < 0.01$ . Pearson Chi-Square Test.

**Table 3. Comparison of pelvic metastases for lympho-vascular space involvement and myometrial invasion.**

		Pelvic metastasis		Total (n)
		Negative (n)	Positive (n)	
LVSI	Negative (n)	41	2	43
	Positive (n)	10	6	16
Myometrial Invasion > 1/2	Negative (n)	26	2	28
	Positive (n)	25	6	31

gression) (Table 2). In comparison with pathological examination results with myometrial invasion more than 1/2 of the myometrium that has 75% sensitivity, 51% specificity, 19% PPV and 93% NPV for pelvic LN metastasis; LVSI seems to have equal sensitivity but more specificity (80 vs 51) ( $p < 0.05$  Mc Nemar's test) (Table 3).

#### 4. Discussion

LVSI is a significant factor for the risk of LN metastasis, tumor recurrence and survival [5, 7, 20–22]. As mentioned in previous studies, we also found that LVSI is a strong predictor of LN involvement. In a pooled analysis of Post-operative Radiation Therapy in Endometrial Carcinoma (PORTEC) 1 and 2 trials, LVSI is found the strongest independent prognostic factor for pelvic regional recurrence, distant metastasis, and overall survival [23]. Same authors conclude that adjuvant external beam radiotherapy (EBRT) and/or chemotherapy should be considered for stage I EC with substantial LVSI. The Gynecologic Oncology Group (GOG) recognized the LVSI for early-stage endometrial cancer as an important prognostic factor for need of adjuvant treatment [10]. European Society of Medical Oncology, European Society of Gynecological Oncology and European Society of Radiotherapy and Oncology (ESMO-ESGO-ESTRO) published guidelines for adjuvant treatment following surgery for stage I EC and LVSI is an important factor whether to decide postoperative adjuvant treatment. Also, for patients with no lymphadenectomy performed, EBRT is recommended in case of LVSI positive and vaginal brachytherapy (VB) is recommended in LVSI negative tumors [16, 24].

Lymphadenectomy increases postoperative complication risks like lower extremity lymphedema, pelvic lymphocele, increases operation times and intraoperative complications such as vessel or nerve injury [25–27]. Routine lymphadenectomy for low risk (Grade 1 and 2, less than 1/2 of the myometrium involved and <2 cm in diameter) EC is controversial and have less than 1% risk of lymphatic spread that increases complication rate without an obvious survival advan-

tage [12, 14, 28]. In our center, we perform pelvic and para-aortic lymphadenectomy if the tumor has high risk features like Grade 3 tumor, non-endometrioid subtype and cervical stromal involvement according to preoperative endometrial biopsy or if the tumor has invasion more than half of the myometrium, cervical stromal involvement, or high-grade histopathological features according to intraoperative frozen section results. We perform only pelvic lymphadenectomy if the tumor does not have high risk features, but largest tumor diameter is more than 2 cm according to intraoperative pathological evaluation.

Still a large proportion of the patients (67%) in our study needed lymphadenectomy according to abovementioned criteria.

Capozzi *et al.* [29] formulated a pre-operative score to predict LVSI in case no sentinel node identification, to guide management for EC patients. Serum CA125 value, Grade of tumor, myometrial invasion prediction, and tumor size were the parameters in scoring. That “lymphovascular space invasion score” demonstrated 79% sensitivity, 65% specificity, 29% PPV (95% CI 0.916 to 0.964) for predicting LVSI. Authors concluded that, with high (94.4%) NPV, this score may be used to avoid unnecessary lymphadenectomy in sentinel node management algorithm.

In our study, LVSI seems to have equal sensitivity but more specificity than myometrial invasion for LN metastasis. If feasible, incorporating LVSI in intraoperative frozen section analysis may be used to decide to perform lymphadenectomy, at least as important as myometrial invasion status of the tumor that LVSI may be a better indicator of LN metastasis. This approach may decrease the rate of lymphadenectomies for patients without LN metastasis, thus lowering operation times and complication rates without taking the risk of under-staging. However, according to a study, interobserver disagreement between pathologist is 32% (kappa 0.6,  $p = 0.01$ ) for LVSI in frozen section analysis [30]. Furthermore, even permanent section analysis may show interobserver variability due to technical issues and lack of clear

definitions or criteria of LVSI with conflicting papers in literature [23, 31, 32].

A strength of our study is that all the patients are evaluated preoperatively and then operated by the same physician, a certified gynecologic oncologist, and all of the histopathological examinations are done at the same center. This may eliminate inter-observer variance.

A limitation of the study is central pathology review is not available and LVSI findings could not be verified, and a small number of tumors may be misclassified. Also, as a limitation of a retrospective study, lymphadenectomy is not done for all low-risk patients, and the actual LN involvement status of the patients with low-risk tumors that  $<1/2$  of myometrium invaded, Grade 1 or 2 and  $<2$  cm in largest diameter with LVSI (5 patients in our study) could not be determined. And finally, we could not analyze survival data with postoperative risk factors and LVSI due to the short amount of time between operations and the paper, which could have been of value.

## 5. Conclusions

This study demonstrates that LVSI is an independent predictor of LN metastasis for apparently Stage 1 endometrioid type endometrial carcinoma.

Further large studies are needed with routine lymphadenectomy for low and intermediate risk EC to compare LVSI with myometrial invasion depth for an algorithm at frozen section analysis with both parameters incorporated to determine which patients will benefit more from lymphadenectomy to detect nodal metastasis.

## Author contributions

BT designed the research study, performed the surgeries, collected the data, and analyzed the data. BT wrote the manuscript, read, and approved the final manuscript.

## Ethics approval and consent to participate

This retrospective study is approved by Ethical Committee and Institutional Review Board at Health Sciences University Samsun Research and Training Hospital. Informed consent is obtained prior to utilization of patients' data. Approval number is: TUEK 67-2019BADK/13-100.

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## Conflict of interest

The author declares no conflict of interest.

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