



HISTOPATHOLOGIC PARAMETERS OF POSITIVE LYMPH NODE PREDICTABILITY IN ENDOMETRIAL CANCER

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SUMMARY – Endometrial cancer is the most common malignancy of the female reproductive tract. Lymph node metastases are an important prognostic factor in endometrial cancer. Several prognostic factors have been shown to correlate with lymph node metastasis, including depth of myometrial invasion, cervical infiltration, histologic grade of the tumor, tumor diameter, histology type, lymphovascular invasion, and positive peritoneal cytology. The aim of the study was to identify the histopathologic parameters that would indicate with greater certainty the possibility of metastases into lymph nodes, which would serve as a basis to assess whether patients should undergo lymphadenectomy or not. This retrospective study included patients with endometrial cancer having undergone surgery at the Oncology Institute of Vojvodina during the 2012–2018 period. The study included 120 patients having undergone hysterectomy with bilateral adnexectomy and pelvic lymphadenectomy. Among patients who had lymph node metastases, there were statistically significantly more patients ($p < 0.01$) with endometrial cancer histologic type 2, depth of myometrial invasion greater than 50%, cervical stroma infiltration, lymphovascular invasion, and positive peritoneal cytology. In conclusion, histopathologic parameters such as type 2 endometrial cancer, myometrial invasion depth greater than 50%, cervical stroma infiltration, lymphovascular invasion and positive peritoneal cytology increased the likelihood of lymph node metastases. Tumor size (> 2 cm), as well as histologic grade did not correlate with a higher incidence of lymph node metastases. In this study, both parametrial infiltration and the number of lymph nodes removed were found to have clinical relevance but not statistical significance.

Key words: *Endometrial cancer; Lymphadenectomy; Lymph node metastases*

Introduction

Endometrial cancer is the most common malignancy of the female reproductive tract and the fourth most common cancer in general, with 300 000 new cases worldwide¹. In the last 10 years, a progressive increase in the incidence rate of all types of endometrial cancer has been reported².

Current international guidelines (ACOG, FIGO, SGO, ESGO and ESMO) recommend systemic surgical staging as an initial approach to treatment for all types of endometrial cancer, i.e., type I (endometrioid) and type II (non-endometrioid)³, as systemic staging offers many diagnostic, prognostic, and therapeutic benefits for these patients⁴.

Pelvic and para-aortic lymphadenectomy are integral parts of systemic surgical staging⁵. The prognosis of endometrial cancer depends on several factors such as histologic subtype and histologic grade of the tumor, tumor stage, lymphovascular invasion, depth of myometrial invasion, and lymph node metastasis⁶. One of

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the most important prognostic factors in endometrial cancer are lymph node metastases^{7,8}.

Several prognostic factors have been shown to correlate with lymph node metastases, i.e., depth of myometrial invasion, cervical infiltration, histologic grade of the tumor, tumor diameter, histology subtype, lymphovascular invasion, and positive peritoneal cytology⁹.

About 10% of patients with clinical stage I and 20% of patients with endometrial cancer that has spread outside the uterus (stages II and IIIA-B) have lymph node metastases¹⁰.

Although lymphadenectomy is the best way to identify lymph node metastases, its clinical value remains controversial¹¹. Although several retrospective studies have shown better survival rates after pelvic and para-aortic lymphadenectomy^{12,13}, the benefit in terms of survival could not be demonstrated in either of the two published randomized controlled studies^{14,15}, thus questioning the routine use of systemic lymphadenectomy in early stage endometrial cancer. The risk of lymphadenectomy is thought to outweigh its benefit in patients with low-risk endometrial cancer, stage IA (G1 and G2) with endometrioid type¹⁶.

There is currently no gold standard for the preoperative grouping of low- and high-risk patients for lymph node metastases¹⁷.

At an early stage, the risk of engraftment of pelvic lymph nodes in endometrial adenocarcinoma depends on the degree of histologic differentiation, ranging from 3% for histologic grade 1 to 12% for histologic grade 3¹⁸. Preoperative tumor grade is an important cornerstone in determining the extent of surgical treatment¹⁹.

Patients with low-risk endometrial cancer have a significantly lower (<1%) risk of lymphatic dissemination²⁰, so lymphadenectomy may be omitted in this group of patients. This prevents unnecessary morbidity and reduces costs²¹.

The aim of this study was to identify the histopathologic parameters that would indicate with greater certainty the possibility of metastases into lymph nodes, which would serve as a basis to assess whether patients should undergo lymphadenectomy or not.

Patients and Methods

The study was conducted as a retrospective analysis of patients with endometrial cancer and operated on

at the Oncology Institute of Vojvodina, Department of Operative Oncology, during the 2012-2018 period. The study included 120 patients having undergone hysterectomy with bilateral salpingo-oophorectomy and pelvic lymphadenectomy.

The following data were analyzed: patient age at the time of surgery, histologic type of tumor based on definitive histopathologic finding (type 1, endometrioid and type 2, non-endometrioid), histologic grade of tumor (G1, G2 and G3), depth of invasion of myometrium, infiltration of cervical stroma, tumor size, and parametrial infiltration. Cytology was analyzed on peritoneal washings.

The IBM SPSS 21 statistical software was used on statistical data processing. The methods of descriptive statistics (absolute and relative numbers, measures of central tendency, measures of variability) and analytical statistics (methods for assessing the significance of difference: Student's test for numerical data, and χ^2 -test for categorical data) were employed. The level of statistical significance was set at $p < 0.05$. Results are presented in tables and figures.

Results

The study included 120 women who had histopathologically confirmed endometrial cancer and had undergone hysterectomy with bilateral salpingo-oophorectomy and pelvic lymphadenectomy. The mean (\pm standard deviation, SD) age of these 120 patients was 62.53 ± 7.27 years. The youngest patient was aged 44 and the oldest 78 years. Of the 120 women having undergone lymphadenectomy, lymph node metastases were absent in 104 (86.67%) and present in 16 (13.33%) patients (Fig. 1).

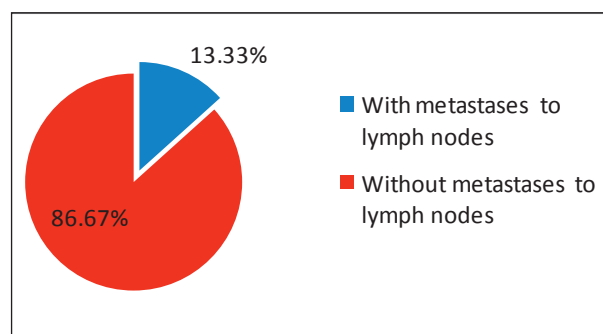


Fig. 1. Percentage of patients with/without metastases to lymph nodes.

Lymph node metastases were more prevalent in patients with histologic type 2 (31.8%) compared to patients with histologic type 1 (9.2%), yielding a statistically significant difference ($\chi^2=6.127$; $df=1$; $p=0.013$) (Table 1).

Table 1. Prevalence of histologic type of endometrial cancer according to lymph node metastases

Metastases to lymph nodes/histologic type			Histologic type		Total
			1	2	
Metastases to lymph nodes	No	n	89	15	104
		%	90.8%	68.2%	86.7
	Yes	n	9	7	16
		%	9.2%	31.8%	13.3%
Total	n	98	22	120	
	%	100%	100%	100%	

Lymph node metastases were present in 10% of G3 patients and 14.8% of G1/G2 patients. This difference between the groups was not statistically significant ($\chi^2=0.123$; $df=1$; $p=0.726$) (Table 2).

Table 2. Prevalence of histologic grade according to lymph node metastases

Metastases to lymph nodes/histologic grade			Degree of differentiation		Total
			G1/G2	G3	
Metastases to lymph nodes	No	n	75	27	102
		%	85.2%	90.0%	86.4%
	Yes	n	13	3	16
		%	14.8%	10.0%	13.6%
Total	n	88	30	118	
	%	100.0%	100.0%	100.0%	

Lymph node metastases were more prevalent in the group of patients who had cervical stroma infiltration (25%) as compared to patients who did not have cervical stroma infiltration (9.1%), yielding a statistically significant difference ($\chi^2=3.855$; $df=1$; $p=0.05$) (Table 3).

Table 3. Percentage of cervical stroma infiltration according to lymph node metastases

Metastases to lymph nodes/cervical stroma infiltration			Cervical stroma infiltration		Total
			No	Yes	
Metastases to lymph nodes	No	n	80	24	104
		%	90.9%	75.0%	86.7
	Yes	n	8	8	16
		%	9.1%	25.0%	13.3
Total	n	88	32	120	
	%	100.0%	100.0%	100.0%	

Lymph node metastases were more prevalent in women who had lymphovascular infiltration (32.6%) compared to patients who did not have lymphovascular infiltration (2.6%), yielding a statistically significant difference ($\chi^2=18.919$; $df=1$; $p=0.000$) (Table 4).

Table 4. Percentage of lymphovascular infiltration according to lymph node metastases

Metastases to lymph nodes/lymphovascular infiltration			Lymphovascular infiltration		Total
			No	Yes	
Metastases to lymph nodes	No	n	75	29	104
		%	97.4%	67.4%	86.7%
	Yes	n	2	14	16
		%	2.6%	32.6%	13.3%
Total	n	77	43	120	
	%	100.0%	100.0%	100.0%	

Lymph node metastases were more prevalent in the group of patients with myometrial infiltration depth greater than 50% (19.2%) compared to the group of patients with myometrial infiltration depth less than 50% (4.7%), yielding a statistically significant difference ($\chi^2=6.413$; $df=2$; $p=0.041$) (Table 5).

Table 5. Myometrial infiltration depth (none, <50%, >50%) according to lymph node metastases

Metastases to lymph nodes/myometrial infiltration depth		Myometrial infiltration depth			Total
		None	<50%	>50%	
Metastases to lymph nodes	No	n	3	41	59
		%	100.0%	95.3%	80.8%
	Yes	n	0	2	14
		%	0.0%	4.7	19.2
Total		n	3	43	73
		%	100.0%	100.0%	100.0%

Lymph node metastases were present in 11.1% of patients with tumor size larger than 2 cm and in 12.5% of patients with tumor size less than 2 cm. This difference was not statistically significant ($\chi^2=0.000$; $df=1$; $p=1.000$) (Table 6).

Table 6. Tumor size (≤ 2 cm / >2 cm) according to lymph node metastases

Metastases to lymph nodes/tumor size		Tumor size		Total
		≤ 2 cm	>2 cm	
Metastases to lymph nodes	No	n	7	40
		%	87.5%	88.9%
	Yes	n	1	5
		%	12.5%	11.1%
Total		n	8	45
		%	100.0%	100.0%

Lymph node metastases were present in 60% of patients with positive peritoneal washing and in 10.7% of patients with negative cytology finding. This difference was statistically significant ($\chi^2=6.460$; $df=1$; $p=0.011$) (Fig. 2).

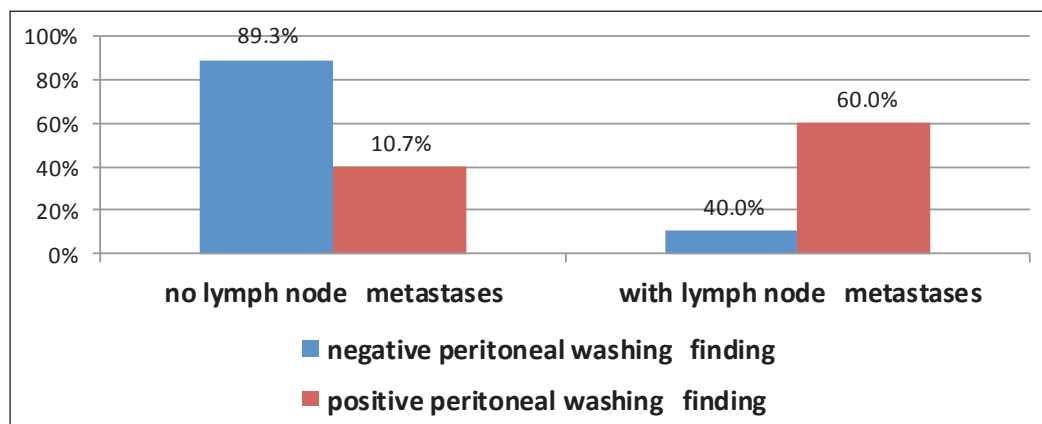


Fig. 2. Peritoneal washings according to lymph node metastases.

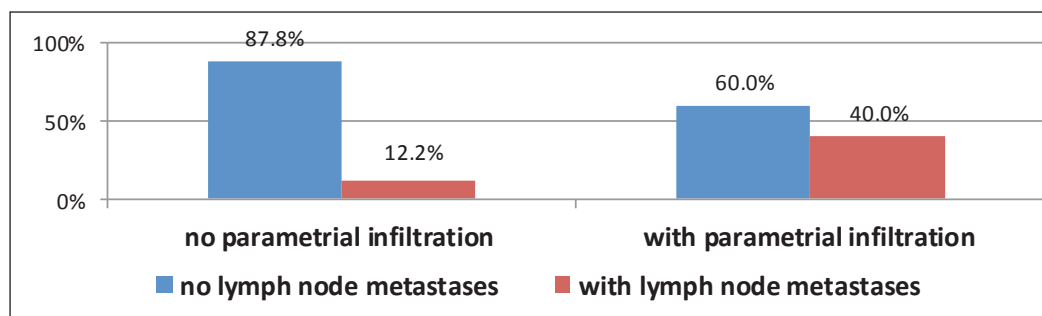


Fig. 3. Parametrial infiltration according to lymph node metastases.

Patients with parametrial infiltration were more likely to have lymph node metastases (40%) than patients who had no parametrial infiltration (12.2%). This difference was not statistically significant ($\chi^2=1.254$; $df=1$; $p=0.263$) (Fig. 3).

Discussion

Lymph node metastases are an important prognostic factor in endometrial cancer²². The most accurate method of assessing the status of retroperitoneal lymph nodes is their surgical removal, followed by histopathologic analysis. This information is crucial for properly defining the prognosis and tailoring adjuvant chemotherapy²³.

In this study, out of 120 women who underwent pelvic lymphadenectomy, 104 (86.67%) did not have lymph node metastases and 16 (13.33%) did. Pollom *et al.*²⁴ evaluated the histopathologic parameters of 296 patients with endometrial cancer who underwent selective lymphadenectomy. On multivariate analysis, lymphovascular invasion, deep myometrial infiltration, and cervical stroma infiltration were significantly associated with lymph node metastases. Tumor size (>4 cm) was marginally significant. These factors have developed a nomogram in which the absence of all four risk factors implies an irrelevant risk of lymph node metastases (<1%)²⁴. Mariani *et al.* have reported a prevalence of lymph node metastases of 16% in endometrioid type endometrial cancer, with an increase to 40% in non-endometrioid type endometrial cancer²⁵. In this study, the parameters associated with a greater likelihood of lymph node metastasis also were tumor histologic type 2 (non-endometrioid), myometrial infiltration depth greater than 50%, cervical stroma involvement, and presence of lymphovascular invasion. Tumor size (>2 cm) was not associated with a higher incidence of lymph node metastases. Our findings are consistent with the conclusions of Widschwendter *et al.* and Akbayir *et al.*^{26,27}. After studying 349 patients with endometrioid endometrial adenocarcinoma who underwent complete pelvic and para-aortic lymphadenectomy, Geisler *et al.*²⁸ concluded that positive lymph nodes occurred equally across all histologic grades. In this study, differences in histologic grades were not associated with the occurrence of lymph node metastases.

Defining the role and extent of lymphadenectomy is one of the major controversies in the treatment of patients with endometrial cancer. Lymphadenectomy

provides pathologic and prognostic data, shows the extent of the disease, and provides information on the need for adjuvant therapy. It can also have a potential therapeutic effect in patients, especially with the prevalence of diseases outside the womb²⁹.

It is generally accepted that in patients with low-grade endometrioid cancer, small tumor size (<2 cm) and without deep myometrial invasion, lymphadenectomy can be omitted without negatively affecting prognosis³⁰. This group of patients has a relatively low risk (1%-3%) of lymphatic dissemination⁹. However, it is difficult to identify these low-risk patients preoperatively, due to differences in tumor histologic grade and depth of myometrial invasion at definitive histopathologic examination³¹.

Agreement rates for tumor grade between preoperative endometrial sampling and final diagnosis vary from 32% to 97%^{32,33}. Discordances in grading and histologic subtype in preoperative and final diagnosis can lead to either undertreatment by underestimating the risk of lymph node metastasis or overtreatment with unnecessary surgical procedures with associated complications³⁴. In 15%-68% of the samples, there is an insufficient amount of tissue for diagnosis³⁵. This insufficiency rate differs *per* sampling method³⁶.

Visser *et al.* report that hysteroscopic biopsies show a higher agreement (89%) compared with dilatation and curettage (70%) ($p=0.02$), suggesting that not only the amount of tissue, but also the accuracy of sampling is important³⁴. Zhu *et al.* report that hysteroscopy is superior with 97.8% accuracy as compared to dilatation and curettage with 88.8% accuracy. These authors found it to be statistically significant. Biggest concerns about hysteroscopy, which is still being evaluated, lie in the fact that endometrial cells have been detected in peritoneal fluid in women with benign disease^{37,38}.

Taskiran *et al.* demonstrated the incidence of metastases in retroperitoneal lymph nodes to differ significantly between patients with and without positive peritoneal cytology (53.1% *vs.* 8.6%, $p<0.001$). Although the revised FIGO criteria for endometrial cancer do not include the finding of cytology in disease staging, data from this study clearly indicate that patients with positive peritoneal cytology are at a significant risk of extrauterine spread³⁹.

In this study, positive peritoneal washings also indicated a higher likelihood that lymph node metastases would develop (60% *vs.* 10.7%, $p=0.011$).

In the group of patients who had lymph node metastases, women with parametrial infiltration were more prevalent (40%) as compared to those without lymph node metastases (12%), however, the difference did not reach statistical significance. In contemporary oncologic surgery, due to the increase in morbidity in patients with complete lymphadenectomy, the concept of sentinel lymph node biopsy has been increasingly applied, showing a high degree of accuracy in the detection of lymph node metastases⁴⁰. Preoperative histology can adequately select low-grade patients in which sentinel lymph node biopsy can be performed with only 8% clinically relevant upgrading. Overgrading leads to more extensive surgical treatment with associated perioperative morbidity in up to 20%⁴¹. Sentinel lymph node biopsy can be a compromise between whether or not to perform lymphadenectomy⁴².

Conclusion

In this study, it was shown that histopathologic parameters such as type 2 endometrial cancer, myometrial invasion depth greater than 50%, cervical stroma infiltration, parametrial infiltration, lymphovascular invasion, and positive peritoneal cytology increased the likelihood of lymph node metastases. Tumor size (>2 cm) and histologic grade did not correlate with a higher incidence of lymph node metastases.

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Sažetak

HISTOPATOLOŠKI PARAMETRI PREDVIDLJIVOSTI POZITIVNIH LIMFNIH ČVOROVA KOD
ENDOMETRIJSKOG KARCINOMA*A. Mandić, D. Kokanov, S. Maričić, T. Ivković Kapicl i N. Šolajić*

Karcinom endometrija je najčešći malignitet ženskog reproduktivnog trakta. Metastaze u limfnim čvorovima su jedan od najvažnijih prognostičkih čimbenika kod karcinoma endometrija. Pokazalo se da je nekoliko prognostičkih čimbenika u korelaciji s metastazama limfnih čvorova: dubina invazije miometrija, infiltracija cerviksa, histološki gradus tumora, promjer tumora, serozna histologija, limfovaskularna invazija i pozitivna peritonejska citologija. Cilj ovoga istraživanja bio je utvrditi one patohistološke parametre koji će s većom sigurnošću ukazati na mogućnost nastanka metastaza u limfnim čvorovima te na temelju kojih se može procijeniti treba li takvim bolesnicama raditi limfadenektomiju ili ne. Provedena je retrospektivna analiza bolesnica s karcinomom endometrija koje su operirane na Institutu za onkologiju Vojvodine u razdoblju od 2012. do 2018. godine. U istraživanje je uključeno 120 bolesnica kod kojih je napravljena histerektomija s obostranom adneksektomijom i pelvičnom limfadenektomijom. U skupini bolesnica koje su imale metastaze u limfnim čvorovima statistički su značajno više ($p < 0,01$) bile zastupljene bolesnice s histološkim tipom 2 endometrijskog karcinoma, dubinom invazije miometrija većom od 50%, infiltracijom cervikalne strome, limfovaskularnom invazijom i pozitivnom peritonejskom citologijom. Zaključeno je kako patohistološki parametri kao što su tip 2 endometrijskog karcinoma, dubina invazije miometrija veća od 50%, infiltracija cervikalne strome, limfovaskularna invazija i pozitivna peritonejska citologija povećavaju vjerojatnost nastanka metastaza u limfnim čvorovima. Veličina tumora (> 2 cm) kao i histološki gradus nisu bili udruženi s većom učestalošću metastaza u limfnim čvorovima. U našem istraživanju se klinički relevantnom pokazala i infiltracija parametrija, kao i broj odstranjenih limfnih čvorova, ali bez statističke značajnosti.

Ključne riječi: *Karcinom endometrija; Limfadenektomija; Metastaze limfnih čvorova*