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ORIGINAL RESEARCH

Lymphadenectomy and Sentinel Lymph Node Biopsy in Patients with Endometrial Cancer in Intermediate and High-Intermediate Risk Groups: The Ukrainian Experience

Olha Khoptiana[1], Valentyn Svintsitskyi[1], Sergiy Nespryadko[1], Natalia P Tsip[1], Teimuraz Gogisvanidze[2], Mikheil Dzimistarishvili[2], Dmytro Krasylenko[2], Mykhailo Serhiiovych Chetverikov[3], Igor Pavlovych Nigutsa[3,4], Dmytro Sumtsov[4], Pavlo Dolyk[5]

[1]Scientific and Clinical Department of the Female Reproductive System Neoplasms, National Cancer Institute, Kyiv, Ukraine; [2]Oncogynecological Department, Kyiv Regional Oncology Center, Kyiv, Ukraine; [3]Department of Obstetrics and Gynecology, Odesa National Medical University, Odesa, Ukraine; [4]Oncogynecological department, Sumy Regional Clinical Oncology Center, Sumy, Ukraine; [5]Oncogynecological department, Medical Center "med-Atlant", Ivano-Frankivsk, Ukraine

Correspondence: Olha Khoptiana, National Cancer Institute, Y. Zdanovska Street, Kyiv, 33/43, Ukraine, Tel +380984614138, Email hoptyana.olha@ukr.net

Purpose: To analyze the oncological safety of sentinel lymph node biopsy compared to lymphadenectomy. Additionally, we evaluated the postoperative complications of the two methods.

Patients and Methods: This retrospective multicenter trial included 118 patients with intermediate and high-intermediate Stage I–II endometrioid endometrial cancer. Patients with non-endometrioid tumors and those with lymphadenopathy detected on computed tomography were excluded. The study group underwent sentinel lymph node biopsy. In contrast, the control group underwent systematic lymphadenectomy up to the renal vessels, the level of the inferior mesenteric artery, or the bifurcation of the iliac vessels. Recurrence-free survival was calculated using the Kaplan–Meier method. Differences were considered statistically significant at $p < 0.05$ (95% confidence interval).

Results: Patients were recruited from 2017 to March 2024. In the control group, six (5.9%) patients experienced disease recurrence and five (4.2%) died. Overall, two (1.7%) patients from both groups died from causes unrelated to recurrence. Recurrence-free survival did not significantly differ between those who underwent sentinel lymph node biopsy (96.3%, SE ± 0.036) and those who underwent lymphadenectomy (89.4%, SE ± 0.045) over 3 years from the date of surgery to the time of the first recurrence ($p = 0.608$). Eighteen postoperative complications were identified: 11 (9.3%) patients experienced complications within 30 days of follow-up, and 7 (5.9%) within 90 days.

Conclusion: Sentinel lymph node biopsy may serve as an alternative to systemic lymphadenectomy for surgical staging without compromising recurrence-free survival.

Keywords: sentinel lymph node biopsy, lymphadenectomy, endometrial cancer

Introduction

The optimal method for lymph node assessment in oncology patients at intermediate and high-intermediate risk remains debatable Several studies report no differences in survival between patients who underwent lymphadenectomy and controls.[1,2] However, several inaccuracies in the experimental data were noted, particularly regarding the number of para-aortic lymphadenectomies performed and the selection of adjuvant treatment methods. Therefore, the lack of efficacy of systematic lymphadenectomy in adequate staging has led to the search for alternatives.

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Sentinel lymph node biopsy using indocyanine green is an alternative method for lymph node assessment in patients with endometrial cancer across different risk groups.[3–5] Prospective studies have shown that this method has a high sensitivity and negative predictive value.[6,7]

The study aimed to perform a comparative analysis of the effectiveness of sentinel lymph node biopsy in patients with endometrial cancer at intermediate and high-intermediate risk compared to systematic lymphadenectomy.

Materials and Methods

This retrospective multicenter study included patients with intermediate and high-intermediate endometrioid endometrial cancer at Stage I–II who were treated at the National Cancer Institute (Kyiv), Sumy Regional Clinical Oncology Center (Sumy), "MED Atlant" (Ivano-Frankivsk), "Esperanto MED" (Odesa), and Kyiv Regional Oncology Center (Kyiv) in Ukraine. The data were obtained from a prospective database. Data collection began in 2017 and ended in March 2024 (Figure 1).

The inclusion criteria were patients with endometrioid cancer Stages I and II with high, moderate, or low differentiation. Patients with non-endometrioid tumors or those with lymphadenopathy described in computed tomography (CT) scans of the abdominal cavity, pelvis, or chest were excluded from the study.

Preoperative preparation of the patients was performed in accordance with the ESMO–ESGO–ESTRO 2016 protocols and ESGO–ESTRO–ESP 2021 guidelines. CT scans of the abdominal and thoracic organs and magnetic resonance imaging (MRI) of the pelvis with intravenous contrast were performed to evaluate the disease spread and myometrial invasion depth.[8]

Patients were divided into two groups: the first (study) group underwent sentinel lymph node mapping and biopsy, while the second (control) group underwent systematic lymphadenectomy. The extent of lymph node removal varied per the surgeon's discretion; it was performed either up to the level of the renal vessels (A2), inferior mesenteric artery, or to the bifurcation of the iliac vessels.

In the sentinel lymph node biopsy group, the Memorial Sloan Kettering Cancer Center algorithm was used.[9]

The primary endpoint was 3-year recurrence-free survival. The secondary endpoints included the number of post-operative complications, number of patients with affected lymph nodes, and complications according to the Clavien–Dindo classification within 30- and 90-days post-surgery. This study was conducted in accordance with the Declaration of Helsinki. Institutional review board approval for the study was granted by the National Cancer Institute in Kyiv, Ukraine (Approval No. 185, May 25, 2021). All participants gave their written informed consent to participate in the study.

Statistical Analysis

Patient data were collected in a prospective database for subsequent comparisons. Categorical data were described using absolute numbers and percentages, and comparisons were performed using Fisher's exact test. Quantitative data were presented as the mean ± standard deviation.

Survival was graphically represented using Kaplan–Meier curves. Statistical differences between the survival curves were assessed using the Log rank test. Differences were considered statistically significant at $p < 0.05$ (95% confidence interval). Time to recurrence was calculated from the date of surgery. Statistical software EZR v. 1.64 (graphical user interface for R statistical software version 4.3.1, R Foundation for Statistical Computing, Vienna, Austria) was used for data analysis.[10]

Results

From September 2017 to March 2024, 118 patients with endometrial cancer who met the inclusion criteria were recruited. The study group (sentinel lymph node mapping and biopsy) and control group (systematic lymphadenectomy) both included 59 patients. The clinical characteristics of the patients are shown in Table 1.

The median patient age was 60 years (range, 27–80 years), and the median body mass index (BMI) was 29.7 (IQR 18–54) kg/m^2. In addition, the median BMI was 29.5 (IQR 22–54) kg/m^2 and 29.5 (IQR 18–53) kg/m^2 in the study and control groups, respectively. There were 29 (47.5%) and 25 (42.4%) patients with obesity (BMI >30 kg/m^2) in the control

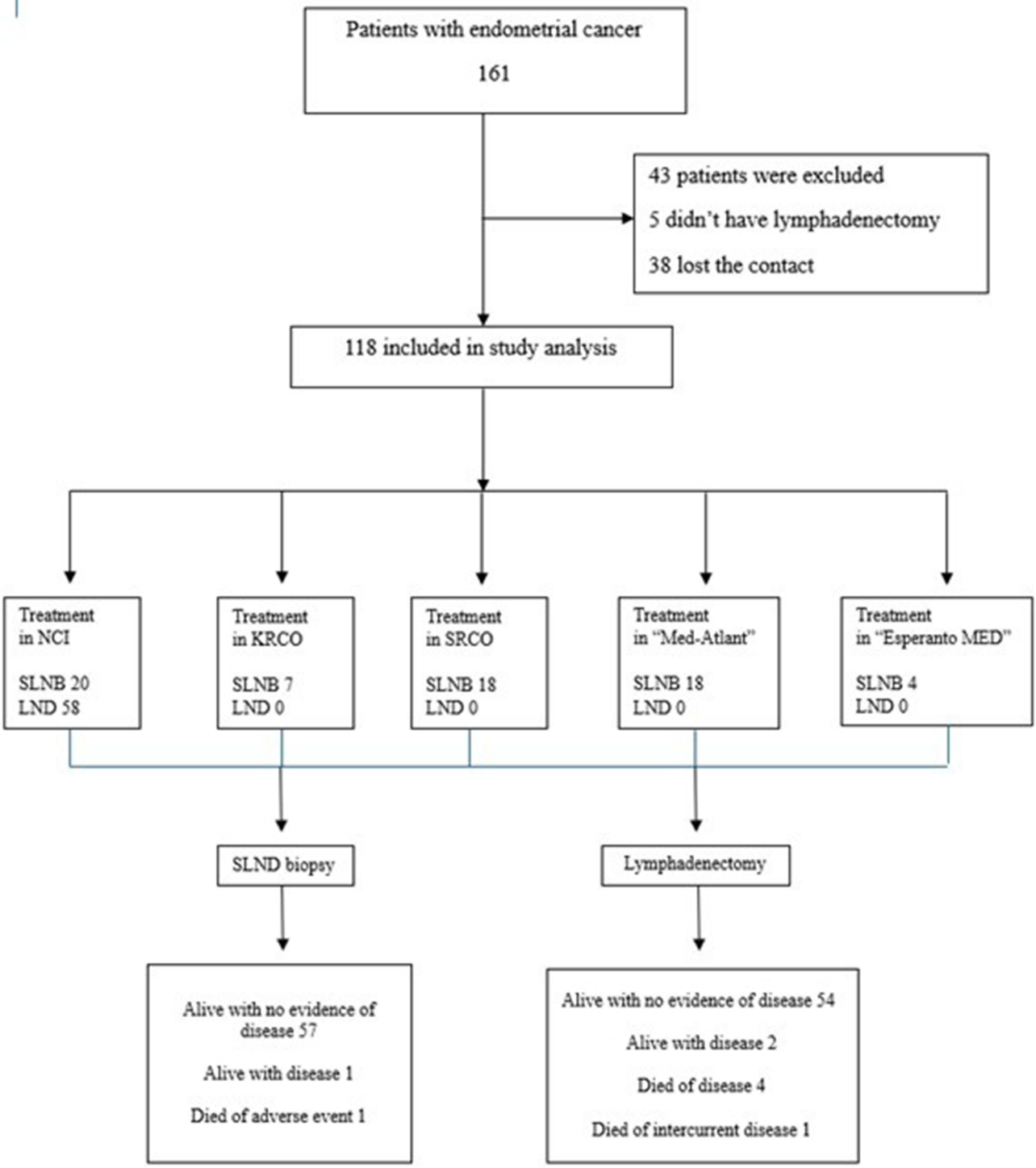

Figure 1 Patient flowchart.
Abbreviations: NCI, National Cancer Institute; SLNB, sentinel lymph node biopsy; LND, lymphadenectomy; KRCO, Kyiv Regional Oncology Center; SRCO, Sumy Regional Clinical Oncology Center.

and study groups, respectively. Nearly half of the patients had concomitant cardiovascular pathology (hypertension stages I–III, heart failure grades 0–II) (n = 57, 47.5%). A significantly smaller proportion of patients had type 2 diabetes mellitus (n =10, 8.3%). No patients had type 1 diabetes.

Table 1 Characteristics of Patients in the Control and Study Groups

	Overall n = 118	**Sentinel Lymph Node Biopsy n (%) = 59 (50%)**	**Lymphadenectomy n (%) = 59 (50%)**
Median ± SD (years)	60 ± 10	60 ± 10	60 ± 9.1
Median ± SD BMI (kg\m^2)	29.7 ± 4.6	29.5±6.8	29.5±5.9
BMI > 30	52 (43.3%)	25 (42.4%)	29 (47.5%)
Cardiovascular disorders	57 (47.5%)	26 (44%)	31 (50.8%)
Diabetes	10 (8.3%)	3 (5%)	7 (11.5%)
ECOG status			
0	104 (88.1%)	55 (93.2%)	49 (83.0%)
1	14 (11.9%)	3 (5%)	11 (18.6%)
Tumor grade			
G1	25 (21.2%)	24 (40.7%)	2 (3.4%)
G2	51 (43.2%)	26 (44.1%)	24 (40.7%)
G3	42 (35.6%)	9 (15.2%)	33 (55.9%)
Myometrial invasion			
>50%	55 (46.6%)	9 (15.3%)	41 (69.5%)
<50%	59 (60%)	48 (81.3%)	11 (18.7%)
Cervical involvement	9 (7.6%)	2 (3.4%)	7 (11.8%)
Surgical treatment			
Pelvic LND	21 (17.8%)	–	21 (35.6%)
LND to a. mesenterica inf	14 (11.9%)	–	14 (23.7%)
LND to a. renalis	24 (20.3%)	–	24 (40.7%)
Surgical approach			
Laparoscopy	67 (56.8%)	59 (100%)	8 (13.6%)
Laparotomy	51 (43.2%)	0 (0%)	51 (86.9%)

Abbreviations: BMI, body mass index; cervix, cervical involvement; LND, lymphadenectomy.

Among patients with endometrioid cancer, 25 (21.2%) had well-differentiated cancer, 51 (43.2%) moderately differentiated, and 42 (35.6%) poorly differentiated. Nine (7.5%) patients had cervical involvement.

In the study group, which underwent sentinel lymph node biopsy, the lowest number of patients had poorly differentiated endometrioid carcinoma (n = 9, 15.2%), while the highest had moderately differentiated tumors (n = 26, 44.1%). Twenty-four (40.7%) patients had well-differentiated endometrial tumors. Myometrial invasion <50% was found in 48 (81.3%) patients on preoperative radiological diagnostics, while cervical involvement was detected in two (3.4%).

In the control group, most patients had poorly differentiated endometrial cancer (n = 33, 55.9%). Only two (3.4%) patients had well-differentiated carcinoma, while 24 (40.7%) had moderately differentiated tumors preoperatively. Myometrial invasion >50% was diagnosed in 41 (69.5%) patients, compared to <50% in 11 (18.7%). Cervical involvement was noted in seven (11.8%) patients.

Laparoscopic access was used in 67 (56.8%) patients, including eight (6.8%) in the control group. Systematic lymphadenectomy was performed from the obturator nerve level to the bifurcation of the iliac vessels in 21 (35.6%)

patients. In 14 (23.7%) patients, lymphadenectomy was extended to the inferior mesenteric artery. The lymphadenectomy extended to the renal vessels in 24 (40.7%) patients.

An important stage of the study was the detection of metastatic lymph node involvement. In the study group, one patient had a metastatic sentinel lymph node. Lymph node mapping did not occur on either side, only on the left side, and only on the right side in three, two, and three patients, respectively. Lymphadenectomy was performed on the side of the detected involvement.

In the control group, where systematic lymphadenectomy was performed, nine patients were found to have metastatic lymph node involvement. Notably, three of these patients had affected para-aortic lymph nodes without pelvic lymph node involvement. Six patients had affected pelvic lymph nodes, with lymphadenectomy limited to the pelvic area in three. One patient had micrometastases detected in a para-aortic lymph node (Table 2).

The next stage of the study was to compare the 3-year recurrence-free survival rates of each group. During the observation period, six (5.9%) patients in the control group experienced disease recurrence, and five (4.2%) patients died. Overall, two (1.7%) patients from both groups died from causes unrelated to the recurrence.

Recurrence-free survival was not statistically significant between patients who underwent sentinel lymph node biopsy (96.3%, SE ± 0.036) and those who underwent lymphadenectomy (89.4%, SE ± 0.045) over a 3-year observation period from the date of surgery to the time of first recurrence ($p = 0.608$) (Figure 2 and Table 3).

An assessment of postoperative complications was conducted according to the Clavien–Dindo classification at 30 and 90 days postoperatively (Table 4).

A total of 18 postoperative complications were identified: 11 (9.3%) patients experienced complications within 30 days, and seven (5.9%) within 90 days of follow-up.

In the sentinel lymph node biopsy group, one patient was found to have an infected wound (Grade I complication), and three patients had Grade IIIa complications (lymphocysts requiring drainage under local anesthesia). Furthermore, one patient died on the second postoperative day from pulmonary embolism (Grade V).

In the systematic lymphadenectomy group, one patient had a Grade I complication (infected postoperative wound), one patient had a Grade II complication (dynamic bowel obstruction), seven patients had Grade IIIa complications (lymphocysts requiring drainage), and three patients had Grade IIIb complications (postoperative ventral hernias requiring surgical intervention, including one vesicouterine fistula).

Discussion

The question of whether to perform lymphadenectomy in endometrial cancer remains debatable Two randomized studies demonstrated that systematic lymphadenectomy did not result in a therapeutic benefit).[1,2] However, the detection of changes in metastasis staging can affect the approach to adjuvant treatment.

Table 2 Comparative Characteristics of Patients with Detected Lymph Node Metastases

	SLNB	Lymphadenectomy								
	Patient 1	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9
Histological type	EM	Serous	EM	EM	EM	Adeno-squamous	EM	EM	EM	EM
Grade	G2	G2	G2	G3	G3	G3	G3	G2	G2	G2
Myometrial invasion	>50%	>50%	>50%	>50%	>50%	>50%	>50%	>50%	>50%	>50%
L\n involvement	N1	N2 (N1-)	N1 (N2-)	N1 (N2-)	N2 (N1-)	N1 (N2-)	N2 (N1-)	N1 (N2-)	N1 (N2-)	N1 (N2-)
LVSI	Yes	No	No	Yes	No	No	Yes	Yes	Yes	Yes
Cervical involvement	No	No	No	Yes	No	Yes	Yes	No	No	No
Ovarian mts	No	No	No	No	No	No	No	No	No	No
Level LND		a.mes.inf.	a.mes.inf.	ren.ves.	ren.ves.	ren.ves.	a.mes.inf.	Common iliac bif.	Common iliac bif.	Common iliac bif.

Abbreviations: EM, edometioid; l\n, lymph node; LVSI, lympho-vascular invasion; N1, pelvic lymph nodes involvement; N2, paraaortic lymph nodes involvement; LND, lymphadenectomy; mts, metastasis; a.mes.inf., arteria mesenterica inferior; ren. ves., renal vessels, common iliac bifurcation.

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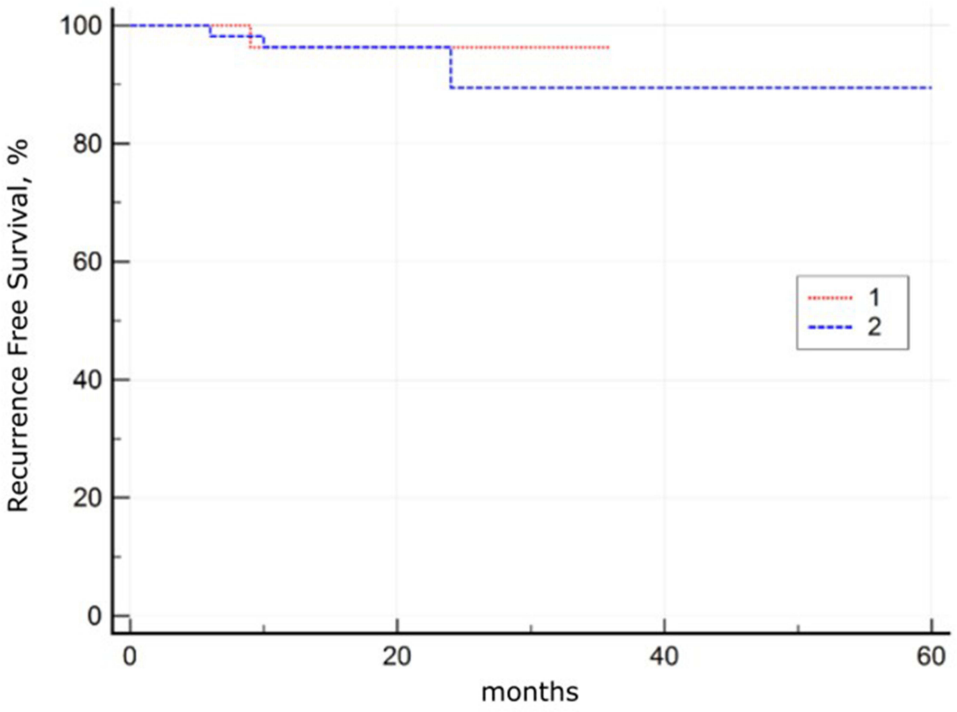

Figure 2 Kaplan–Meier curve for recurrence-free survival in patients from the two groups: 1 – sentinel lymph node biopsy, 2 – systematic lymphadenectomy.

The extent to which lymphadenectomy should be performed to detect possible lymph node involvement and its impact on patient survival remains unclear. Currently, sentinel lymph node biopsy is considered the optimal method for assessing lymphatic spread in endometrial cancer. The use of indocyanine green dye has shown a high detection sensitivity (97%) with a negative predictive value of 99.6%.[6]

Table 3 Types of Recurrence

	Sentinel lymph node biopsy n = 1	**Lymphadenectomy n = 7**	**P value**
3-years free survival	96.3 (SE ± 0.036)	89.4 (SE ± 0.045)	p = 0.608
Lymphogenous	-	1	
Hematogenous	1	3	
Peritoneal	-	2	

Table 4 Postoperative Complications Within 30 and 90 days

	30 days n = 11 (9.3%) p = 0.528		**90* days n = 7 (5.9%) p = 0.114**	
Type of complication	SLNB, n = 4 (3.4%)	LND, n = 7 (5.9%)	SLNB, n = 1 (0.84%)	LND n = 6 (5.08%)
Lymphocyst's infection	2 (19.2%)	3 (27.4%)	1 (14.3%)	4 (57.1%)
Dynamic bowel obstruction	0 (0%)	1 (8.9%)	0 (0%)	0 (0%)
Abdominal hernia	0 (0%)	1 (8.9%)	0 (0%)	1 (14.3%)
Vesico-vaginal fistula	0 (0%)	1 (8.9%)	0 (0%)	0 (0%)
Wound infection	1 (8.9%)	1 (8.9%)	0 (0%)	1 (14.3%)
Pulmonary artery thrombosis	1 (8.9%)	0 (0%)	0 (0%)	0 (0%)

Note: * *Postoperative complications within 30 and 90 days.*

Li et al demonstrated that the probability of isolated metastases in para-aortic lymph nodes with negative pelvic nodes is 2.8% (114/4001).[11] Therefore, the question remains whether avoiding systematic lymphadenectomy up to the levels of the renal vessels might impact patient survival. There are already studies that have demonstrated the beneficial role of sentinel lymph node biopsy in various sites, such as melanoma and breast cancer, where it remains the standard method for lymph node assessment.[12,13] However, in the context of endometrial cancer, this approach remains debatable.

This study is the first to present an analysis of a prospective database of data on sentinel lymph node biopsy and lymphadenectomy from Ukrainian centers. We found that the 3-year recurrence-free survival in the sentinel lymph node biopsy group did not statistically differ from the lymphadenectomy group (96.3% (SE ± 0.036) and 89.4% (SE ± 0.045) ($p = 0.608$), respectively). Lymphatic metastasis was observed in only one case among the patients with recurrence. Peritoneal spread was observed in two patients and hematogenous spread in four. Interestingly, in the lymphadenectomy group, nine patients had lymph node metastases, three of whom had para-aortic involvement without pelvic node metastasis. In addition, six patients had pelvic-only metastases. Despite this, survival between the two groups did not differ.

Schlappe et al examined the recurrence-free survival of a cohort of patients with negative lymph nodes and endometrioid endometrial cancer with >50% myometrial invasion; they found no difference in survival between the sentinel lymph node biopsy and systematic lymphadenectomy groups (hazard ratio (HR) for lymphadenectomy vs sentinel lymph node biopsy, 0.87; 95% CI, 0.40–1.89). However, in the univariate analysis, Stage III disease was associated with higher overall survival (HR, 12.70, 95% CI, 3.63–44.46) among patients who received chemotherapy.[14]

The GOG-0249 study, which included patients with high-intermediate and high-risk endometrial cancer, found no significant difference in survival between the brachytherapy and chemotherapy group versus the external beam radiation group, with reported survival rates of 88% and 91%, respectively. Patients with endometrioid cancer accounted for 71%, 74% of whom were in Stage I. Recurrence in pelvic or para-aortic lymph nodes was 9.2% in the chemo/brachytherapy group compared to 4.4% in the radiation-only group. However, the subgroup analysis did not reveal a significant correlation between lymphadenectomy and the choice of adjuvant therapy.[15]

Our data did not show a significant association between recurrence risk and the type of adjuvant therapy ($p > 0.05$ for all factors) One advantage of our study is that patient selection was based not only on a single criterion but also according to the risk groups outlined in the ESGO–ESTRO–ESP 2021 guidelines, specifically the intermediate and high-intermediate groups,[8] which is important due to the heterogeneity of inclusion criteria.

Cuccu et al analyzed patients in the high-intermediate and high-risk groups and did not observe a difference in the 5-year recurrence-free survival rate between the sentinel lymph node biopsy group and the pelvic lymphadenectomy group, with or without para-aortic lymphadenectomy (74.3% and 78.6%, respectively, $p = 0.690$). Furthermore, no differences were observed after patient stratification by risk group.[16]

Several studies have shown no difference in recurrence-free survival between patients with different levels of lymph node assessment, including sentinel lymph node, sentinel lymph node with backup lymphadenectomy, and systematic lymphadenectomy.[17,18]

Several prospective studies have aimed to investigate the oncological safety of sentinel lymph node biopsy compared to systematic lymphadenectomy up to the level of the renal vessels.[19–21] One such study aimed to analyze patients with various histological forms of Stages I and II disease, comparing the two surgical methods while considering adjuvant treatment choices, including six courses of chemotherapy following surgery and brachytherapy.[22]

Several studies have demonstrated the impact of lymphovascular invasion (LVI) on disease-free survival in endometrial cancer. Positive LVI has been identified as a predictor of reduced progression-free survival (PFS) and may independently contribute more to distant recurrences than to local ones.[23–25] In our study, the impact of LVI on disease recurrence was not analyzed. Further data are needed to clarify this association.

However, our study results indicate that systematic lymphadenectomy did not demonstrate an advantage in recurrence-free survival in patients with endometrioid Stage I–II cancer, which is in agreement with the results of previous studies.

Our study included patients based on myometrial invasion depth or histological type, any grading, Stage I–II disease, and any invasion depth. It should also be noted that indocyanine green dye was used as the marker in the sentinel lymph node group, and no backup lymphadenectomy was performed.

Due to the recent registration of indocyanine green in Ukraine, the follow-up duration is relatively short; however, these results are promising for future data analysis and in planning prospective studies.

Limitations

First, the study was conducted on a limited number of patients, which could potentially influence the survival outcomes. Second, since the study was retrospective in design, it was not possible to assess the MRI/CT diagnostic results regarding lymph node involvement, which might have contributed to the observed differences in the number of affected lymph nodes between the two groups due to diagnostic errors and the detection of suspicious nodes. Third, a video recording of the lymph node mapping sequence during surgery was not available for analysis. Fourth, this was a multicenter study, and there was no single reference center for the histological evaluation of postoperative material. This could have resulted in the low number of detected affected lymph nodes in the study group. Finally, 86.9% of patients underwent laparotomy in the control group, while 100% of the study group underwent laparoscopy. This heterogeneity in the choice of surgical access could have influenced the incidence of postoperative complications in the two groups.

Conclusion

Systematic lymphadenectomy in intermediate and high-intermediate risk patients with endometrial cancer remains a topic of debate. Sentinel lymph node biopsy may be an alternative that does not compromise recurrence-free survival; however, further prospective studies with a larger patient sample and a standardized choice of adjuvant treatment are needed.

Disclosure

The authors report no conflicts of interest in this work.

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