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Diagnostic accuracy of sentinel lymph node biopsy in women with early-stage endometrial cancer

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Summary

Objective: The objective of the present study was to evaluate the accuracy of the sentinel lymph node (SLN) detection procedure in Serbian sample of women with early-stage endometrial cancer (EC). *Materials and Methods:* In the period from March, 2015 to May 2016, all consecutive patients with histologically confirmed EC, were considered for enrolment in the study. Exclusion criteria included preoperative FIGO Stages II-IV, previous surgery that could influence the uterine lymphatic drainage, history of congenital uterus anomalies, duplex malignancies or deep vein thrombosis on lower extremities, and allergies to the contrast agent. Finally, 27 patients underwent SLN detection, followed by systematic pelvic lymphadenectomy. Demographic, surgical, and pathologic data on all patients were evaluated. *Results:* The SLNs were identified in 25 patients, with overall detection rate of 92.6%. Twenty-two (81.5%) patients had bilateral, while 11.15% had unilateral intraoperative visualization of SLNs. Of the seven females with positive SLNs, at definitive histology evaluation, pelvic non-SLNs were metastatic in four (57.1%) cases and negative in three (42.9%) cases. The false-negative rate of sentinel procedure was 0%. The evaluation of prognostic values of SLN status, for prediction of presence of metastases in non-SLNs showed the negative predicive value of 100%, and the positive predictive value of 57.1%. Additionally, the sensitivity of SLN method in sample of women with early-stage EC was 100%, while the specificity was 86.9%. *Conclusions:* SLN procedure has good diagnostic performance and is reliable in prediction of the metastatic status of the regional pelvic lymph nodes in women with early-stage EC.

Key words: Sentinel nodes; Endometrial cancer; Pelvic lymphadenectomy

Introduction

Endometrial cancer (EC) is the most common gynecologic malignancy and the fourth most common cancer in women in developed countries [1-3]. Additionally, during the past decades, the frequency of this tumor in developing countries has increased significantly and is currently ranked second within the group of female reproductive system cancers [4, 5]. Despite this high prevalence, recommendations and the surgical treatment of patients with a preoperative diagnosis of early-stage EC remain an area of considerable debate and controversy, with wide variations in the intraoperative management of the regional lymph nodes (LN) [3, 6, 7].

It has been well recognized that the presence of LN metastasis is one of the main prognostic factors of survival in women suffering from EC, and LN status is a major determinant of the treatment strategy [8, 9]. The results from numerous studies highlighted that the five-year disease-free survival in patients with early-stage (Stage I) EC with positive pelvic LNs is about 50%, compared to 90% for those with negative LNs [9]. However, the incidence of LN metastases in patients with Stage I disease is approximately 10%. Although the rate of metastases in these patients is low, the standard treatment, in many practices, still includes a comprehensive regional lymphadenectomy, resulting in prolonged operating time, additional cost, and potential side effects including blood loss, neural injuries, lymphocysts, and long-term lymphedema. It is estimated that the most of these patients are over-treated and consequently subjected to potential postoperative complications that could be avoided [6-9].

Keeping in mind all mentioned above, in the field of EC surgery, there is a considerable interest in identifying a valid and reliable technique that provides accurate staging information about nodal status, with the aim to avoid the over-treating of low-risk patients and under-treating patients with metastatic disease [10]. In this regard, sentinel lymph node (SLN) mapping procedure seems to be a challenging alternative to complete pelvic lymphadenectomy as it might decrease treatment-related morbidity while preserving the benefits of correct LN staging [11-15]. SLN mapping is based on the concept that LN drains in a specific pattern away from the malignant mass. According to this assumption, it is expected that if the SLN is found negative

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for metastasis, then the nodes following the SLN should also be found negative. Namely, in SLN, the identification of micro-metastases and isolated tumor cells is possible through comprehensive histopathological assessment and the use of immunohistochemical (IHC) analyses, offering an ultrastaging of the malignancy. The SLN approach has become the standard of care in patients with melanoma and breast cancer [15], and more recently, the encouraging results have also been observed in cohorts of patients with early stage of different gynecological cancers [11-14]. Thus, it could be hypothesized that the SLN procedure offers more accurate staging and less chance for post-operative complications in females with EC. However, there has been no clear evidence of its diagnostic performance in this specific cohort of patients.

The objective of the present study was to evaluate the accuracy of the SLN detection procedure in Serbian sample of women with early-stage EC.

Table 1. — *Socio-demographic characteristics of the patients (n=27).*

Variable		Value
Age (years)	Median	65
	Range	47-79
BMI (kg/m^2)	Mean ± SD	28.7±4.9
	Range	21.9−41.5
Education (years), n. (%)	Primary (1-8)	6 (22.2)
	Secondary (9-12)	17 (63.0)
	University (>12)	4 (14.8)
Marital status, n. (%)	Single (never married)	4 (14.8)
	Married/cohabiting	17 (63.0)
	Widowed	5 (18.5)
	Separated/divorced	1 (3.7)
Place of residence, n. (%)	Urban	25 (92.6)
	Rural	2 (7.4)

BMI: body mass index.

Materials and Methods

In the period from March, 2015 to May 2016, all consecutive patients with histologically confirmed EC, referring to the University Obstetrics and Gynecology Clinic "Narodni front" in Belgrade, Serbia, were considered for enrolment in the study. Inclusion criteria were as follows: EC of medium (G2) and high risk (G3), in Stage I according to the FIGO classification and written informed consent. Exclusion criteria included preoperative FIGO Stages II-IV, previous surgery that could change the uterine lymphatic drainage (conisation, ceasarean section, metroplasty, myomectomy), history of congenital uterus anomalies, duplex malignancies or deep vein thrombosis on lower extremities and allergies to the contrast agent. The study was approved by the Ethical Committee of the Faculty of Medicine, University of Belgrade.

All patients experienced preoperative MRI of pelvis, as well as RTG of lungs and abdomen US examinations. Additionally, completed biochemical, laboratory, and urine analyses were performed in each participant. After the consent for the type of anesthesia, the females were subjected to surgical treatment, with the signed consents for conducting the same.

The SLNs mapping was performed using intracervical injection (at thre and nine o'clock positions) of *isosulfan blue*, with the superficial and deep infiltration in the quantity from two- to three cm^3 per position. This procedure was performed in the period of ten minutes prior to the commencement of the surgery, and after placing the female patient under anesthesia. Patients underwent SLNs biopsy followed by systematic pelvic lymphadenectomy by each side, as well as classic hysterectomy with adnexectomy, all by laparotomy,.

The removed uterus with ovaries, oviducts, SLNs, and non-SLNs were sent for histopathological testing - Hematoxylin and Eosin (HE) by dyeing with the description of the size of tumor, tumor position, depth with lymphovascular infiltration, and the degree of maturity of the tumor, establishing of a definitive stage of the disease according to the FIGO classification. Both groups of lymph nodes – SLNs and non-SLNs – were sent for an additional IHC testing – pancytokeratin AE1:AE3, for the purpose of verification of the existence of macro and micrometastases (> 0.2 mm and ≤ 2 mm) including isolated tumor cells (≤ 0.2 mm).

Data were presented as arithmetic mean ± standard deviation for continues variables and as absolute number, percentage, and median with corresponding range for discrete variables. The relationship between the presence of metastatic SLNs and detection of lymphovascular invasion was assessed by Spearman's rank correlation coefficient.

The accuracy of SLN biopsy in women with early-stage EC was estimated by assessing following parameters: false-negative rate, positive predictive value (PPV), negative predictive value (NPV), sensitivity, and specificity. The sentinel procedure was considered as true positive if the both, SNLs and non-SLNs had metastatic disease. Moreover, the test was considered as false negative if the SLNs were free of metastases, but non-SLNs showed metastases. Finally, the method was considered as true negative if all lymph nodes were free of metastatic disease. The detection rate was calculated as the number of females with at least one identified SLN divided by total number of patients. Sensitivity was assessed as the proportion of true positives among the patients with pelvic lymph-node metastases, while specificity was estimated as the proportion of true negatives among the patients without pelvic lymph-node metastases. NPV was calculated by dividing the true negatives by the total number of patients without lymph node metastases, while PPV was found by dividing the true positives by the total number of patients with lymph node metastases. Finally, the false-negative rate was defined as the number of patients with the negative SLN and one or more positive non-SLNs divided by the total number of patients with any positive pelvic lymph nodes.

Results

Twenty-seven women with early-stage EC were included in the study. Socio-demographic characteristics of the study population and tumor-related characteristics are summarized in Tables 1 and 2. The majority of females had endometroid adenocarcinoma (70.4%) and presence of invasion to more than one half of the myometrium (59.3%). The lymphovascular invasion was detected in seven (25.9%) patients.

The SLNs were identified in 25 patients, with overall detection rate of 92.6%. Twenty-two (81.5%) patients had bilateral, while three (11.15%) had unilateral intraoperative

Table 2. — *Tumor-related characteristics.*

Variable		Value
Histology, n. (%)	Endometroid	19 (70.4)
	Serous papillary	4 (14.8)
	Clear cell	1 (3.7)
	Endometroid+ Serous papillary	1 (3.7)
	Other	2 (7.4)
Postoperative FIGO Stage, n. (%)	IA	9 (33.3)
	IB	11 (40.7)
	II	5 (18.5)
	IIIC1	2 (7.4)
Maximal tumor size (mm)	Mean ± SD	38.1±17.3
	Range	(1−80)
Lymphovascular invasion, n. (%)	Present	7 (25.9)
	Absent	20 (74.1)
Myometrial invasion, n. (%)	Absent	1 (3.7)
	< 1/2	10 (37.0)
	> 1/2	16 (59.3)

Table 3. — *Lymph node characteristics.*

Variable	Value
Overall SLN detection	25/27 (92.6%)*
Bilateral SLN detection	22/27 (81.5%)*
Unilateral SLN detection	3/27 (11.1%)*
No SLN detection	2/27 (7.4%)*
Total number of SLNs detected	163
Median number of SLNs/patients (range)	6 (0-15)
Total number of non-SLNs removed	319
Median number of non-SLNs /patients (range)	10 (2-26)

SLN: sentinel lymph node;
*Data are presented as proportion with corresponding detection rate.

visualization of SLNs. The SLN mapping failed in two (7.4%) cases. The total number of SLNs, which were detected and removed in the sample of 27 women with early-stage EC, was 163. The median number of SLNs per patient was six. During surgical interventions the total of 319 non-SLNs were removed, with median number of non-SLNs per patient of ten (Table 3).

Thirty-nine SLNs (23.9%) from seven (25.9%) patients were found to be metastatic. At final histopathology assessment, three of these seven patients (42.8%) with positive SLNs had macrometastases, confirmed by HE staining in two cases and IHC in one. Four remaining patients (58.2%) had micrometastases, identified by IHC alone. Additionally, the presence of metastatic SLNs statistically significantly correlated with detection of lymphovascular invasion ($p = 0.421$, $p = 0.029$).

Of the seven females with positive SLNs, at definitive histology evaluation, pelvic non-SLNs were metastatic in four (57.1%) cases and negative in three (42.9%) cases. The SLNs of 18 patients (66.7%) were negative by both, HE and IHC staining, and their pelvic non-SLNs were also extensively examined, using the same histopathological approaches. These histological assessments were also performed on two patients (7.4%) whose intraoperative SLN mapping was unsuccessful. A total of 247 non-SLNs from these 20 patients were assessed, and none were found to be positive (meaning the absence of macrometastases, micrometastases or isolated tumor cells). Therefore, the results in the present study showed that there were no females with negative SLN status, but whose non-SLN status was positive, suggesting the absence of false-negative cases. Therefore, the false-negative rate of sentinel procedure in this study was 0%. Finally, the evaluation of prognostic values of SLN status, for prediction of presence of metastases in non-SLNs showed a NPV of 100%, and a PPV of 57.1%. Additionally, the sensitivity of this method in the present sample of women with early-stage EC was 100%, while the specificity was 86.9% (Table 4).

Table 4. — *Presence of metastases by lymph node type in patients with endometrial cancer (n=27).*

SLNs	Non-SLNs Positive	Non-SLNs Negative	Total	Predictive values
Positive	4	3	7	PPV=57.1%
Negative	0	20	20	NPV=100%
Total	4	23	27	
Validity	Sensitivity =100%	Specificity =86.9%		

SLN: sentinel lymph node, PPV: positive predictive value,
NPV: negative predictive value.

Discussion

Over the last few years, SLNs mapping has emerged as an increasingly popular option in the surgical treatment of the EC patients. The main challenge in introduction of sentinel node concept in patients with early-stage EC is to reduce the morbidity of surgical staging by comprehensive lymphadenectomy, while accurately identifying patients who will benefit from adjuvant therapy.

The findings from the present study showed the overall and bilateral SLN detection rates of 92.6%, and 81.5%, respectively. These results are in line with previous investigations that reported wide variation of these rates, ranging from 45% to 96% [16, 17]. Morover, Hasanzadeh *et al.* showed detection rate of even 100%, suggesting that this method is highly applicable for SLNs identification in EC [18]. Similarly, the high overall and bilateral detection rates of 96% and 88% were also observed in two recent studies [19, 20]. However, Desai *et al.* suggested an overall and bilateral detection rate of 86% and 56% [21], while in SENTI-ENDO study these rates were 89% and 69%, respectively [17]. Finally, in evaluation of the SLN approach efficacy, it has been emphasized that the value of detection rate is highly important due to its possible influence on the clinical usefulness, and the diagnostic accuracy of this

method [22]. Therefore, it is important to note that this identification rate can be depended by numerous factors including the injection site, the type and amount of tracers, and the time between injection and surgical intervention [16].

An important issue in the SLN mapping of the midline tumors (including EC) is the side of the sentinel node identification [18, 23, 24]. Namely, although it is expected that lymphatic flow from the EC should be bilateral in the pelvic area, it is recognized that some of the patients have unilateral visualization of lymphatic drainage during surgery. In the present investigation 11.15% of the patients also had unilateral mapping of SLNs. This finding should take into consideration the possibility of metastatic SLN involvement on detection failure side, which could lead to underestimation of prevalence of positive lymph nodes. Keeping in mind this issue, Haupsy *et al.* postulated that SLN detection should be considered per hemipelvis rather than per patient. According to this assumption, in case of unilateral detection of SLNs, the contralateral hemipelvis requires a complete lymphadenectomy [25]. Another essential concern in the SLN procedure of the EC is the injection site of the mapping material. It has been pointed out that in this group of patients, detection rates strongly vary depending on the route of administration and the tracer used [17, 18]. However, there is still no consensus regarding the most accurate and reliable method for identification of SLN in patients suffering from EC. In the present study the authors performed cervical injection technique which has shown to be simple and reproducible [17]. Furthermore, the results from meta-analysis of 26 studies reported that the use of cervical injection was associated with the highest detection rates, both unilateral and bilateral [22]. On the other hand, cervical injection has been criticized due to possibility that it might not reflect expected uterine lymphatic drainage, resulting in a low detection rate in para-aortic area [17, 22]. Hence, it is debatable whether cervical injection can provide the complete picture about SLN status in patients with EC.

A false-negative rate has been recognized as the most important outcome measure in SLN procedure. Namely, it is well-known that false-negative finding under-stages the EC patients, and therefore may result in an incorrect decision concerning the need for adjuvant therapy [18]. Thus, achieving an acceptable low false-negative rate is crucial if lymph mapping is to be considered as potential alternative to standard treatment option. In the present investigation there were no patients with negative SLN status, but whose non-SLN status was positive, suggesting the absence of false-negative cases. Therefore, the false-negative rate of sentinel procedure in this study was 0%, and both the NPV and the sensitivity of SLN biopsy was 100%. The same results were also registered in others studies [16, 18], indicating high diagnostic performance of this methodological concept in identification of EC patients who will not require comprehensive regional lymphadenectomy. However, these results should be interpreted with caution bearing in mind the fact that this finding could be due to small simple size in most of these investigations with relatively low incidence of metastatic SLNs in early-stage EC. Therefore, a large number of patients would be needed to calculate clinically meaningful sensitivity and false-negative rates, since statistical analysis of these indicators is based on the absolute number of patients with confirmed metastases in lymph nodes [16].

Ultrastaging of lymph node, using additional and more sensitive histological approach, such as the IHC, is a core of sentinel-node idea. In the present study, more than half of the patients with positive SLNs had micrometastases, which were not detected by conventional histology. These are in agreement with previous findings showing that the rate of occult metastases varied from 0% to 15% with the combination of serial sectioning, HE and IHC [16, 22]. The prognostic significance of micrometastases in patients with early-stage EC has not been deeply explored [16]. However, the results from case-control study are promising and showed that removal of this occult metastases was associated with a significant increase in disease survival in group of females with EC [25].

Some limitations of the present study need to be kept in mind during interpretation of the results. Firstly, this study could have benefitted from a larger sample size. However, the consecutive sampling design, in a well-defined period, ensures the representativeness of the sample and the generalizability of the results. Secondly, application of cervical injection alone might have given a lower SLN detection rate, particularly those located in para-aortic pelvic region. Finally, another possible limitation of this study is the absence of the para-aortic lymphadenectomy which is needed for more precise assessment of the true false-negative rate.

Conclusion

In conclusion, the results from the present study suggest that SLN procedure has good diagnostic performance and is reliable in prediction of the metastatic status of the regional pelvic lymph nodes in Serbian sample of women with early-stage EC. However, further studies are required to evaluate cost-effectiveness of SLN procedures compared to systematic lymphadenectomy, as well as to assess the effect of the SLN approach on adjuvant therapies and quality of life in this group of patients.

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