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The Evaluation of Sentinel Lymph Node Biopsy Using Radiocolloid in First Stage Endometrial Cancer

Birinci Evre Endometrial Kanserde Radyokolloid Kullanılarak Yapılan Sentinel Lenf Nodu Biyopsisinin Değerlendirilmesi

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Abstract

Objectives: Detection of a sentinel lymph node (SLN) in patients with endometrial cancer (EC) reduces the rate of unnecessary systemic lymph dissection. The aim of this study was to assess the SLN detection rate, accuracy of the method using Tc-99m-SENTI-SCINT and the rate of metastatic nodal involvement in patients with preoperative first stage EC.

Methods: A prospective study of SLN biopsy of 41 patients with stage I EC was conducted after cervical application of 4mCi Tc-99m-SENTI-SCINT. Planar lymphoscintigraphy and single-photon emission computed tomography/computed tomography (SPECT/CT) of the pelvis were performed, followed by site-specific lymphadenectomy in intermediate-risk patients if no SLN was detected per hemipelvis and pelvic lymphadenectomy in all high-risk patients.

Results: Pre-operative detection rate of planar lymphoscintigraphy was 80.49 [95% confidence interval (CI): 68.36-92.62] and of SPECT/CT 95.12 (95% CI: 88.52-101.7). The total intraoperative SLN detection rate was 95.12 (95% CI: 88.52-101.7) per patient and 26.83 (95% CI: 19.91-33.75) bilaterally. The average number of SLNs removed was 1.6±0.8. The most common anatomical location of SLN was the right external iliac region. The SLN metastatic rate was 17%. Both sensitivity and negative predictive value regarding metastatic involvement were 100%.

Conclusion: The SLN detection rate, sensitivity and negative predictive value using Tc-99m-SENTI-SCINT in patients with EC in our study were high. The application of ultra-staging in the histopathological analysis of SLN increases the detection of nodal metastases and improves the staging in these patients.

Keywords: Endometrial carcinoma, sentinel lymph node, ultra-staging, SPECT/CT

Öz

Amaç: Endometriyal kanserli (EK) hastalarda sentinel lenf nodu (SLN) saptanması gereksiz sistemik lenf diseksiyonu oranını azaltır. Bu çalışmanın amacı, preoperatif birinci evre EK'li hastalarda SLN saptama oranını, Tc-99m-SENTI-SCINT kullanılan yöntemin doğruluğunu ve metastatik nodal tutulum oranını değerlendirmekti.

Yöntem: 4mCi Tc-99m-SENTI-SCINT'nin servikal uygulamasından sonra evre I EK'li 41 hastanın SLN biyopsisini içeren prospektif bir çalışma yapıldı. Pelvisin planar lenfosintigrafisi ve tek foton emisyonlu bilgisayarlı tomografisi/bilgisayarlı tomografisi (SPECT/BT) çekildi, ardından hemipelvis başına SLN saptanmadıysa orta riskli hastalarda bölgeye özgü lenfadenektomi ve tüm yüksek riskli hastalarda pelvik lenfadenektomi uygulandı.

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Bulgular: Planar lenfosintigrafinin ameliyat öncesi saptama oranı 80,49 iken [%95 güven aralığı (GA): 68,36-92,62] SPECT/BT'nin saptama oranı 95,12 (%95 GA: 88,52-101,7) idi. Toplam intraoperatif SLN saptama oranı hasta başına 95,12 (%95 GA: 88,52-101,7) ve bilateral olarak 26,83 (%95 GA: 19,91-33,75) idi. Çıkarılan ortalama SLN sayısı 1,6±0,8 idi. SLN'nin en yaygın anatomik yerleşim yeri sağ eksternal iliak bölge idi. SLN metastatik oranı %17 idi. Metastatik tutulumla ilgili hem duyarlılık hem de negatif öngörü değeri %100 idi.

Sonuç: Çalışmamızda EK'li hastalarda Tc-99m-SENTI-SCINT kullanılarak SLN saptama oranının ve Tc-99m-SENTI-SCINT'nin duyarlılığının ve negatif prediktif değerinin yüksek olduğu gösterildi. Ultra evrelemenin SLN'nin histopatolojik analizinde uygulanması nodal metastazların saptanmasını arttırır ve bu hastalarda evrelemeyi geliştirir.

Anahtar kelimeler: Endometriyal karsinom, sentinel lenf nodu, ultra evreleme, SPECT/BT

Introduction

Endometrial carcinoma (EC) is the sixth most common cancer among women worldwide, with 417,367 new cases registered in 2020 (1). The surgical treatment includes hysterectomy with adnexectomy for histopathological analysis of the tumor, further with pelvic lymphadenectomy, with or without para-aortic lymphadenectomy, for nodal staging (2). Radical lymphadenectomy in EC is a current topic of a debate and is very controversial, on one hand due to lack of impact on the overall survival and recurrence of the disease, while on the other could lead to frequent complications such as lymphedema/lymphocyst, pelvic infections, nerve injury, and/or deep vein thrombosis (3,4).

To improve the quality of EC treatment in 2020, the existing guidelines have been updated and new recommendations have been established in terms of patient management. Sentinel lymph node (SLN) biopsy has been proposed as a viable alternative to conventional lymphadenectomy to evaluate the nodal status in tumor stage I/II (5). The SLN, as first described by Gould et al. (6), is the first drainage lymph node of the tumor area and thus has the highest probability to be the carrier of metastatic cells. Therefore, if the SLN is negative for metastatic disease, it is assumed that all lymph nodes in the same lymph pathway are also free of metastasis. This concept of SLN removal in EC patients would provide an adequate approach between sub-treatment (no lymphadenectomy) and over-treatment (radical lymphadenectomy) with a significant risk of complications.

The cervical application of Tc-99m labeled colloid particles 2-24 hours before the operation allows the tracer to be trapped by phagocytosis by the SLNs so they can be detected preoperatively either on planar lymphoscintigraphy and/or single-photon emission computed tomography/computed tomography (SPECT/CT), which is not the case when other tracers/techniques are being used. Planar images show two-dimensional mapping of the lymphatic drainage and the SLN, while SPECT/CT provides important information about its anatomical location, facilitating surgical detection (7). SLNs are detected intraoperatively with a hand-held gamma detector probe, following its acoustic signal and determining the counts per second (8). In this way, lymph nodes at atypical locations are detected, especially locations where lymphadenectomy would not commonly be performed, in the immediate vicinity of blood vessels. An important advantage of the SLN concept is the possibility of detecting small-volume metastases by detailed histopathological analysis that otherwise would have been missed by routine procedures (9).

SLN mapping with radiocolloid has already been established at our Institution and incorporated as a part of the surgical staging of patients with breast cancer, melanoma, and colorectal cancer. Using this knowledge, we established a nuclear medicine method for SLN biopsy in EC patients with presumed first stage of the disease. Furthermore, purpose of our study was to evaluate the detection rate of SLN in preoperative imaging and intraoperative during SLN biopsy using the Tc-99m-SENTI-SCINT as a tracer, the diagnostic accuracy of SLN biopsy procedure for detecting nodal metastases (sensitivity and negative predictive value), lymphatic drainage, and the rate of metastatic lymph nodes in these patients.

Materials and Methods

Study Design

This is a prospective interventional study that included 41 patients with preoperative (presumed) International Federation of Gynecology and Obstetrics first stage EC who met the inclusion criteria (histopathologically verified EC, T1; N0; M0; patients over 18 years of age, signed informed consent for the procedures and participation in this study) for the SLN biopsy. Patients with EC who had any of the following exclusion criteria were not included in the study: presumed disease stage II-IV (confirmed by ultrasound, computed tomography or magnetic resonance imaging); patients who refused to sign the informed consent for the procedure and participation in this study; a documented contraindication for application of radioactive tracer; existence of contraindications for surgical treatment; and patients who have received neoadjuvant therapy).

The study was approved by the Ethics Committee of the Medical Faculty in Skopje (approval number: 03-366/8).

Procedures

In the morning on the day of the surgical intervention, 37MBq Tc-99m-SENTI-SCINT (Tc-99m marked human serum albumin millimicroaggregate-colloidal particles with a diameter of 100-600 nm) was applied in four cervical quadrants (3, 6, 9 and 12 o'clock positions) by a specialist in gynecology and obstetrics. Planar lymphoscintigraphy and SPECT/CT for SLN detection were than performed to the following acquisition protocol as recommended by the EANM guidelines (8):

- Static images (600 seconds) at 30, 60 and 120 min after application (anteroposterior) position, and if necessary in left lateral and/or right lateral position (gamma camera Mediso DHV Nucline Spirit).

- SPECT/CT at 120-180 minutes (SPECT/CT camera OPTIMA NM/CT 640 GE Healthcare dual detector/4 slice CT).

Intraoperative detection of SLN was performed with a hand-held gamma detector probe (EUROPROBE SYSTEM III), taking into account the results of lymphoscintigraphy and SPECT/CT. In patients with more than one hot node per hemipelvis, we followed the 10% rule. In this regard, all lymph nodes that had 10% higher counts per second than those of the hottest node were also treated as SLNs and were removed (8).

In intermediate-risk patients (endometrioid histology with histological grade 1-2 and more than 50% myometrial invasion or histological grade 3 and less than 50% myometrial invasion) where no SLN was detected in either half of the pelvis, site-specific lymphatic dissection was performed. Pelvic lymphadenectomy was performed in all high-risk patients (non-endometrioid histology; grade 3 endometrioid adenocarcinoma with more than 50% myometrial invasion). The surgical method was laparotomy. After SLN biopsy, all patients underwent abdominal hysterectomy with bilateral salpingo-oophorectomy.

Histopathological Evaluation

The operative material was analyzed at the Institute of Pathology, where a macroscopic evaluation was performed with isolation of SLNs. After fixation in 10% neutral formalin, tissue specimens were paraffin embedded, serially cut, and stained with standard hematoxylin and eosin (H&E) staining for microscopic analysis.

In SLNs where no metastatic deposits were found on the initial sections, two additional sections were done, every 20 microns deep, one of which was stained with standard H&E staining, and the second immunohistochemically for cytokeratin AE1/AE3, in order to detect the presence of low-volume metastasis. Briefly, the paraffin tissue sections were cut (3-5 μm) and mounted on silanized glass slides, followed by deparaffinization in the thermostat at 58-60 °C. PT Link pretreatment was performed in Autostainer Link instrument with diluted EnVision Flex Target Retrieval solution in deionized water for 30 minutes at 97 °C. After cooling the slides to 65 °C, the sections were rinsed in diluted EnVision Flex Wash Buffer for 5 min. DAKO FLEX Ready to Use primary antibody-cytokeratin AE1/AE3 by using Dako EnVision FLEX+ detection system was applied by pre-programmed Autostainer Link Software on Autostainer PT LINK platform. We used Flex + Mouse and Flex+ Mouse 2x5 DAB (Linker) protocol. When the staining procedure was completed, the specimens were mounted with Neo-clear (xylene substitute) after the procedure of dehydrating and clearing the sections. Positive and negative tissue controls were used at the same time.

Detection of malignant cells in the lymph nodes was defined according to the recommendations of the American Joint Committee on Cancer:

- The presence of macrometastasis (MM): focus on metastatic tumor cells larger than 2 mm in diameter,

- The presence of micrometastasis (Mm): focus on metastatic tumor cells 0.2-2 mm in diameter,

- The presence of isolated tumor cells (ITCs): microscopic clusters and single cells less than 0.2 mm in diameter.

Statistical Analysis

Statistical analysis was performed using SPSS 23.0. Categorical (attributive) variables were represented by absolute and relative numbers. Numerical (quantitative) variables were represented by average, standard deviation, minimum, and maximum values. The detection rate of SLN on planar lymphoscintigraphy, SPECT/CT, and intraoperatively was defined as the ratio between the number of patients with at least 1 detected SLN on planar lymphoscintigraphy, SPECT/CT, and intraoperatively with the total number of subjects in the study. Bilateral detection rate was defined as the ratio between the number of patients with at least 1 intraoperatively removed SLN in each hemipelvis and the total number of subjects in the study. The status of the SLN after histopathological examination was defined as true positive-if SLN contained malignant cells regardless of the pathological status of the subsequent non-SLNs in the pelvis (the other lymph nodes in the pelvis); true negative-if SLN did not contain malignant cells and the subsequent non-SLNs in the pelvis were also negative for metastasis or false negative- if SLN did not contain malignant cells but at least one subsequent removed non-SLN in the pelvis was

positive for metastasis. No false positive SLN status was evaluated because positivity of the SLN guaranties nodal metastatic disease. The sensitivity and negative predictive value of SLN biopsy for detecting nodal metastasis were analyzed on a per-patient basis. We used and compared the pathological status of SLNs and non-SLNs to determine if radionuclide mapping and SLN biopsy accurately detected SLN (through finding if the pathological status of the SLN reflects the same pathological status of the non-SLNs). Considering this, the estimated sensitivity and negative predictive value were referred to the SLN biopsy procedure and consequentially (secondarly) to the imaging modality (planar lymphoscintigraphy and SPECT/CT). The sensitivity of SLN biopsy was calculated as the ratio between patients with true positive SLN and patients with true positive SLN and false negative SLN. Negative predictive value of SLN biopsy was calculated as the ratio between patients with true negative SLN and all patients with negative SLN (true negative and false negative).

Results

Demographics

The mean age of the patients was 60.2±7.9 years. The body mass index (BMI) had a mean value of 32.3±5.9 kg/m^2, while the average age of menarche was 12.9±1.3 years. Thirty nine patients were in menopause at the time of EC diagnosis with an average age at menopause occurring at 50.1±4.0 years. Only four patients had a family history of malignancy (9.8%).

Endometrial Carcinoma Characteristics

The characteristics of EC are shown in Table 1. The results of fractional curettage of the endometrium presented endometrioid adenocarcinoma as the most common histopathological type (78.05%). Preoperatively, most carcinomas were intermediate differentiated (46.34%) and in stage IA (82.92%). Endometrioid adenocarcinoma was also the dominant postoperative histological type, proven in 82.9% patients, followed by serous type in 9.75% patients. Postoperative histopathological analysis presented the largest number of carcinomas in stage IA (70.7%) and grade 2 (68.3%) with a size of 2 cm and larger (63.4%). Lymphovascular space invasion and invasion of the myometrium greater than 50% were in 11 (26%) carcinomas. The mean duration of surgery with SLN biopsy was 2.26±0.5 hours, ranging from 1.15 to 3.35 h.

Sentinel Lymph Node Detection

The detection rate of the SLN (hot spots referred as SLNs) on planar lymphoscintigraphy was 33/41=80.49% [95% confidence interval (CI): 68.36-92.62]; while on SPECT/CT 39/41=95.12% (95% CI: 88.52-101.7); the total intraoperative detection rate of SLN was 39/41=95.12% (95% CI 88.52-101.7); the bilateral intraoperative detection rate of SLN was 11/41=26.83% (95% CI: 19.91-33.75). The SLN presentation on planar lymphoscintigraphy and on SPECT/CT is shown in Figures 1 and 2. Table 2 presents the distribution of SLNs detected on planar lymphoscintigraphy and SPECT/CT. Comparing the pre-operative SPECT/CT and intraoperative findings, total concordance was obtained in 35 patients (85.4%), while partial concordance was noticed in 6 patients (14.6%). In these 6 patients, we removed the "hottest" SLN detected by both preoperative imaging and gamma probe (fist echelon). The additional hot spots (n=10), detected on SPECT/CT were not registered by the gamma probe or had activity below 10% counts from the "hottest" SLN and thus were not removed. These nodes were characterized as second echelon nodes and were located in the common iliac region (9) and internal iliac region (1) on SPECT/CT. In two patients, no SLN was detected by both preoperative imaging and gamma probe (4.8%).

Table 1. Characteristics of EC (n=41). Results are present as number and percent

	Preoperative characteristics	Postoperative characteristics
Histological type n (%)		
Endometrioid adenocarcinoma	32 (78.05)	34 (82.93)
Serous	4 (9.75)	4 (9.75)
Mixed form	1 (2.44)	1 (2.44)
Undifferentiated	1 (2.44)	1 (2.44)
Mucinous	3 (7.32)	1 (2.44)
Grade n (%)		
1	13 (31.70)	5 (12.19)
2	19 (46.34)	28 (68.29)
3	9 (21.95)	8 (19.51)
Stage n (%)		
IA		29 (70.73)
IB	34 (82.92)	7 (17.07)
II	7 (17.07)	1 (2.44)
IIIC		4 (9.76)
Size of the carcinoma (cm)		
<2		15 (36.58)
≥2		26 (63.41)
Lymphovascular space invasion		
Present		11 (26.83)
Absent		30 (73.17)
Myometrial invasion		
None		2 (4.88)
<50%	30 (73.17)	28 (68.29)
>50%	11 (26.83)	11 (26.83)

EC: Endometrial cancer

In half of the patients, more than one SLN was removed. The total number of SLNs removed was 66, and the average number was 1.6±0.8. Metastatic deposits in the SLN were detected in 8 SLNs in 7 (17.1%) patients, of which 3 were MM, 1 Mm, and 4 were ITCs. Micrometastatic deposit in a SLN is shown in Figure 3. The total number of non-SLNs removed during site-specific lymphadenectomy (in 4 patients) and pelvic lymphadenectomy (in 8 patients) was 154. In 2 patients, metastatic deposits were in both SLNs and non-SLNs. The sensitivity of the SLN biopsy regarding nodal metastasis was 100%. The true negative rate was 100%. No false negative SLN was found, and the negative predictive value was 100%. The data for intraoperative SLN detection are presented in Table 3. There were no adverse events during cervical application of the tracer, SLN mapping on nuclear medicine imaging, and during surgery regarding radiocolloid and SLN biopsy.

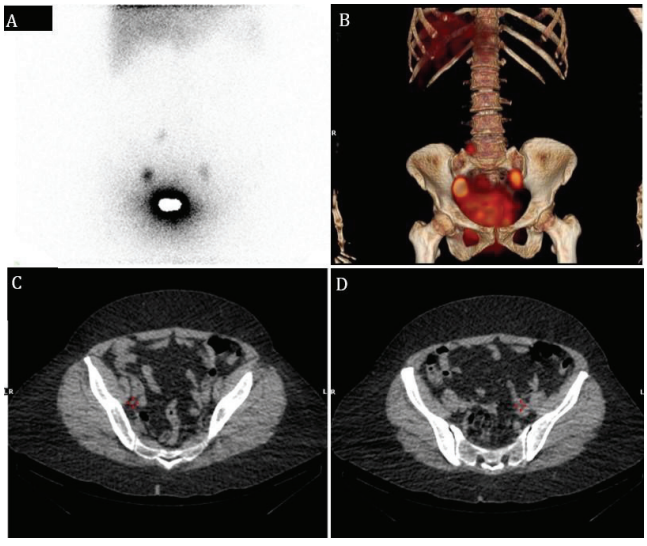

Figure 1. Planar lymphoscintigraphy and SPECT/CT in a 51-year-old patient with grade 3 mixed form of endometrial adenocarcinoma. Planar lymphoscintigraphy (A) and SPECT/CT (B) showed drainage to the bilateral pelvic regions. The hot spots refereed as SLNs were further localized on the axial CT image in the right external iliac region (C) and in the left external iliac region (D). The second hot spot in the right hemipelvis was characterized as second echelon node and was located in the right common iliac region

SPECT/CT: Single-photon emission computed tomography/computed tomography, SLN: Sentinel lymph node

The most common anatomical location of the SLN was the right external iliac region, followed by the left external iliac region and the right obturator regions. SLNs with metastatic deposits were most often located in the right external iliac region. Only in the left obturator region was no SLN with metastatic deposits found. Data for the anatomical localization of the SLN and the distribution of the SLN with metastatic deposits are presented in Table 4.

Discussion

The concept of SLN detection in the EC has been controversial for a long time due to the central position of the uterus and thus the complex lymphatic drainage as well as the heterogeneity of the used techniques. Although it was first applied in 1996 by Burke et al. (10), this procedure was not accepted as a possible alternative to complete lymphadenectomy until 2014 (11). Two uterine lymphatic drainage pathways are identified in the pelvis: the upper paracervical pathway with drainage to the external iliac and/or obturator lymph nodes and the lower paracervical pathway with drainage to the internal iliac and/or presacral lymph nodes (12). Mainly the upper lymph nodes and only part of the lower paracervical pathway are removed by conventional lymphadenectomy, which leaves the possibility of some nodal metastases to be missed. During SLN biopsy, a specific lymph node is removed regardless of the location, including those detected in less typical places such as parametrium, interiliac region, presacral region etc. (13,14). At the same time, the detection

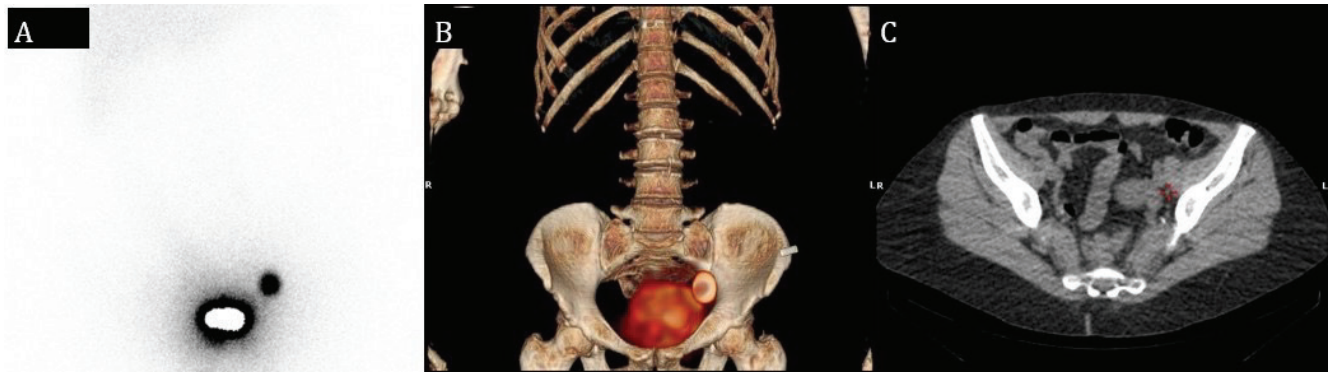

Figure 2. Planar lymphoscintigraphy and SPECT/CT in a 54-years old patient with grade 2 endometrioid adenocarcinoma. Planar lymphoscintigraphy (A) and SPECT/CT (B) showed intensive focal accumulation in the left hemipelvis, corresponding to a left obturator node on the axial CT image (C)

SPECT/CT: Single-photon emission computed tomography/computed tomography, SLN: Sentinel lymph node

Table 2. Patients (n=41) distribution according to the number of SLNs detected on planar lymphoscintigraphy and SPECT/CT. Results are presented as number and percent

Visualization of hot spots referred as SLNs on gamma camera	Number of hot spots referred as SLNs	
	Planar lymphoscintigraphy n (%)	SPECT/CT n (%)
0	8 (19.51)	2 (4.88)
1	17 (41.46)	18 (43.90)
2	12 (29.27)	13 (31.71)
3	3 (7.32)	5 (12.19)
4	1 (2.44)	3 (7.32)
Total number of hot spots referred as SLNs	62	72
Mean ± SD	1.3±0.9	1.7±0.9

SLN: Sentinel lymph node, SPECT/CT: Single-photon emission computed tomography/computed tomography, SD: Standard deviation

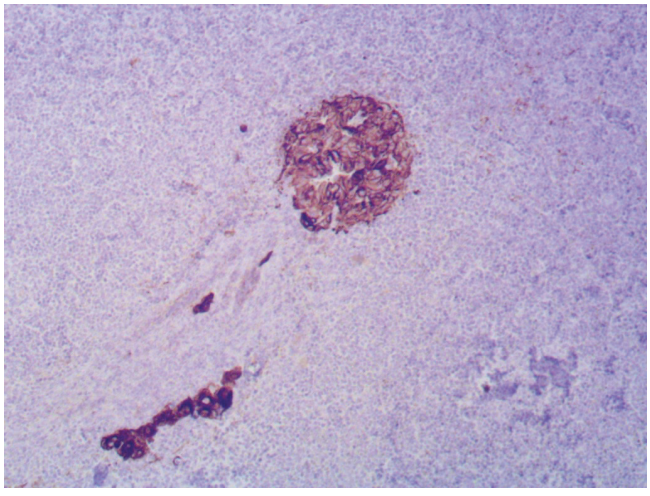

Figure 3. A positive sentinel lymph node for micrometastasis (immunohistochemistry with cytokeratin 7; magnification, x40)

rate of nodal metastases was increased compared with lymphadenectomy (14.7% vs. 9.9%; p=0.002) (15).

Several tracers for identification of the SLN and techniques for their application have been reported (16,17,18,19,20). The total detection rate varies and it is lowest for blue dye as a single tracer 71-76% (14,16), while the best results are obtained using the double-tracer (dual detection) method, which combines radiocolloid and indocyanine green, with a detection rate of 91-100% and a bilateral detection rate of 69-87.3% (17,18,19). Furthermore, future studies concerning SLN biopsy in EC with hybrid tracer (fluorescent and radioactive tracer) would be beneficial as this tracer contains advantages of both compounds.

Table 3. Data for intraoperative SLN detection. Results are presented as number and percent

Variable	Statistical parameter
SLN detection n (%) Unilateral pelvic Bilateral pelvic Unsuccessful detection	 28 (68.29) 11 (26.83) 2 (4.88)
Number of removed SLNs Total number Mean ± SD	 66 1.6±0.8
Lymphatic metastases in SLN n (%) Yes No	 7 (17.07) 34 (82.93)
Macrometastasis Micrometastasis Isolated tumor cells	3 (7.32) 1 (2.44) 3 (7.32)

SLN: Sentinel lymph node

Table 4. Distribution of the SLNs in the pelvis by anatomical regions and localization of SLNs with metastatic deposits

Anatomical location of the SLN in the pelvis	Total number of SLN	Positive for metastatic deposits
Right hemipelvis n (%)	37	5/37 (13.51%)
Right common iliac region	8/37 (21.62%)	1/5 (20%)
Right external iliac region	15/37 (40.54%)	2/5 (40%)
Right internal iliac region	4/37 (10.87%)	1/5 (20%)
Right obturator region	10/37 (27.03%)	1/5 (20%)
Left hemipelvis n (%)	29	3/29 (10.34%)
Left common iliac region	7/29 (24.14%)	1/3 (33.33%)
Left external iliac region	11/29 (37.93%)	1/3 (33.33%)
Left internal iliac region	3/29 (10.34%)	1/3 (33.33%)
Left obturator region	8/29 (27.59%)	0/3 (0%)

SLN: Sentinel lymph node

Several places of tracer application are being proposed: cervical, hysteroscopic-endometrial, and subserosal/myometrial. Cervical injection is most commonly used because of its easy access to the cervix and the highest pelvic detection rate (20). However, the para-aortic SLN count is significantly lower compared with endometrial injection (21). Another concern is that the cervical injection site of Tc-99m-colloid can stimulate gamma detectors, making it difficult to distinguish it from parametrial SLNs (22).

In our study, we used Tc-99m-SENTI-SCINT applied cervically at the 3, 6, 9 and 12 o'clock positions of the uterine cervix, and the total intraoperative detection rate was high, 95.12%. A lower detection rate of 80% was published when only two cervical injections of Tc-99m-labeled tracer were used at the 3 and 9 o'clock positions (21).

Various factors affecting the SLN detection rate have been published. In their study, Restaino et al. (23) pointed out that older patients with higher BMI and non-endometrioid histology were more likely to have no SLN mapping. The SLN in our study was not detected by both SPECT/CT and handheld gamma probes in two patients. Both patients had low grade endometrioid type adenocarcinoma on final histopathology, but were obese as the possible reason for mapping failure.

For a hot spot to be considered as SLN on preoperative imaging, some criteria should be fulfilled, such as lymphatic duct visualization, first appearing node in the lymphatic basin, and high intensity of lymph node uptake. These factors further determine the probability of SLN identification (24). Total concordance between preoperative imaging and intraoperative SLN detection was achieved in 85.4% and partial concordance in the rest of the cases in our study. Elisei et al. (25) published a moderate concordance (73% of the cases) between SPECT/CT and intraoperative findings with a gamma probe, with SPECT/CT having the highest detection rate. Furthermore, Sawicki et al. (26) found 35 false-positive hot spots detected on SPECT/CT that were not found by gamma probe intraoperatively. This could be due to misinterpreting a lymphatic duct or a lymphatic lake for an SLN or a higher echelon lymph node with mild activity below 10% of the counts of the hottest node.

The diagnostic accuracy of SLN biopsy in EC was evaluated by a meta-analysis (34 studies) of How et al. (27), with a pooled sensitivity of 94% (95% CI: 91-96%) and negative predictive value of 100% (95% CI: 99-100%). To calculate the above mentioned parameters, a complete pelvic lymphadenectomy is required. However, lymph node dissection does not provide any therapeutic benefit except adding prognostic information in low-risk ECs. Considering this, we decided not to perform lymphadenectomy besides SLN biopsy in these patients. Complete pelvic lymphadenectomy and site-specific lymphadenectomy were performed in 12 patients. These non-SLNs were further analyzed for sensitivity and negative predictive value of the procedure. Specificity and positive predictive values were not analyzed because false-positive results for SLN can not occur. If a SLN is found positive for metastasis, it would remain unchanged by histopathological analysis of the additional non-SLNs removed at systematic lymphadenectomy. The sensitivity and negative predictive value was 100% in our study, which indicates the high accuracy of the technique although the sample of patients was small.

The most common anatomical localization of SLN in the pelvis regardless of the tracer used is the external iliac region, followed by the obturator region (17,20). These results were also confirmed .

The second advantage of SLN detection is the extensive histopathological analysis with the possibility of detecting low volume deposits of tumor cells (Mm and ITCs). Ultra-staging is expensive and prolongs the processing time, making it impossible to apply to several lymph nodes. In contrast to radical lymphadenectomy, SLN biopsy removes a few lymph nodes, which can be histopathologically analyzed in more detail. Thus, the SLN concept offers an increase in the sensitivity of detecting nodal metastases, especially since Mm is also considered N1 and such patients are classified into stage III of the disease (5,28).

In our study, 57% of the patients positive for nodal metastases had low-volume metastases, of which Mm was found in one patient, with the final stage being IIIC. This patient would have been missed and misclassified as stage I by conventional histopathology. Patients with Mm/ITCs have a higher relative risk of recurrence compared with patients without nodal metastases. However, the importance of the ITCs is still not clear enough, so it does not affect the staging for the time being. In addition, it is recommended that ITCs be noted in the surgical pathology report but designated as pNo(i+) (29). Large, randomized studies are needed to assess their impact on recurrence and overall survival (30).

Study Limitations

Limitations of the study include the small sample size and not performance of para-aortic lymph node dissection as there was no case of first echelon para-aortic lymph node visualization on planar lymphoscintigraphy/SPECT/CT. Additionally, pelvic lymphadenectomy was not performed in patients with low-risk EC. Therefore, we could not analyze the sensitivity and negative predictive value of the method in low-risk EC.

Conclusion

Our study indicates that SLN biopsy is a safe, non-invasive, and effective alternative for lymph node assessment in EC patients. The present results point out the high detection rate and diagnostic accuracy of the lymphoscintigraphy method for detecting SLN with cervical application of Tc-99m-SENTI-SCINT in patients with apparently uterine-confined EC. Furthermore, the application of immunohistochemical analysis of the SLN increases the detection of low-volume metastases in the lymph nodes, contributing to more

accurate staging and thus appropriate adjuvant treatment in these patients. Additionally, since the lymphatic drainage of the uterus is complex and there could be more than one drainage region and therefore more than one SLN, we recommend following the 10% rule and removal of all lymph nodes with counts per second higher than 10% of the counts of the hottest SLN.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of the Medical Faculty in Skopje (approval number: 03-366/8).

Informed Consent: Consent has been taken.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.J., S.S., Sa.S., I.A., R.J., M.T., S.K.K., N.M., G.P., D.M., Concept: A.J., D.M., Design: A.J., S.S., Sa.S., I.A., G.P., D.M., Data Collection or Processing: A.J., D.M., Analysis or Interpretation: S.S., G.P., D.M., Literature Search: A.J., D.M., Writing: J.A., N.M., S.S., G.P., D.M.

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