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Sentinel lymph node biopsy in early stage endometrial cancer: a Turkish gynecologic oncology group study (TRSGO-SLN-001)

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HIGHLIGHTS

- A sentinel lymph node (SLN) algorithm detected all pelvic nodal metastases and decreased unnecessary systematic lymphadenectomy.
- Indocyanine green and blue dye provided comparable bilateral mapping rates.
- The risk of non-SLN involvement in patients with macrometastatic SLNs was 61.2%.

ABSTRACT

Objective The aim of this multicenter study was to evaluate the feasibility of sentinel lymph node (SLN) mapping in clinically uterine confined endometrial cancer.

Methods Patients who underwent primary surgery for endometrial cancer with an SLN algorithm were reviewed. Indocyanine green or blue dye was used as a tracer. SLNs and/or suspicious lymph nodes were resected. Side specific lymphadenectomy was performed when mapping was unsuccessful. SLNs were ultrastaged on final pathology.

Results 357 eligible patients were analyzed. Median age was 59 years. Median number of resected SLNs was 2 (range 1–12) per patient. Minimal invasive and open surgeries were performed in 264 (73.9%) and 93 (26.1%) patients, respectively. Indocyanine green was used in 231 (64.7%) and blue dye in 126 (35.3%) patients. The dyes were injected into the cervix in 355 (99.4%) patients. The overall and bilateral SLN detection rates were 91.9% and 71.4%, respectively. The mapping rates using indocyanine green or blue dye were comparable (P=0.526). There were 43 (12%) patients with lymphatic metastasis. The SLN algorithm was not able to detect 3 of 43 patients who had isolated paraaortic metastasis. After SLN biopsy, complete pelvic lymphadenectomy was performed in 286 (80.1%) patients. Sensitivity and negative predictive value were both 100% for the detection of pelvic lymph node metastases. In addition, 117 (32.8%) patients underwent completion paraaortic lymphadenectomy after SLN biopsy. In these patients, sensitivity for detecting metastases to pelvic and/or paraaortic lymph nodes was 90.3% with a negative predictive value of 96.6%. The risk of non-SLN involvement in patients with macrometastatic SLNs, micrometastatic SLNs, and isolated tumor cells in SLNs were 61.2%, 14.3% and 0%, respectively.

Conclusions SLN biopsy had good accuracy in detecting lymphatic metastasis. However, one-third of cases with metastatic SLNs also had non-SLN involvement and this risk increased to two-thirds of cases with macrometastatic SLNs. The effect of leaving these nodes in situ on survival should be evaluated in further studies.

INTRODUCTION

Lymph node dissection is part of surgical staging and aims to determine lymph node status and tailor adjuvant treatment in endometrial cancer. However, most endometrial cancers are diagnosed in the early stages and lymphatic metastasis is seen in only a minority of cases.[1 2] Thus many patients face unnecessary systematic lymphadenectomy.

Intraoperative uterine frozen section examination based lymphadenectomy has been used in many centers to avoid unnecessary lymphadenectomy.[3–5] Nevertheless, this approach may miss some cases of metastasis. On the other hand, the lymphatic metastasis rate in patients who have the highest risk for lymphatic spread is only 34%.[6] Therefore, two-thirds of cases with the highest risk on frozen section are still metastasis free and this approach does not eliminate unnecessary systematic lymphadenectomy sufficiently.

As a third way, a sentinel lymph node (SLN) algorithm was suggested by the National Comprehensive Cancer Network (NCCN) that includes steps to increase detection rates of lymphatic metastasis and reduce misdiagnosis.[7 8] It could be a rational approach for patients with endometrial cancer to reduce the number of systematic lymphadenectomy procedures with a high accuracy in detecting lymph node metastasis.

In this multicenter study, the aim was to evaluate implementation of the SLN algorithm in early stage endometrial cancer. Success with different tracers and surgery types were also evaluated in 357 cases.

METHODS

Patients from six institutions with a diagnosis of clinical early stage endometrial cancer were included in the study between February 2016 and April 2019. This was a retrospective review of data that were collected prospectively at these institutions and each center had experience of the SLN algorithm in at least 30 endometrial cancer cases. Ethics committee approval and informed consent from the patients were obtained to use their data for the scientific studies. Transvaginal ultrasonography and chest X-ray were routine preoperative tests. Additional imaging studies were not routine but in high risk tumors, imaging studies were performed to exclude extrauterine disease at the clinician's discretion. Patients were excluded if they had a contraindication to any of the dyes (elevated bilirubin, or bilirubin or iodine allergy) or were treated without lymphadenectomy due to morbid obesity and/or medical comorbidities. Clinical early stage cancer was defined as the disease confined to the uterus.

Surgeries were performed by conventional laparoscopy, robotic surgery, or laparotomy. Methylene blue dye was used in three centers and indocyanine green (1.25 mg/mL, Pulsion Medical Systems, Feldkirchen, Germany) in the other three centers. A total of 4 mL of the solution were injected into the cervix, at 3 and 9 o'clock locations, 1 mL deep (1 cm) and 1 mL superficial (3–4 mm), using a 22 gauge spinal needle. The dyes were injected slowly, at a rate of 10 s, in each site. Injections were done at the beginning of the operation, and before laparotomy incision and carbon dioxide insufflation.

SLNs were checked by the naked eye in open surgery or by endoscopic white light in patients injected with blue dye. Near infrared/indocyanine green compatible endoscopic systems ((i) Spies Full HD D-Light P ICG technology, Karl Storz, Tuttlingen, Germany; (ii) PINPOINT near infrared fluorescence imaging system, Stryker, Kalamazoo, Michigan USA; or (iii) Da Vinci Xi robotic system, Intuitive Surgical Inc, Sunnyvale, California, USA) were used in surgical procedures for patients injected with indocyanine green. During the laparotomy operations, laparoscopic endoscope or an endoscope developed for open surgery was used in the same manner.

All cases were managed according to the steps in the SLN algorithm.[7] Briefly, after observing the peritoneal cavity, and pelvic and abdominal structures, the retroperitoneum was entered. Anatomical spaces were created and then SLN mapping was visualized. In addition to the mapped SLNs, any suspicious lymph nodes were also removed, regardless of the mapping. Side specific pelvic lymphadenectomy was performed for the unmapped pelvic side. The majority of cases also underwent at least bilateral pelvic systematic lymphadenectomy after applying the SLN algorithm, as this was the first time the attending institutions had used the algorithm and they needed to calculate the diagnostic performance of the algorithm and false negative rate by comparing the SLN algorithm steps and systematic lymphadenectomy. Paraaortic lymphadenectomy was performed at the surgeon's discretion. In general, preoperative non-endometrioid histology, grade III endometrial cancer, positive lymph nodes on intraoperative frozen section, or enlarged paraaortic nodes suspicious of malignancy were the main indications for paraaortic lymphadenectomy. Hysterectomy with or without adnexectomy was performed as a last step.

Histopathologic Evaluation and Ultrastaging

SLNs were routinely sectioned and stained with hematoxylin and eosin. The ultrastaging protocol for SLNs was implemented if the SLN was negative on initial hematoxylin and eosin staining. Serial sections were performed at intervals of 100–200 μm until the lymph node was exhausted. At each level, two slides were created, one stained with hematoxylin and eosin and one stained with the cytokeratin (clone AE1/AE3, Neomarkers) for immunohistochemical analysis. Non-SLNs were evaluated only by hematoxylin and eosin staining. Tumor foci >2 mm in the lymph node was considered as macrometastasis. Micrometastasis was defined as tumor foci 0.2–2 mm in size. Isolated tumor cells were defined as tumor deposits <0.2 mm.

Statistical Analysis

SLN mapping rates were calculated according to the presence or absence of lymph node on final histopathologic examination of SLN labeled specimens. The performance of the algorithm for the detection of lymph node metastasis was assessed by calculating sensitivity, false negative rate, and negative predictive value in patients who underwent at least systematic bilateral pelvic lymph node dissection after applying the SLN algorithm. Each woman served as her own control in terms of nodal status. Specificity and positive predictive value and false positive rate could not be reported because all positive SLNs have to be positive for lymph node metastasis. True positivity was defined as a positive SLN or algorithm in a patient with lymph node metastasis. Categorical variables were compared using the χ^2 test. Descriptive data are presented as median (minimun–maximum) for continuous variables and as frequency (percentage) for categorical variables. A P value <0.05 was considered statistically significant. All statistical analyses were performed using Stata V.9.0 (StataCorp, College Station, Texas, USA).

RESULTS

A total of 357 patients were included in the study (Figure 1). Median age of the patients was 59 years and median body mass index was 30.9 kg/m^2. Laparoscopic, open, and robotic surgery were

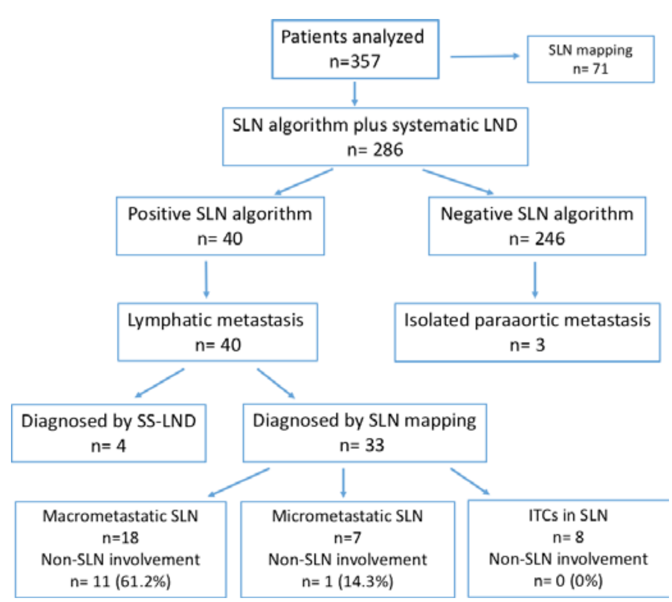

Figure 1 Summary of the study results. The SLN algorithm was able to detect all pelvic metastases. ITCs, isolated tumor cells; LND, lymph node dissection; SLN, sentinel lymph node; SS-LND, side specific lymph node dissection.

Table 1 Characteristics of the patients

Age (years) (median (range))	59 (36–87)
BMI (kg/m^2) (median (range))	30.9 (17.9–57)
Menopausal status (n (%))	
Premenopausal	74 (20.7)
Postmenopausal	283 (79.3)
Surgical route (n (%))	
Laparotomy	93 (26.1)
Laparoscopy	225 (63)
Robotic	39 (10.9)
Type of lymphadenectomy (n (%))	
Only SLND	71 (19.9)
BPLND	169 (47.3)
BPPALND	117 (32.8)
No of SLNs removed per patient (median (range))	2 (1–12)
No of pelvic LNs removed (median (range))	19 (3–74)
No of paraaortic LNs removed (median (range))	11 (1–61)

BMI, body mass index; BPLND, bilateral pelvic lymph node dissection; BPPALND, bilateral pelvic and paraaortic lymph node dissection; LN, lymph node; SLN, sentinel lymph node; SLND, sentinel lymph node dissection.

performed in 225 (63%), 93 (26.1%), and 39 (10.9%) patients, respectively. All patients underwent hysterectomy and bilateral salpingectomy with or without oophorectomy depending on age and intraoperative findings. While in 71 (19.9%) patients only SLNs were removed, bilateral pelvic lymphadenectomy was performed in 169 (47.3%) and bilateral pelvic and paraaortic lymphadenectomy in 117 (32.8%) patients. The characteristics of the patients are shown in Tables 1 and 2.

Indocyanine green was used in 231 (64.7%) patients and methylene blue dye in 126 (35.3%) patients to detect SLNs. The dyes were injected into the cervix in 355 (99.4%) patients and into the cervix and the fundus in 2 (0.6%) patients. In 328 patients (91.9%) at least one SLN was detected. The median number of resected SLNs was 2 (range 1–12) per patient. There was no lymph node in resected tissue labeled as SLN in 29 patients (4% of 714 hemipelvises) (empty packets) and these sides were considered as unmapped. Nineteen and 10 of the 29 patients were injected intracervically with indocyanine green and methylene blue dye, respectively. The overall, unilateral, and bilateral SLN detection rates were 91.9%, 20.5%, and 71.4% respectively.

Patients with successful mapping were younger (median 59 years vs 64 years, P=0.03) and had a lower median body mass index (kg/m^2) (30.4 vs 35.4, P=0.037) compared with patients with mapping failure (Table 2). But the significance of age disappeared in the multivariate analysis, and body mass index was the only independent factor related to mapping (odds ratio 1.0 (95% confidence interval 1.0 to 1.1), P=0.04). The overall, unilateral, and bilateral SLN detection rates were 92.2%, 22.5%, and 69.7% for indocyanine green and 91.3%, 16.7%, and 74.6% for blue dye, respectively (Table 3), and there was no statistically significant differences (P=0.422). There was no difference in mapping rates between the centers (P=0.068).

There were 43 (12%) patients with lymphatic metastasis. SLNs were found to be metastatic in 36 of 43 patients. Four of the 43 cases were diagnosed by side specific lymphadenectomy However, the SLN algorithm was not able to detect 3 of 43 metastatic patients who had isolated paraaortic metastasis.

Seventy-one cases underwent SLN mapping only and were excluded from the analysis. Three of the 43 lymphatic metastases were seen in this group and these cases were also not included in our calculations. Thirty-one cases with lymphatic metastasis were in the group in whom pelvic and paraaortic lymphadenectomy was performed and 9 were in the group in whom bilateral pelvic lymphadenectomy was performed.

Diagnostic Efficacy of the SLN Algorithm for Pelvic Nodes

Data from 286 patients who underwent at least systematic bilateral pelvic lymphadenectomy following implementation of the SLN algorithm were used for this analysis. The SLN algorithm was negative for pelvic node metastasis in 249 cases and final pathology of all lymph nodes was negative in all cases. The SLN algorithm was positive for pelvic node metastasis in 37 cases and final pathology was also positive in all of these cases. The sensitivity, negative predictive value, and false negative rate were 100% (95% confidence interval 90.5-100%), 100% (98.1-100%), and 0%, respectively. These rates were the same in the analysis of 169 cases who underwent systematic bilateral pelvic lymphadenectomy only (without paraaortic lymphadenectomy).

Diagnostic Efficacy of the SLN Algorithm for Pelvic and Paraaortic Nodes

Data from 117 cases who underwent bilateral pelvic and paraaortic systematic lymphadenectomy following implementation of the SLN algorithm were as follows: the SLN algorithm was negative for metastasis in 89 cases and 86 were also negative in the final pathology for all lymph nodes but 3 had isolated paraaortic metastasis; the SLN algorithm was positive for metastasis in 28 cases, and the final pathology confirmed these results. The sensitivity, negative predictive value, and false negative rate were 90.3% (95% confidence interval 74.2–97.9%), 96.6% (90.7–98.8%), and 9.6%, respectively.

Eighteen of the 36 cases with metastatic SLN had macrometastasis while the other 18 cases had micrometastasis and/or isolated tumor cells. Lymphatic spread was confined to the SLN in 24 patients (63.6%) while 12 patients (36.3%) also had metastasis in non-SLN(s). The risk of non-SLN(s) involvement in patients with macrometastatic SLN, micrometastatic SLN, and isolated tumor cells in SLN was 61.2%, 14.3%, and 0%, respectively. There were higher rates of lymphovascular space invasion (94% vs 63%, P=0.04) and grade III disease (70% vs 26%, P=0.01) in macrometastatic SLN patients compared with those who had low volume lymphatic metastasis. However, median body mass index was higher in patients with low volume metastatic SLN (33 vs 30 kg/m^2, P=0.038).

DISCUSSION

This multi-institutional study showed that the SLN algorithm for endometrial cancer had high diagnostic efficacy for detecting pelvic lymphatic metastases, thus avoiding unnecessary systematic

Table 2 Comparison of patient and tumor characteristics between mapped and unmapped patients

	All patients (n (%)) 357 (100)	Patients with at least 1 SLN (n (%)) 328 (91.9)	Patients with no mapping (n (%)) 29 (8.1)	P value
Age (years) (median (range))	59 (36–87)	59 (36–87)	64 (45–78)	0.030
BMI (kg/m^2) (median (range))	30.9 (17.9–57)	30.4 (17.9–57)	35.4 (22.7–49)	0.037
Menopausal status (n (%))				0.336
Premenopause	74 (20.7)	70 (21.3)	4 (13.8)	
Postmenopause	283 (79.3)	258 (78.7)	25 (86.2)	
Dye (n (%))				0.757
ICG	231 (64.7)	213 (64.9)	18 (62.1)	
MB	126 (35.3)	115 (35.1)	11 (37.9)	
Tumor size (mm) (median (range))	25 (1–100)	25 (2–100)	30 (1–80)	0.394
Histology (n (%))				0.312
Endometrioid	315 (88.2)	288 (87.8)	27 (93.1)	
Serous	10 (2.8)	10 (3)	0	
Clear cell	3 (0.8)	3 (0.9)	0	
Mucinous	4 (1.1)	4 (1.2)	0	
Carcinosarcoma	11 (3.1)	11 (3.4)	0	
Mixed	7 (2)	5 (1.5)	2 (6.9)	
Other	7 (2)	7 (2.1)	0	
Myometrial invasion (n (%))				0.458
None	46 (12.9)	41 (12.5)	5 (17.2)	
<1/2	211 (59.1)	197 (60.1)	14 (48.3)	
>1/2	100 (28)	90 (27.4)	10 (34.5)	
Grade (n (%))				0.647
I	164 (45.9)	149 (45.4)	15 (51.7)	
II	121 (33.9)	111 (33.8)	10 (34.5)	
III	72 (20.2)	68 (20.7)	4 (13.8)	
LVSI (n (%))				0.520
Negative	292 (81.8)	267 (81.4)	25 (86.2)	
Positive	65 (18.2)	61 (18.6)	4 (13.8)	
Stage (n (%))				0.257
IA	234 (65.5)	214 (65.2)	20 (69)	
IB	58 (16.2)	52 (15.9)	6 (20.7)	
II	12 (3.4)	12 (3.7)	0	
IIIA	9 (2.5)	9 (2.7)	0	
IIIC1	27 (7.6)	26 (7.9)	1 (3.4)	
IIIC2	15 (4.2)	14 (4.3)	1 (3.4)	
IV	2 (0.6)	1 (0.3)	1 (3.4)	

. BMI, body mass index; ICG, indocyanine green; LVSI, lymphovascular space invasion; MB, methylene blue;SLN, sentinel lymph node.

lymphadenectomy procedures and its morbidities. More than two-thirds of cases would need bilateral SLN biopsy without systematic lymphadenectomy and most of the remaining cases would need one sided pelvic systematic lymph node dissection. It is a valid option for the management of endometrial cancer to avoid unnecessary systematic lymphadenectomy with the ability to diagnose all pelvic lymphatic metastases.

The lymphatic metastasis rate was 12%. Although most of the metastases were diagnosed by SLN mapping, our results also confirmed the importance of side specific lymphadenectomy as nearly 10% of the metastases were diagnosed by this step in the SLN algorithm.

A substantial number of patients (60%) with macrometastatic SLNs also had non-SLN involvement, and this rate varied between

Table 3 Comparison of dyes in sentinel lymph node detection

	All patients (n (%)) 357 (100)	ICG patients (n (%)) 231 (64.7)	MB patients (n (%)) 126 (35.3)	P value
Bilateral	255 (71.4)	161 (69.7)	94 (74.6)	0.422
Unilateral	73 (20.5)	52 (22.5)	21 (16.7)	
None	29 (8.1)	18 (7.8)	11 (8.7)	

ICG, indocyanine green; MB, methylene blue.

50% and 64% in previous reports.[9–11] Chemotherapy is given as adjuvant treatment in such cases to improve survival.[12 13] However, there are no data to suggest that leaving these nodes in situ has a detrimental effect on survival. Until clarification of this controversial issue by further studies, the decision to perform systematic lymphadenectomy could be made by intraoperative frozen section examination of SLNs. Sometimes dilated lymphatic channels or adipose tissue are excised instead of SLNs, and failure of excision of the true nodes means the lymph node status of the hemipelvis cannot be determined. 'Empty packets' were found in 4% of hemipelvises in this study.

Nearly half of the lymphatic metastases were diagnosed by the SLN ultrastaging procedure as low volume metastasis (micrometastasis or isolated tumor cells). The risk of non-SLN involvement was low compared with patients who had macrometastatic SLNs, and it was 14% for micrometastasis, 0% for isolated tumor cells, and the overall risk was 5% in our cohort. The overall risk was 0–29% in other studies.[10–12 14] Micrometastasis was considered as lymphatic metastasis and managed accordingly, and isolated tumor cells were managed according to uterine risk factors in our centers, as generally suggested. However, there is no standard management for this new entity, and it is also suggested that low volume metastasis should be to ignored and the ultrastaging procedure omitted as it is not a determinant of adjuvant treatment and it increases workload.[14] Detailed evaluation of this topic was not a major objective of this study, but it should be investigated in further studies.

There was no clinical or histopathologic factor related to mapping rate except obesity. Surgery and retroperitoneal observation may be difficult in obese patients and previous studies reported similar results.[15 16] Mapping rates were not affected by the tracers used in this study and were comparable with previously reported rates. In contrast with using radiocolloid/scintigraphy for SLN detection, indocyanine green and blue dye can be used easily and there is no need for preoperative preparation. But indocyanine green/near infrared mapping requires fluorescent imaging systems and indocyanine green is more expensive than the blue dye. Although previous studies mostly reported that using indocyanine green has higher mapping rates compared with blue dye,[10 15 17 18] this study suggests that indocyanine green and blue dye have similar bilateral SLN mapping rates. In our multicenter study, surgeons in the blue dye group had SLN experience of at least 3 years. They had already completed their learning curve prior to initiation of this study. We believe that this is the most important factor that may explain the discordance between published data and our study. Both tracers can be used according to the center's potentials and it is important for widespread implementation of the SLN algorithm, particularly in low resource settings.

The NCCN SLN algorithm is a pelvis focused algorithm and has excellent diagnostic performance for pelvic metastases. The main reason for the false negativity is due to isolated paraaortic metastasis. This rate was 2.6%, and paraaortic area assessment is left to the surgeon's discretion. Obesity and many other morbidities make surgery difficult, and paraaortic assessment may be ignored due to the low probability of isolated metastasis. Most of the isolated paraaortic metastases were diagnosed in high risk cases, and preoperative imaging for these cases can decrease misdiagnosis of isolated paraaortic metastasis.[19] Another possible suggestion is to look for upper SLNs, especially in the presacral area, in cases where pelvic mapping has failed.[20]

The multicenter design of the study provided a large number of patients and allowed us to compare many parameters. However, possible heterogeneous surgical techniques may be a limitation of this study. Although the injection technique used was based on the suggestion of the NCCN, different surgeons injected the dyes which may have affected the mapping rate. Bilateral mapping rates varied between 63% and 75% in the centers. However, the differences were not statistically significant.

In conclusion, the SLN algorithm detected all pelvic lymphatic metastases. Although most of the metastases were diagnosed by resection of the mapped SLNs, the other steps in the algorithm (ie, side specific lymphadenectomy) were also essential to reach maximum diagnostic efficacy. Evaluation of the paraaortic area is not a mandatory step in the algorithm and isolated paraaortic metastasis is the main reason for false negativity. There was non-SLN metastasis in two-thirds of cases with macrometastatic SLNs. As there are no data on whether or not to leave metastatic non-SLNs in situ, intraoperative frozen section examination of SLNs could help in deciding if lymphadenectomy should be performed.

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