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Paraaortic sentinel lymph node detection in intermediate and high-risk endometrial cancer by transvaginal ultrasound-guided myometrial injection of radiotracer (TUMIR)

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ABSTRACT

Objective: We aimed to evaluate the accuracy of sentinel lymph node (SLN) mapping with
transvaginal ultrasound-guided myometrial injection of radiotracer (TUMIR) to detect lymph
node (LN) metastases, in patients with intermediate and high-risk endometrial cancer (EC),
focusing on its performance to detect paraaortic involvement.

Methods: Prospective study including women with preoperative intermediate or high-risk
EC, according to ESMO-ESGO-ESTRO consensus, who underwent SLN mapping using
the TUMIR approach. SLNs were preoperatively localized by planar and single photon
emission computed tomography/computed tomography images, and intraoperatively by
gamma-probe. Immediately after SLN excision, all women underwent systematic pelvic and
paraaortic lymphadenectomy by laparoscopy.

Results: The study included 102 patients. The intraoperative SLN detection rate was
79.4% (81/102). Pelvic and paraaortic drainage was observed in 92.6% (75/81) and 45.7%
(37/81) women, respectively, being exclusively paraaortic in 7.4% (6/81). After systematic
lymphadenectomy, LN metastases were identified in 19.6% (20/102) patients, with 45.0%
(9/20) showing paraaortic involvement, which was exclusive in 15.0% (3/20). The overall
sensitivity and negative predictive value (NPV) of SLNs by the TUMIR approach to detect
lymphatic involvement were 87.5% and 97.0%, respectively; and 83.3% and 96.9%, for
paraaortic metastases. After applying the MSKCC SLN mapping algorithm, the sensitivity
and NPV were 93.8% and 98.5%, respectively.

Conclusion: The TUMIR method provides valuable information of endometrial drainage

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Author Contributions

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in patients at higher risk of paraaortic LN involvement. The TUMIR approach showed a detection rate of paraaortic SLNs greater than 45% and a high sensitivity and NPV for paraaortic metastases in women with intermediate and high-risk EC.

Keywords: Genital Neoplasms, Female; Endometrial Neoplasms; Sentinel Lymph Node; Lymph Node Excision; Sensitivity and Specificity; Surgery

INTRODUCTION

Lymph node (LN) involvement is one of the most important prognostic factors in endometrial cancer (EC) and its evaluation is essential for treatment planning. To assess the risk of LN involvement, patients are stratified based on preoperative criteria as having low, intermediate or high-risk of LN metastases [1]. According to the current European clinical guidelines, systematic pelvic and paraaortic lymphadenectomy should be considered in intermediate-risk patients and is recommended in women with high-risk [1]. The prognosis of women with EC showing paraaortic LN metastases is worse than in patients with only pelvic involvement [2] and extended-field radiotherapy to the aortic area is indicated, in addition to adjuvant chemotherapy [1]. Thus, adequate assessment of paraaortic LN status is crucial in patients at higher risk of LN metastases.

However, the risk of pelvic LN metastases is about 20% [3-6], and in the paraaortic area it is of about 15% (4% for isolated paraaortic involvement) in patients with intermediate and high-risk EC [5]. Considering that lymphadenectomy entails a non-negligible morbidity [7], this would imply a high rate of overtreatment even in women at higher risk of LN involvement. Sentinel lymph node (SLN) detection has emerged as an alternative to systematic lymphadenectomy in these patients [3,4,8-10].

Cervical tracer injection is the most common technique used for SLN assessment in EC [11]. However, this approach can miss lymphatic endometrial drainage to the paraaortic area, which implies that paraaortic LN metastases may be underdiagnosed. In 2013, we described a safe and feasible method for SLN detection using transvaginal ultrasound-guided myometrial injection of radiotracer (TUMIR). This pilot study showed that this approach significantly increased the rate of paraaortic SLN detection and adequately reflected the expected endometrial drainage [12].

In the present study, we aimed to analyze the performance of SLN mapping using the TUMIR approach in patients with intermediate and high-risk EC and to evaluate the diagnostic accuracy of this method in the detection of LN metastases, particularly in the paraaortic area.

MATERIALS AND METHODS

1. Patients and study design

Between March 2006 and March 2017, we prospectively enrolled women with histologically confirmed EC who were candidates for systematic surgical staging because of the presence of intermediate or high-risk of LN involvement, defined by fulfilling at least one of the following inclusion criteria: 1) unfavorable histology (serous, clear cell or International Federation of Gynecology and Obstetrics [FIGO] grade 3 endometrioid adenocarcinoma); 2) myometrial

invasion $\geq 50\%$ suspected by imaging techniques (magnetic resonance imaging [MRI] or 3-dimensional [3D]-ultrasound); 3) cervical stroma involvement confirmed by biopsy or suspected by imaging techniques. Patients with any of the following criteria were excluded: 1) contraindication for surgical staging; 2) suspicion of pelvic or paraaortic LN metastases by imaging techniques (computed tomography [CT] or MRI) due to a short-axis diameter larger than 8 mm for pelvic LNs, 10 mm for paraaortic LNs, or due to a round appearance [13]; 3) suspicion of distant metastases at imaging or histologically confirmed; 4) previous surgery or radiotherapy in the pelvic or paraaortic regions.

All patients were informed and signed a consent form. The study was approved by the Institutional Review Board of the Hospital Clinic of Barcelona (HCB/2006/3112).

2. Radiotracer injection methodology

As previously described, [^{99m}Tc] Tc-nanocolloid (Nanocoll[®]; GE Healthcare, Saluggia, Italy) was injected into the myometrium guided by transvaginal ultrasound imaging 18 to 24 hours prior to surgery, with the patient awake after the application of local anesthesia [12]. The volume injected ranged from 4 to 8 mL, and the dose was of 3 to 6 MCi [14]. The Aspen (Siemens-Acuson Inc., Mountain View, CA, USA) or Voluson (Voluson v730Expert; General Electric, Frankfurt am Main, Germany) ultrasound imaging devices, equipped with a 4–9 MHz 2D vaginal probe with an attached needle guide, were used for the injection. In an anteverted uterus, a 20-gauge biopsy needle (Gallini Medical Devices, Mantova, Italy) crossed the anterior wall to inject half of the volume in the posterior wall. The remaining volume of radiotracer was injected into the anterior myometrial wall (**Fig. 1**). Once the radiotracer was administered, the needle was flushed with saline solution. In a retroverted uterus, the injection of radiotracer was first performed into the anterior uterine wall and secondly into the posterior uterine wall [12]. All the procedures were performed by experienced gynecological sonographers together with nuclear medicine physicians. Tolerance to the procedure was assessed using a visual analog scale (range 0–10; no pain to severe pain).

3. Preoperative lymphoscintigraphy

After radiotracer injection, pelvic and abdominal planar images (256×256 matrix, anterior and lateral views of 300 s/frame each) were acquired using single-head (E-Cam; Siemens, Erlangen, Germany) or dual-head (Infinia Hawkeye 4; General Electric, Milwaukee, WI, USA) gamma cameras fitted with a low energy-high resolution collimator. The images were obtained 30 minutes and 2–4 hours after tracer injection. Subsequently, single photon emission computed tomography (SPECT) (128×128 matrix, 120 frames, 3°/frame, 20 s/frame) and low-dose CT (512×512 matrix, 140 kV and 2.5 mAs) images were acquired using a hybrid camera (Infinia Hawkeye 4; General Electric) (**Supplementary Fig. 1**). Since 2012 volume-rendering images were generated using an Osirix Dicom viewer (Pixmeo SARL, Geneva, Switzerland) in a Unix-based operating system (MAC OS X, MacPro; Apple, Cupertino, CA, USA) to obtain a 3D presentation to improve the localization of SLNs.

SLNs were defined as the first LN observed in sequential images in a specific LN basin, those directly connected with the injection site by a lymphatic channel or if a combination of these criteria was present. LNs appearing later in the same lymphatic basins were considered to be second echelon nodes. If SPECT/CT showed other hot spots in areas without drainage on the planar images or in regions close to the injection site but without visualization in previous planar images, these hot spots were also considered SLNs. Images were examined by 2 nuclear medicine physicians and discussed with the surgeon prior to surgery.

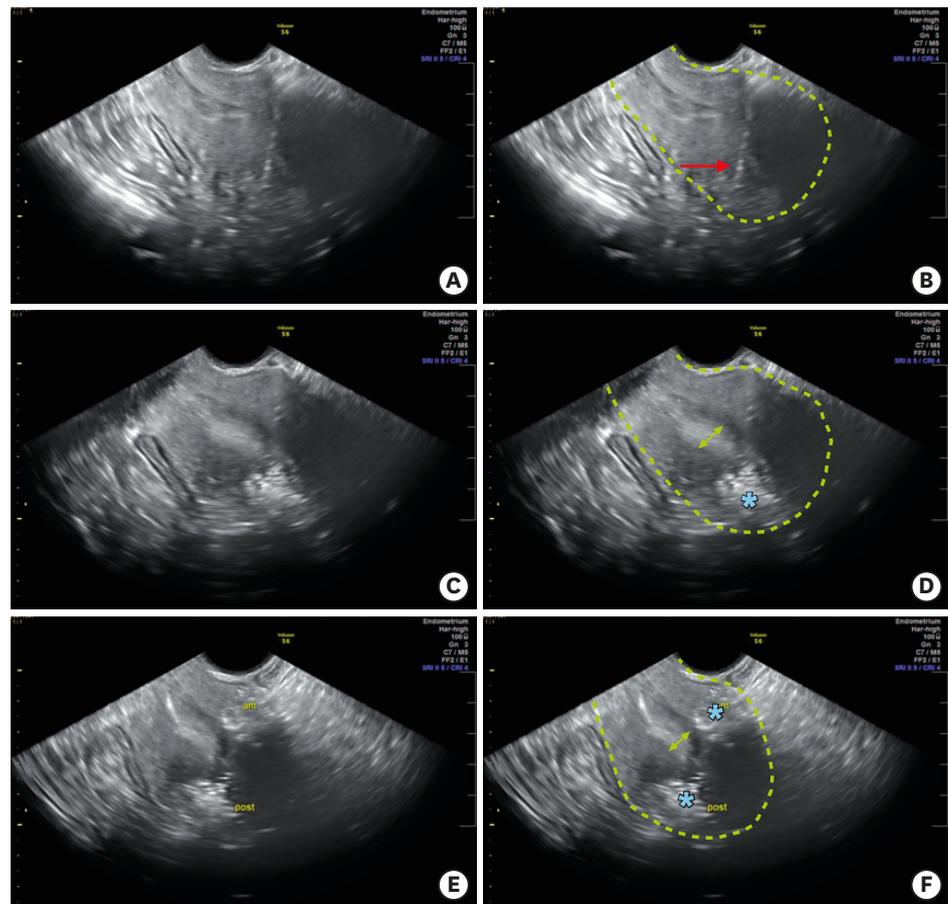


Fig. 1. Transvaginal ultrasound-guided myometrial injection of radiotracer. In the first step the needle penetrates through the anterior vaginal fornix, crossing the anterior myometrium and the endometrial cavity until reaching the posterior myometrium (A). Half of the volume of radiotracer is injected into the outer two-thirds of the myometrium (C). Then, the needle is partially removed, and the remaining volume of radiotracer is injected into the outer two-thirds of the anterior myometrium (E). (B) Needle crossing the endometrial cavity towards the posterior wall (red arrow). Discontinuous green line delimits the uterus. (D) Tracer accumulation (cyan asterisk) in the posterior wall of the myometrium. Discontinuous green line delimits the uterus. Green double-headed arrow indicates the endometrium. (F) Tracer accumulation (cyan asterisk) in the anterior and posterior walls of the myometrium. Discontinuous green line delimits the uterus. Green double-headed arrow indicates the endometrium.

4. Surgical procedure: Intraoperative SLN detection with gamma probe and paraaortic plus pelvic lymphadenectomy

Laparoscopic surgery began with an intraperitoneal approach to rule out carcinomatosis. Then, a left retroperitoneal access was created to first localize the paraaortic SLNs with a laparoscopic gamma probe (Navigator; USSC, Norwalk, CT, USA) inserted through a 12 mm-trocar. The SLNs previously visualized in the lymphoscintigraphy or the SPECT/CT were identified and removed. All LNs depicted in the preoperative images and those found during surgery with an activity greater than 10% of the hottest LN were considered SLNs. After selective excision of paraaortic SLNs, a systematic paraaortic LN dissection was carried out. Lymphadenectomy included the removal of the LNs located at the presacral, aortic bifurcation, precaval, preaortic and paraaortic areas, both below and above the inferior mesenteric artery up to the level of the left renal vein as the upper limit of dissection.

The procedure continued through a transperitoneal approach to perform selective excision of pelvic SLNs. The pelvic regions were carefully scanned with the gamma probe, angled

laterally to avoid detection of radioactivity at the injection site. The exact location of each SLN excised in relation to the pelvic vessels, vena cava, or aorta was recorded. Then, bilateral transperitoneal pelvic lymphadenectomy was performed, including removal of external and internal iliac, obturator fossa, and common iliac LNs. Finally, total vaginal hysterectomy and bilateral salpingo-oophorectomy assisted by laparoscopy was performed.

5. Histological SLN ultrastaging and evaluation of the lymphadenectomy specimens

The SLNs were cut into 2 mm-thick serial sections following their shortest diameter, submitted completely for histology, and routinely embedded in paraffin. The first two 4 μm-thick sections were stained one with hematoxylin and eosin (H&E) and the second by immunohistochemistry for cytokeratin 7 (Dako Pathology; Agilent, Santa Clara, CA, USA) and examined under a light microscope (conventional evaluation). If these first 2 sections were negative, 6 additional sections were performed at an interval of 400 μm (ultrastaging). Each level included one section stained with H&E and another for cytokeratin 7. Immunohistochemical studies were performed with the automated immunohistochemical system Autostainer Link 48[®], using the EnVision system (Dako, Glostrup Municipality, Denmark).

The lymphadenectomy specimens were fixed in 10% neutral-buffered formalin and macroscopically dissected to isolate all LNs, which were cut into 2 mm-thick sections following their largest diameter and routinely processed. The 4 μm-thick histological sections were obtained with a microtome, which were stained with H&E and examined under a light microscope.

Metastatic LN involvement was defined as at least one LN (either SLN or one non-SLN) positive for metastases detected either in the evaluation of the H&E and/or the immunohistochemical section (in case of SLN). When present, the size of the metastasis was recorded. Macrometastases were defined as tumor clusters >2 mm, while micrometastases were defined as tumor clusters between 0.2 and 2 mm in size, and isolated tumor cells (ITC) were defined as single tumor cells or small tumor clusters ≤0.2 mm [15].

6. Statistical analysis

Data are presented as absolute number and percentage for categorical variables. For continuous variables, data were shown as median and range for the pain scale score and LNs, and as mean±standard deviation for age and body mass index (BMI). Intraoperative SLN detection rate was defined as the number of patients with at least one SLN identified during surgery divided by the number of patients in whom the SLN dissection was attempted during surgery.

The Memorial Sloan Kettering Cancer Center (MSKCC) algorithm includes the excision of all mapped SLNs analyzed with ultrastaging, the excision of any suspicious LN during surgery regardless of the mapping and side-specific LN dissection in case of no mapping in the hemi-pelvis [16]. Analysis of accuracy of the TUMIR was performed considering exclusively the women in whom SLN detection was successfully carried out, and it was conducted following the standardization proposal by Cormier et al. [17] by reporting both “overall” and “algorithm” results. Lack of drainage was considered as a failure of the technique and these cases were not considered for the evaluation of diagnostic accuracy.

The overall sensitivity was estimated as the proportion of patients with positive SLNs among the patients with LN metastases. Overall, the negative predictive value (NPV) was defined as

the fraction of patients without LN involvement within the group of patients with negative SLNs. A false negative (FN) result was defined as a patient with negative SLNs who had at least one metastatic non-SLN.

The sensitivity of the MSKCC SLN mapping algorithm was estimated as the proportion of algorithm-positive patients among those with LN involvement. In the MSKCC SLN mapping algorithm, the NPV was defined as algorithm-negative patients without LN involvement divided by all algorithm-negative patients. The FN rate of the MSKCC SLN mapping algorithm was defined as algorithm-negative patients with LN involvement divided by patients with LN involvement.

The analysis of para-aortic SLN accuracy with the TUMIR approach was performed considering exclusively the women in whom at least one para-aortic SLN was found. The sensitivity of TUMIR to detect para-aortic involvement was estimated as the proportion of patients with positive para-aortic SLNs among the patients with para-aortic LN metastases. The NPV for para-aortic involvement was defined as the fraction of patients without para-aortic involvement among the group of patients who had negative para-aortic SLNs. A FN result was defined as a patient with negative para-aortic SLNs who had at least one para-aortic metastatic non-SLN. The sensitivity and NPV were calculated for the SLNs evaluated by conventional evaluation (only H&E) and with ultrastaging.

The Wilson's method was used to estimate 95% confidence intervals (CIs). For all the statistical tests, differences were considered significant at the level of 5%, and all reported p-values were 2-sided. The statistical analyses were conducted using STATA 13.1 software (StataCorp, College Station, TX, USA).

RESULTS

1. Patients' characteristics

The inclusion criteria were fulfilled by 107 patients and TUMIR injection was performed. No major adverse effects were observed during injection and interruption of the procedure did not occur in any of the cases. The median score in the pain scale was 4 (range 0–10).

Of the 107 women initially enrolled, the procedure was abandoned in 5: due to the detection of peritoneal carcinomatosis not identified in preoperative imaging in 3 patients, due to severe intraoperative bleeding in one patient, and due to technical failure of the gamma probe in another patient. Thus, 102 women were finally included in the study.

The mean age of the 102 women undergoing the SLN procedure was 66.0±9.9 years and the mean BMI was 28.2±5.2 kg/m². Sixty-four (62.7%) women were preoperatively diagnosed with intermediate-risk EC and 38 (37.3%) had high-risk EC. Preoperative risk, the definitive histological characteristics, and FIGO stage are summarized in **Table 1**.

2. Surgical SLN detection: successfulness of the TUMIR technique

Of the 102 patients in whom SLN dissection was attempted, the procedure was successful in 81 women (79.4%: detection rate), whereas in 21 (20.6%) SLN detection failed. In 15 patients there was no drainage of the radiotracer, and in 6 women the radiotracer spilled out through the peritoneal cavity. **Fig. 2** shows the flow chart with the women initially recruited (n=107),

Table 1. Histological characteristics of the 102 patients included in the study

Characteristics	No. (%)
Preoperative assessment	
Preoperative risk*	
Intermediate	64 (62.7)
High	38 (37.3)
Definitive histological data	
Histological type and grade	
Endometrioid grade 1	25 (24.5)
Endometrioid grade 2	32 (31.4)
Endometrioid grade 3	20 (19.6)
Serous	10 (9.8)
Carcinosarcoma	6 (5.9)
Clear cell	3 (2.9)
Mixed†	6 (5.9)
Tumor size (cm)	
<4	58 (56.9)
≥4	44 (43.1)
Myometrial invasion ≥50%	
Yes	53 (52.0)
No	49 (48.0)
Lymphovascular space involvement	
Yes	28 (27.5)
No	74 (72.5)
Postoperative FIGO‡ 2009 stage	
IA	42 (41.2)
IB	30 (29.4)
II	9 (8.8)
IIIA	0 (0.0)
IIIB	1 (1.0)
IIIC1	11 (10.8)
IIIC2	9 (8.8)
IV	0 (0.0)

FIGO, International Federation of Gynecology and Obstetrics.

*Preoperative risk was assessed according to European Society for Medical Oncology-European Society of Gynaecological Oncology-European Society for Radiotherapy & Oncology; †Mixed endometrioid and serous or endometrioid and clear cell; ‡In our study, we considered low-volume metastases as lymph node involvement.

the women in whom the dissection was attempted (n=102), and the patients in whom the technique was successful and were considered for accuracy analysis (n=81).

3. Anatomical area of SLN drainage and histological evaluation

A median number of 3 (range 1–8) SLNs were identified per patient in the 81 women in whom at least one SLN was detected. Overall, 244 SLNs were intraoperatively identified among the 81 patients. Pelvic drainage was observed in 75 (92.6%) women and paraaortic drainage in 37 (45.7%) patients. Forty-four (54.3%) patients showed exclusively pelvic drainage, 31 (38.3%) showed both pelvic and paraaortic drainage, and 6 (7.4%) had exclusively paraaortic drainage. Among the 75 patients in whom pelvic drainage was observed, the drainage was bilateral in 24 (32.0%), exclusive to the right pelvis in 23 (30.7%), and exclusive to the left pelvis in 28 (37.3%).

The topographic distribution of the 244 SLNs retrieved is shown in **Fig. 3A**. The external iliac was the most common site of SLN drainage. Among the 81 patients with SLN, metastatic involvement of at least one SLN was identified in 14 (17.3%) patients (24/244, 9.8% metastatic SLNs). A single metastatic SLN was identified in 8 patients, and in 6 patients 2 or more SLN with metastasis were detected. The location of the metastatic SLNs is shown in **Fig. 3B**. Most

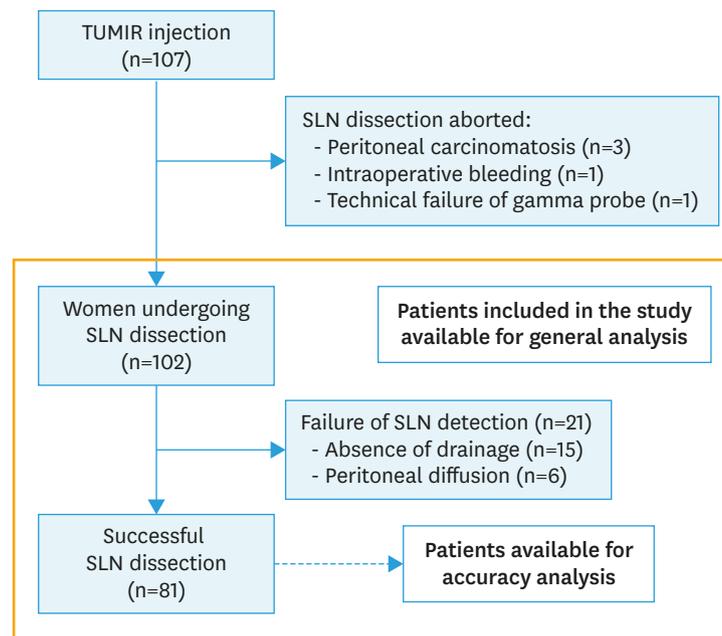


Fig. 2. Flow chart of the patients included in the study and available for the analyses. SLN, sentinel lymph node; TUMIR, transvaginal ultrasound-guided myometrial injection of radiotracer.

of the positive SLNs were found in the obturator fossa or around the external iliac vessels. All the paraaortic metastatic SLNs were located in the inframesenteric area.

SLN metastases were detected in the initial histological evaluation in 8 patients, and in other 6 patients, SLN metastases were detected with ultrastaging (1 patient with macrometastasis, 1 with micrometastasis and 4 cases of ITC).

4. Histological evaluation of pelvic and paraaortic lymphadenectomy

After SLN excision, a systematic lymphadenectomy was performed in all 102 patients. A total of 2,489 non-SLNs were retrieved: 1,478 pelvic and 1,011 paraaortic LNs. The median number of LNs per patient was 24 (range 14–51) with 14 (range 8–31) pelvic LNs and 10 (range 5–37) paraaortic LNs. Twenty or more LNs were removed in 70.6% (72/102) of the patients.

Metastatic involvement of one or more LN (either SLN or non-SLN) was identified in 20/102 (19.6%) women. Exclusive pelvic LN involvement was found in 11/20 (55.0%) cases, while exclusive paraaortic lymphatic involvement was observed in 3/20 (15.0%), and involvement of both areas in 6/20 (30.0%). Thus, 9/20 (45%) patients with LN involvement had paraaortic metastases. Overall, paraaortic metastases were identified in 9/102 (8.8%) patients and exclusive paraaortic involvement in 3/102 (3%).

Four of the 21 (19.0%) women in whom non-SLN was retrieved (SLN technique failure) had at least one metastatic LN. All 4 women showed macrometastases. Three women had pelvic metastases (2 unilateral, 1 bilateral), and the last patient had exclusive paraaortic involvement.

5. Analysis of overall and MSKCC SLN mapping algorithm accuracy

The 81 women in whom the TUMIR procedure was successfully performed and showed at least one SLN were considered in the analysis of accuracy. Sixteen of these 81 (19.7%) women

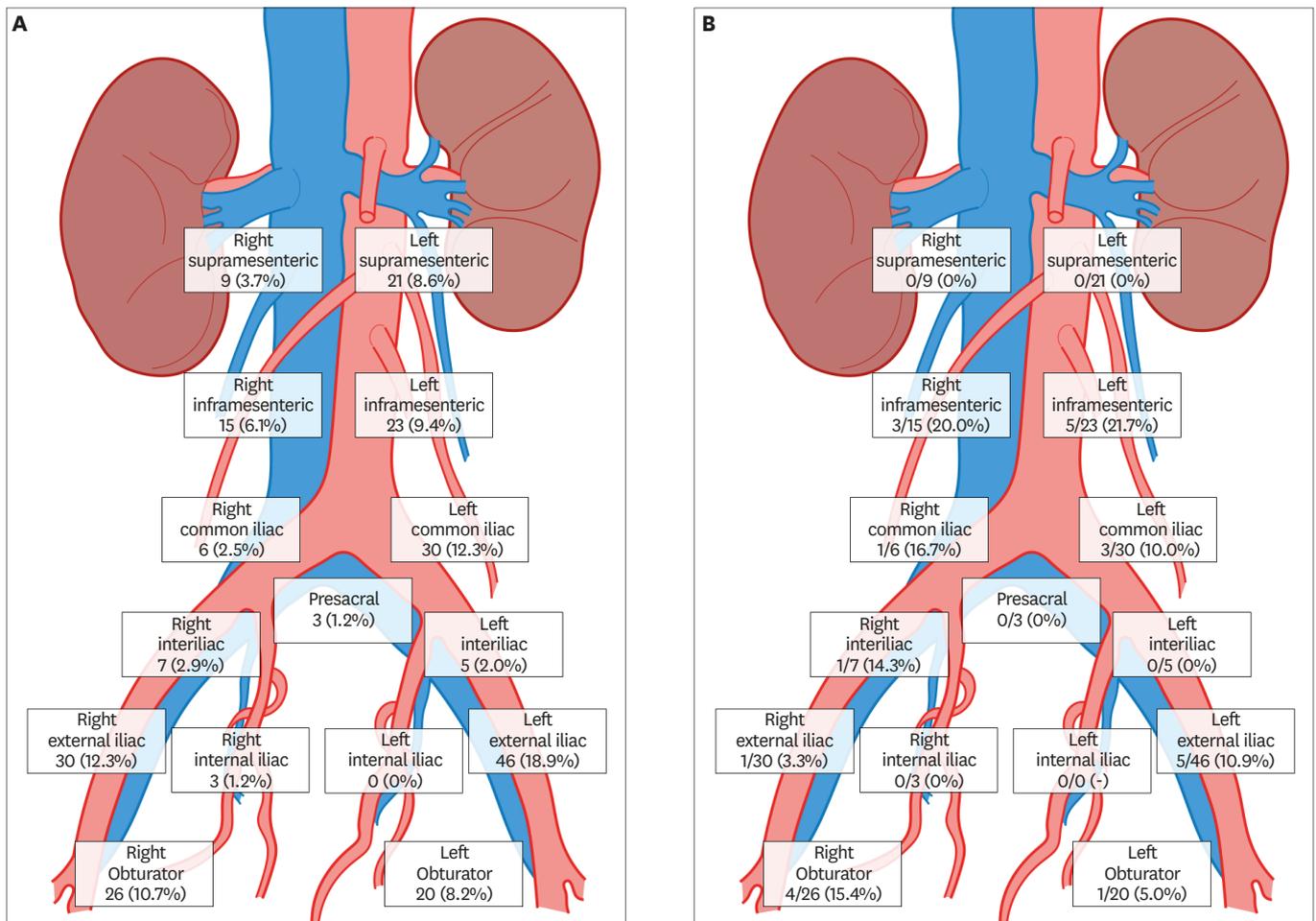


Fig. 3. Topography and lymphatic status of the SLNs identified in the different anatomical areas of lymphatic drainage (n=244) in the 81 patients with at least one SLN. (A) Number and percentage of SLNs retrieved per anatomic area. (B) Number and percentage of involved SLNs per anatomic area. SLN, sentinel lymph node.

had at least one metastatic LN (either SLN or non-SLN). Among these 16 patients, 14 had a positive SLN, while in 2 patients the SLNs were negative (2/16, overall FN rate of 12.5%). In one of these 2 FN cases, one suspicious macroscopic LN was identified during surgery and, therefore, would have been identified by the MSKCC SLN mapping algorithm. The other FN patient had bilateral pelvic drainage and would not have been detected by the algorithm. Thus, the FN rate of the MSKCC algorithm was 1/16, 6.3%. Among the 14 patients with metastatic SLNs, 8 (57.1%) cases showed involvement of SLNs and non-SLNs by H&E, and in 6 (42.9%) cases metastatic involvement was exclusively detected in the SLN by ultrastaging.

The overall sensitivity and NPV of the SLNs identified by TUMIR to detect LN involvement in the conventional evaluation (H&E alone) were 50.0% (95% CI=28.0–72.0) and 89.0% (95% CI=79.8–94.3), respectively. After adding ultrastaging, the overall sensitivity and NPV increased to 87.5% (95% CI=64.0–96.5) and 97.0% (95% CI=89.8–99.2), respectively. The sensitivity and NPV of the MSKCC SLN mapping algorithm to detect LN metastases were 93.8% (95% CI=71.7–98.9) and 98.5% (95% CI=91.9–99.7), respectively.

6. Analysis of paraaortic SLN accuracy

The 37 women with at least one paraaortic SLN were considered in the analysis of paraaortic SLN accuracy by the TUMIR approach. Six of these 37 (16.2%) women had at least one metastatic paraaortic LN (either paraaortic SLN or paraaortic non-SLN). Among these, 5 had a positive paraaortic SLN, while in one patient the paraaortic SLN was negative (1/6; 16.7% FN rate for paraaortic LN involvement). This patient had pelvic and paraaortic LN involvement but showed FN pelvic and paraaortic SLNs. Among the 5 women with metastatic paraaortic SLNs, one patient was only detected by ultrastaging and another, with exclusive paraaortic LN involvement, showed exclusive paraaortic SLN drainage.

The sensitivity and NPV of paraaortic SLN to detect paraaortic lymphatic disease using H&E staining versus the addition of ultrastaging were 66.7% (95% CI=30.0–90.3) vs. 83.3% (95% CI=43.6–97.0) and 93.9% (95% CI=80.4–98.3) vs. 96.9% (95% CI=84.3–99.4), respectively.

Supplementary Tables 1-5 show the accuracy analyses.

In 3 out of the 9 patients with paraaortic LN involvement, no paraaortic SLN was identified and, therefore, these patients were not included in the paraaortic SLN accuracy analysis. One of these patients presented exclusive pelvic SLNs and showed isolated paraaortic LN involvement in the lymphadenectomy. In 2 women non-SLN was identified during surgery: one presented pelvic and paraaortic LN involvement in the lymphadenectomy and the other woman presented exclusive paraaortic involvement (**Supplementary Fig. 2**).

7. Intraoperative complications

In one patient severe bleeding occurred after a lumbar vein injury when searching for the SLN in the paraaortic area, requiring conversion to laparotomy. No other intraoperative complication was observed during SLN excision.

Conversion to laparotomy was required in 2 additional patients. In one case this was due to a ureteral lesion during paraaortic lymphadenectomy, and in the second due to damage of the left renal vein during paraaortic lymphadenectomy.

DISCUSSION

The intraoperative SLN detection rate in the present series was almost 80%, being slightly lower than the rate observed in previous studies performed with cervical tracer injection in intermediate or high-risk EC, in which the SLN detection rate ranged from 83% to 100% [3,4,6,8,18-25]. Two studies evaluating the SLN procedure with subserosal injection of blue dye in intermediate and/or high-risk EC patients showed detection rates of 73% and 89% [26,27]. The decreased overall SLN detection in our series could be explained not only by the site of tracer injection but also by the type of tracer, as indocyanine green (ICG) has shown to provide higher SLN detection rates [11]. **Table 2** displays the recent studies assessing the SLN procedure in patients with intermediate and/or high-risk EC. Regarding the TUMIR approach, in a previous study, we showed that 25 procedures were needed to achieve the learning curve of this technique. From this point on the detection rate stabilized and only slightly increased with the accumulation of experience [14].

Remarkably, paraaortic SLN detection with the TUMIR approach was greater than 45%, being significantly higher than the rate reported in most previous studies using cervical injection,

Paraaortic SLN detection in endometrial cancer by TUMIR
Table 2. Studies assessing SLN procedure in patients with intermediate and/or high-risk endometrial cancer from 2015 to date

Study, country (patients included)	Year	Number*	Preoperative risk	Surgical approach	Injection site	Type of tracer	Overall DR (%)	Bilateral DR [†] (%)	Paraaortic DR [†] (%)	Overall sensitivity (%)	Overall NPV (%)	Algorithm sensitivity (%)	Algorithm NPV (%)
Angeles et al. [19], Spain (all cohort)	2020	102	Intermediate or high-risk	Laparoscopy	TUMIR	RT	79.4	32.0	45.7	87.5 [‡]	97.0	93.8	98.5
Cusimano et al. [27], Canada (all cohort)	2020	156	Intermediate or high-risk	Laparoscopy	Cervical	ICG	97.4	79.6	N/A	88.9 [‡]	97.7	96.3	99.2
Persson et al. [28], Sweden (all cohort)	2019	257	High-risk	Robotic-assisted laparoscopy	Cervical	ICG	100	95.0	N/A	96.3 [‡]	99.0	N/A	N/A
Wang et al. [29], China (all cohort)	2019	98	High-risk	Laparoscopy	Cervical	ICG	95.9	89.9	23.4	88.2 [‡]	97.3	90.9	N/A
Ye et al. [12], China (subgroup)	2019	25	High-risk	Laparoscopy	Cervical	ICG	100	72.0	3.1	20.0 [‡]	83.3	N/A	N/A
Buda et al. [30], Italy and Switzerland (subgroup)	2018	105	High-risk	N/A	Cervical	ICG; BD+RT	N/A	N/A	N/A	85.3 [§]	93.4	91.2	96.0
Papadia et al. [23], Switzerland (all cohort)	2018	42	High-risk	Laparoscopy	Cervical	ICG	100	90.5	N/A	90.0 [‡]	97.1	100	100
Rajanbabu et al. [9], India (subgroup) [¶]	2018	25	High-risk	Robotic-assisted laparoscopy	Cervical	ICG	N/A	N/A	N/A	57.1 [‡]	85.7	100	100
Rajanbabu et al. [9], India (subgroup) [¶]	2018	20	Intermediate risk	Robotic-assisted laparoscopy	Cervical	ICG	N/A	N/A	N/A	100 [‡]	100	100	100
Baiocchi et al. [24], Brazil (subgroup)	2017	75	High-risk	Laparoscopy or robotic-assisted laparoscopy	Cervical	BD	85.3	70.3	3.1	90.0 [‡]	95.7	90.0	95.7
Soliman et al. [6], USA (all cohort)	2017	101	High-risk	Laparoscopy, robotic-assisted laparoscopy or laparotomy	Cervical	ICG; BD; BD+RT	89.1	57.8	2.0	95.0 [‡]	98.6	95.7	N/A
Tanner et al. [25], USA (all cohort)	2017	52	High-risk	Robotic-assisted laparoscopy	Cervical	ICG; BD	86.5	68.9	9.0	77.8 [‡]	94.7	77.8	94.7
Touhami et al. [7], Canada (all cohort)	2017	128	High-risk	Laparoscopy, robotic-assisted laparoscopy or laparotomy	Cervical	ICG; BD; RT; RT+ICG or BD	89.8	70.4	4.3	95.8 [§]	98.2	N/A	N/A
Ehrisman et al. [26], USA (all cohort)	2016	36	High-risk	Laparoscopy or robotic-assisted laparoscopy	Cervical	ICG; BD	83.3	66.7	3.3	77.8 [‡]	91.3	100	100
Farghali et al. [31], Egypt (all cohort)	2015	93	High-risk	Laparotomy	Subserosal	BD	73.1	55.9	0	94.1 [‡]	98.1	N/A	N/A
Naoura et al. [11], France (subgroup)	2015	34	High-risk	N/A	Cervical	BD+RT	88.2	60.0	N/A	62.5 [‡]	70.0	N/A	N/A
Valha et al. [32], Czech Republic (all cohort)	2015	18	Intermediate or high-risk	Laparotomy	Subserosal	BD	88.9	N/A	N/A	100 [‡]	100	N/A	N/A

BD, blue dye; DR, detection rate; ICG, indocyanine green; N/A, not available; NPV, negative predictive value; SLN, sentinel lymph node; RT, radiotracer; TUMIR, transvaginal ultrasound-guided myometrial injection of radiotracer.

*Patients included for evaluation of the DR; [†]Bilateral and paraaortic DR were calculated in patients with at least one SLN; [‡]Sensitivity was calculated considering all patients with at least one SLN; [§]Sensitivity was calculated considering only patients with bilateral SLNs; [¶]Ultrastaging was not done in this study. DR for risk subtypes was not specified.

which was of less than 10% [3,4,9,19-21,26,28]. A recent prospective multicenter study—the FIRES trial—described an unusually high detection rate of paraaortic SLNs of 23% with cervical injection using ICG. The high rate of paraaortic SLNs in this study was probably due to secondary drainage from the pelvic LNs as ICG rapidly drains through the lymphatic channels. This is concordant with the extremely low detection of isolated paraaortic SLNs of less than 1% [29], which is inferior to the exclusive paraaortic drainage with the TUMIR approach (7.4%). This low percentage is not surprising, since it has been already pointed out that cervical injection does not adequately represent endometrial drainage, because it misses the lymphatic drainage to the paraaortic area [30]. The uterine corpus has 2 simultaneous lymphatic pathways: the first drainage is through the lymphatic channels together with the uterine vessels to the pelvic LNs -located in the lateral part of the parametrium and/or under the external iliac vein-, and the second drainage goes directly to the paraaortic area

through the lymphatic vessels of the gonadal vasculature and the infundibulopelvic ligament [31], explaining the possibility of having SLNs in both areas independently. However, when exclusive paraortic SLN drainage is obtained, it cannot be determined whether it is due to direct drainage to the paraortic area or a second echelon after pelvic LNs. Thus, bilateral pelvic lymphadenectomy would be required in these cases to avoid undetected pelvic LN metastases. Recently, it has been suggested that paraortic lymphadenectomy should be considered only in patients in whom paraortic SLN mapping does not occur [2,30]. The TUMIR approach would allow avoiding systematic paraortic LN dissection and its associated morbidity in almost half of patients with SLN mapping. With this high rate of paraortic SLNs obtained with TUMIR, SPECT/CT plays an important role in identifying a higher number of lymphatic areas and paraortic SLNs, which enables planning of the surgical approach and guiding the surgical team during intraoperative SLN detection.

In the present series, the TUMIR approach showed a low bilateral SLN detection rate (32%) compared to the abovementioned studies using the cervical injection approach (58%–95%) [3,4,6,8,9,18-25]. Bilateral detection obtained with myometrial injection techniques is usually lower than with cervical injection [11,26]. Since the uterus is a central organ, bilateral drainage is expected. Therefore, side-specific lymphadenectomy should be performed in case of unilateral SLN detection [32]. Hypothetically, combining the TUMIR method with cervical injection would increase the bilateral pelvic detection rate through the parametrium.

Other techniques have also been described for SLN detection in EC in an attempt to better reflect endometrial drainage. One of these techniques is intraoperative subserosal-intramyo-metrial injection. This technique is easy to perform but compared with cervical or other myometrial injection approaches, subserosal injection has shown a lower sensitivity [33] and overall detection rate [26,27]. Moreover, the detection rate of paraortic SLNs is about 30%, being significantly lower than the rate reported in the present series [11,34]. Moreover, subserosal injection needs to be performed during surgery by an open approach [26,27,33], which increases surgical morbidity and precludes preoperative surgical planning. Preoperative hysteroscopic injection has also been described as an alternative to increase the detection rate of paraortic SLNs. The detection rate of this technique ranges from 50% to 95% [11,35]. A recent study has reported a paraortic SLN detection rate by hysteroscopic injection with radiotracer or ICG similar to the present series [30]. However, a randomized trial comparing cervical and hysteroscopic injections showed better identification of pelvic SLNs after cervical injection with a non-significant higher detection rate of paraortic SLNs after hysteroscopic injection [36]. Moreover, this last approach is complex and less reproducible compared with the TUMIR method. Hysteroscopic radiotracer injection is performed without local and/or general anesthesia, which may be uncomfortable for the patient [30]. Although the TUMIR method showed a median moderate score in the pain scale with the application of local anesthesia, it is also performed with the patient awake and this discomfort is not negligible. Dual injection techniques combining cervical injection with transcervical fundal or cornual injections have also been proposed to increase paraortic SLN detection in EC patients. Dual approaches have shown paraortic SLN detection rates of 60%–86%, together with a pelvic detection rate of 60%–94% [37,38]. However, none of these techniques (hysteroscopic, transcervical fundal or cornual injections) have been evaluated and validated exclusively in the subset of patients with intermediate and high-risk EC.

In keeping with previous reports [3,4,8,18,21,23], the rate of LN involvement in the present series was 19.6%. This relatively low percentage of LN involvement highlights that

performing systematic pelvic and paraaortic LN dissection, as currently recommended [1], implies overtreatment in up to 80% of these women at higher risk of LN involvement. Moreover, a recent study has suggested that adding lymphadenectomy to SLN mapping has no survival benefit as it does not reduce the risk of relapse [30].

The overall sensitivity and NPV for the detection of LN metastases in women with intermediate and high-risk EC were 87.5% and 97.0%, respectively. However, after applying the MSKCC SLN mapping algorithm, the sensitivity in our series increased to 93.8%. This is in line with most previous studies using cervical or subserosal injection in women with intermediate and/or high-risk EC, which have reported sensitivities ranging from 85% to 100% [3,4,6,18,19,22-27]. However, other studies have reported lower sensitivities of less than 80% after cervical injection in high-risk women [6,8,20,21]. The NPV of the MSKCC SLN mapping algorithm of the present series was 98.5%, which is similar to the values reported in most previous studies [3,4,6,18,22-24,26,27] (**Table 2**).

It has been shown that patients with paraaortic LN metastases have an impaired outcome compared to patients with LN metastases limited to the pelvic area, thereby making assessment of paraaortic LN status essential [2]. The TUMIR approach would allow obtaining reliable information of paraaortic LN status with a high sensitivity and NPV of 83.3% and 96.9%, respectively. Although paraaortic SLNs only identify a few isolated paraaortic metastases, the TUMIR technique provides reliable information of paraaortic status in a significantly higher proportion of patients than cervical injection, which is crucial to assess clinical outcomes and to address the need for the addition of extended-field radiotherapy in cases of paraaortic involvement.

In line with previous series, in the current report, ultrastaging of the SLN increased the sensitivity of the technique (37.5% to detect overall LN and 16.6% to detect paraaortic LN involvement) [8,39]. Some studies have reported that patients with low-volume metastases (both micrometastasis and ITC) have a higher risk of recurrence compared with LN negative patients [40]. Thus, ultrastaging should be mandatory in SLNs, as the detection of low-volume metastases might provide important prognostic value.

The main strengths of the present study are its prospective design and the homogeneous management of the patients included. All the women underwent a complete pelvic and paraaortic LN dissection up to the renal vessels, which was not systematically performed in most of the previous studies evaluating the validity of SLN mapping in high-risk EC [4,19,21]. However, the present series also has some limitations. The first is the relatively low number of patients included during the study period. This is due to the strict inclusion criteria that were considered for this series. Another weakness of our study is its unicentric design, which does not allow evaluating the reproducibility of the procedure in other settings. However, the unicentric design ensures homogeneous patient management and processing of the LNs, thereby increasing the internal validity of the study. Moreover, we used a single injection of radiotracer which may produce lower detection rates than combined injection but allows evaluation of the performance of the radiotracer alone.

In conclusion, the present study shows that the TUMIR approach has an adequate SLN detection rate with a high rate of SLNs in the paraaortic area (45%), providing reliable information of endometrial lymphatic drainage. Moreover, the TUMIR approach shows a high sensitivity and NPV in pelvic and paraaortic areas. Combining the TUMIR approach with

cervical injection of tracer would hypothetically allow increasing bilateral pelvic drainage and could be considered in future studies. In addition, the use of ICG alone, combined injection of tracers, or hybrid tracers containing both the radiotracer and ICG should be evaluated in order to increase the overall detection rate. Theoretically, the TUMIR approach by open surgery might provide similar results; however, its performance should be evaluated before any conclusions can be drawn. Prospective multicenter studies including a larger number of women are needed to assess the reproducibility and optimization of this novel approach.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Performance analysis of overall SLNs with H&E alone

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Supplementary Table 2

Performance analysis of overall SLNs with H&E and ultrastaging

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Supplementary Table 3

Performance analysis of the MSKCC SLN mapping algorithm with H&E and ultrastaging

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Supplementary Table 4

Performance analysis of paraaortic SLNs with H&E alone

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Supplementary Table 5

Performance analysis of paraaortic SLNs with H&E and ultrastaging

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Supplementary Fig. 1

Preoperative lymphoscintigraphy. Early planar image (A) shows bilateral pelvic nodes, while in late planar lymphoscintigraphy (B), paraaortic drainage is also visualized (arrows). Single photon emission computed tomography/computed tomography images (C) allow better identification and localization of sentinel lymph nodes in the external iliac chains, precaval and supramesenteric areas (C) (white arrows).

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Supplementary Fig. 2

Flow chart of patients with LN involvement. Results of SLNs are shown in blue and results related to LN involvement (including data of the SLN and the systematic lymphadenectomy) are shown in red.

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