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ORIGINAL ARTICLE

Sentinel-node mapping in endometrial cancer patients: comparing SPECT/CT, gamma-probe and dye

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Abstract
Objective The aim of this study was to compare preoperative SPECT/CT with gamma-probe and methylene blue-dye (MBD) in the identification of sentinel lymph node (SLN) in early stage endometrial cancer.
Methods 40 stage-I EC patients (66.7 ± 9.7 years) underwent preoperative lymphoscintigraphy. After about 3 h from Tc-99m-albumin nanocolloid cervical injection, all patients underwent SPECT/CT study. MBD was injected into the cervix just before surgery under general anesthesia. All patients underwent SLN biopsy, hysterectomy, bilateral salpingo-oophorectomy, and radical regional lymphadenectomy. SPECT/CT findings were compared to those of gamma-probe and MBD techniques.
Results In 2 patients no nodal migration was observed, neither with MBD nor radiotracer. Detection rate of at least one SLN was 90% (36/40 patients) with SPECT/CT, 88% (35/40) intra-operatively with gamma-probe and 80% (32/40) with MBD. Only in 7/40 patients a bilateral migration was obtained with all considered modalities. In particular, bilateral detection was achieved in 26 patients with SPECT/CT, in 24 with gamma-probe and in 10 patients with MBD. The concordance site between SPECT/CT and intraoperative gamma-probe was 73% (29/40 patients: 2 without migration, 21 bilateral and 6 monolateral SLNs); while concordance site with MBD was found in 40% (16/40: 8 bilateral, 6 monolateral SLNs, 2 without SLNs). Overall, 628 LNs were dissected (mean 18 LNs per patient). The median number of SLNs removed was 2 (mean 2.5 per patient). Out of 91 SLNs: 43 were "hot and blue (HB)", 10 were blue only and 38 were hot only. LN metastases rate was 16%: 9/90 SLNs (7 HB, 2 hot only) were positive for metastases in 6 patients. Four non-SLNs were found positive in 3 patients, and all presented concomitant positive SLNs. False negative rate was 0%.
Conclusions SPECT/CT had the highest detection rate and achieved the highest rate of bilateral mapping, compared to gamma-probe and MDB. SPECT/CT had moderate concordance with gamma-probe, and it can help the intraoperative detection of SLNs providing important information about their anatomic location.

Keywords Sentinel lymph node · SPECT/CT · Endometrial cancer

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Introduction

Endometrial cancer (EC) is the most common gynecological cancer in western countries [1]. Lymph node (LN) status remains one of the main prognostic factors; however, two randomized trials and meta-analysis concluded that pelvic lymphadenectomy had no impact on survival for patients with early stage EC, mainly corresponding to low and intermediate European Society of Medical Oncology (ESMO) risk groups [2–5]. Thus, to minimize the treatment related morbidity, and maintain the benefit of surgical staging, the sentinel lymph node (SLN) concept has received increasing interest in EC. The low accuracy of imaging techniques such as magnetic resonance imaging and positron emission tomography (PET)-2-fluoro-D-deoxy-glucose for prediction of nodal status reinforces the potential relevance of SLN in endometrial cancer [6].

According to the National Comprehensive Cancer Network and ESMO guidelines 2016 [7, 8], SLNL can be considered (category 3) for the surgical staging of apparent uterine-confined malignancy when there are no metastases demonstrated by imaging studies or no obvious extra-uterine disease at exploration. A cervical injection with dye has emerged as a useful validated technique for the identification of LNs [9, 10]. The traditional techniques of SLN mapping are visible blue dyes (such as isosulfan or methylene blue-MBD) and radiolabeled tracers (such as Tc 99m albumin Nanocolloid) [11], that allows preoperative imaging with planar scintigraphy and SPECT/CT [12]. Recently, the use of near infrared imaging to detect fluorescing dye, such as indocyanine green (ICG), is a feasible alternative to the traditional methods of SLN mapping in endometrial cancer [13, 14]. Low-volume nodal metastases at SLN detected only by enhanced pathological ultrastaging and the less invasive surgery technique than lymphadenectomy are other important approaches to staging with SLN, although the best technique for nodal mapping has not been defined yet.

The aim of this study was to compare preoperative SPECT/CT with gamma-probe and methylene blue-dye (MBD) for the identification of SLN in early stage EC patients. In particular the concordance of these techniques was evaluated.

Materials and methods

Patient population

Patients with apparent early stage endometrial cancer were considered in this prospective study. Inclusion criteria were: (a) biopsy proven endometrial cancer with apparent clinical stage I; (b) magnetic resonance imaging or transvaginal ultrasound performed to evaluate the myometrial invasion and abdominal/pelvic staging, (c) signed informed consent, (d) performance of SLN technique using both methods, lymphoscintigraphy with 99mTc-Nanocolloid and MBD, followed by surgery.

Sentinel LN mapping with lympho-scintigraphy

In the nuclear medicine department, preoperative lymphoscintigraphy was performed (within 20 h before surgery) with 4 submucosal cervical injections (3, 6, 9, and 12 o'clock positions) of 12 MBq of radiolabeled filtered 99mTc albumin nanocolloid in 0.2–0.3 ml volume.

After 3 h, SPECT/CT scan was performed with a hybrid system (Infinia Hawkeye 4,GE Medical Systems), according to the protocol described in a previous study [15]. Images were analyzed on a Xeleris Workstation (GE Healthcare Medical Systems, Waukesha, WI, USA). Nodal migration was described as a focal uptake of radiotracer, and CT was used to define the site. In particular, pelvic nodal chains (common iliac, external iliac and obturator nodes) and abdominal sites (precaval and paracaval, superficial and deep intercavoaortic and para-aortic nodes) were considered.

Sentinel LN mapping with blue dye

Under general anesthesia and just before surgery, all patients were injected with methylene blue dye (methylene blue 1%, Bioindustria L.I.M, Novi Ligure, Italy). A total of 2 mL of blue dye (1 mL per injection) was injected into the cervix through a 20-gauge spinal needle at 3 and 9 o'clock positions.

Intraoperative surgical sentinel node mapping

SLN detection was the first surgical step with either open or laparoscopic approach. First, the pelvic and the aortic regions were carefully explored using a gamma-probe (C-Trak Galaxy CW4000 System, Southern Scientific, Ltd, UK). For laparoscopic procedures, the 10-mm OmniProbe EL 90-degree detection system was inserted through a 12-mm accessory trocar. Afterwards, the peritoneum was opened, and paravesical and pararectal spaces were delivered.

SLNs were then identified as radioactive and/or blue nodes and removed individually. We used the Reiffenstuhl LN nomenclature for the anatomic location of the SLNs [16]. In addition, any suspicious nodes were removed regardless of mapping. Patients underwent an extrafascial hysterectomy and bilateral salpingo-oophorectomy with pelvic lymphadenectomy. Para-aortic lymphadenectomy was recommended in case of pathological pelvic nodal uptake at preoperative PET/CT or in case of suspicious enlarged nodes at surgery.

Pathological evaluation

All LNs were handled in a standardized manner. LNs with macroscopic metastases were sectioned, and SLNs that appeared normal were cut perpendicular to the long axis. From each paraffin block lacking metastatic carcinoma detectable in a routine section stained with hematoxylin and eosin (H&E), 2 adjacent 5-km sections were cut at each of 2 levels 50-km apart. At each level, one slide was stained with H&E and the other with immunohistochemistry using the AE1/AE3 anticytokeratin antibody (DAKO Company, Glostrup, Denmark), as well as one negative control slide for a total of 5 slides per block. All other non-SLNs were examined only by routine H&E. The size of LN metastases was estimated with an eyepiece micrometer. The term micrometastasis was defined as a metastatic deposit within the LNs ranging from 0.2 mm to no more than 2 mm in size. Isolated tumor cells were defined as single tumor cells or a cluster of malignant epithelial cells less than 0.2 mm. SLNs were considered positive if they contained macrometastasis, micrometastasis, or ITC (isolated tumor cells).

Data analysis

Absolute and percentage frequencies were used to describe categorical items of patients' population while mean values, standard deviation and range were used for continuous characteristics.

The concordance between the 3 techniques: SPECT/CT, intra-operatively gamma-probe and methylene blue dye was determined by evaluating the detection rate of SLN and the sites of nodal migration. Nodal mapping was classified as "not obtained", "bilateral" and "monolateral".

Sum rank test and Fisher's exact test were used to analyze the differences amongst the methods. A level of $p < 0.05$ was adopted for significance. In addition, Cohen's kappa index was used to determine the power of concordance between the 3 techniques, using Landis and Koch interpretation. Stata software 9.0 (Stata Corporation, College Station, Texas, USA) was used for performing the statistical analysis.

False negative SLNs (SLN negative with non-SLNs positive for metastases) were also considered.

Results

From July 2010 to July 2014, 40 patients with apparent stage I endometrial cancer met the inclusion criteria, and their clinical/histo-pathological features are summarized in Table 1.

Table 1 Clinical and histo-pathological features of patients population

Age	66.7 ± 9.7 years (range 48–90)
Pathological stage	
IA	16 pts (40%)
IB	10 (25%)
II	5 (12.5%)
IIIA	1 (2.5%)
IIIB	2 (5%)
IIIC	6 (15%)
Histology	
Endometrioid adenocarcinoma	38 pts (95%)
Squamous carcinoma	1 (2.5%)
Sarcoma	1 (2.5%)
Grade	
G1	9 pts (22%)
G2	19 (48%)
G3	12 (30%)

Detection rate

In 2/40 patients no nodal migration was observed, neither with MBD nor radiotracer. The detection rate of at least one SLN was 90% (36/40 patients) with SPECT/CT, 88% (35/40) intra-operatively with gamma-probe and 80% (32/40) with MBD. In particular, bilateral detection was achieved in 26 patients with SPECT/CT, in 24 with gamma-probe and in 10 patients with MBD. A SPECT/CT scan is shown in Fig. 1.

Agreement

Comparing SPECT/CT and intra-operatively gamma-probe SLN mapping, no statistical differences were observed in nodal mapping (classified as "no migration", "monolateral" and "bilateral"). In particular concordance was obtained in 29/40 patients (73%), Cohen's $K = 0.48$, (moderate agreement). Conversely a statistical significance was obtained comparing SLN mapping of SPECT/CT vs. MBD ($p = 0.001$) with 40% agreement ($K = 0.11$, poor agreement), and comparing gamma-probe vs. MBD ($p = 0.005$) with 45% of agreement ($K = 0.18$, poor agreement). Results were shown in Table 2.

LNs analysis

Overall, 628 LNs were dissected (mean 18 LNs per patient). The median number of SLNs removed was 2 (mean 2.5 per patient). Out of 91 SLNs: 43 (47%) were "hot and blue (HB)", 10 (11%) were blue only and 38 (42%) were hot only.

The sites of migration were shown in Table 3. LN metastasis rate was 16%: 9/90 SLNs (7 HB, 2 hot only) were positive for metastases in 6 patients. In particular, 4 patients had nodal macrometastases (metastatic deposits ranging from 2380 to 7 mm) while in the remaining 2 patients micrometastases were found (ranging from 0.598 to 1.228 mm).

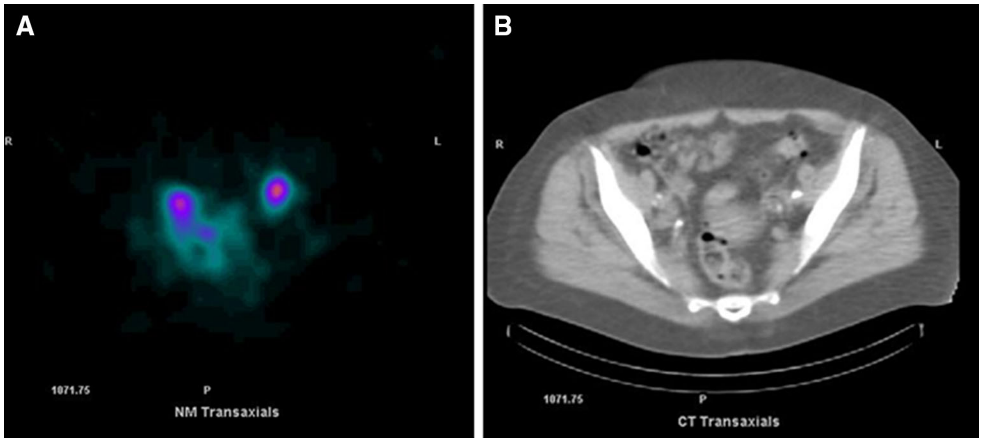

Fig. 1 Transaxial SPECT (**a**) and CT (**b**) images of a bilateral nodal migration; gamma-probe detected SLNs at both external-iliac sites, while no dye migration was found

Table 2 Nodal migration and comparison of SPECT/CT, gamma-probe and MBD

	SPECT/CT				MBD			
	NO	Mono	Bil	Tot	NO	Mono	Bil	Tot
γ-probe								
NO	2	3	0	5	3	1	1	5
Mono	0	6	5	11	3	7	1	11
Bil	2	1	21	24	2	14	8	24
Tot	4	10	26	40	8	22	10	40
MBD								
NO	2	2	4	8	Comparison		Fisher	*K*
Mono	2	6	14	22	SPECT vs γ-probe		0.89	0.48
Bil	0	2	8	10	SPECT vs MBD		0.001	0.11
Tot	4	10	26	40	γ-probe vs MBD		0.005	0.18

Cohen's kappa index was used to determine the power of concordance between the 3 techniques, using Landis and Koch interpretation ($k < 0.2$ = poor agreement, 0.21–0.4 = fair, 0.41–0.6 = moderate, 0.61–0.8 = good, 0.81–1 = very good)

NO no migration, *Mono* monolateral migration (SN in one hemi-pelvis), *Bil* bilateral migration

Table 3 Sites of nodal migration

Site	TOTAL (91 SLNs) (%)	HOT (81 SLNs) (%)	BLUE (53 SLNs) (%)
External iliac			
Right	30	27	29
Left	45	45	49
Internal iliac			
Right	5	6	6
Left	1	1	0
Common iliac			
Right	4	4	2
Left	5	6	4
Obturator fossa			
Right	4	4	6
Left	3	4	2
Paraortic	1	1	2
Paracaval	2	2	0

Four non-SLNs were found positive in 3 patients, and all patients presented concomitant positive SLNs. False negative rate (SLN negative with non-SLNs positive for metastases) was 0%.

Discussion

Lymph node involvement remains one of the most important prognostic factors for women with EC and the diagnosis of nodal invasion can modify management with the introduction of adjuvant therapy. In this setting, SLN mapping has the advantage of providing surgical staging and decreasing surgical complications by limiting the extent of lymphadenectomy (without increasing the number of complications that can result from complete lymphadenectomy). This is an important key point as the majority of patients with EC are at high surgical risk due to obesity and associated comorbidities. In addition, the use of an SLN algorithm with pathologic ultra staging using extensive immunochemistry has led to increased detection of low-volume LN metastasis (ITCs and MMs) [9, 10]. However, the clinical significance of these findings in endometrial cancer is still under investigation [17, 18]. Finally, SLNs can be localized in less-common regions, which are not universally approached during systematic lymphadenectomy.

The traditional methods of SLN mapping are visible dyes (such as MBD) and radiolabeled tracers (such as Tc 99 m nanocolloid).

Three techniques of SLN have been described: pericervical injection, hysteroscopic peritumoral injection, and fundal peritumoral injection. The cervical injection of tracer is adequate for EC, as the main lymphatic drainage to the uterus is from the parametria; a well-known lymphatic pathway is composed of a complex network of bilaterally independent lymphatic channels, draining the uterine cervix and corpus primarily from the lateral parametrial regions [10]. A meta-analysis (26 studies) did not detect a significant difference between the various detection methods [19]. Cervical injection has these advantages: the cervix is easily accessible, rarely distorted by anatomic variations (such as myomas), and rarely scarred from prior procedures, such as conization or bulky tumor infiltration in endometrial cancer patients [10].

Radiotracer technique allows preoperative imaging with planar scintigraphy and SPECT/CT. The addition of a SPECT/CT study has been demonstrated to increase the number of detected SLNs [15, 20]. In our experience, the main advantage of SPECT/CT scan resides in providing anatomical information about the SLN location and its relation to other abdominal structures [15]. This is especially important in endometrial cancer because of complex lymphatic drainage from the uterine corpus and because SLNs might be found over an extensive area, from the obturator fossa to para-aortic region [20, 21]. Thus, the surgeons can be better guided to the mapped regions, which is very helpful, in particular, during the learning curve. However, studies demonstrated a low correlation between imaging done the day before surgery and the intra-operative findings [22, 23]. In our series, a moderate agreement was found between SPECT/CT findings and gamma-probe, with 29/40 concordant cases in terms of migration and bilateral/monolateral migration, in particular: 21 cases with bilateral migration detected by both techniques, 6 cases with monolateral migration and 2 cases without migration.

The clinical significance of the comparison between SPECT/CT and gamma-probe resides in the contribution of these techniques to achieve the best accuracy in identification and removal of SLNs. Adding SPECT/CT to conventional lymphatic mapping gives the surgeon and nuclear medicine physician much more accurate anatomical information, which can facilitate the process of intraoperative SLN resection [24]. However, accuracy is also required with the use of laparotomic or laparoscopic gamma-probe to attain higher sensitivity in the intraoperative SLN detection. Divergence between SPECT/CT and gamma-probe has been reported: SPECT/CT detected 75.5–96.2% of SLNs found during surgery [22]. It is crucial that scanning of the pelvis and para-aortic region with an intraoperative gamma-probe be performed, regardless of the SPECT-CT results.

The correlation was worse comparing gamma-probe with blue dye (concordant cases 18/40 cases) [25]. Of 22 discordant cases: 5 cases without MBD migration had SLNs detected by isotopic technique, 2 cases without radiotracer migration had MBD SLNs detection, 14 had monolateral MBD and bilateral radiotracer migration, 1 had bilateral MBD and monolateral tracer migration.

Radiotracer techniques had a higher detection rate than blue dye (90% for SPECT, 88% for gamma-probe vs 80% for blue dye) and a higher rate of bilateral migration (65% for SPECT, 60% for gamma-probe vs. 25% for blue dye), with these results consistent with previously published data [26, 27].

Difficulties reported in identifying SLN with BD are due to the dissemination of dye into parametria [28], bleeding covering the retroperitoneal fat and staining of the operative field [14].

Recently, near infrared (NIR) fluorescent imaging with ICG has been widely investigated and has emerged as a promising alternative technique for real-time intraoperative SLN mapping in gynecologic cancer [14, 29–31].

This method is expensive because, it requires the use of specialized equipment. As ICG contains sodium iodine, iodine allergy constitutes the main contraindication. However, reports on its use in cervical and endometrial cancer suggest very high SLN detection rates. Buda et al. found a DR of 100% if compared to radiotracer technique

Table 4 Summary of the main advantages and disadvantages of techniques for sentinel node mapping

Technique	Advantages	Disadvantages
Blue-dyes	Low cost: easiness, lack of need for specialist equipment	Need to open the retroperitoneal space to visualize lymph nodes and the requirement for a degree of subjectivity with visual assessment [34]; stain of the operative field [14] Allergic reaction (1–1.6%) including anaphylaxis and hypotension [35]
Radio-isotopic	Preoperative detection of SLNs with SPECT/CT scan Detection of “uncommon” site of nodal migration Allergic reactions very rare (estimated rate of 1–10/100.000) [36]	High cost: need of Nuclear Medicine Department Radiation exposure Discomfort for patients
Fluorescent-dye	Combination of the advantages of both colorimetric technique (visibility) and radio-isotopic techniques (penetration of signal through intact tissue) [35]	High cost: need of instrumentation Contraindication in case of iodine allergy (estimated risk of anaphylactic reaction 1/42.000) [37]

(97% with blue dye) and blue dye only (89%), with the highest rate of bilateral migration (85%) [14].

Another technique that would help identify SLNs consists of a hybrid fluorescent-radioactive tracer such as ICG-99mTc-nanocolloid. How et al. in 100 endometrial cancer patients, using a mixture of 99mTc-Sulfur colloid, BD and ICG, found that ICG had a significantly higher SLN detection rate and bilateral detection than BD, but similar SLN detection rates compared to technetium-99 in both overall (87 vs 88%, respectively; $p = 0.83$) and bilateral (65 vs 71%, respectively; $p = 0.36$) detection [32]. 99mTc-tracer provided a helpful tool for surgeons during the development of their SLN mapping technique while BD was not essential for SLN detection if ICG is performed [32]. In addition, the use of radiotracer can aid SLN detection by acting as a confirmation that the targeted tissue is the SLN, in addition to primarily detecting the SLN when direct visualization with other methods fails. In particular 99mTc-SC was the only method that detected all 13 SLNs containing metastatic disease (ICG detected 77% and blue dye 53%) [32]. Similarly, in our series, all pathologic SLNs were hot (7 hot and blue and 2 hot only).

Radiotracer and dye techniques can be complementary, and our study confirmed this synergy. Even though the majority of SLNs could be detected by isotopic technique, 11% of SLNs have been detected only thanks to MBD. Thus, considering that dye technique is less costly and is performed intra-operatively (without additional discomfort for patients), it can be performed together with isotopic method with important diagnostic advantages for nodal status assessment. Indeed, in our population (median follow-up 28.3 months), of the 4 patients with a relapse of disease 3 of them had positive SLNs.

According to a recently published meta-analysis about SLN mapping in cervical and endometrial cancer [33], the pooled analysis data showed a significant increase in overall detection rate for ICG respect to BD; while ICG seemed to be equivalent both to 99Tc alone and to the combination of BD + 99TC, in terms of overall and bilateral detection rates. Thus, its safety profile and ease of use may favor the employment of ICG with respect to conventional tracers [33], although this technology is still not available for most patients and surgeons around the world. Table 4 summarized the main advantages and disadvantages for each technique [34–37].

In conclusion, the detection rate of at least one SLN was 90% with SPECT/CT, 88% intra-operatively with gamma-probe and 80% with MBD. SPECT/CT achieved the highest rate of bilateral mapping (65%), providing important information about the anatomic location of SLNs that can help the intra-operative detection. Considering the promising results of new dyes such as ICG, comparative studies in the same population are needed to define the best approach for SLN mapping in endometrial cancer patients that might be possible with complementary techniques.

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