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Original

Lymphatic mapping and sentinel node biopsy in endometrial cancer — a feasibility study using cervical injection of radiotracer and blue dye

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Abstract

BACKGROUND: The aim of this study was to evaluate the feasibility and accuracy of sentinel lymph node (SLN) detection using preoperative lymphoscintigraphy and intra-operative gamma probe/blue dye for endometrial cancer patients.
MATERIAL AND METHODS: Twenty four consecutive patients with endometrial cancer were recruited. All patients underwent lymphatic mapping and sentinel node biopsy using combined intracervical radiotracer and blue dye injections. Pelvic lymph node dissection was performed for all patients. Para-aortic lymphadenectomy was done in high risk patients. All SLNs were examined by frozen section and Hematoxylin and Eosin (H&E) permanent sections.
RESULTS: Pre-operative lymphoscintigraphy showed at least one SLN in 21/24 patients. Intra-operatively, at least one SLN could be harvested by gamma probe and/or blue dye methods. A total of 95 SLNs were detected. Four SLNs were detected only by blue dye, 42 only by radiotracer, and 49 were hot/blue. Median number of SLN per patient was 3. Three patients had positive pelvic lymph nodes. All of them had positive SLN (no false negative case). Frozen section could identify SLN involvement in two of three patients with positive pathology.
CONCLUSION: Lymphatic mapping and sentinel node biopsy is feasible and accurate in endometrial cancer patients using combined radiotracer and blue dye methods. Frozen section accuracy was lower and underscores the importance of expert pathologists for SLN mapping technique.

KEY words: sentinel node, endometrial cancer, blue dye, cervical injection, radiotracer, endometrium, uterine

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Background

Gynecological cancers are important female life-threatening malignancies among which endometrial cancer is the most common in most areas of the world [1]. The primary surgical procedure for endometrial cancer patients include total hysterectomy with bilateral salpingo-oophorectomy [2]. A controversial issue in the management of the endometrial cancer is whether or not to perform systematic pelvic lymphadenectomy and paraaortic lymphadenectomy because of the inability to predict those patients who would benefit from lymph node dissection [3–5].

Complete pelvic and paraaortic lymphadenectomy may cause severe surgical complications which can considerably affect the quality of life of the patients [6]. In order to avoid lymphadenectomy, the sentinel lymph node (SLN) concept has been applied to the treatment of several solid tumors [7–9]. This concept has also been used in endometrial cancer patients since 1996 and many groups reported their experience on this technique thus far [10, 11].

The aim of this study was to evaluate the feasibility and accuracy of sentinel lymph node detection using preoperative lymphoscintigraphy and intra operative gamma probe/blue dye for endometrial cancer patients.

Material and methods

From October 2010 to December 2012, consecutive patients who had a histologically verified endometrial cancer and early stage on pre-operative evaluation underwent lymphatic mapping and were enrolled into the study. The study was approved by the ethics committee of Mashhad University of Medical Sciences under the approval number of 89 706 and all patients were required to sign an informed consent. The procedures followed were in accordance with the Helsinki Declaration.

Preoperative lymphoscintigraphy was obtained following intracervical injection (at 3 and 9 o'clock positions) of 2 mCi radiotracer (Tc-99m-Antimony Sulfide Colloid in 15 patients and Tc-99m-Phytate in 9 patients) in 0.4 mL volume divided to two aliquots. Imaging was done 15 minutes post-radiotracer injection (ANT-POST and Lat views 5 min/view using low energy high resolution collimator and Tc-99m photopeak) with a dual head variable angle gamma camera (E.CAM, Siemens) [12, 13].

The day after radiotracer injection (18–24 hours post injection), the patients underwent surgical operation. In all patients, methylene blue dye was injected directly into the cervix in the operating room. The injection was performed just before incising the skin. Two 2 ml syringes, each containing methylene blue dye (0.5 ml) were used for each patient. Injection sites were the same as the radiotracer.

Detection of SLNs was accomplished through direct visualization of blue colored lymphatics and nodes, and/or by detection of radioactivity, using a handheld gamma probe (EUROPROBE, France). All hot and/or blue nodes were harvested and sent for intra-operative frozen section evaluation. The surgeon then proceeded to do a complete pelvic lymphadenectomy in all cases regardless of the SLNs frozen section results. Para-aortic lymphadenectomy was done only in selected cases (clear cell, serous or adenosquamous types, grade 2 or 3 endometrioid carcinomas). Bilateral lymphadenectomy was followed by total hysterectomy and bilateral salpingo-oophorectomy.

Results

Overall, 24 patients were included in the study. Table 1 shows the characteristics of the included patients. All patients were injected with both radiotracer and blue dye. However, gamma probe was defective during surgery of one patient and only blue dye technique was used for this specific patient.

Table 1. Characteristics of the study population

Age (years)	56 (33–86)
BMI [kg/m^2]	32 (25–35)
Histology	
Endometrioid	20
Papillary serous	3
Clear cell	1
Grade	
I	9
II	7
III	4
Stage	
I	14
II	4
III	5
IV	1
Lymphovascular invasion	
Present	9
Absent	15
Myometrial invasion	
< 1/2	10
> 1/2	14
Lymph node surgery	
Pelvic lymph node dissection	10
Pelvic and para-aortic lymph node dissection	14

Preoperative lymphoscintigraphy visualized SLN in 21/24 patients (Figure 1). Intraoperative localization of the SLN was possible in all 24 patients (100% surgical detection rate). A total of 95 SLNs were identified (median SLNs per patient of 3). SLNs were detected bilaterally in 16 and unilaterally in 8 patients. The anatomic distribution of the SLNs is shown in Table 2. No para-aortic SLN was detected intra-operatively. Four SLNs were detected only by blue dye, 42 only by radiotracer, and 49 were hot/blue.

Pelvic lymph nodes were pathologically involved in 3 patients. SLNs of these three patients were also positive on pathological examination (2 were positive by frozen section and 1 by H&E examination). The false negative rate for H&E was 0% and for frozen section examination was 33%. Two of these patients had pathologically involved non-SLN too.

Discussion

Our results revealed a 100% detection rate, suggesting that SLN detection is feasible using intra-operative and preoperative cervical injections for endometrial cancer. Furthermore, SLN detection was not related to histological type or grade of endometrial carcinoma. Preoperative lymphoscintigraphy with cervical injection of radiotracer visualized SLN in 21/24 patients. More importantly, intraoperative localization of the SLN was possible in all patients even those with lymphoscintigraphy detection failure. In another study, Abu-Rustum et al. reported that preoperative lymphoscintigraphy visualized SLN in 30

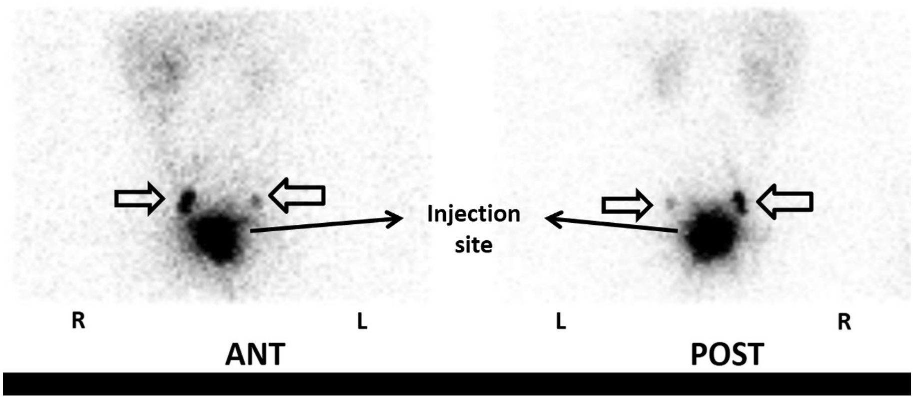

Figure 1. Anterior-Posterior lymphoscintigraphy images of a patient after cervical injection of the radiotracer. The sentinel nodes are shown in open arrows. At surgery two hot/blue external iliac nodes on the right side and one hot internal iliac node on the left side were detected

Table 2. Anatomical distribution of the SLNs

Anatomic sites of SLN	Number of SLNs
External iliac	
Right	12
Left	7
Internal iliac	
Right	16
Left	13
Obturator	
Right	26
Left	15
Common iliac	
Right	5
Left	1

out of 42 endometrial cancer patients. Intraoperative localization of the SLN was successful in 36 patients [14]. Niikura et al. also reported the same findings as lymphoscintigraphic SLN detection was 68% despite 82% detection rate at surgery [15]. The above-mentioned findings can be due to proximity of injection site to the lymphatic basin which can mask the sentinel nodes on lymphoscintigraphy images [16, 17]. This problem can be overcome by SPECT/CT to some extent [18–20]. By improving the localization ability of the nuclear medicine imaging, SPECT/CT can contribute a lot to the sentinel node mapping of gynecological cancers. Lymphatic flow to the unusual anatomical sites can be also detected by SPECT/CT. It seems that SPECT/CT is becoming an integral part of sentinel node mapping in surgical oncology.

The mapping method was highly related to SLN detection rate in our study, as the majority of harvested SLNs were detected by radiotracer and contribution of blue dye was minimal. The blue only SLNs were found during surgery of a patient without gamma probe at hand. Several other reports also supported our findings as detection rate using radiotracer or combined radiotracer and blue dye was higher than blue dye alone [21–24]. Considering the potential risks of blue dye injections (such as life threatening anaphylaxis reactions), radiotracer alone may be sufficient for SLN mapping in endometrial cancer [25].

An important issue in the SLN mapping of endometrial cancer is the injection site of the mapping material. We used cervical injection technique which is much easier than the fundal or sub-endometrial injections. High detection rate and sensitivity of our study was in accordance to other studies used cervical injection [19, 26]. Cervical injection is associated with extremely low para-aortic lymphatic drainage and some groups argue against this technique due to this fact. For example Solima et al. reported that 56% of their patients had para-aortic SLNs using sub-endometrial injection of the radiotracer [27]. However, frequency of isolated para-aortic without pelvic lymph node involvement in endometrial cancer patients is reported to be low. This was only 2% in Abu-Rustam et al. study [28]. We didn't have any para-aortic node involvement in the patients underwent para-aortic lymph node dissection.

False negative rate is the most important outcome measure in all SLN mapping studies. Two recent systematic reviews evaluated the sentinel node concept in endometrial cancer and showed sensitivity about 90% or more [23, 29]. We didn't have any false negative results in our study either, as all 3 patients with involved pelvic nodes had positive SLNs too. However, the frozen section accuracy was lower with 1 (33%) false negative results. This false negative case occurred in the beginning of our study and can be attributed to the learning curve effect. This finding underscores the importance of expert pathologist in the evaluation of SLNs. The discrepancies between frozen section and permanent H&E evaluation are not unknown in the literature [30], and can reach as high as 27% [27]. In the most recent study, Ballester et al. reported 56.3% sensitivity for intra-operative diagnostic methods [31]. For introduction of SLN mapping to any gynecological oncology center, this finding should be taken into account [32, 33].

Another important issue in the sentinel node mapping of midline tumors is the side of sentinel node identification [34, 35]. As midline tumors, lymphatic flow of the endometrial cancer should be bilateral in the pelvic area, however not all patients have bilateral lymphatic drainage during surgery. For example in our study, bilateral drainage could be detected in 16 out of 24 patients.

Bilateral drainage in midline tumors (including endometrial cancer) is very important. In case of sentinel node detection failure on one side, possibility of pathological lymph node involvement on the detection failure side should be considered. In other words, each patient is considered as two separate units and decision to continue to regional lymphadenectomy should be based on the pathological condition of sentinel nodes of each side separately. This strategy has proven to decrease the false negative rate of sentinel node mapping in midline tumors [36]. Our study had relatively low sample size and the effect of unilateral drainage on the accuracy of sentinel node mapping was not apparent.

Conclusion

Lymphatic mapping and sentinel node biopsy is feasible and accurate in endometrial cancer patients using combined radiotracer and blue dye methods. Frozen section accuracy was lower and underscores the importance of expert pathologists for SLN mapping technique.

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