RESEARCH ARTICLE

Value of Sentinel Lymph Node (SLN) Mapping and Biopsy using Combined Intracervical Radiotracers and Blue Dye Injections for Endometrial Cancer

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Abstract

Background: Lymphadenectomy, as part of the initial surgical staging of patients with endometrial carcinoma, remains a controversial topic in gynecologic oncology. Sentinel lymph node (SLN) mapping has become a well-accepted procedure for melanomas and breast cancer; a number of investigators have begun to explore the utility and accuracy of this technique with regard to endometrial cancer. **Aim:** This study was conducted to evaluate SLN mapping of early stage endometrial cancer with blue dye in conjunction with a radioactive tracer. **Subjects and methods:** In this prospective cross-sectional study, patients with stage I and II endometrial cancer who were candidates for systemic lymph node dissection during surgery were enrolled, some underwent lymph node mapping and SLN biopsy using combined intra cervical radiotracer and blue dye injections and some applying only an intra cervical radiotracer. SLNs and other lymph nodes were sent for pathological assessment. Sensitivity, specificity, the positive predictive value, and the negative predictive value were calculated as predictive values for the radiotracer and blue dye. **Results:** Pre-operative lymph node mapping showed SLN in 29 out of 30 patients. Intra operations in 29/30 patients, SLNs were harvested by gamma probe; in 13 out of 19 patients SLNs were detected by blue dye. The median number of SLNs per patient was 3 and the total number of SLNs detected was 81. Four patients had positive pelvic lymph nodes. All of the positive nodes were SLNs. Using this technique (radiotracer and blue dye) an overall detection rate of 96.7%, an NPV of 100%, a sensitivity of 100% and a specificity of 3.85% were achieved. **Conclusion:** Results of SLN research for endometrial cancer are promising and make feasible the possibility of avoiding unnecessary aggressive surgical procedures in near future by advances in SLN mapping.

Keywords: Sentinel lymph node- radiotracer- blue dye- cervical injection- endometrial cancer

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Introduction

Uterine cancer is the most common gynecologic malignancy in developed countries, and second most common gynecologic cancer in developing countries. At the time of beginning of this study, in the United States it is estimated that 54870 new uterine cancer cases will occur in 2015, with 10,170 deaths resulting from this disease. The incidence of endometrial cancer is increasing because of increased life expectancy and obesity (Koh et al., 2015).

68% of women with endometrial cancer are diagnosed with disease confined to the uterus and 81.7% have 5–year survival rate, thus, a considerable longevity of person after treatment will be achieved. The improvement of patients' life quality is of high importance (Koh et al., 2015; Khoury-Collado et al., 2016).

When disease confine to the uterus, the likelihood of cure with surgery alone is relatively high. In the minority of these cases occult metastatic disease will be found at the time of surgical staging, and this will have a considerable impact on prognosis and survival. The status of the regional lymph nodes is acknowledged as being one of the primary determinants of prognosis, and national guidelines including national comprehensive cancer network (NCCN) recommend their removal at the time of surgery. As this information is used post operatively to tailor adjuvant therapy, some expert advocate full lymphadenectomy on all patients at the time of surgery. Though generally a safe procedure, it is not without risks (Khoury-Collado et al., 2016). This procedure is associated with prolonged operating time, additional cost, deep vein thrombosis, lymphocyst, lymphedema, lymphangitis and rarely nerve and vascular injury. This complications may negatively affect survival and quality of life in many patients for whom the procedure would have been of minimal or no benefit (Allameh et al., 2015).

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Sentinel lymph node (SLN) mapping has become a well-accepted procedure in melanoma and breast cancer. The intention of this procedure is to avoid the morbidity of full-scale lymphadenectomy, while still identifying meaningful metastatic disease. This technique has recently gained acceptance in vulvar cancers as well. More recently, a number of investigators have begun to explore the utility and accuracy of this technique in endometrial cancer (Allameh et al., 2015).

The current study is planned to evaluate the SLN mapping in early stage endometrial cancer with blue dye in conjunction with radiotracer.

Materials and Methods

Subjects and Methods

Study Design

This is a prospective cross-sectional study which conducted in Gyneco-Oncology Department of Imam Hossein hospital affiliated to Shahid Beheshti University of Medical Sciences, Tehran, Iran, between October 2015 and October 2016.

Ethical consideration

The study followed the principles of the declaration of Helsinki and was approved by the Medical Ethics Review Board of Shahid Beheshti University of Medical Sciences. All information about the patients was fully kept confidential, also all information will be released as a group without participants' name. Study participants did not incur any costs and the study protocol did not have any harm to participants. The written informed consent was obtained from volunteers and details and purpose of the study were disclosed.

Subjects

All consecutive Patients with pathologic report of endometrial cancer based on D and C or pippelle who refer to Gyneco-oncology Department was evaluated; patients with clinically suspicious stage I or II endometrial cancer who were candidate for systemic lymph node dissection during surgery after filling consent form and demographic questionnaire enrolled in the study. Patients who were done incomplete surgery previously, are now candidate for surgical staging, and patients at clinically stage III or IV are excluded from this study.

Tracer injection

Deep intra cervical injection at 3 and 9 o'clock positions of 2mCi radiotracer Technetium colloid 99 (Tc99) in 4 ml volume divided to two 2ml syringes. The day before surgery, methylene blue dye was injected directly into the cervix in the operating room before incising the skin. Two 10ml syringes, each containing 4ml blue dye; the injection sites were the same as radiotracer.

Imaging

For all patients, preoperative lymphoscintigraphy was done 1 hour and 17-24 hours post radiotracer injection.

Surgical technique

The surgeon proceeded to do a complete bilateral pelvic lymphadenectomy in all cases and para-aortic lymphadenectomy in selected cases (clear cell, papillary serous, grade 2 or 3 endometrioid adenocarcinomas, stage II).

Pathological examination

The samples with the following labels send to pathologic ward in separate containers: 1- SLN with gamma probe 2-SLN with blue dye 3- SLN with both detection method 4- other lymph nodes.

SLN mapping

Detection of SLNs was accomplished through direct visualization of blue colored nodes. And by detection of radioactivity, using a handheld Spanish gamma probe.

Statistical analysis

Continuous data were represented as mean and standard deviation, frequency and proportion is used to show categorical variables. 95% confidence interval was calculated with Wald or score test method for proportions). Sensitivity, specificity, Positive predictive value, and negative predictive value were calculated as predictive values. All analysis were done using R-package version 3.0.1.

Results

Overall, 30 patients were included in the study, mean age and body mass index was 53.9±8.9 (39-80) years and 31.6±4.4 (21-40) kg/m^2. Pre-operative lymph node mapping showed SLN in 29 out of 30 patients. Lymphoscintigraphy of one patient is shown in figure-1 Intra operative in 29/30 patients, SLNs were harvested by gamma probe; in 13 out of 19 patients SLNs were seen by blue dye.

SLN detection rate was 96.7% by radiotracer and 72.2% by blue dye. Median number of SLN per patient was 3 and total number of SLNs detection was 81. The most common site of SLN was the obturator node (Table 1).

Most of the patients with endometrial cancer were stage IA, and most histologic type were endometrioid adenocarcinoma (Table 2).

The final results such as sensitivity, specificity, positive predictive value and negative predictive value are summarized in (Table 3).

None of the patients with histologically negative SLN had other lymph node metastasis; as all 4 patients with involved pelvic nodes had positive SLNs too. In this study, there was not any para-aortic node involvement in the

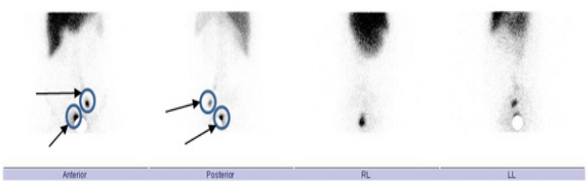

Figure 1. Anterior-Posterior, Lateral Lymphoscintigraphy of one Patient 17 Hours after Cervical Injection of Radioactive Tracer (TC99)

Table 1. Anatomical Distribution of the SLNs

		Nothing N (%)	Right N (%)	Left N (%)	Both N (%)
Blue dye	External iliac	17 (94.4)	1 (0.6)	0 (0.0)	0 (0.0)
	Internal iliac	15 (83.3)	1 (5.6)	2 (11.1)	0 (0.0)
	Obturator	11 (61.1)	6 (33.3)	1 (5.6)	0 (0.0)
	Common iliac	16 (88.9)	2 (11.1)	0 (0.0)	0 (0.0)
TC99	External iliac	28 (96.6)	1 (3.4)	0 (0.0)	0 (0.0)
	Internal iliac	22 (75.9)	6 (20.7)	0 (0.0)	1 (3.4)
	Obturator	7 (24.1)	10 (34.5)	8 (27.6)	4 (13.8)
	Common iliac	27 (93.1)	2 (6.9)	0 (0.0)	0 (0.0)

Table 2. FIGO Stage and Histologic Type of Patients

FIGO Stage	TC99 N (%)	TC99 and Blue dye N (%)	Total N (%)
1A	9 (75)	12 (66.7)	21 (70)
1B	2 (16.7)	2 (11.1)	4 (13.3)
II	1 (8.3)	4 (22.2)	5 (16.7)
Histologic type			
Endometrioid	10 (83.3)	15 (83.3)	25 (83.3)
Papillary serous	2 (16.7)	3 (16.7)	5 (16.7)

patients underwent para-aortic lymph node dissection.

Discussion

Our research applied cervical injection of both methylene blue and Tc99, Using this technique, a detection rate of 96.7% was achieved in endometrial cancer. None of the patients with histologically negative SLN had other lymph node metastasis; as all 4 patients with involved pelvic nodes had positive SLNs too, resulting in a 100% NPV and 100% sensitivity and 3.8% specificity. Meta-analyses of the SLN mapping data in patients with endometrial cancer report a broad range in SLN detection rates and false negative rates (Ansari et al., 2013; Levinson and Escobar, 2013; Touboul et al., 2013; Koh et al., 2015).

A systematic review of seventeen studies with n>30 patients revealed detection rates of 60% to 100%; Retrospective application of a surgical algorithm revealed a sensitivity of 95%, a negative predictive value of 99%, and a false negative rate of 5% (Cormier et al., 2015).

One of the difficulties with SLN mapping in endometrial cancer has been identifying the best injection site. Melanoma, vulvar cancer, and cervical cancer all lend themselves to direct peri-tumoral injection. In endometrial cancer, direct tumoral injection is more challenging and can only be accomplished by hysteroscopy or transvaginal ultrasonography (Cormier et al., 2015).

In this research, cervical injection technique was used which is much easier than the fundal injection. High detection rate and sensitivity of our study was in accordance to other studies used cervical injection (Ballester et al., 2011; Garcia et al., 2012; Kadkhodayan et al., 2014; Kadkhodayan et al., 2015). Cervical injection is associated with extremely low para-aortic lymphatic drainage and some groups argue against this technique duo to this fact. However frequency of isolated para-aortic without pelvic lymph node involvement in endometrial cancer patients is reported to be low (Kadkhodayan et al., 2014; Kadkhodayan et al., 2015). This was only 2% in Abu-Rustam et al., study (2009). We did not have any para-aortic node involvement in the patients underwent para-aortic lymph node dissection.

Multiple injection agents have been described for

Table 3. Sensitivity, Specificity, NPV, and PPV of SLN Status

		Pathology of Lymph nodes positive	negative	
SLN	Positive	4	25	PPV=13.8% 95%CI: (3.9%-31.7%)
	Negative	0	1	NPV=100% 95%CI: (2.5%-100.0%)
		Sensitivity=100.0% 95% CI: (39.8%-100.0%)	Specificity=3.8% 95%CI: (0.1%-19.6%)	Disease prevalence:13.3%

PPV,Positive predictive value; NPV,Negative predictive value; CI,Confidence interval

identification of SLNs, blue dye and/or radionuclide tracers (Cormier et al., 2015).

Technetium colloid 99 (Tc99) can be detected for a longer period of time and therefore is often injected pre-operatively. Surgeons can be guided to the mapped regions by a pre-operative lymphoscintigram, however correlation between imaging done the day before surgery and the intra-operative findings is low. It may be more difficult to detect SLNs close to the cervix as the gamma-probe picks up high activity from the injection site. The resources and equipment required for Tc mapping are cumbersome, costly, and are not available to all surgeons.

Blue dye is a much cheaper product and is widely available in most hospitals. It also is more convenient to use because it is injected intra-operatively, however it may be more difficult to detect in obese patients. Allergic reactions are known to occur; but severe reactions are very rare (< 0.1%). Overall detection rates were satisfactory for products. However, detection rates were higher when blue dye was combined with Tc99 (Cormier et al., 2015).

Kadkhodayan et al., reported 100% detection rate, as the majority of harvested SLNs were detected by radiotracer and contribution of blue dye was minimal (2015). Several other reports also supported our finding as detection rate using radiotracer or combined radiotracer and blue dye was higher than blue dye alone (Echt et al., 1999; Holub et al., 2000; Barlin et al., 2012; Ansari et al., 2013; Kadkhodayan et al., 2014). Shiravani et al., reported 92.5% detection rate by Tc99 and 42.5% detection rate by blue dye (Shiravani et al., 2014). Barlin et al., in a major group of endometrial cancer patients (498 patients) reported 95% detection rate (Barlin et al., 2012).

Allameh et al., applied fundal injection of blue dye; reported 80% detection rate and found para-aortic basin (SLN) only in one out of fifteen patients (6.7%) (2015). Solima et al., reported that 56% of their patients had para-aortic SLNs using sub-endometrial injection of the radiotracer (2012).

Sentinel node procedure in endometrial cancer has been studied for more than 10 years but has yet to be established as a standard of care (Cormier et al., 2015). SLN mapping may be most appropriate for those patient at low to intermediate risk for metastases and/or for those who may not tolerate a standard lymphadenectomy (Koh et al., 2015). Patients without nodal involvement can be identified by the examination of SLNs. As a result, they benefit from limited surgery and associated risk of complications (Allameh et al., 2015).

SLN mapping should be done in institution with expertise in this procedure, the main contraindication for SLN mapping is uterine sarcoma. Additionally, SLN mapping should be done with particular caution in patients with high-risk histology (eg, serous carcinoma, clear cell carcinoma, carcinosarcoma). It is important to note that the system-wide long-term outcomes data are not available for SLN mapping in endometrial cancer (Koh et al., 2015).

The limitation of this study is low sample size can effect on results such as sensitivity and specificity, and pathologists were not aware of SLNs from other lymph nodes, that may need specific consideration; because the samples send in labeled container. Also SLNs were not send for frozen section.

Considering the lower risk of metastases in early stage of endometrial cancer, SLN technique allows for confident and accurate staging of cancer. Continuing further in these studies, it could be anticipated to avoid aggressive surgical procedure in near future by advances infeasible and reliable SLN mapping technique and intraoperative histological methods.

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Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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