ORIGINAL ARTICLE

Sentinel lymph node mapping in early stage of endometrial and cervical cancers

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Background: The sentinel lymph node (SLN) is defined as the first chain node in the lymphatic basin that receives primary lymphatic flow. If the SLN is negative for metastatic disease, then other nodes are expected to be disease-free. SLN techniques have been extensively applied in the staging and treatment of many tumors, including melanoma, breast and vulvar cancers. This study aims to evaluate our technique in SLN mapping in early stage endometrial and cervical cancers. **Materials and Methods:** We scheduled a cross-sectional pilot study for patients undergoing staging surgery for endometrial and cervical cancer from November 2012 to February 2014 in Beheshti and Sadoughi Hospitals. Our SLN mapping technique included 1 h preoperative or intraoperative injection of 4 ml of 1% methylene blue dye in the tumor site. At the time of surgery, blue lymph nodes were removed and labeled as SLNs. Then systematic lymph node dissection was completed, and all of the nodes were sent for pathologic examination concerning metastatic involvement. All of the sentinel nodes were first stained with hematoxylin and eosin and examined. Those negative in this study were then stained with immunohistochemistry using anti-keratin antibody. Descriptive statistics, sensitivity, negative predictive values (NPV), false negative (FN) and detection rates were calculated. **Results:** Twenty-three patients including 62% endometrial and 38% cervical cancers enrolled in the study. Median of SLN count in the endometrial and cervical cancers was 3 and 2, respectively. Among endometrial and cervical cancers, detection rate of metastatic disease was 80% and 87.5%, respectively. The FN rate for this technique was 0 and the sensitivity and NPV are 100% for both endometrial and cervical cancers. **Conclusion:** Considering the lower risk of metastases in early stage of both endometrial and cervical cancers, SLN technique allows for confident and accurate staging of cancer.

Key words: Cervical cancer, endometrial cancer, lymph node, metastasis, sentinel node

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INTRODUCTION

Lymph node metastasis is one of the main prognostic factors in patients suffering from cancer[1,2] and lymph node status is a major determinant of the strategy of treatment.[3-5] It is common to remove the entire lymphatic basin draining a tumor to obtain a histological diagnosis of nodal spread.[6] In order to decrease complications related with lymph node dissection, sentinel lymph node (SLN) techniques have been developed and widely studied in many oncologic fields and gained importance in the treatment of solid tumors. SLN mapping is based on the concept that lymph node drains in a specific pattern away from the tumor. It is expected that if the SLN or the first node is negative for metastasis, then the nodes after the SLN should also be negative.[7]

As a result, the standard treatment guidelines for the management of cancers such as breast and melanoma include SLN technique.[8,9] In recent decades, several surveys on SLN dissection for early stage vulvar cancer have been done that suggest to introduce this technique as a safe alternative for inguinofemoral lymphadenectomy[10-16] with a negative predictive value (NPV) approaching 100%.[12-16]

After the first report in 1999, the use of SLN mapping procedure in cervical cancer has also been examined in several studies.[11,17-19] The standard surgical lymph node assessment in early cervical cancer is a systemic pelvic lymphadenectomy. This procedure is associated with prolonged operating time, additional cost, lymphocyst, lymphedema and rarely neural or vascular injury. Meanwhile, the majority of patients with early-stage disease does not have lymph node metastases and may undergo unnecessary lymph node dissection and hence some studies have been conducted on cervical cancer to analyze SLN concept feasibility, finding high detection rates of 78-100%.[20-22]

It is known that identification of nodal metastasis has a profound influence on postoperative management and adjuvant therapy in endometrial cancer. Two large, randomized trials studying the role of systematic lymphadenectomy in patients with clinically early-stage

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endometrial cancer report that the benefit of this procedure is limited to better surgical staging without an additional therapeutic effect.[23,24] Hence, the SLN concept has gained importance in endometrial cancer as a reproducible and accurate technique in determining lymph node status.[25]

Our study planned to evaluate the SLN mapping in early stage endometrial and cervical cancers with a feasible method.

MATERIALS AND METHODS

We conducted a cross-sectional pilot study between November 2012 and February 2014. Twenty-three patients with stage I and II endometrial or cervical cancer who were candidate for systematic lymph node dissection during the initial surgery at Shahid Beheshti and Sadoughi Hospitals (Isfahan, Iran) enrolled in the study. Patients with prior radiotherapy were excluded. Patients underwent radical hysterectomy and surgical staging. All patients signed consent upon enrollment.

Sentinel lymph node mapping for endometrial cancer was done at laparotomy by deep uterine subserosal injection of 4 ml of 1% methylene blue in the fundus after clamping the fallopian tubes using a 25 gauge needle. To prevent spillage of dye, fundal gentle pressure on the sites of injection was used.[26]

Our technique for cervical cancer was slow injection of 4 ml of 1% methylene blue at 4 cervical regions including the 2, 4, 8, and 10 O'clock positions using a 25 gauge needle 30-60 min before operation.[27]

After accessing the retroperitoneum at the time of surgery, the blue lymphatic channels were considered and followed to their designated SLN. Then stained and nonstained lymph nodes were removed and sent to the pathology lab. The total number of dissected lymph nodes was counted. Sections from nodal tissue, including SLN were first stained with hematoxylin and eosin (H and E) and studied for metastatic involvement. SLNs showing metastatic involvement on H and E stained sections were considered as positive for metastatic disease. One extra section from the deeper levels of SLN was then prepared and stained with immunohistochemistry (IHC) technique using anti-cytokeratin (AE1/AE3) antibody if results from the initial study of SLN for metastatic disease were negative. If the SLN section stained with IHC technique was positive for keratin immunoreactivity, SLN was considered to have metastatic disease. False negative (FN) result was defined as finding metastatic disease in the lymphadenectomy specimen in the absence of SLN metastatic involvement. Eventually, obtained data were classified in stained and nonstained groups and in terms of negative and positive metastases in histopathologic examination. Descriptive statistics were performed on the entire cohort.

Sensitivity, NPVs, FN and detection rates with 95% confidence interval for their differences were calculated. The SPSS System version 20 (SPSS Inc., Chicago) was used for statistical analysis.

RESULTS

A total of 23 patients enrolled in the study including 15 endometrial and 8 cervical cancers. Mean age and body mass index was 63.47 ± 1.09 years and 29.13 ± 0.50 kg/m^2 for endometrial and 39 ± 1.22 years and 24 ± 0.73 kg/m^2 for cervical cancer. Median of SLN count in endometrial and cervical cancers were 3 (range, 1-4) and 2 (range, 1-3), respectively.

Sentinel lymph node detection rate was 80% in patients with endometrial cancer and 87.5% in those with cervical cancer [Table 1].

Most of the patients with endometrial carcinoma or cervix malignancy were surgically staged as IA (46.7%) and IB (50%) based on lymph node status, respectively [Table 2].

The most common site of SLN in endometrial cancer was the obturator node that was identified in 53.3% of cases. With regard to cervical cancer, the most predictive sites of sentinel nodes were obturator (50%) [Table 3].

Table 4 shows histological findings. Pathological evaluations showed that majority of patients with endometrial cancer had the conventional endometroid carcinoma (86.7%). In cervical cancer, half of the patients were identified with squamous cell carcinoma (50%).

Metastatic disease was documented in 20% and 25% of patients with endometrial and cervical cancer, respectively [Table 5].

The final results of this technique are summarized in Table 5a and b. The FN rate for the technique seems to be 0 in this cohort and the sensitivity and NPV are 100% for both endometrial and cervical cancers.

Table 1: SLN detection rate in endometrial and cervical cancers

Type of cancer	Positive	Negative
	Frequency (%)	Frequency (%)
Endometrial cancer	12 (80)	3 (20)
Cervical cancer	7 (87.5)	1 (12.5)

SLN = Sentinel lymph node

Table 2: FIGO stage in endometrial and cervical cancers

Stage	Endometrial cancer	Cervical cancer
	Frequency (%)	Frequency (%)
1A	7 (46.7)	2 (25)
2A	1 (6.7)	1 (12.5)
3A	1 (6.7)	–
1B	3 (20)	4 (50)
2B	2 (13.3)	1 (12.5)
1C	1 (6.7)	–

FIGO = Federation of gynecology and obstetrics

Table 3: Location of SLN in endometrial and cervical cancers

Site	Endometrial cancer	Cervical cancer
	Frequency (%)	Frequency (%)
Obturator	8 (53.3)	4 (50)
External iliac	–	2 (25)
Internal iliac	6 (40)	–
Common iliac	–	2 (25)
Para-aortic	1 (6.7)	–

SLN = Sentinel lymph node

Table 4: Histologic subtypes of endometrial and cervical cancers

Histology	Endometrial cancer	Cervical cancer
	Frequency (%)	Frequency (%)
Endometroid carcinoma	13 (86.7)	
Clear cell carcinoma	1 (6.7)	
papillary serous carcinoma	1 (6.7)	
adenocarcinoma		3 (37.5)
Squamous cell carcinoma		4 (50)
Adenosquamous carcinoma		1 (12.5)

Table 5a: Sensitivity, specificity, NPV, PPV and FNR of SLN status in endometrial cancer

Metastasis SLN	Positive	Negative	Predictive rates
	Frequency	Frequency	
Positive	3	9	PPV=25% 95% CI: (6.69-75.16)
Negative	0	3	NPV=100% 95% CI: (30.10-100)
	Sensitivity=100% 95% CI: (30.10-100)	Specificity=25% 95% CI: (6.69-57.16)	FNR=0% 95% CI: (0-69)

CI = Confidence interval; PPV = Positive predictive value; NPV = Negative predictive value; FNR = False negative rate; SLN = Sentinel lymph node

Table 5b: Sensitivity, specificity, NPV, PPV and FNR of SLN status in cervical cancer

Metastasis SLN	Positive	Negative	Predictive rates
	Frequency	Frequency	
Positive	2	5	PPV=28.6% 95% CI: (5.11-69.74)
Negative	0	1	NPV=100% 95% CI: (5.46-100)
	Sensitivity=100% 95% CI: (19.79-100)	Specificity=16.7% 95% CI: (0.87-63.52)	FNR=0% 95% CI: (0-94.54)

CI = Confidence interval; PPV = Positive predictive value; NPV = Negative predictive value; FNR = False negative rate; SLN = Sentinel lymph node

No perioperative complication was observed. Uneventful light blue urine was made in most of patients that resolved until 24 h later.

DISCUSSION

Research on SLN mapping has gained popularity in gynecological oncology. 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. Data on the gynecological cancers strongly supports the need for an accurate selection of patients for more aggressive surgical procedures.[1,2]

Various studies have been published with regard to sentinel node detection in cervical and endometrial cancer.[6,7,17-25,28] These reports show SLN biopsy as a promising technique in both types of cancers.[28] Although many surgeons concern about false-negative rate of SLN technique, the rate has been shown to be low.[20,29]

Our study on SLN technique achieved 80% and 87.5% detection rate in endometrial and cervical cancers, respectively. None of the patients with histologically negative SLN had other lymph node metastasis resulting in a 100% NPV and 100% sensitivity. Another study on 36 cervical cancers with negative bilateral SLN showed no lymph node metastases on the nonsentinel nodes after thorough ultrastaging by both H and E and IHC staining. This study achieved a false-negative and NPV of 0% and 100%, respectively.[30]

Multiple techniques have been described in the identification of SLNs in endometrial cancer. These techniques include cervical and/or fundal injection of dye, all providing dye penetration to the uterine vessels; use of laparoscopy for staging,[20,28] hysteroscopy[1] and radionuclide tracers[6,25,31] for SLN mapping are some of the other applied techniques, which need more equipment and experience of gynecologic oncologist to achieve acceptable results. Khoury-Collado *et al*. who applied cervical injection of tracer emphasize that high detection rates of SLN are determined by both the optimal method used for lymphatic mapping and the experience of the surgeon.[25]

The blue dye is a low-cost and accessible tracer. It is very useful when the SLN is located in the parametrium, which is a rare finding in early-stage disease.[31] Our research applied fundal injection of methylene blue for endometrial cancer. It achieved NPV of 100%. The results of study by Khoury-Collado *et al*. demonstrated that following a cervical injection of dye, sentinel nodes are three times more likely to yield metastatic tumor cells than randomly sampled nodes.[32] However, both methods were adequately satisfactory.

In this study, the most predictive sites of sentinel nodes for endometrial cancer were the area of obturator and internal iliac arteries. This finding is in concordance with other studies where a dual-labeling method has been used.[28,32-34] In a study of 47 patients with endometrial cancer and single lymph node metastases, 61.8% of the lymph node metastases were located in the obturator fossa and the area of internal iliac artery, whereas 10.9% were located in the para-aortic basin.[35] We found para-aortic basin only in one subject. A study reported the bifurcation of iliac vessels and/or the obturator fossa as the most frequent sites of SLNs in cervical cancer and levels above the bifurcation of iliac vessels and para-aortic area were the less frequent sites of sentinel nodes[31] that our results were similar to it.

One SLN mapping algorithm is offered by Cormier *et al*. for cervical cancer to detect microscopic metastases. It is based upon a comprehensive study using a valid surgical method and is admissible. According to this algorithm, all mapped SLN should first be studied with H and E staining and considered for ultrastaging if negative in H and E staining. Moreover, any suspicious node regardless of mapping should be excised and finally if there is no mapping on a hemipelvis, a side-specific lymph node dissection (including interiliac/subaortic nodes) should be performed.[6]

Sentinel lymph node technique seems to go to revolutionize surgical staging in gynecologic oncology. One of the comprehensive studies on the subject suggests introducing this technique as the gold standard for staging of cervical cancer.[2] Although several studies on both endometrial and cervical cancers have confirmed SLN technique reliability,[1,2,23,36-38] it sounds that more evaluations are needed to follow up the patients who underwent this technique for long-term recurrence.

The limitation of SLN technique is frozen section. When a SLN is negative on intraoperative frozen section, sensitivity of detection micrometastasis is low. It has been suggested that complete lymphadenectomy could possibly be avoided only in patients with tumors less than 2 cm when bilateral SLNs are identified and reported as negative on frozen section in cervical cancer.[31] Hence, our study gained the role of SLN mapping as an adjunct to surgical staging and lymphadenectomy, not to replace it. However, now the significant role of SLN lies in its ability to identify nodes outside the usual field of complete lymphadenectomy (e.g., presacral nodes in cervical carcinoma).[39,40] Our study as a pilot study had limitations for access to trained surgeons and also enough candidate cases for this technique.

CONCLUSIONS

Considering the lower risk of metastases in early stage of both endometrial and cervical cancer, SLN technique allows for confident and accurate staging of cancer. We are hopeful to avoid aggressive surgical procedures in near future by advances in intraoperative histological methods. Our SNL mapping technique with ultrastaging offers a feasible and reliable method parallel to other techniques of SLN mapping for early stage of endometrial and cervical cancers.

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AUTHOR'S CONTRIBUTIONS

TA and VH carried out the design and coordinated the study, participated in most of the experiments and prepared the manuscript. FM and FB provide assistance in the design of the study, coordinated and carried out all the experiments and participated in manuscript preparation. FB helped us in surgical division of study. All authors have read and approved the content of the manuscript.

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