



Feasibility of Sentinel Lymph Node Sampling in Early-Stage Carcinoma Endometrium: Single-Institution Experience

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Abstract

Introduction Accurate surgical staging is an essential component in the management of carcinoma endometrium to assess the stage of disease and to tailor adjuvant treatment. Sentinel node technique was introduced as an alternative for extensive lymphadenectomy in early stages to avoid complications associated with lymphadenectomy.

Aims and Objectives To assess the detection rate and diagnostic accuracy of SLN mapping in patients with early-stage carcinoma endometrium

Materials and Methods Prospective validation study involving 30 patients diagnosed to have early-stage carcinoma endometrium. Sentinel nodes were detected by combined methods of radio colloid dye and isosulphan blue dye injection

Results Sentinel lymph node was detected in 19 patients (63.4%). 11 patients had no sentinel nodes. Total number of sentinel nodes isolated was 68 with a mean of 2.26 per patient (range 0–4). Ten (33.33%) patients had single sentinel node location, while 9 (30%) had more than 1 sentinel lymph nodes. Twelve patients had bilateral sentinel nodes, and the most frequent location of sentinel node was obturator, 19 (63.3%) especially on right hemi-pelvis. One patient had a hot para-aortic node, while none had blue para-aortic sentinel node. Average number of lymph nodes obtained by lymphadenectomy was 13 per patient (range 7–22). All patients with sentinel node had negative frozen report as well as in histopathology. Two patients in whom no sentinel nodes were detected by either techniques had metastatic nodes in histopathology report.

Conclusion Detection rate was maximum with radiocolloid dye, and it is better to utilize the technique for less graded tumours and endometrioid variants.

Keywords Carcinoma endometrium · Sentinel nodes · Detection rate

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Introduction

Carcinoma endometrium is the commonest genital tract malignancies in females in developed countries. In India, it ranks third most common genital tract malignancy [1]. Accurate surgical staging is an important prognostic factor in the management of carcinoma endometrium. The incidence of metastasis to the pelvic lymph nodes in patients with corpus-confined endometrial cancer varies from 5 to 18% [2]. Retroperitoneal lymph node involvement, including either pelvic or para-aortic lymph nodes, results in a worse prognosis. Patients with lymph node metastasis usually have 5-year survival rate as low as 44% to 52% compared to 95% when the disease is localized [1]. However, the therapeutic role of lymphadenectomy has not been well established with two randomized trials, in fact failing to show a survival benefit. After MRC-ASTEC EN 5 [3] and study by Panici et al. [4], it was proved that there is no evidence of benefit in terms

of overall or recurrence-free survival for pelvic lymphadenectomy in women with early endometrial cancer. Retrospective studies suggested that complete lymphadenectomy may be associated with improved survival outcome [5], and prospective trials evaluating the same are ongoing [6]. Lymphadenectomy as a part of staging in early-stage carcinoma endometrium is still controversial. Lymphatic mapping using various injection techniques is currently being practiced.

Aims and Objectives

To assess the detection rate and diagnostic accuracy of SLN mapping in patients with early-stage carcinoma endometrium.

Materials and Methods

This study was conducted as a validation study in a tertiary care referral hospital in south India to assess the feasibility of sentinel lymph node sampling in early-stage carcinoma endometrium after getting Institution review board and ethics committee approval. It was done as a prospective observational study from January 2018 to January 2019.

Patient Selection

Patients with histological diagnosis of carcinoma endometrium confined to uterus clinically and radiologically were included. Magnetic resonance imaging (MRI) was taken for all patients to assess myometrial invasion and lymph node involvement. MRI showing enlarged lymph nodes (more than 10 mm) were excluded from the study. Representative slides and blocks of referred cases were reviewed by our pathologists to confirm diagnosis as well as grade of lesion.

Patients with Endometrioid adenocarcinoma grade 1 with less than 50% myometrial invasion (radiologically), history of prior chemotherapy or radiotherapy, history of other malignancies, and previous surgeries that could change lymphatic drainage of uterus (e.g. myomectomy) were excluded.

Procedure

After taking informed consent, 0.2 ml technetium-99 injections were administered at 3'o clock and 9'o clock positions of cervix the day before surgery. The injection was prepared in the department of Nuclear medicine, on the morning of injection day. All patients underwent single photon emission computed tomography (SPECT-CT) one hour after injection to assess the location of lymph node with two dynamic and two static images taken at fifteen minutes interval.

On the day of surgery, under general anaesthesia, after opening nodal spaces a hand-held gamma probe was used to detect hot nodes and the site of hot nodes was marked. Blue dye- isosulphan blue 3 ml was injected intracervically at 3 and 9 o'clock positions. All nodes which turned blue immediately and within twenty minutes of injection were considered as blue sentinel nodes. All blue and hot nodes were removed, properly labelled and submitted for frozen examination and then proceeded with bilateral pelvic lymph node dissection, para-aortic node dissection up to the level of renal vein along with hysterectomy and bilateral salpingo-oophorectomy. Data were managed with an Excel database (Microsoft) and analysed by SPSS software.

Results

Number of patients included was 30. Mean age of patients was 58.7 (range 48–73), and median BMI was 26.44. Twenty-eight were postmenopausal. None of them had previous history of infertility treatment or hormonal exposure. Most frequent co-morbid conditions were Diabetes Mellitus 2 (6.7%), Systemic hypertension 6 (20%) and Hypothyroidism 4 (13.3%). Seven patients (23.3%) had diabetes and hypertension. Clinical and radiological evaluation details are given in Table 1.

All patients underwent laparotomy. None of the patients had allergic reactions to technetium-99 or isosulphan blue dye. Sentinel lymph node was detected in 19 patients (63.4%). Eleven patients had no sentinel nodes in the initial SPECT-CT or intraoperatively. Total number of sentinel nodes isolated was 68 with a mean of 2.26 per patient (range 0–4). Ten (33.33%) patients had a single sentinel node location, while 9 (30%) had more than 1 sentinel lymph node. Twelve patients had bilateral sentinel nodes, and the most frequent location of sentinel node was obturator 19 (63.3%), especially on right hemi-pelvis. One patient had a hot para-aortic node, while none of the patients had blue para-aortic sentinel node. The average number of lymph nodes obtained by lymphadenectomy was 13 per patient (range 7–22) [Table 2].

All patients with sentinel node had a negative frozen report as well as in final histopathology. Two out of eleven patients in whom no sentinel nodes were detected by either techniques had metastatic nodes in final histopathology report.

There were no major complications in the intraoperative or postoperative period. While giving isosulphan blue dye injection, there was a transient SPO2 fall which recovered quickly without any interventions. Ninety percentage of patients had a mean hospital stay of 4.5 days, while 2 had post-op stay more than 5 days in view of paralytic ileus.

Table 1 Baseline characteristics of patients and diagnostic evaluation

Age mean + SD (range)	58.7 ± 6.7 (48 – 73)	
ECOG score	0 or 1	
BMI mean + SD (range)	26.44 ± 1.95 (23 – 29)	
Pre-operative endometrial sampling	Frequency	Percentage
Type of endometrial cancer		
Endometrioid adenocarcinoma	26	86.7
Uterine papillary serous	3	10
Clear cell carcinoma	1	3.3
Grade of endometrioid cancer		
Grade 1	8	26.7
Grade 2	16	53.3
Grade 3	2	6.6
MRI	Frequency	Percentage
Myometrial infiltration		
< 50% MI	10	33.3
> 50% MI	20	66.67
Enlarged lymph nodes		
Pelvic		
Yes	2	6.7
No	28	93.3
Para-aortic		
No	30	100

Table 2 Sentinel node detection rate

Sentinel node	Right hemi-pelvis		Left hemi-pelvis	
	No	%	No	%
No. of patients with SPECT CT detected sentinel nodes	8	26.67	4	13.33
No. of patients with hot node	19	63.4	12	40
No. of patients with blue node	9	30	8	26
Site of hot node				
Int. iliac	4	13.33	1	3.33
Ext. iliac	12	40	7	23.33
Com. iliac	1	3.3	2	6.67
Obturator	8	26.7	4	13.33
Site of blue node				
Int. iliac	1	3.33	1	3.3
Ext. iliac	5	16.67	5	16.67
Com. iliac	0	0	0	0
Obturator	3	10	2	6.67

Patients were staged based on FIGO 2009 staging report, and histopathology report was summarized in Tables 3 and 4, and adjuvant treatment was decided after multidisciplinary tumour board decision.

Table 3 Final histopathology report

Final histopathology report	Frequency	Percentage
Type of endometrial cancer		
Endometrioid adenocarcinoma	26	86.7
Uterine papillary serous	3	10
Clear cell carcinoma	1	3.3
Grade of endometrial cancer		
Grade 1	3	10
Grade 2	21	70
Grade 3	2	6.6
Myometrial infiltration		
< 50% MI	15	50
> 50% MI	15	50
Cervical stromal invasion		
Yes	1	3.3
Adnexal/parametrial invasion		
Yes	3	10
No	27	70

Discussion

Use of sentinel lymph node technique was already established in managing melanoma [7] and carcinoma breast [8]. Sentinel lymph node technique is based on the

Table 4 Stage of disease

Stage of disease	Frequency	Percentage
I A	15	50
I B	9	30
II	1	3.3
III A	1	3.3
III B	2	6.6
III C		
III C1	1	3.3
III C2	1	3.3
IV	0	0

hypothesis that sentinel lymph node is the first regional draining node from the primary tumour. Thus, the histological status of the sentinel node could accurately predict the pathological status of the regional lymph node basin.

Detection rate of sentinel node using SPECT-CT was low (26.6%, 8/30 patients on right hemi-pelvis and 13.3%, 4/30 patients on left hemi-pelvis) in our study compared to other studies. Based on a study by Hoogendam et al. [9], SPECT-CT is more sensitive in detecting sentinel nodes comparing planar lymphoscintigraphy. The median detection rate with SPECT-CT for more than one lymph node in a patient was 98.6% compared with 85.3% for lymphoscintigraphy. Most common sentinel node detected was obturator node on right hemi-pelvis.

By combined injection technique using technetium-99 and isosulphan blue dye, detection rate was 63.4% on right hemi-pelvis and 40% on left hemi-pelvis. In cases where sentinel nodes were detected, final histopathology report was also in agreement with frozen report. Two cases where final histopathology report showed metastatic nodes had no sentinel nodes intraoperatively by either methods. One was a case of uterine papillary serous carcinoma, and other was a poorly differentiated endometrioid adenocarcinoma. One patient had metastatic deposits at pelvic and para-aortic areas. Same patient's histopathology report showed lymphovascular space invasion and left parametrial tumour deposits. Second case had metastatic pelvic and para-aortic nodes with diffuse lymphovascular emboli and dense parametrial tumour infiltration. The possible reason for non-detection of sentinel node might be due to occlusion of lymphatic drainage channels by tumour cells.

Abu-Rustum et al. [10] compared subserosal myometrial injection techniques with cervical injection of tracer to detect sentinel nodes in carcinoma endometrium. With myometrial injection, detection rate varies between zero [11] to ninety-two per cent [12]. In the above-mentioned article, when tracer was given as cervical injection, detection rate was as high as 86%. The author himself gave cervical injection in their institutional study. Similar technique was used

in our case also. In order to avoid bias, the same investigator injected technetium-99 as well as blue dye at 3'o clock and 9'o clock positions to all thirty patients and still detection rate was almost similar to average detection rate obtained by myometrial detection technique. But in the study by Fady Khoury-Collado et al. [13] lymph node mapping was performed using blue dye injection to cervix in 71% cases while combined cervical and uterine fundal injection in 29% cases. In their analysis, they found that detection rate increased from 78% (on cervical injection alone) to 94% by combined technique ($p=0.033$).

Hysteroscopic injection of tracer is another technique, but the procedure is more complicated and demanding. It requires hysteroscopic evaluation of tumour, and usually dye is given as peritumoural injection. In developing countries with limited resources, utilization of hysteroscopic injections will be cumbersome and financially challenging. Multiple studies utilized hysteroscopic injection technique to detect sentinel lymph node in early-stage carcinoma endometrium with varying detection rate from zero [14] to hundred per cent [15, 16].

As proficiency in minimal access surgery increases and there was adequate robust evidence for staging in cancer endometrium without survival compromise, more and more studies are now focussing on sentinel node detection by minimal access methods. FIRES trial [17] was a one multi-centric prospective cohort study involving 340 patients with clinical stage 1 endometrial cancer of all histologies. They used indocyanin green injection on cervix followed by robotic detection intraoperatively and then proceeded with hysterectomy and node dissection based on ultra-staging results. This study showed a sensitivity of 97.2% to detect node positive disease and a negative predictive value of 99.6%. Study mentions neurological disorders and post-operative respiratory distress and failure as most common grade 3–4 adverse events. They could not identify metastasis in 3% of patients with node positive disease. The same study concludes with the interpretation that sentinel lymph node detection in endometrial cancer using indocyanin green has a high degree of diagnostic accuracy.

Our study was conducted as a validation study with minimum patients. Compared to similar studies, average detection rate was less. Probable explanation for low detection rate might be due to disruption of lymphatic channels while opening peritoneal spaces. Hot node detection and blue dye injection was performed after opening peritoneal spaces in all cases. In two cases, sentinel nodes were negative for malignancy but harboured metastatic nodal disease. Both were of high-grade variants. As per NCCN guidelines, complete lymphadenectomy including pelvic and para-aortic nodes up to renal vein has to be done for Type II endometrial cancers. Whether to improve detection rate by considering additional uterine injection or using indocyanin green dye by minimal access methods has to be further validated.

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Declarations

Conflict of interest The authors have no conflicts of interest relevant to this article to disclose.

Ethical Statement This study was conducted after Institute review board and Ethical committee clearance—IRB no. 12/2016/09, HEC no. 03/2017.

Informed Consent Informed consent was obtained from all the participants in this study.

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