



A Feasibility Study of Sentinel Lymph Node Biopsy in Endometrial Cancer Using Technetium 99m Nanocolloid

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Abstract

To study the feasibility of sentinel node biopsy in early-stage endometrial cancer and to analyse the detection rate of sentinel lymph node (SLN) using preoperative cervical injection of Tc99m nanocolloid. Thirty-five patients with preoperative histological diagnosis of endometrial cancer without any extrauterine involvement on imaging were included in the study. Sentinel node mapping was done by cervical injection of Tc99m nanocolloid on the evening before surgery. Scintigraphic images were taken using gamma camera. Intraoperatively, nodes showing radioactivity were detected using hand-held gamma probe, dissected out separately and labelled as sentinel lymph nodes. Detection rate was calculated and analysed with respect to various parameters. Sentinel lymph node biopsy (SLNB) is feasible in endometrial cancer using cervical injection of Tc99m nanocolloid. SLN detection was done in 33 (94.3%) out of 35 patients. Bilateral detection was feasible in 19 patients (54.3%) with detection in left and right hemipelvis being 74.3%. Detection rate of SLN was 93.7% in endometrioid adenocarcinoma. Sentinel node was detected in all the patients with non-endometrioid histology. The SLNB using cervical injection of Tc99m nanocolloid is feasible in endometrial cancer. It is a safe and easily reproducible technique with good detection rate and high sensitivity. Stage of the tumour, grade and myometrial invasion do not seem to have an influence on sentinel node detection. Cervical involvement, enlarged lymph nodes and obstructed lymphatics can affect sentinel node mapping adversely.

Keywords Endometrial cancer · Sentinel node biopsy · Tc99m nanocolloid

Introduction

Endometrial cancer is the second most common gynaecological malignancy in India, next to cervical cancer. Majority of cases of endometrial cancer are diagnosed at an early stage—nearly 68% being confined to the primary site at the time of diagnosis [1]. Lymph node status and lymphovascular space invasion remains one of the most significant prognostic factors [2]. The rate of nodal metastasis in patients with endometrioid type of endometrial cancer with less than 50% myometrial invasion

is as low as 5.5% [3]. Despite the low incidence of lymph node involvement in early-stage disease, complete lymphadenectomy has been recommended as the only way to accurately stage endometrial cancer [4].

Analysis of the postoperative morbidity resulting from increased operating time, blood loss, nerve injury and lymphadenectomy-related complications has led to a lot of studies in recent years [5]. The focus of research has therefore shifted to sentinel lymph node biopsy which is a less invasive modality to assess the lymph node status and thereby avoiding conventional complete lymphadenectomy in patients at low risk for lymph node metastasis.

Sentinel lymph node biopsy has been well-established in carcinoma breast and melanoma for several years. Its role in gynaecological malignancies like endometrial cancer and cervical cancer is being validated.

Several techniques have been studied for mapping of sentinel lymph nodes in endometrial cancer including hysteroscopic injection, peritumoral and pericervical injection of radiocolloid or dyes with varying results. The aim of our study was to analyse the feasibility of sentinel lymph node biopsy in women with endometrial cancer using intracervical injection of technetium 99m nanocolloid.

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Materials and Methods

This is a prospective observational study, conducted on patients diagnosed to have endometrial cancer in the Department of Gynecologic Oncology at Valavadi Narayanaswamy Cancer Centre (VNCC), G. Kuppaswamy Naidu Memorial Hospital, Coimbatore. The study was done over a period of 2 years between June 2015 and May 2017.

From a review of previous studies, it was found that the detection rate of sentinel lymph node biopsy is 90% [6]. Therefore, to estimate the detection rate of 0.90 with 5% precision and 95% confidence interval, the minimum sample size required was determined to be 35 in this feasibility study. Patients with histologically confirmed endometrial cancer on a preoperative biopsy and patients with presumed FIGO stages I and II based on preoperative MRI who were planned for a staging laparotomy were included in the study. Patients with extrauterine involvement on preoperative imaging, pregnant women and patients who had undergone surgeries like conisation or myomectomy that may alter lymphatic drainage were excluded.

Four injections of 0.5 ml each of technetium nanocolloid which contained 1 mCi or 37 Mbq was prepared in the Department of Nuclear Medicine at our hospital. With the patient in lithotomy position, cervix was visualised through a Cusco's speculum. The injections were given intracervically into the substance of the cervix using a 23G spinal needle at 2, 4, 8 and 10 O'clock positions. The positions were chosen so as to avoid inadvertent injection into the cervical arteries which can cause entry of the dye into the systemic circulation. Combined superficial (1–3 mm) and deep (1–2 cm) injection techniques were followed as per the NCCN 2016 (National Comprehensive Cancer Network) guidelines which ensure dye delivery to the main lymphatic channels [7].

Technetium nanocolloid was chosen in view of its small particle size of 100–600 nm which ensures rapid transit and faster clearance from the nodes. Injection was done preoperatively on the previous evening, approximately 18–22 h prior to surgery. One hour after injection, scintigraphic static images were taken using a dual head gamma camera to know the sites of lymph node uptake, if any (Figs. 1 and 2). Intraoperatively, after hysterectomy, the nodes showing radioactivity were detected using a hand-held gamma probe. Nodes were considered radioactive only if the counts emitted from them was ten times greater than the background counts. The probe was usually directed away from the cervix so as to avoid detection of radioactivity at the site of injection. Those radioactive nodes were resected out separately, labelled as sentinel nodes and sent for histopathology. Then, we proceeded with complete pelvic and lower para-aortic lymphadenectomy. Lymph nodes were studied by haematoxylin-eosin staining.

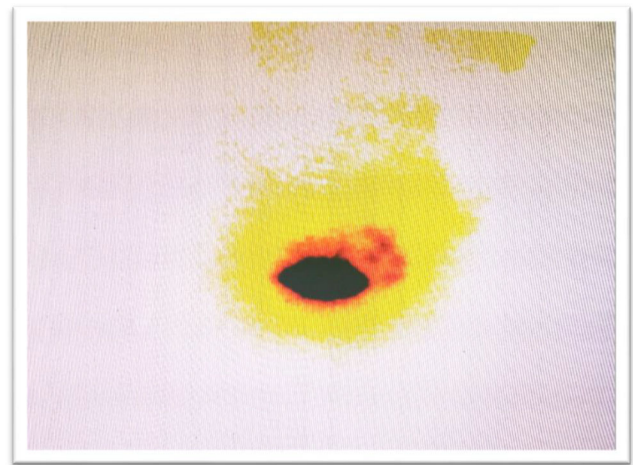


Fig. 1 Scintigraphic image—multiple nodes on the left side (obturator and iliac)

Results

From June 2015 to May 2017, thirty five patients with histologically confirmed endometrial cancer were enrolled into the study. All of them had a sentinel lymph node mapping by preoperative injection of technitium 99m nanocolloid followed by a scintigraphy scan on the evening before surgery. There were no anaphylactic reactions following the injection of technitium 99m nanocolloid and no other complications during the procedure. Next day, they underwent staging laparotomy with sentinel lymph node biopsy followed by complete lymphadenectomy. The demographic details of the patients are shown in Table 1.

As per our inclusion criteria, we enrolled patients who did not have any extrauterine involvement on preoperative MRI. Majority of our patients were stage I (88.6%) which included 19 of them (54.3%) with stage IA (< 50% myometrial invasion on MRI) and 12 patients (34.3%) with stage IB (> 50% myometrial invasion on MRI). Four patients (11.4%) were stage II, with cervical involvement based on preoperative MRI. The most common histological subtype was

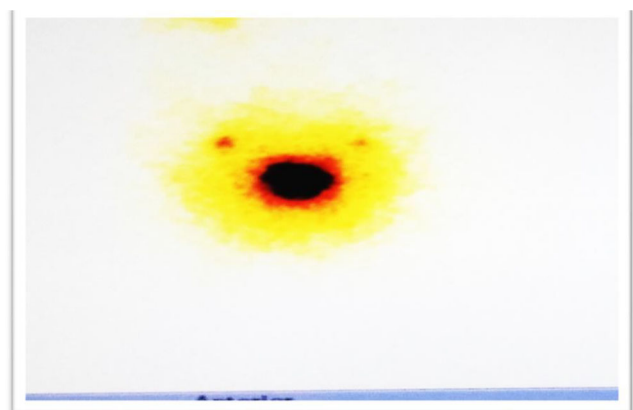


Fig. 2 Bilateral iliac nodes

Table 1 Demographic details

Total number of cases	35
Age in years	37–68
Mean age	57.6 years
BMI Range	22.5–37
Mean BMI	28.5
Postmenopausal	33
Premenopausal	2
Comorbid conditions	
Systemic hypertension	12
Diabetes mellitus	18
Overweight (BMI 25–29.9)	15
Obese (BMI > 30)	9
Hypothyroid	3
Coronary artery disease	1
Rheumatoid arthritis	6
FIGO stage as per preoperative MRI	Number (%)
Stage IA	19 (54.3)
Stage IB	12 (34.3)
Stage II	4(11.4)

endometrioid adenocarcinoma ($n = 30$) which amounted to 85.7% of the total cases. There were also 5.7% cases of papillary serous carcinoma and 2.8% each of other histological subtypes as mentioned in the Table 1. The histopathological details along with the sentinel detection rates are shown in Table 3.

Thirty-three of thirty-five patients (94.3%) had at least one sentinel node detected while sentinel lymph node (SLN) detection was not feasible in 2/35 patients (5.7%). A hemipelvis-wise analysis of SLN detection rate was done for the purposes of analysis. Bilateral detection was feasible in 19 out of 33 patients (57.6%). Twenty-six patients (74.3%) had sentinel node detection in left hemipelvis and right hemipelvis each. Pelvic lymph node detection was possible in 31 patients with two of them having combined pelvic and para-aortic sentinel nodes. Detection rate of para-aortic node was 5.7% using the same technique. According to our study, the most common sentinel lymph node detected was obturator node (25/35 = 71.4% of cases) followed by external iliac node (18/35 = 51.4% of cases).

SLN detection was not feasible in two patients with endometrioid adenocarcinoma. There were three patients with non-endometrioid histology. Sentinel node detection was feasible in all of them. Both the patients with failed SLN mapping had a grade II disease while detection rate was 100% in patients with grade I and grade III disease. Studying the SLN detection with respect to myometrial invasion, both patients with failed SLN detection had > 50% myometrial invasion. SLN mapping was successful in all patients with stage IA. Analysing the patients with

failed SLN mapping, one patient was stage II while the other patient belonged to stage IB but had enlarged pelvic lymph nodes intraoperatively. These nodes showed reactive histiocytosis on histopathology. There was one patient with stage III C1 on final histopathology (Table 3). SLN mapping was feasible in this patient with a positive pelvic node. This node was also detected by lymphoscintigraphy.

The main aim of the study was to determine the feasibility and detection rate of SLN biopsy in endometrial cancer. Detection rate was calculated considering patient as a unit and also for each hemipelvis separately. The test was considered true positive if at least one of the sentinel lymph nodes detected was histologically positive for metastatic disease and false negative if any of the non-SLN had metastasis on histological examination. Detection rate was calculated as the ratio of number of patients with at least one SLN detected to the total number of patients who underwent mapping. Detection rate when considering patient as a unit was 94.3%. While taking into account each hemipelvis, the detection rate was 74.3% for left and right hemipelvis separately. Rate of bilateral sentinel lymph node detection was 54.3%. One patient had a histologically positive node, i.e. left obturator node. The final histopathology with the true positive sentinel lymph node was papillary serous adenocarcinoma, stage III disease with adnexal involvement. In this case, the positive node was detected by lymphoscintigraphy as well as intraoperatively using gamma probe.

Sensitivity of the technique was calculated as the proportion of true positives to the total patients who tested positive for sentinel nodes. Hence, sensitivity of this procedure in our study was 100%. Negative predictive value was calculated as the proportion of patients who tested negative for sentinel nodes to the number of patients with negative pelvic nodes. None of the non-sentinel nodes had metastatic disease.

Table 2 Final histopathological findings

HPE	Number	%
Endometrioid adenocarcinoma	32	91.4
Endometrioid adenocarcinoma with foci of mucinous differentiation	1	2.9
Papillary serous carcinoma	2	5.7
Total	35	100
Grade of tumour		
Grade I	13	37.1
Grade II	14	40
Grade III	8	22.9
Total	35	100
Myometrial invasion		
< 50%	12	34.3
> 50%	23	65.7
Total	35	100

Table 3 Sentinel lymph node detection statistics

Sentinel node(SLN) detection	Number of cases			%
SLN detected	33			94.3
Not detected	2			5.7
Total	35			100
SLN detection per hemipelvis				
Left hemipelvis	26			74.3
Right hemipelvis	26			74.3
Bilateral detection	19			54.3
Unilateral detection	16			45.7
Pelvic vs para-aortic SLN				
Pelvic SLN detection	31			88.6
Combined pelvic and para-aortic SLN detection	2			5.7
Not detected	2			5.7
Total	35			100
Type of tumour and SLN detection				
	Total number	SLN detection		
Endometrioid adenocarcinoma	32	30	93.7	
Adenocarcinoma with foci of mucinous differentiation	1	1	100	
Papillary serous	2	2	100	
Tumour grade and SLN detection				
	Total number	SLN detection		
Grade I	13	13	100	
Grade II	14	12	85.7	
Grade III	8	8	100	
Myometrial invasion and SLN detection				
	Total number	SLN detection		
< 50% myometrial invasion	12	12	100	
> 50% myometrial invasion	23	21	91.3	
FIGO stage and SLN detection				
	Total number	SLN detection		
IA	16	16	100	
IB	14	13	92.8	
II	4	3	75	
IIIA	–	–	–	
IIIB	–	–	–	
IIIC1	1	1	100	

Therefore, the negative predictive value of the procedure in our study was 100.

Discussion

This prospective observational study has shown that SLN biopsy using cervical injection of Tc99m nanocolloid alone can be an effective alternative to avoid complete lymphadenectomy along with its related complications in early stage endometrial cancer.

We decided to use Tc99m nanocolloid as it has been in use for sentinel node mapping in breast cancer for over 2 years in our institution, yielding good results. Due to reports of anaphylactic reactions following injection of methylene blue and difficulty in procuring it in the purest form, we have used only Tc99m nanocolloid for SLN detection [8]. To the best of our knowledge, this is the first study done on the feasibility of

cervical injection of using Tc99m nanocolloid alone without the use of methylene blue. Ballester et al. used a cervical dual injection technique using Tc99m sulphur colloid and methylene blue [6]. Maccauro et al. used Tc99m nanocolloid in his study but used a peritumoral injection technique through hysteroscopy 3–4 h prior to surgery [9]. However, the procedure may be cumbersome and resulted in vasovagal reaction in some patients.

The technique used in our study was cervical injection technique. This technique has been already proven to have higher detection rates according to the meta-analysis of Kang et al. [10]. Various studies employing hysteroscopic, peritumoral and myometrial injections have not shown good results [11]. Most commonly described positions in cervical injection technique are four-quadrant injection at 3, 6, 9 and 12 O'clock [6]. Some studies using indocyanine green have used a two-quadrant injection at 3 and 9 O'clock [12]. However, we discovered that with usage of these positions,

there was an increased chance of inadvertent entry of radiotracer into the cervical vessels and into the systemic circulation. Hence, 2, 4, 8 and 10 O' clock positions in the cervix were chosen. 23G spinal needle was used for injection as against 25G which is described in studies [6]. We found that comparatively less resistance was observed while injecting into the cervix, and at the same time, there were less chances of bleeding from the injection site. Rapid injection against resistance sometimes resulted in spillage and contamination of vagina, which obscured the nodes in the scintigraphic imaging. Hence, a slow injection with a wide bore needle is recommended based on our experience.

The technique was adopted from a large multicenter study called the SENTI-ENDO study by Ballester et al., in which cervical dual injection technique was used wherein preoperative Tc99m sulphur colloid injection was done followed by intraoperative injection of patent blue [6]. However, our study differs by the fact that we did not use patent blue and employed a single-injection protocol. The median time interval between lymphatic mapping and surgery was 18–22 h. While radiocolloids require an injection on the day before surgery, colorimetric dyes like patent blue and ICN injection are done just before the procedure after induction of anaesthesia [13] [14].

We proceeded with complete pelvic and lower para-aortic lymphadenectomy in all the patients irrespective of the sentinel node dissection. In our study, the most commonly detected SLN was obturator node (71.4%) ($n = 25$), followed by external iliac node (51.4%) ($n = 18$). This finding coincides with the results of most of the studies wherein the obturator is the most commonly detected SLN [6] [14].

Successful SLN mapping was feasible in 93.7% of endometrioid adenocarcinoma; 6.3% had failed mapping of SLN. SLN biopsy was feasible in both the patients with non-endometrioid histology. Analysing the SLN detection with respect to stage of the disease, all patients with stage IA had sentinel lymph nodes detected, while detection was not feasible in one patient with stage IB and stage II each. A positive node was detected in one patient with stage III disease on final pathology; the same was detected by mapping as well. Both patients with failed mapping had a grade II disease and more than 50% myometrial invasion. However, due to small sample size, we could not do any statistical analysis for these parameters and draw a conclusion. Other studies have also not commented on the relationship between these parameters and feasibility of sentinel node mapping.

We analysed the detection rate of SLN per hemipelvis in our study. The detection rate on the left and right hemipelvis was 74.3% in our study. This kind of an analysis is important, because according to the NCCN guidelines 2016 for sentinel node mapping, a side-specific dissection is recommended in case of failed mapping on one side [7]. Our results are comparable with the results of larger studies like the SENTI-

ENDO study where the overall detection rate was 89% and bilateral detection rate was 69% [6]. How et al. had a detection rate of 92% with a similar technique with bilateral SLN detection being 72% [15].

Among the 35 cases, sentinel node detection was feasible in 33 (94.3%) which included a case of papillary serous carcinoma, 3 cases of stage II, one case with IIIC disease and 8 high-grade endometrial cancers. Among the SLN detected cases, one had a histologically positive node which was detected on scintigraphy as well as intraoperatively by the gamma-probe. None of the non-sentinel nodes were involved by tumour. Therefore, the sensitivity of the procedure was 100% and there was no false negative node, making the negative predictive value 100% in our study. Larger studies like that of Ballester et al. and How et al. had false negative rates of 16% and 11%, respectively. Larger study numbers would probably increase our false negative rates as well.

Of the two cases wherein SLN detection was not feasible, one had a stage II disease with cervical stromal involvement, which probably prevented the transit of radiotracer. The other case was an early-stage endometrioid cancer with > 50% myometrial invasion but had enlarged iliac nodes intraoperatively. These nodes were not involved by tumour but showed evidence of reactive histiocytosis on histopathology. It is likely that lymphatic channels were blocked or altered due to the enlarged lymph nodes and this could be a reason for negative SLN biopsies.

The main drawback of our study apart from our sample size was that the pathological analysis of nodes was done by routine haematoxylin-eosin staining. Ultrastaging which is recommended to detect micro-metastasis of sentinel lymph node procedure was not performed [16].

Recently, the advent of indocyanine green (ICN) has brought about a drastic improvement in detection rate of SLN in endometrial cancers to as high as 100% [14, 17]. However, ICN needs an infrared imaging or a robotic platform. In a developing country like India, where out-of-pocket expenses for cancer treatment are extremely high, it becomes important to develop a cost-effective, safe and efficacious method of SLN mapping in endometrial cancer which will lead to optimum patient care.

Conclusions

SLN biopsy in endometrial cancer using intracervical injection of Tc99m nanocolloid is a safe and easily reproducible technique with good detection rates and high sensitivity. Stage of the tumour, grade and myometrial invasion do not seem to have an influence on sentinel node detection. Cervical involvement, enlarged lymph nodes and obstructed lymphatics could affect sentinel node mapping adversely though more data is needed to prove this. More studies on this are required

before it is accepted as a standard of care in the treatment of women with endometrial cancer.

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