

Influence of Tumor Size on Sentinel Lymph Node Detection in Operable Uterine Cervical Carcinoma Patients.Vijaya Lakshmi V V¹, Narendra Hulikal², Amit Kumar Chowhan³¹Assistant Professor, Department of Surgical Oncology, Oncology Block, St Johns Medical College and Hospital, Johnnagara, Bengaluru, Karnataka²Professor and Head, Department of Surgical Oncology, Sri Venkateswara Institute of Medical Sciences, Tirupati, Andhra Pradesh³Professor and Head, Department of Pathology, All India Institute of Medical Sciences, Tatibandh, Raipur

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Abstract:**Background and objectives:** The National Comprehensive Cancer Network (NCCN) cervical cancer guidelines presents Sentinel lymph node (SLN) mapping as an alternative for the surgical management of early stage cervical cancer less than 2 cms in diameter. This study was conducted to evaluate the impact of tumour size in detecting SLN in early stage operable cervical cancer, using low cost methylene blue dye alone in a prospective manner.**Methods:** This prospective study was conducted in biopsy proven female patients with early stage operable cervical cancer meeting the selection criteria and attending the surgical oncology department of a tertiary care center in south India, from June 2016 to December 2017. After induction of anesthesia, 4 ml of 1% methylene blue was injected into the cervix peritumorally under direct observation. This was followed by laparotomy or laparoscopy, identification and removal of SLN, pelvic lymph node dissection and radical hysterectomy.**Results:** In this study, 20 patients with operable cervical cancer were analyzed. SLN detection rate was 90%. Mean SLN per patient was 3.1. Obturator group (45%) was the most common SLN station. SLN detection in relation to tumor size less than 2cms and more 2 cms was 90.9% and 88.9% respectively (p value 0.88).**Conclusion:** The tumour size of the patient does not significantly influence the SLN detection using methylene blue dye alone undergoing radical hysterectomy in early stage operable cervical carcinoma. There was a trend towards higher SLN detection with smaller size tumour.**Keywords:** Cervical Cancer, Tumor Size, Methylene Blue Dye, Sentinel Lymph Node Biopsy, Pelvic Lymph Node Dissection, Radical Hysterectomy.

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Introduction

Cervical cancer is the third most common cancer among women, worldwide. It is the second leading cause of cancer death in women in developing countries. [1] In India, the incidence of cervical cancer is 123000, contributing to about 25% of global count, with 67000 deaths per year, and a 5yr prevalence of 309000. [2,3]

Sentinel lymph node biopsy (SLNB) is a diagnostic technique used to determine the local and regional lymph node involvement of cancer by identifying and examining a targeted lymph node sample. Sentinel lymph node (SLN) is the first node draining the primary tumor. The concept is that, lymph drains in an orderly pattern away from the tumor, hence a histologically negative SLN predicts the absence of tumor metastasis in the non-sentinel nodes [4].

The incidence of nodal metastases in women with early-stage cervical cancer is only 15%–20% [5,6,7], meaning that 80%–85% of patients undergo an unnecessary complete pelvic lymphadenectomy, a procedure associated with increased blood loss, neurovascular and ureteral injuries, infections, lymphedema, lymphocyst formation, and venous thromboembolism [8].

The factors known to affect SLN identification rates include the age, lymphovascular invasion (LVI), body mass index (BMI), tumor grade, tumor size, SLN mapping methods, and tumor location [9].

The current management for patients with early stage operable cervical cancer (upto Federation Internationale de Gynecologie et d'Obstetrique

FIGO IIA) is radical hysterectomy and pelvic lymph node dissection.

The different techniques available for SLN detection are radioisotope labelling with Tc 99m and dyes, alone or combined. In India and other developing countries, cervical cancer is more prevalent. It may not always be possible to have availability of the required isotopes, nuclear medicine facility and expensive infrastructure to perform radio labelling for SLN detection. In India, it is more practical for the detection of SLNs using, readily available, low-cost methylene blue dye. Although tumor size is of prognostic importance in cervical carcinoma patients, its role in the detection of SLN is unclear. We therefore evaluated the influence of uterine cervical tumor size in identifying the SLN using methylene blue dye alone, in a prospective manner

Aims:

The influence of tumor size on the detection of sentinel lymph node using methylene blue dye alone in clinically node negative FIGO stage I-IIA cervical carcinoma

Materials & Methods:

This prospective study was conducted after ethical committee approval, in biopsy proven early stage operable cervical carcinoma patients of Sri Venkateswara institute of Medical Sciences, Tirupathi, from June 2016 to December 2017.

After obtaining informed consent from the patients, clinical examination findings, tumour extent, biopsy report, blood investigations and image findings of all the patients were recorded.

After induction of anaesthesia, patient was placed in lithotomy position, under direct observation, 4ml of 1% methylene blue was injected into the cervix

peritumorally (1ml each at 12, 3, 6 and 9 O' clock position) with a 25gauge spinal needle. A SLN was defined as any blue node or a blue lymphatic leading to a node. The absence of a lymph node identified by blue dye was documented as a failed sentinel lymph node mapping. After injection, laparotomy or laparoscopy was done and a careful inspection for SLN was done in the bilateral pelvic region about 20 minutes after injection of the dye. [10] A note was made as to whether a SLN was identified or not. If identified the location of the node was noted. All the sentinel lymph nodes that were identified, were dissected and sent for frozen section.

All patients regardless of the outcome of the intraoperative pathology report underwent bilateral complete pelvic lymphadenectomy, the boundaries of which are given in the table no.1 below. Following the bilateral pelvic node dissection, radical hysterectomy was performed. The SLN, the pelvic node dissection and radical hysterectomy specimen were analysed with final paraffin section.

SLN was serially sectioned perpendicular to the long axis at 2.0mm intervals. Blocks were examined through routine hematoxylin and eosin (H&E) staining. If sentinel node had a metastasis in the initial H&E stained section, no further workup was performed on that lymph node. If a sentinel node was negative on the initial section, ultrastaging was performed. This entailed performing 5 wide H&E levels at 250 micrometer intervals. With each level, 2 unstained slides were cut (total of 10 unstained slides). If in ultrastaging H&E intervals were negative, 1 unstained slide at each level was subjected to immunostaining with pancytokeratin [11].

Table 1: Anatomic boundaries Bilateral Pelvic lymphnode dissection:

Lateral	Genitofemoral nerve
Medial	Anterior division of the hypogastric artery and the ureter
uperior	Bifurcation of the aorta
Inferior	Deep inferior epigastric vessels.

Inclusion Criteria:

All patients with newly diagnosed, early cervical cancer (FIGO stage I - IIA) confirmed on final histopathology and willing to participate in the study aged 18-70 years with Squamous cell, adenocarcinoma or poorly differentiated histology.

Exclusion Criteria:

1. Patients with FIGO stage IIB and higher cervical cancer on conventional imaging.
2. Those patients who are pregnant, medically unfit for surgery.

3. Unequivocal evidence of nodal involvement on preoperative imaging
4. Those who have received RT or chemotherapy before surgery.
5. Pre-invasive stage of cervical carcinoma, non-epithelial histology, small cell carcinoma etc.
6. Patients not willing for the procedure.

Statistical Analysis:

At the end of study, patient characteristics were compared using *t* tests for continuous variables and a χ^2 test for categorical variables.

Results

In this one and half year prospective study, 45 patients with cervical lesions who underwent surgery (radical hysterectomy) were studied. Twenty patients were analyzed and remaining 25 patients were excluded from the study in view of not fulfilling the inclusion criteria.

Mean age of the studied patients was 52.85 years (32-70years) and common histology was squamous cell carcinoma (19) followed by adenocarcinoma (1). Three-fourth of the patients underwent open radical hysterectomy (15) and remaining patients operated through laparoscopic radical hysterectomy (5)

Table 2: Tumour characteristics of patients (n=20)

Parameters	values
Clinical staging (FIGO)	n (%)
Stage IA1	4 (20%)
Stage IB1	12 (60%)
Stage IB2	2 (10%)
Stage IIA	2 (10%)
SLN location, n (%)	
Obturator	40 (72.7%)
Exetrnal iliac	12 (21.8%)
Internal iliac	3 (5.5%)
FIGO Federation Internationale de Gynecologie et d'Obstetrique; SLN sentinel lymph node	

SLN detection rate was 90% (18 patients). SLN detected was higher in laparoscopic radical hysterectomy than open radical hysterectomy (100% > 86.87%). Total SLNs detected were 55(1-8). Median and Mean SLN detected per patient was 3. Total pelvic lymph nodes including the sentinel lymph nodes assessed in the final HPE were 342.

Ten percent (2) of study population had metastatic deposits in the SLN. Fifty percent (1) of stage IIA and 8.3% (1) of stage IB1 patients had sentinel lymph node metastasis, detected by ultra-sectioning the lymph node and confirmed by histopathological examination. Of the detected metastatic deposits one was micrometastatic (0.2-2.00mm) and the other macrometastasis (5.0 mm in size.)

Stage based lymph node positivity

Table 3: showing stage based SLN detection and correlation with lymph node metastasis

Stage of cervical cancer	No. of cases	SLN not detected	No. of SLN detected cases	Metastasis
IA1	4	-	4	-
IB1	12	2	10	1 macro metastasis
IB2	2	-	2	-
IIA	2	-	2	1 micro metastasis
Total	20	2	18	2

Tumour size and SLN detection rate

In the present study, out of the 20 patients, 11 patients had cervical lesion less 2cms and 9 patients had cervical lesion more than 2 cms.

SLN was detected in 10 out of the 11 patients with cervical lesion size less than 2 cm. This accounts for SLN detection in 90.9% of the cases with lesion size less than 2cms. In the 9 patients that had cervical lesion size more than 2 cm, SLN was detected in 8 patients, accounting for 88.9 % detection in tumor > 2 cm. (p value 0.88)

Discussion

The National Comprehensive Cancer Network (NCCN) cervical cancer guidelines presents SLN

mapping as an alternative for the surgical management of early stage cervical cancer less than 2 cms in diameter. [1]

In the present study, the mean age was 52.85 years, which was comparable with D Stefano et al study [14] with 49 years and Yuan et al [10] study with 42 years. D Stefano et al [14] and Yuan et al [10] had used single agent methylene blue to detect sentinel lymph node biopsy.

In the present study, the most common stage of presentation was FIGO stage IB cervical cancer. In early operable cervical carcinoma, FIGO stage IB was the most common stage of presentation as seen in other studies. Operable cervical carcinoma is not a very common disease.

Table 4: comparing the most common stage of cervical carcinoma presentation and sample

Author	Technique	Number of patients	Stage
D Stefano et al. (D) [14]	Dye alone	50 (double center)	IB
Yuan et al. (D) [10]	Dye alone	77 (31 cases post chemotherapy or radiation therapy for bulky disease)	IB
Present study	Dye alone	20	IB

quamous cell carcinoma and adenocarcinoma are the most common histologic types of cervical cancer. Squamous cell carcinoma was the most common histology in the present study, accounting for 95 % of the patients. Squamous cell carcinoma was the most common histology in D Stefano et al [14] study with 82 % and Yuan et al [10] study with 90.1%

In our present study on patients with early stage cervical cancer who underwent lymphatic mapping and SLN biopsy followed by complete pelvic lymphadenectomy, we were able to detect at least one SLN in 90% of the patients using single dye technique. D Stefano et al [14] and Yuan et al [10] study had a SLN detection rate of 90% and 93.9% respectively. The mean SLN detected in present study was 3 similar to Yuan et al study [10] and higher than D Stefano et al [14] study which was 1.9. The most common group of pelvic lymph node where SLN was found was obturator group in the present study and Yuan et al study. In D Stefano et

al study external iliac group was the most common site of SLN detection.

In S.Kadkhodayan et al retrospective study, laparoscopic surgery (93.9%), including robotic assisted (90.8%) method was associated with higher detection rate and sensitivity comparable to open surgery (88.5%). [12] In our study, SLN was detected in all the patients undergoing laparoscopic surgery (5/5, 100%) and in 13 of the 15 patients undergoing open surgery (86.7%)

A larger tumour size and an advanced stage were associated with lower detection rate and sensitivity. In these patients, the lymphatic tract may be destroyed and the rate of lymph node metastasis is higher, which hampers lymphatic flow, than with the smaller tumours. [12]. When nodes are replaced with tumor often they do not take up mapping substances and lymphatic mapping fails or the non-involved lymph nodes may be detected as SLNs, because the original SLN is completely replaced with cancer cells [13]

Table 5: Showing comparison of size based SLN detection

Author	Tumor size \leq 2 cm	Tumor size $>$ 2 cm
Di Stefano et al [14] (methylene blue)	72%	28%
Rob et al [15] (patent blue + Tc 99m colloid albumin)	95 %	80%
Fader et al [16] (isosulfan blue + Tc 99 m sulfur colloid)	100%	
Altagassen et al [17] (patent blue + Tc 99m albumin)	94%	83.6%
Present study (methylene blue)	90.9 %	88.9 %

Altagassen et al [17] included all the stages of cervical carcinoma for SLN detection and 32% of their study population had tumour stage more than stage IB2 which must have contributed to lower detection rate in patients with tumour size $>$ 2 cm Rob et al [15] conducted an extensive literature review and found that for tumours $<$ 2 cm, the SLN detection rate was 95% and in tumours $>$ 2cms , the SLN detection was 80% Fader et al [16] study included patients with tumour size $<$ 2 cms and used combined mapping technique for SLN identification and had a 100% detection rate.

In a recent retrospective review and metaanalysis from MD Anderson Cancer Center including 188 early stage operable cervical cancer, there was no difference in SLN detection rate between patients with tumours $<$ 2 cm and \geq 2 cms [18]

In the present study, SLN detection was not significantly affected by tumour size in early stage operable cervical carcinoma (p value 0.88), though there was a trend towards higher SLN detection with smaller size tumours

The major limitation of the present study is the sample population. There are limited number of studies similar to our study for comparison. A larger prospective study is required to validate these findings.

Conclusion

The tumour size of the patient does not significantly influence the SLN detection using methylene blue dye alone undergoing radical hysterectomy in early stage cervical carcinoma.

There was a trend towards higher SLN detection with smaller size tumours.

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