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AN OBSERVATIONAL ANALYTICAL STUDY OF SENTINEL NODE MAPPING AND BIOPSY IN PATIENTS WITH STAGE I AND IIA CERVICAL CANCER

General Surgery

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ABSTRACT

AIMS AND OBJECTIVES: The observational analytical study was conducted in the Department of Surgical Oncology of Omega Hospital, Hyderabad

***Aim*:** To reduce the morbidity associated with pelvic node dissection in early stage cervical cancer.

***Objectives*:**

- Inject methylene blue dye at 3'0 clock and 9' 0 clock positions into the stroma of cervix and identify the sentinel node.
- Frozen section analysis of the sentinel node and its correlation with the final histological findings
- Subject the detected sentinel node, pelvic nodes to standard histopathological examination and detect correlation if any.

KEYWORDS

Sentinel Node , Cervical Cancer , Hyterectomy

Materials and methods

The study included 50 random patients of carcinoma of cervix operated between 1/8/2014 and 31/03/2016 at Omega hospital

Study design

New cases of suspected carcinoma cervix were seen in the Out Patient Department. Diagnosis and stage of the tumour was assessed by clinical examination. Cases diagnosed elsewhere as carcinoma cervix were assessed clinically to ascertain the stage. If there was any suspicion of tumour spread to bladder or rectum it was confirmed by biopsy and histological examination. After confirming that the patient is having carcinoma cervix with stage I or IIA, patient was counseled to undergo primary radiation or radical hysterectomy. Those patients chose to have the operation were given the option of enrolling into the study. Preoperatively all patients were investigated in the same manner with hematological and biochemical investigations, chest radiograph, electrocardiogram and a colposcopy with biopsy.

Inclusion criteria:

This is a prospective study which would recruit patients presenting at Omega hospital with Stage I and IIA cervical cancer between 2014 and 2016.

Patients undergoing open radical hysterectomy for stage I and IIA of cervical cancer.

Exclusion criteria:

- Patients who received Neo-adjuvant chemo radiation
- Patients who refuse to take part in the study
- Patients who have undergone surgery elsewhere.
- Stage IIb and higher of cervical cancer.
- Patients with a known allergy to Methylene Blue.
- ASA grade 3 and 4

Anesthesia and Incision

Spinal anesthesia was administered with epidural analgesia to all the patients. Patients were placed in the low lithotomy position to allow intraoperative vaginal access for cervical dye injection. Laparotomy was performed using a transverse (Maylard) midline incision to ensure adequate exposure to pelvic and low paraortic tissues.

Surgery procedure:

All patients underwent per vaginal examination under anesthesia before starting surgery for assessment of tumor and stage. After Laparotomy, assessment was done. Metastasis excluded. Cervix was visualized by placing a large speculum in the vagina ,took methylene blue 2ml ,diluted with 2 ml of normal saline. Made it two halves, methylene blue dye injected at 3' 0 clock and 9'0 clock positions into the stroma of cervix with the help of a spinal needle/IV needle and the sentinel nodes identified before opening the posterior peritoneum over the pelvic and para aortic area. Once dye uptake was observed in parametrial lymphatics, pelvic and lower paraaortic nodal regions were carefully inspected for dye uptake in lymphatic channels and specific lymph nodes .Up to 25 min were allowed for nodal dye uptake. The number and location of SLN are recorded on a standard proforma. Surgical findings, including specific locations of lymphatic dye uptake, were recorded on a diagram. Prior to lymphadenectomy, the lymph node(s) with obvious dye uptake was separately excised and designated the "sentinel" node. The pelvic nodal "basin" was defined as all lymph node-bearing tissue in the internal and external iliac, obturator, and distal common iliac nodal chains. A complete bilateral pelvic lymphadenectomy and radical hysterectomy (type III) were then performed.

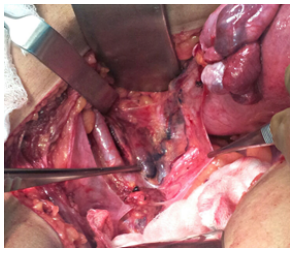

Figure:1 showing blue nodes and blue channels

All SLNs were sent for frozen section biopsy. Surgical findings were correlated with final pathology reports.

Figure 2: Blue node along with blue channel

Figure 3:Blue node

Patients were advised to undergo adjuvant chemoradiation therapy if they had high-risk tumor characteristics (serosal penetration of tumor, parametrial extension, etc.) or nodal metastases.

Histopathological examination of specimen:

Sentinel lymph nodes are sent to the pathology department for Frozen biopsy. No fixatives were added Lymph nodes are cut and touch imprints are taken for imprint cytology and then lymph nodes processed for frozen sectionImprint cytology and frozen section slides are stained with rapid H&E stain and observed under microscope and reported as

- Total number of sentinel lymph nodes isolated
- lymph nodes are involved by tumor/Not involved/showing

reactive hyperplasia

The tissue is further processed for routine histo pathological examination (paraffin sections are stained with H &E) and examined under microscope for further confirmation of frozen reports along with entire Radical hysterectomy specimen Final histopathology report consists of

1. Number of sentinel lymph nodes and total number of lymph nodes from each side of the pelvis were recorded.
2. Type of cancer, Grade, extent of invasion, angiolymphatic and perineural invasion and margin status(vaginal cuff/ parametrium/ lower uterine segment)
3. Pathological stage of the disease mentioned in the report Tumor assigned to Final Histo pathological TNM staging according to the 7th edition of the American Joint Committee on Cancer Staging 2010

Statistical Analysis

Statistical analysis was performed by SPSS23.0 version and statistical test chi square to find the association between study parameters. Sensitivity, Specificity, Positive Predictive value and Negative Predictive Value calculated for frozen section biopsy considering final histopathology as gold standard.

Results

A total of 50 patients with early cervix cancer agreed to participate in the study and underwent exploratory laparotomy for planned radical hysterectomy. The age range of the patients was 30-70 years(Table 5). Among them, 12 patients are between 30-40 years (23%),16 patients are between 40-50 years(32%),15 patients are between 50-60 years and above 60 years are 7(14%).Minimum age of the patients is 30 years and maximum age is 70 years (average 49, SD± 9.731)(figure 7).

Table 5

Age (Yrs)	No. of Patients	Percentage
30 - 40	12	24.00%
40 - 50	16	32.00%
50 - 60	15	30.00%
Above 60	7	14.00%
Total	50	

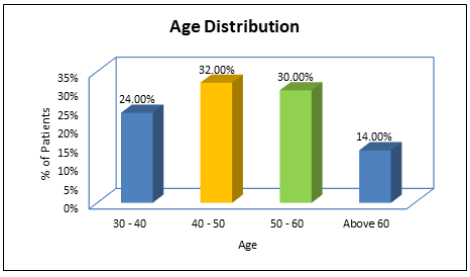

Figure 7: Bar chart of Age distribution

The clinical stages of patients were listed as Ib 1-34(68%), stage IB2 are 8(16%) and stage IIA are 8(16%)(Figure 8)

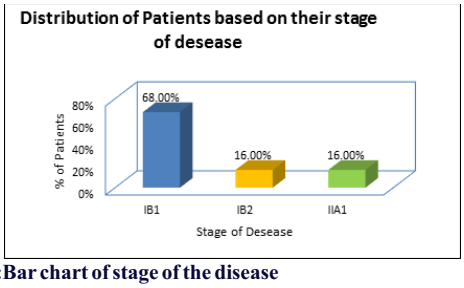

Figure 8:Bar chart of stage of the disease

Intra operative findings

All 50 patients were given blue dye pre operatively and seen for blue nodes and blue channels. It has taken 15-20 minutes to get the results. Those cases, where after 25 minutes if there are no blue nodes, declared in adequate for study .Blue nodes and channels were observed and their location carefully recorded. Of all 50 patients, blue nodes and /or blue channels are noted in 41patients (82%).No dye was seen in 9 patients (Table 6)

Table 6

blue nodes/blue channels detected	No. of Patients	Percentage
Yes	41	82.00%
No	9	18.00%
Total	50	

Blue nodes are seen in 38 patients' i.e, Sentinel Node detection rate is 76%

.Only these blue nodes in 38 patients are sent for frozen biopsy. Three patients had visible uptake into lymphatic channels but no clearly identifiable sentinel node (Figure 9&10)

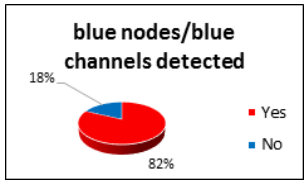

Figure 9: Pie chart blue nodes/channels

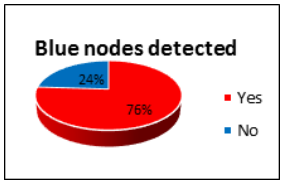

Figure 10: Pie chart- only Blue nodes detected

Dye uptake was seen in the parametrial lymphatic channels of 17 of 41 patients (41.46%)

Only Blue channels were developed more or less on both sides in 3 cases.

SLN (Blue nodes) were detected in 11(28.95%) cases in the right side, 25 (65.79%) cases in the left side and 2 (5.26%) cases in both sides.

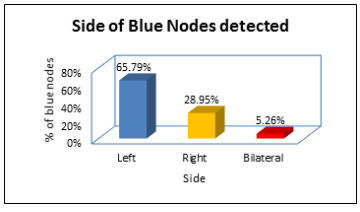

Figure 11:comparision of nodes on both sides detected

The locations of detected SLN were in, obturator area, internal iliac area, external iliac area, in the order of frequency. No aberrant Sentinel lymph nodes detected in our study. The commonest site was the obturator nodes (76.32%) followed by internal iliac node (28.95%). (Table 7). Bilateral obturator Sentinel nodes are seen in 1 patient (3.45%). In obturator area, on left side sentinel nodes are identified in 20 patients (68.97%) ,right side in 8 (27.59%) patients (Figure12).

Table 7 percentage of various blue nodes detected

Type of Blue Nodes Detected	No. of Patients	Percentage
Obturator	29	76.32%
Int Iliac	11	28.95%
Ext Iliac	2	5.26%

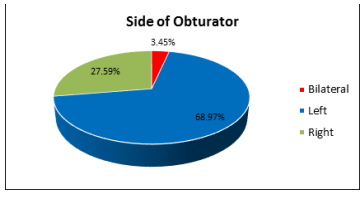

Figure 12 Side of obturator(Pie chart)

Internal iliac Sentinel nodes are noticed in 11 patients.left side noticed in 8 patients(72.73%) and right side noticed in 3 patients(27.27%)

Table 8 percentage of internal iliac blue nodes on either side

Int Iliac_Side	No. of Patients	Percentage
Left	8	72.73%
Right	3	27.27%
Total	11	

External iliac Sentinel nodes are seen in 2 patients.in both patients it was noted on right side.In one case nodes are assosiated with blue channels along the parametrium.A total number of 71 lymph nodes

identified in 38 patients.53 obturator nodes were identified in 29 patients with maximum numrer of 4 nodes in one(3.45%) patient, 3 nodes in 2(6.9%) patients,one node in 9 (31.03%) patients and 2 nodes in 17(58.62%) patients. A total number of 16 nodes were identified in 10 patients.A single node was observed in 4(40%) patients.2 nodes were observed in 6(60%) patients.In only 2 patients ,External iliac sentinel nodes were observed and in both cases only one node was identified in that basin.

Pathology

Blue nodes detected in all38 patients were sent for frozen biopsy.Sub capsular metastatic deposits were seen in 3 patients out of 38(7.89%).In all 3 cases, though 4 nodes were sent for frozen bopsy, only one node is positive for tumor deposits.In 35 (91.11%)cases frozen biopsy didn't show any tumor deposits. All tumors in our study turned out sqamous cell carcinoma.

Microscopic nodal metastasis were confirmed by final histopathology in 4 of 38 patients (10.53%). In three of these cases, nodal metastases were identified in the sentinel lymph nodes, accurately reflecting the pathologic status of the involved nodes. In the fourth patient only one node out of 24 nodes was positive for tumor on final histopathology ,where a retrieved sentinel lymph node didn't show any tumor on frozen biopsy. Thirty four (89.47%) histologically negative SLNs were retrieved from lymphatic basins in which nodal disease was absent on final histo pathology (Table 9) . In remaining cases where blue nodes were not detected, they didn't show any metastasis.

Table 9 frozen biopsy compared with final histopathology

Fozen	FINAL HPE		Total
	Positive	Negative	
Positive	3	0	3
Negative	1	34	35
Total	4	34	38

Sentinel node sensitivity of this study is75.00%,specificity is 100%,positive predictive value is 100% and negative predictive value is 97.14% (p value <0.001)(CI 95%)

Size of the tumor

In our study, 3 cm or less than 3 cm tumors are noticed in 30 patients (90%). Above 3 cm tumors are noted in 20 patients (40%). Sentinel node detection rate is 90% in patients with tumors ≤3 cm (26 patients), where as it is only 55% in patients with tumor >3 cm (55%)(Table 10). Final histopathology showed metastasis in 2 patients (6.67%) which coincided with frozen biopsy of Sentinel nodes in patients with tumor less than or equal to 3 cm. Metastasis were detected in 2 patients of tumor > 3 cm (11%) on final histology of which only one case was detected in frozen section biopsy.

Size of the tumor	no of pts %	SLN detected %	HPE + ve
≤3 cm	30(60%)	26 (90%)	2(6.67%)
>3 cm	20 (40%)	11 (55%)	2(11%)

Table 10 size of tumor and Sentinel nodes detected

A total number of 71 nodes detected in 37 patients.2 nodes were detected in 20 patients (52.63%).A single node was detected in 12 patients (31.58%), 3 nodes were detected in 5 patients(13.16%) and in one patient 4 nodes were detected(Figure 12)

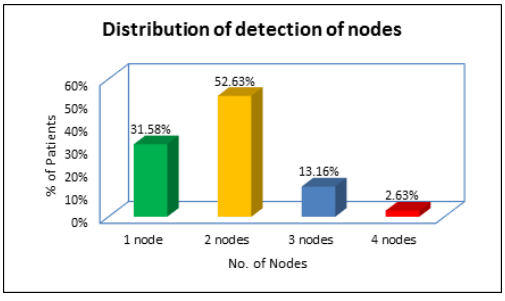

Figure 13: Bar chrt showing distribution of detection of nodes

Nodes on both sides detected in 2 patients.In both the patients frozen biopsy was negative and final histopathology also not detected any metastasis.(100% specificity and 100% negative predictive value (95% CI))

Discussion and Analysis

At present, the NCCN guidelines have not endorsed Sentinel lymph node identification and biopsy for cervix cancer. But panel recommends consideration of Sentinel node biopsy for IA1 individuals with LVSI, select patients with IA2-IB cervical cancer with tumors less than or equal to 2cmm (category 2B-appendix).They proposed a SLN mapping algorithm and advised the surgeon to follow it strictly .They also suggested that surgeon should perform side specific node dissection in any case of failed mapping and remove all suspicious and grossly enlarged nodes regard less of mapping. The two common methods for sentinel node dissection are using vital dyes and radioactive tracers. The vital dyes commonly used are isosulfan blue, patent blue violet, and methylene blue. Any blue-dyed node is considered to be a sentinel node. Radioactive tracers contain the 99m technetium radioisotope. In our study we used only methelene blue dye to detect the sentinel nodes. Any blue node is considered sentinel node. Sentinel node was detected in 76% of cases in our study. Robotic laparoscopic 3D vision and magnification is thought to facilitate the identification of lymph nodes in general and nonsentinel lymph node tumour suspect nodes in particular adding extra accuracy to the SLN concept.More recently, a novel mapping technique for cervical cancer SLN biopsy using indocyanine green (ICG) imaging and near-infrared (NIR) fluorescence imaging has been described. ICG is an agent that emits fluorescence which is generated from the contact of ICG with plasma proteins. The fluorescence signal is captured by a NIR laser and NIR camera, which transcribes the signal into a black and white image. The real-time laparoscopic images are then merged with the NIR fluorescence images and displayed on the screen. Therefore, the peri tumoural cervical injection of IGC will lead to the identification of the SLN by the use of NIR fluorescence imaging. almost all of them describe excellent negative predictive values ranging from 88% – 100%. Sensitivity appears to be more inconsistent.

Table11 sentinel node studies showing detection rate, sensitivity and negative predictive value

Study	Patients	Technique	Detection rate %	Sensitivity %	NPV
Dargent 2000(85)	70	dye	N/S	100	100
Levenback 2002(88)	39	Dye +technetium	100	88	97
Buist 2003	25	Dye +technetium	100	90	94
Rob et al 2005(86)	100	Dye	80	100	100
Wydra2006(87)	100	Dye +technetium	84	100	100
Altgassen et al 2008(93)	590	Dye +technetium	89	77	98
SENTICOL study 2011(92)	139	Dye +technetium	97.8	92	98.2
Present study	50	Blue dye	76%	75%	97

Conclusion

We finally conclude that Sentinel lymph node biopsy in stage I and IIA patients by injecting methylene blue dye is feasible and safe. However our results show a detection rate of 76% and negative predictive value of 97.14%%. In view of this, sentinel lymph node biopsy can be considered as a reliable marker of pelvic node involvement whenever it is identified Main limitations of this study are lack of sufficient number of patients, mapping with blue dye only instead of combination with technetium, open laparotomy approach (not laparoscopic or robotic pelvic node surgeries) and no facility for ultra staging of sentinel nodes, which were important factors noted in previous studies. An important consideration for sentinel lymph node mapping is the learning curve faced by those who will be performing them. Proficiency in the execution of sentinel lymph node mapping increases with experience as intracervical injection is technically challenging. We found that intra operative histological examination (frozen section and imprint cytology) is very much helpful because it correlated with final histopathology in 100% of cases in our study. Further research is needed in the field of Sentinel node biopsy in the form of Prospective, observational, multicentre studies are important to confirm the validity of Sentinel lymph node assessment. Until then it is recommended that sentinel lymph node mapping for cervix cancer can be conducted within a setting of controlled trial at high volume experienced centers.

References

1. Bray F, Jemal A, Grey N, Ferlay J, Forman D. Global cancer transitions according to the Human Development Index (2008-2030): a population-based study. The Lancet Oncology. 2012;13(8):790-801.
2. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. International journal of cancer Journal international du cancer. 2010;127(12):2893-917.
3. Asthana S, Chauhan S, Labani S. Breast and cervical cancer risk in India: An update. Indian journal of public health. 2014;58(1):5-10.
4. Bosch FX, Lorincz A, Munoz N, Meijer CJ, Shah KV. The causal relation between human papillomavirus and cervical cancer. Journal of clinical pathology. 2002;55(4):244-65.
5. Deacon JM, Evans CD, Yule R, Desai M, Binns W, Taylor C, et al. Sexual behaviour and smoking as determinants of cervical HPV infection and of CIN3 among those infected: a case-control study nested within the Manchester cohort. British journal of cancer. 2000;83(11):1565-72.
6. Henriksen E. The lymphatic spread of carcinoma of the cervix and of the body of the uterus; a study of 420 necropsies. American journal of obstetrics and gynecology. 1949;58(5):924-42.
7. Sakuragi N, Satoh C, Takeda N, Hareyama H, Takeda M, Yamamoto R, et al. Incidence and distribution pattern of pelvic and paraaortic lymph node metastasis in patients with Stages IB, IIA, and IIB cervical carcinoma treated with radical hysterectomy. Cancer. 1999;85(7):1547-54.
8. Barranger E, Darai E. Lymphatic mapping for gynecologic malignancies. Seminars in oncology. 2004;31(3):394-402.
9. Fuller AF, Jr., Elliott N, Kosloff C, Hoskins WJ, Lewis JL, Jr. Determinants of increased risk for recurrence in patients undergoing radical hysterectomy for stage IB and IIA carcinoma of the cervix. Gynecologic oncology. 1989;33(1):34-9.
10. Delgado G, Bundy B, Zaino R, Sevin BU, Creasman WT, Major F. Prospective surgical-pathological study of disease-free interval in patients with stage IB squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. Gynecologic oncology. 1990;38(3):352-7.
11. Yin YJ, Li HQ, Sheng XG, Li XL, Wang X. Distribution Pattern of Circumflex Iliac Node Distal to the External Iliac Node Metastasis in Stage IA to IIA Cervical Carcinoma. International journal of gynecological cancer : official journal of the International Gynecological Cancer Society. 2014.
12. Corn BW, Lanciano RM, Greven KM, Noumoff J, Schultz D, Hanks GE, et al. Impact of improved irradiation technique, age, and lymph node sampling on the severe complication rate of surgically staged endometrial cancer patients: a multivariate analysis. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 1994;12(3):510-5.
13. Bats AS, Mathevet P, Buenerd A, Orliaguet I, Mery E, Zerdoud S, et al. The sentinel node technique detects unexpected drainage pathways and allows nodal ultrastaging in early cervical cancer: insights from the multicenter prospective SENTICOL study. Annals of surgical oncology. 2013;20(2):413-22.
14. Scheidler J, Hricak H, Yu KK, Subak L, Segal MR. Radiological evaluation of lymph node metastases in patients with cervical cancer. A meta-analysis. Jama. 1997;278(13):1096-101.