Role of Sentinel Lymph Node Biopsy in Early Cervical Cancer

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Background

Sentinel lymph node (SLN) is defined as the first echelon lymph node for an anatomical region reached by the lymphatic drainage [1]. In breast cancer and melanoma, the role of sentinel lymph node mapping and biopsy using peritumoral injection of radioactive colloid in combination with a blue dye is well established [2, 3]. A histologically negative SLN predicts the absence of tumor metastasis in the non sentinel nodes. [4, 5]

In cervical cancer, involvement of regional lymph nodes is one of the most reliable prognostic factors [6, 7]. Presently radical hysterectomy with complete pelvic lymphadenectomy is the standard surgical procedure for patients with early cervical cancer. In patients with early cervical cancer (FIGO Stage IB1, IB2) pelvic lymph node metastasis is expected in 10–15 % of cases [8]. In node negative group of patients, pelvic lymphadenectomy has low benefit, but increases the risk of complications like lymphocyst formation and lymphedema. SLN mapping using peritumoral injection of radio-isotope and blue dye with or without lymphoscintigraphy, followed by intraoperative detection using a gamma probe has been proposed to be a useful technique for identification of SLNs in patients with early cervical cancers. Several blue dyes like cyalume, methylene blue and isosulfan blue were investigated for SLNB initially. Methylene Blue has been found to be one of the suitable and feasible dyes for sentinel node mapping [9]. The purpose of

this study is to evaluate the feasibility, usefulness and clinical impact of this technique in twenty consecutive patients with early cervical cancer.

Methods

Between January 2004 and January 2006, twenty patients with biopsy proven early stage cervical cancer (FIGO Stage IB1 and IB2) were taken up for study at Manipal Comprehensive Cancer Centre. Informed written consent was taken from the patient to participate in the study. Patients with carcinoma cervix stage-II and above, previous pelvic radiotherapy, previous retroperitoneal surgery and previous chemotherapy were excluded from the study. A total of 20 patients were included in this study. Stage and histology of the tumor are given in Table 1.

A combination of Methylene blue dye and radioactive ^{99}Tc -Sulphur nano-colloid was used. Two hours prior to surgery radioactive ^{99}Tc -Sulphur nano-colloid was injected in all four quadrants of tumor submucosally ($0.2\text{ ml} \times 4 = 0.8\text{ ml}$ 1mci) using a 25 gauge hypodermic needle. Methylene blue was injected on table after induction of anesthesia ($1\text{ ml} \times 4 = 4\text{ ml}$) at the same locations as the radioactive colloid with help of speculum (Fig. 1). On opening the abdomen and exposure of pelvis, SLN were localized using hand held gamma probe (Europrobe) (Fig. 2). The entire lymphatic tissue was also examined visually for presence of blue stained lymph nodes (Fig. 3). All the hot or blue nodes were dissected, labeled and sent separately for histopathological examination. Their relationship with major vessels was recorded. This was followed by radical hysterectomy with lymphadenectomy in all cases. After bisecting the nodes, they were sectioned at 2 mm intervals; further these slices are serially sections at $200\text{ }\mu\text{m}$ depth to evaluate the sentinel node as per college of American pathologist guidelines for sentinel nodes. The SLN and other lymphadenectomy nodes

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Table 1 Stage and histology of patients in the study

	Number of patients(<i>n</i> =20)
Stage	
Stage IB1	14
Stage IB2	6
Histology	
Squamous cell carcinoma	18
Adenocarcinoma	1
Collision (adenosquamous)	1

were assessed separately by the pathologist using hematoxylin and eosin staining and the results were compared.

Results

The SLN was detected in all cases (Identification rate—100 %). The mean number of sentinel nodes was 2.7. Methylene blue dye could detect sentinel node (blue node) in 90 % cases (*n*=18). Gamma probe could detect SLN (hot node) in 95 % of cases (*n*=19) (Table 2). In one patient, only blue dye identified the SLN which was a parametrial node. This was because of the shine through effect from primary site of injection of radioactive colloid since the sentinel node was very close to the cervix and in the parametrium. In 16 patients (80 %) sentinel nodes were located in pelvis only whereas 10 % they were detected at the aortic bifurcation and in further 10 % they were detected in pelvis as well as at aortic bifurcation. Of the 16 patients were sentinel node were located in pelvis only, in 4 they were at the obturator area, in 8 at the origin of the uterine artery, in 3 at the division of the common iliac artery and in parametrial region

Fig. 1 Methylene blue being injected per speculum on table after induction of anaesthesia

Fig. 2 Sentinel lymph node being located using hand held gamma probe (Europrobe)

in one. In three patients bilateral drainage was identified. In 6 patients (30 %) the SLNs were positive for metastasis, of these two had stage IB1 and remaining four had stage IB2 disease. There were no false negative cases. These results completely correlated with the final histopathology of the pelvic lymphadenectomy specimens (Table 3). In 33.3 %(*n*=2) cases the Sentinel node was the only positive node. The mean size of positive sentinel node was 0.8 mm

Discussion

Lymph node status is both a major prognostic factor and decision criteria for adjuvant therapy in patients with

Fig. 3 Visual detection of blue stained nodes

Table 2 Sentinel lymph node identification rate with blue dye and gamma probe

Technique	Sentinel node detection
Blue dye	90 % (<i>n</i> =18)
Gamma probe	95 % (<i>n</i> =19)
Blue dye + Gamma probe	100 % (<i>n</i> =20)

cervical cancer. Pelvic node metastases are only detected in upto 17 % in stage IB and 12–27 % in Stage IIA in cervical cancer. Thus, as many as four out of five patients derive no benefit from pelvic lymphadenectomy; this procedure increases morbidity, especially when post operative radiotherapy is required. Cervical cancer patients with negative pelvic nodes benefit from radical hysterectomy while those with histologically proven lymph node metastases require primary chemoradiation.

In our study, it was found that SLN detection in women with early cervical cancer is a feasible and safe technique. It is a promising surgical technique to confirm nodal status and minimize post operative morbidity through avoidance of unnecessary lymphadenectomy in the presence of a negative SLN.

A number of authors have published their work on SLN in the early stages of cervical cancer using the blue dye and/or radioisotope [10–13]. Initially, blue dye was used in open surgery for guidance of SLN biopsy, yielding identification rates in the range of 15.4 to 60 % [14]. Now it has been proved that a combination of blue dye and radioactive colloid is superior to blue dye alone. [15] Studies using blue dye and radioactive colloid in combination have been done with or without lymphoscintigraphy. In our study we have used blue dye and radio isotope without lymphoscintigraphy. Verheijen et al used preoperative lymphoscintigraphy with 99mTc-colloidal albumin and blue dye injection at the start of surgery in ten stage IB cervical cancer patients, among whom intraoperative gamma probe detection was successful in eight and visual detection in only four [10]. In our study, gamma probe could detect sentinel lymph node in 95 % of cases whereas blue dye was successful in identifying SLN in 90 % of cases. A 100 % identification of SLN was achieved with a combination of the two techniques. In a study of 50 patients with cervical cancer of FIGO

stages I-IV by Malur et al., a combination of radioactively labeled albumin and blue dye yielded an SLN detection rate of 78 %. [11]

Barranger et al. emphasised in several publications that in cervical cancer, regional lymph node status is a major prognostic factor and a criterion for the use of adjuvant therapy [16]. They asserted that the SLN procedure based on blue dye and radiocolloid is suitable for evaluation of lymph node status. Plante and Niikura published their experience with 20–30 patients with early cervical cancer [17, 18]. They achieved a detection rate of nearly 100 % using a combination of 99mTc-colloid and blue dye, without any false negative results. These authors found that SLN biopsy is less aggressive than complete pelvic lymph node dissection and decreases both post operative morbidity and cost. Angioli et al., however achieved a lower SLN detection rate both by lymphoscintigraphy (89 %) and during surgery (70 %) than other groups [19].

In the present study, in one case we found that the SLN in the parametrial region was identified only by the blue dye. SLN in this location is difficult to locate using gamma probe because of the proximity of the cervical tumor and the peritumoral area of increased radioactivity. In our study, we used methylene blue as the vital blue dye. Cyalume, methylene blue and isosulfan blue were the initial dyes investigated for sentinel lymph node biopsy (SLNB). Cyalume (a fluorescent dye) stains the lymphatics and surrounding tissue, generating a high background. Methylene blue, a water soluble dye, demonstrated poor lymphatic uptake in initial studies but recent work shows that it can be a substitute for isosulfan blue and is less expensive [9]. No adverse reactions with methylene blue were observed in our study. However there are reports of adverse reactions in studies, the incidence being as high as 21 % [20].

Conclusion

Validation of sentinel lymph node concept in carcinoma cervix opens the door to various possibilities in the management of carcinoma cervix. Sentinel lymph node can be subjected to more extensive histopathological assessment including the use of immunohistochemistry to detect metastases more accurately. SLNB along with intra-operative frozen section analysis of the sentinel node in early stages of cervical cancers could be utilized as a promising surgical technique to identify occult nodal metastasis and to minimize post-operative morbidity by avoiding unnecessary lymphadenectomy in presence of negative SLN. Successful implementation of lymphatic mapping techniques is dependent on the operator's experience. Good co ordination between the surgeon and nuclear medicine physician is required.

Table 3 Pattern of nodal metastases on final histopathology

Sentinel node	Lymphadenectomy nodes	No. of patients
+	+	<i>n</i> =6*
–	–	<i>n</i> =14
–	+	<i>n</i> =0

In 2 patients sentinel nodes were the only sites of nodal metastases

However ours is a small study and for the clinical validity of this technique large randomized multi institutional trials are required. Until then this should be done under clinical protocol as a part of trials until it becomes standard of care.

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