Sentinel Lymph Node Biopsy in N0 Neck for Squamous Cell Carcinoma of Oral Cavity: a Prospective Study

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Abstract Oral cancers in India are very common. SLNB (sentinel lymph node biopsy) for the management of the cN0 neck provides proper staging with less morbidity. The study aims at assessment of the technical feasibility and accuracy of SLNB. Two by two table and Kappa statistic was used to compare SLN and END. In 14 cases out of 16 cases, SLN was identified. Sensitivity and specificity of 100 % were found. One hundred percent agreement was observed between SLN and END using kappa statistics. A meta-analysis of 19 studies showed 97.7 % sentinel node identification rate and 92.6 % sensitivity with a false negative rate of 3 %. In patients with N0 neck and negative SLN, neck dissection can be avoided decreasing morbidity of SOND. SLN biopsy has potential to become standard of care for managing N0 neck; however, long-term oncological results need to be evaluated.

Keywords Oral cancer · Sentinel lymph node · Neck dissection

Introduction

Oral cancers are one of the commonest cancers and ranks number one in terms of incidence among men and third among women [1]. In the west, cancer of the tongue and the

floor of the mouth are common, whereas in the Indian sub-continent, the cancers of gingival and buccal mucosa are common due to placement of tobacco quid in the oral cavity. Among all risk factors for survival, lymph nodal status is the most important reason. Twenty-five to forty percent of patients with lymph node metastasis will achieve 5-year survival, in contrast to about 90 % of patients without metastasis showing poor outcome with lymph node involvement [2]. According to published data, the incidence of occult metastases in the neck with clinical N0 can range from 15 to 60 % depending on different prognostic factors [3]. Management of cases with clinically positive node is straight forward, treatment being radical/modified radical neck dissection. Management of clinically node-negative cases is controversial, options being observation, radiation or surgery. Elective neck dissection improved overall survival by 12.5 % and reduced risk of death by 36 % when compared with observation for node-negative, squamous cell carcinoma of the oral cavity [4]. These findings made strong evidence to decide treatment for N0 neck. A staging supraomohyoid neck dissection (SOND) is recommended for all patients with T2 disease at the primary site and possibly in T1 disease with greater than 4 mm depth of invasion.

SLNB (sentinel lymph node biopsy) in the management of the cN0 neck is introduced to lessen the morbidity associated with neck dissection, while still providing proper staging of the neck. SLN is the first node among all nodes in drainage area where metastasis spread first. So, if SLN is negative for malignancy, assumption is that the rest of the nodal area is free of tumour. Identification of SLN is done by radio colloid alone, blue dye alone or combination of both radio colloid and blue dye. Studies have shown identification rate of 97 % (range 90–100 %), negative predictive value of 96 % (range 88–100 %) [5]. There are very limited studies where they have used only blue dye to identify SLN. Results with the use of

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methylene blue dye is important because the radioisotope technique is costly and is not available everywhere; in addition, shine-through effect seen with radioisotope technique makes identification of SLN difficult. Logistics management represents another major obstacle for using radio colloid for the identification of SLN biopsy.

With respect to pathological examination, SLN undergoes detail examination. Step sectioning and immunohistochemistry analysis of SLN can be done because of low sample volume. The exact importance of micro-metastases and isolated tumoural cells in the lymph node is not known presently, but in the future, it may be a treatment-changing factor.

Aim and Objectives

This study aims to assess the technical feasibility of SLNB in patients with squamous cell carcinoma of the oral cavity with N0 neck using methylene blue dye only.

The study also aims to assess accuracy of SLNB by testing sensitivity, specificity, positive predictive value and negative predictive value.

Material and Methods

Study Area and Design

The prospective experimental study included patients treated at the tertiary care centre between 1st August 2012 and 30th April 2014. Ethical committee suggestions and clearance taken before the study was started.

Inclusion Criteria

The inclusion criteria are histopathological-proven cases of oral SCC and clinically N0 neck who is a candidate for END (cT2 and above lesions for all oral sub-sites; for carcinoma tongue and floor of mouth carcinoma lesions with cT1 having endophytic growth pattern or/and size more than 1 cm were included as chances of metastasis to the neck is more than 20 % of these cases).

Exclusion Criteria

The exclusion criteria are clinically node positive patients, clinically N0 neck who is eligible for observation (in cases of carcinoma lip, RMT, hard palate and GB patients with cT1; for carcinoma tongue and floor of mouth size less than 1 cm), recurrent cancers and history of any previous surgery or RT to neck.

Study Methodology

The incision is placed and flaps are raised in the subplatysmal plane. Flaps are raised before injecting dye as lymphatics run in the subplatysmal plane so raising flaps in this plane will not disrupt the lymphatics, and if the time taken for raising the flaps is longer, non-SLN nodes become blue. Two millilitres of sterile methylene blue dye is injected in the peritumoural area (Fig. 1). Within 5 min of the injection, all the nodes which turn blue is removed (Fig. 2); the stations are labelled and sent for frozen section and histopathological evaluation. Subsequently, END is performed. The lymph node stations are labelled and sent for histopathological evaluation.

Statistic Method

Sentinel lymph node identification rate is calculated. The two by two table is used for evaluating data. True positive, true negative, false positive and false negative percentage is calculated with the help of the two by two table. With the help of these values, sensitivity, specificity, positive predictive value and negative predictive values were calculated. Kappa statistic is used to compare SLN and END.

Results

Age/Sex Distribution, Clinical Stage

A total of 16 cases were seen over the study period. Overall mean age was 48.8 years (range 25–75 years). In women, mean age was 41 years and in men, mean age was 56 years. Among the 16 cases, there were 8 men and 8 women in study making sex ratio 1:1. Site distribution and clinical stage are as shown in Fig. 3. There were no cases of carcinoma of the floor of the mouth, RMT, lip or hard palate.

Fig. 1 Injection of sterile methylene blue dye in the peritumoural area

Fig. 2 Removal of the sentinel lymph node identified

Sentinel Lymph Node

In 14 out of 16 cases, SLN is identified, making the SLN identification rate of 88 % (Fig. 4). In two cases, SLN was not identified. The two cases where lymph node was not identified were both cT4, each G. B sulcus and buccal mucosa. The number of lymph node harvested ranged from one to eight nodes. Mean number of lymph node harvested was two. Following are neck levels in the neck where the sentinel lymph node was identified; in the tongue, seven SLN were identified at Level 2a and one case of carcinoma tongue lymph node was identified at level 1a, in which this patient had a lesion at the tip of the tongue. In B. M, two SLN were identified at Level 1b and in one case, lymph node was not identified. In G.B sulcus, four SLN were identified at Level 1b and in one case, lymph node was not identified. Among 14 patients where SLN was sent for frozen, section 2 came positive for metastasis; both cases were of carcinoma tongue. SLN has upstaged in 12 % of patients where SLN was performed.

Histopathology of Primary Lesion

With respect to the grade of tumour, among eight cases of tongue lesion, two were well differentiated and six cases were moderately differentiated. Among three cases of buccal mucosa, one was well differentiated and two cases were moderately differentiated. Among five cases of G. B sulcus lesion, three were well differentiated and two cases were moderately

differentiated. With respect to the margin of resection in 14 cases, among 16, margin was free, but in two cases, margins were positive, both cases being cases of the buccal mucosa.

Histopathology of Elective Neck Dissection

Mean number of lymph nodes harvested in END were 17.6 nodes (range 11–39 nodes). One case among 16 cases where SOND was done had metastatic to neck nodes. This case had SLN also positive. One case where SLN was positive and rest of SOND had no metastatic lymph node was counted as positive for lymph node metastasis. If SLN was not done in this case, this node would have been removed with SOND. Hence, when calculating statistic percentage, this case is also taken as positive. In calculating variables, we found zero false positive and zero false negative cases, making sensitivity and specificity of 100 %. One hundred percent agreement is observed between SLN and END using the kappa statistic ($k = 1$) (Fig. 5). Considering all indications for adjuvant treatment, adjuvant treatment was given to eligible patients after discussion of case in tumour board meeting.

Complications

Two cases complained of shoulder pain; one case had shoulder dysfunction. Numbness over the neck is complained by four cases; there was no case of deviation of the mouth or dribbling of saliva.

Discussion

Feasibility and Accuracy

The combination of methylene blue and radioisotope is the most common method described in papers for detection of SLN. Previous studies showed the low detection rate and high false negative rate for detection of SLN when methylene blue only is used for detection of SLN when methylene blue only is used for detection of SLN [6]. In contrast, our study where methylene blue dye is used for identification of SLN had a high identification rate of 88 and 0 % false negative rate. Our study is in agreement with a study by Seema Singh et al. from India showing SLN using the blue dye alone is feasible and has a high detection rate [7]. In one of the bigger study,

Fig. 3 Site distribution and clinical stages of 16 cases

Fig. 4 Sentinel lymph node identification

SLN identification rate was 95 %; 25 % patients were upstaged based on SLN biopsy [8]. Two patients were upstaged based on SLN biopsy. In the same study [8], overall sensitivity was found to be 90 %. Eight patients (4 %) were found to have false negative SLN biopsy. We found zero false positive and zero false negative cases, making sensitivity and specificity of 100 %. One hundred percent agreement was observed between SLN and END using the kappa statistic ($k = 1$). A meta-analysis of 19 studies showed 97.7 % sentinel node identification rate and 92.6 % sensitivity with a false negative rate of 3 % [9]. Mahima Rakheja et al., in his study, showed that sentinel lymph node biopsy is feasible and helpful in N0 necks for detecting in lymphatic spread of oral malignancy [10]. We had no cases of carcinoma of the floor of the mouth where other studies showed low sensitivity and specificity for these sub-sites. We do not have long-term follow-up of our patients. Results are available where the SLN biopsy is done, without SOND in SLN negative cases. In patients with negative pathologic results, 3.8 % subsequently developed a disease within 24 months showing low recurrence rate with SLN [11].

Fig. 5 Measuring the agreement rate between SLN and END using the kappa statistic

Complications

Since all our SLNB cases also underwent elective SOND, it is difficult to identify complications specific to SLNB. We assume that complications in our cases were mainly attributed because of SOND part of the neck dissection. The amount of dissection and nerve handling is more in SOND. Complications in our case could have been avoided; only SLN was done, avoiding SOND in node-negative cases. All patients had a bluish discoloration of urine; none of our patients had allergic reaction to blue dye.

Limitations

Our study is having small numbers. As study is not sufficiently powered, statistical data is not used to interpret results. Larger randomized studies are required to substantiate our conclusion. We presently do not have long-term follow on our cases. All these patients are on follow-up. As concluded in some studies, use of radiocolloid increases sensitivity of SLN; maybe we could have picked some extra SLN with the use of radiocolloid along with methylene blue dye.

Conclusion

Identification of SLN by methylene blue in squamous cell carcinoma of the oral cavity is feasible and accurate. In patients with N0 neck and negative SLN, neck dissection can be avoided decreasing morbidity of SOND. The SLN biopsy may contribute to predict lymph node metastasis in oral squamous cell carcinoma in the future but requires further validation by larger multi-institutional studies before it is recommended as a reliable diagnostic tool or standard of care.

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