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Sentinel lymph node biopsy in Early Oral Squamous cell carcinoma: A Review

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ABSTRACT
Sentinel lymph node is defined as the first lymph node(s) at a potential risk to receive tumor cells from the primary tumour. Hypothetically when the sentinel lymph node is free of tumor, the regional nodal basin is considered to be free of tumor. The identification of sentinel lymph node and its histopathological examination reduces the need of radical surgical procedure and its morbidity, if found free of tumor. In other words, sentinel lymph node biopsy (SNB) is considered a triage procedure. The concept of SNB has been designed since 1960 and in present era it is considered the most important advance in cancer management. Subsequently it was used in the management of penile carcinoma and malignant melanoma. With the passage of time its use was extended in the treatment of breast, vulvar, cervical, endometrial cancers and so on. Lymph node metastasis is important prognostic factor in the management of head and neck cancers. The status of the cervical lymph nodes is a crucial factor in determining the staging, management, and prognosis of oral cavity squamous cell carcinomas (OSCCs). The role of sentinel lymph node biopsy in patients with head and neck cancers has been studied and found useful in accurately predicting the nodal status of the rest of basin, thereby avoiding elective lymph node dissection in patients with early head and neck cancers. We are discussing various studies to demonstrate the accuracy and usefulness of SNB in such patients in this paper.

Keywords: Head, Neck, Cancer, Oral, Sentinel lymph node biopsy

INTRODUCTION

Sentinel lymph node (SLN) is defined as the first lymph node(s) receiving the tumor cells from the primary. This node is likely to be the first lymph node to harbour the metastasis and can provide information about the rest of the nodal basin. Hypothetically when sentinel lymph node is free of tumor, the rest of nodal basin is considered to be free of tumor.

The concept of SNB has been designed since 1960 and in present era it is considered the most important advance in cancer management [1]. Subsequently it took long time before it was used in the management of penile carcinoma and malignant melanoma [2,3]. With passage of time its use was extended in various other malignancies, like breast, vulvar, cervical, endometrial cancers and so on. Since the management of neck in patients with early head and neck squamous cell carcinoma (HNSCC) is controversial, the application of SNB may be of help in such patients. Same principle of SNB have been used by various authors in the management of early (T1-T2, N0) head and neck squamous cell carcinoma to reduce the morbidity and hospital expenses of unnecessary elective lymph node dissection. The neck node metastasis is important prognostic factor in

the management of these patients [4]. The five year survival rate of patients with HNSCC is reduced to 50% in presence of regional lymph node metastasis in neck [5]. The lymph node metastasis in patients with early head and neck cancers (T1-T2, N0) is in the range of 15-20% in elective lymph node dissection specimen [6].

The status of the cervical lymph nodes is a crucial factor in determining the staging, management, and prognosis of oral cavity squamous cell carcinomas (OSCCs). . Despite physical examination and various imaging techniques the i.e. ultrasonography (USG), computerised tomography (CT), Positron emission computerised tomography (PET-CT), magnetic resonance imaging (MRI), the lymph node metastasis can be missed. This inaccuracy of clinical examination and imaging to reliably detect occult cervical lymph node metastasis along with the evolving evidence from randomized clinical trials has resulted in elective neck dissections (ENDs) becoming the standard of care for the vast majority of patients with early stage OSCC (cT1/2, N0) [7]. However, close to 70% of the patients with early staged OSCC will not have cervical lymph nodal metastases and risk being subjected to overtreatment by an END thereby increasing morbidity and hospital costs as well as compromising the patient quality of life. Compared to elective neck dissection, sentinel node biopsy is minimal invasive, less morbid, cost effective and with better patient quality of life [8] The procedure involves combination of peri-tumoral injection of Tc-99 sulphur colloid and blue dye, hand-held gamma probe, although use of blue dye in floor of mouth with short distance between primary tumor and lymph node is problematic as it obscure the edges of tumor during resection [9]. The sentinel lymph node obtained is subjected to histopathological examination with or without use of immunohistochemistry to identify the lymph node metastasis for staging N0 neck. We are discussing various studies to find out the role and accuracy of sentinel lymph node biopsy in patients with T1-T2, N0 oral squamous cell carcinoma.

Discussion:

A number of single-institution retrospective studies, a few prospective multi-institutional studies, and a few meta-analyses have clearly demonstrated the efficacy of SLNB in the detection of occult cervical lymph node metastases in OSCCs. The most recent meta-analysis of 66 studies comprising >3500 patients showed a pooled SLNB identification rate of 96.3%, a pooled sensitivity of 0.87, a pooled negative predictive value of 0.94, and an area under curve of 0.98[10]. A subgroup analysis from the meta-analysis had shown the application of immunohistochemistry to increase the sensitivity of sentinel lymph node (SLN) detection by 11%. Further analysis showed no significant difference between the “serial sectioning” subgroup and “no serial sectioning” subgroup.

It has been further found that additional non-SLN metastases are detected in up to a third of the neck dissections following a positive SLNB, the percentages being 13% for isolated tumor cells, 20% for micrometastasis, and up to 40% for macrometastasis in SLNs[11]. A few authors have suggested that any type of neoplastic spread to the SLN has an adverse impact on survival; a completion neck dissection is hence currently recommended in all the SLN-positive patients[12]. Although an intraoperative frozen section can identify a proportion of patients with a positive SLNB, there remains a group of patients with occult disease which will only become apparent on the postoperative histopathology. Apart from the physical and psychological concerns about the necessity for a completion surgery in patients with positive SLNs, questions were also raised from the health economics perspective despite a few studies suggesting that SLNB is in fact more cost-effective when compared to END[13].

In a multi-institutional prospective study, the validity of SNB result was compared viz-a-viz with lymph nodes harvested after elective lymph node dissection in patients with T1-T2,N0 oral cancers. The trial involved 25 institutions over a period of 3 years enrolling 140 patients with invasive oral cancers(T1-T2N0), comprising of 95 cases of tongue cancer, 26 floor of mouth and 19 other oral cancers. Out of 106 negative SNB on haematoxylin and eosin staining, 100 Patients were found to have no additional pathological positive lymph nodes on ELD, corresponding to negative predictive value of 94%. In 40 patients with proven cervical metastasis, the true positivity rate was 90.2%, with high sensitivity for tongue tumors as compared to floor of mouth tumors. For T1 lesions, metastases were correctly identified

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in 100%. With the use of additional sectioning and IHC, NPV was 96%. (14)

A meta-analysis was conducted to systematically assess the accuracy of SNB in cT1/T2, N0 oral cavity and oropharyngeal SCC patients. 21 studies enrolling 827 patients were included neck dissection as reference test for SNB. Majority of patient had oral cavity SCC. The pooled data of meta-analysis demonstrated an overall sensitivity of 0.93 [95% CI 0.90-0.95]. No significant difference was shown in subgroups on subgroup analysis (15)

Martina and colleagues analysed the reliability of negative SNB and impact SLN metastases on regional control and survival of patients with early oral and oropharyngeal SCC. In their prospective cohort analysis, they included 111 patients between 2003-2010. The end point of the study was neck control rate, overall survival (OS), disease- specific survival (DSS), and disease- free survival (DFS), depending on the size of occult metastases. 42 of 111 patients (38%) were reported to have positive SNB (10 had isolated tumor cells (ITCs), 19 had micrometastases, and 13 had macrometastases). OS, DSS, and DFS at 3 years for SLN- negative and SLN- positive patients was 98% and 71%, 95% and 76%, and 98% and 73%, respectively. Statistically significant difference was found between the SLN- negative group and SLNs showing ITCs in DSS as well as between the SLN- negative group and patients with micrometastases in OS and DSS and between the SLN- negative group and patients with macrometastases in all 3 survival estimates (16).

An European Organisation for Research and Treatment of Cancer (EORTC) conducted prospective, observational study to establish, whether the technique of SLNB is reliable in staging N0 neck and a safe oncological procedure in patients with early stage oral SCC. A total of 415 patients with radiologically staged T1-T2, N0 SCC were enrolled by fourteen European centres. SNB technique was performed with an average of 3.2 nodes removed per patient. Patients were excluded if the sentinel node (SN) could not be identified. Patients with positive SLN were subjected to neck dissection within 3 weeks. The study was analysed after 3 years of follow-up. SLN detection rate was 99.5%. SLN was found to be positive in 23% (94 in 415) and false negative rate in 14% (15 in109) patients. Among false negative, eight patients were subsequently rescued by salvage therapy. Twenty two patients with recurrence after positive SLNB underwent neck dissection of whom 16 (73%) were in in the neck and only six patients were rescued. Only minor complications were reported following SLNB in 3% of patients. The sensitivity of SLNB was 86% and NPV of 95%. DSS was reported to be 94% (17).

In another prospective study, a total of twenty eight patients of ca buccal mucosa with clinically N0 nodes to evaluate the feasibility and role of SLNB using blue dye was carried out in India. SNB was performed after injecting 1-2 ml of 2.5% isosulphan blue dye peritumorally. During neck dissection, blue colored nodes were dissected out and sent for HPE and IHC for cytokeratin which was performed using peroxidase and anti-peroxidase method. A total of 37 SLNDs were identified in 27 patients with 1.3 LNs per neck. Of thirty seven SLNs, fourteen were positive including one detected by IHC and twenty three were negative. Six patients had only sentinel node positive for metastasis while as seven patients had other nodes positive in the neck apart from SLNs. Sensitivity and negative predictive value of sentinel node biopsy was 100%, while the specificity was 93.3% positive predictive value was 92.8. None of the patients with negative SLN had node positivity in other nodes. Thus, concluded a definite role of SLNB in patients with clinically N0 buccal mucosa cancer (18).

A meta-analysis of 66 studies was conducted to evaluate the diagnostic efficacy of SLNB in neck negative T1-T2 oral SCC. 3566 patients were included in the meta-analysis. On pooled analysis SLN identification rate was 96.3% (95%CI :95.3%-97.0%). The pooled sensitivity was 0.87 (95% CI: 0.85±0.89), pooled negative predictive value was 0.94 (95% CI:0.93±0.95), and AUC was 0.98 (95% CI: 0.97±0.99). Subgroup analysis suggested that SLN assessment using IHC resulted in significantly higher sensitivity (19).

The proposed advantages of SLNB are its ability to identify skip metastases and metastases in unpredictable lymphatic basins (which would not have been otherwise dissected in a standard END), a focused histologic evaluation of the identified nodes at risk, a decreased morbidity and an improved health-related quality of life. A few studies have

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further suggested SLNB to be an oncological safe alternative to END given the lack of a significant survival difference between both the groups[20]. However, it must be noted that there exists no adequately powered randomized clinical trial comparing SLNB and END in the setting of *N* zero neck in OSCC.

Over the years, there have been many technical innovations aimed at improving the intraoperative SLN localization, and these advances can possibly help clear some of the hurdles to the widespread implementation of SLNB in OSCCs. The advances include the development of novel radiotracers (^{99}mTc-tilmanocept), near-infrared light tracers (indocyanine green), improved imaging techniques (freehand single photon emission computed tomography), molecular assays, and the use of sentinel node navigation surgery.

CONCLUSION:

Surgical management of clinically neck negative patients of head and neck squamous cell carcinoma is controversial. Traditionally patients are subjected to elective or comprehensive lymph node dissection especially when the risk of occult lymph node metastasis is 15-20%. The said procedure is associated with significant morbidity, health care expenses and low patient quality of life. SNB is an alternative to neck dissection. Since various small studies to large prospective studies and meta-analyses have demonstrated SNB identification rate of more than 95%. Furthermore, the procedure has been useful in detecting occult metastases in the range of 25%-40% and thus clinically useful in staging N0 neck. False negative rate is within acceptable limits (<15%). NCCN guidelines 2020 also approves SNB technique for such patients with the caveat that its sensitivity is lower for patients with floor of mouth tumors ,which however can be overcome by first resecting the tumor before proceeding for SNB. given the potential for overtreatment by an END and the decreased survival of watchful waiting policy, clinicians must be aware of the growing body of evidence that suggests that adopting the philosophy of SLNB is a reasonable alternative to END in the management of *N* zero necks of early staged OSCCs provided it is performed by a dedicated multidisciplinary team. Although the routine use of SLNB over END may not be entirely justified in clinical practice as yet, the future scope of SLNB in advancing the concept of surgical minimalism in OSCC is indeed promising and exciting.

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