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Factors affecting lymph node yield in squamous cell carcinoma of mandibular Gingivo-Buccal sulcus.

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ABSTRACT

Lymph node yield (LNY) is a valid marker of prognosis in oral cancer. Precise estimation of LNY in Indian patients with T3/T4 gingivobuccal sulcus squamous cell carcinoma (GBS-SCC) has not been well documented. Hence, the primary objective of the study was to determine the LNY in patients with T3/T4 SCC of mandibular GBS, and the secondary objective was to study the association of LNY with clinicopathological factors such as tumor thickness, histological differentiation, number of positive nodes, and extracapsular spread (ECS). Study patients comprised biopsy proven T3/T4 SCC of mandibular GBS that underwent unilateral surgery (composite or bite composite resection with level I to level V-neck dissection and pectoralis major flap reconstruction) at sree balaji dental college and hospital,chennai in between year 2014 to 2016. Grossing of surgical specimens was done as per the guidelines established by the Royal College of Pathologists (December 2009). The surgical specimens of 12 patients yielded 320 lymph nodes with the mean LNY of 21.00 ± 5.00. Higher mean LNY of over 21 was significantly associated with ECS, number of positive nodes, delay in surgery over 15 days, skin involvement by the tumor, and presence of oral potentially malignant disorders. With the single surgeon, pathologist and same surgical procedure, the mean LNY in Indian patients with T3/T4 SCC of mandibular GBS is 21.00 ± 5.00. Although clinicopathological factors affect the estimation of LNY, further studies are needed to validate the findings of this study.

Keywords: Factors, gingivobuccal sulcus, lymph node yield, squamous cell carcinoma

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INTRODUCTION

Gingivobuccal sulcus (GBS) is a major subsite for oral squamous cell carcinoma (SCC) in the Indian subcontinent, and these tumors are known to recur locoregionally the following treatment.[1],[2] Accurate pathological staging is a critical factor in determining the prognosis in these patients. Like SCC of any other oral subsite, lymph node metastasis is a single most important independent prognostic factor in patients with GBS-SCC.[2] Apart from tumor node metastasis (TNM) staging, recent studies have shown the importance of other lymph node associated factors such as the exact number of positive nodes, total number of harvested nodes in the neck dissection, and the presence of extracapsular spread (ECS) as determinants of prognosis in oral SCC.[3]

Lymph node ratio (LNR) has emerged not only as a marker of prognosis [4],[5] but as a reliable tool in determining the extent of cancer spread, extent of clearance, and the need for adjuvant therapy following surgery for cancers of the stomach, esophagus, bladder, and colorectum, in addition to head and neck cancer.[5],[6],[7],[8],[9],[10] The LNR has been successfully validated as a strong predictor of survival in oral cancer.[4] However, accurate estimation of LNR depends on the lymph node yield (LNY) which has been shown to vary depending on anatomical, surgical, and pathological factors.[4],[5],[11]

Although previous studies have thoroughly evaluated the efficacy of LNR and LNY as prognostic markers in oral SCC, there is a lack of uniformity in these studies with regard to specific oral subsite of SCC, TNM stage-specific distribution of cases, neck dissection procedure, and standardization of harvesting lymph nodes from the neck dissection specimens.[4],[5],[11],[12] To date, there is a lack of specific data regarding LNY and LNR in advanced GBS-SCC.

Locally, advanced GBS-SCC is the most common malignancy at our center and bite composite resection with comprehensive neck dissection, and pectoralis major myocutaneous flap reconstruction has remained as a surgical procedure of choice for this type of cancer due to the workload, nonavailability of microvascular expertise, and socioeconomic reasons. Thus, removal of sternocleidomastoid muscle to facilitate inset of pectoralis major myocutaneous flap and clearance of level I to level V cervical lymph nodes is commonly done at our center for most of the node-positive necks. This enables us to assess the LNY in locally advanced GBS-SCC. The primary objective of this prospective study was to determine the LNY in T3/T4 GBS-SCC. The secondary objectives were to study the association of LNY with age, tumor thickness, histological differentiation, number of positive nodes, and ECS.

MATERIALS AND METHODS

The patients with biopsy proven, T_3/T_4 SCC that have classical extension into the mandibular GBS as defined by the previous studies [1],[2] were included. These patients were operated at our center between 2014 to 2014 and had undergone *en bloc* composite or bite composite resection, modified comprehensive neck dissection with clearance of level V to level I neck nodes as per the centre protocol. The modifications in neck dissection included preservation of the internal jugular vein and/or spinal accessory nerve whenever it was oncologically safe. The patients with recurrence, previous therapy, tuberculosis or chronic inflammatory diseases of head and neck and those with non-SCC were excluded from the study.

The clinical details included were clinical extent of the tumor, cTNM (AJCC 2009), findings in the high-resolution contrast computed tomography scan.The pathological details obtained were pT_3 or pT_4 status, histological differentiation, gross tumor thickness, skin infiltration by the tumor, total number of lymph nodes harvested per specimen, and number of positive nodes and nodes with ECS.

The surgical specimens were oriented by the operating surgeon, and nodal levels were identified as defined by their anatomical extent. Following dissection of each nodal level, suture ligatures bearing labels marked with nonwashable ink were tied around each dissected group of lymph nodes to demarcate the individual levels. After completion of *en bloc* dissection, the specimens were washed in flowing water to remove blood clots and loose tissues. The individual levels were transected, and the lymph nodes from each level were harvested by a senior pathologist. These nodes were transferred to separate labeled bottles denoting individual nodal level, completely immersed in 10% of buffered formalin solution.

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The grossing of the specimens was performed as per the modified standard protocol established by the Royal College of Pathologists, Standards and Datasets for reporting head and neck cancers (December 2009).[13] The specimens were sectioned after 48 h of fixation, and all the lymph nodes in the specimens were processed. The lymph nodes >2 mm in size were sectioned along the long axis and those with <2 mm in size, transverse sections were made. Four µm sections of all the lesional and lymph node sections were stained by routine eosin and Hematoxylin and Eosin staining.

RESULTS

The patient and surgical variables studied are mentioned in [Table 1]. This study included 12 subjects with T_3 and T_4 SCC of mandibular GBS. The age of the patients was ranged between 30and 60 years. Overall, 9 of the patients were males and 3 were females. There were (7patients) in T_{4a} stage and (5 patients) in T_3 stage, with (6 patients) showing skin involvement. The mean tumor size was 4.0 cm × 3.5 cm . Overall, 310 lymph nodes were harvested from 12 patients that underwent unilateral neck dissections, and the mean LNY was 21.00 ± 5.00.

Table 1: Patient and surgical variables

Variables	All patients n=20(%)
Age (years)	
Range	35-65
Mean	40.95
Males	14
Females	6
Duration(days)	
<15	7
>15	13
Side of disease	
Right	11
Left	9
Premalignant disorders	
Absent	5
Oral submucous fibrosis	9
Leukoplakia	4
Erythroplakia	2
Neck dissection type	
Modified neck dissection type	14
Radical neck dissection	6
Total positive nodes	80
SD	24.8
Mean	2.75
LNY	
Mean	21.00
SD	5.00
TOTAL	320

*time between the patients first visit to the hospital and surgery; ** preservation of spinal accessory nerve and / or internal jugular vein. LYN= Lymph node yield ; SD= standard deviation

The pathological variables are shown in [Table 2]. In 4 of the patients, the tumor thickness ranged from 0.4 to 0.9 cm whereas in 8 of patients, the tumor thickness was over 1 cm. ECS of the tumor in the lymph nodes was seen in 4 of patients.

	Table 2: Pathological variables and their association with lymph node yield		
VARIABLES	ALL PATIENTS	MEAN LYN	SD
Differentiation			
Well	9	21.33	5.88
Moderate	7	22.85	5.38
Poor	4	20.86	3.89
Tumor thickness			

0.4-0.9	5	21.84	5.52
1.0-1.9	11	22.04	5.64
>2.0	4	20.07	5.48
Pathological T stage(S)			
PT3 cases	6	20.63	4.75
PT4 cases	14	22.72	5.88
Skin involvement(S)			
Present	8	24.14	5.75
Absent	12	19.35	4.05
Extracapsular			
Present	11	23.68	5.03
absent	9	20.76	5.65
Number of positive nodes (S)			
None, pn0	6	18.45	4.38
1-4	10	23.02	6.00
>5	4	21.97	5.57
Delay in treatment(S)			
1-15	9	18.94	3.76
16-30	11	24.78	5.52
OPMD(S)			
Absent(n=6)	6	17.44	2.74
OSF (n=10)	10	25.56	5.05
Leukoplakia (n=3)	3	18.56	3.42
Leuko erythroplakia(n=1)	1	24.50	2.97

OPMD= Oral potentially malignant disorders ; OSF= oral sub mucous fibrosis; S= significant; SD= Standard deviation; LYN= lymph node yield

In 75% of patients, only level I nodes were positive; in 37.74% of patients, level I and level II nodes were positive; in 29.25% of patients, level I, level II, and level III were positive; in 16.98% of patients, all the nodal levels from level I to level IV were positive; whereas, in 9.43% of patients, all the nodal levels from level I to level V were positive.

Overall in 12 patients, the total number of patients with pN+ status was 70.75% (8 patients) whereas the number of patients with pN0 status were 29.25% (4 patients).

In Our study , association of clinicopathological variables and LNY, ECS, number of positive nodes, delay in surgical treatment for more than 15 days after diagnosis, skin involvement by the tumor, and presence of oral potentially malignant disorder (OPMD) were significant factors that contributed to higher LNY [Table 1] and [Table 2]

DISCUSSION

When the protocol for grossing the specimen proposed by the Royal College of Pathologists [13] was followed, the mean LNY in our patients was 21.00 (range 10–42). Whereas, as per the Royal College of Pathologists,[13] in the absence of previous chemotherapy, radiotherapy or neck dissection, and radical neck dissection yields 20 lymph nodes (range 10–30) on an average. The range of lymph nodes retrieved in our study was comparable to that proposed by the Royal College of Pathologists [13] although the surgical procedure in our study, in the majority of cases, was modified neck dissection.

The role of pathologists, surgeons, pathology technicians, method of handling the surgical specimen and the extent of training of these specialists have shown to influence the harvest of lymph nodes from the surgical specimens, thereby affecting the overall LNY.[14],[15],[16] The surgical technique is yet another factor contributing to the variability of LNY.[11],[12] Thus, a wide variation exists in the reports on the LNY and LNR in the current literature. However, in our study, the lymph node dissection and their retrieval from surgical specimens were done by the most experienced single surgeon and single pathologist, to prevent the bias in most of the studies. Despite specific consensus-based definitions of various neck dissection procedures in the current literature,[17] there is still a possibility of variation in the neck dissection fields by the surgeons, depending on the individual judgment, expertise, and decision-making. Comparing the LNYs obtained by a

uniform, standard neck dissection procedure among different centers can help in determining the factors responsible for varied reports. Nevertheless, on multivariate analysis, a significant variation in the rate of lymph node metastasis among Asian and non-Asian gastric carcinoma patients was found in a study,[18] the literature is sparse with regard to the contribution of racial and ethnic factors in the variability of cervical lymph node metastasis in head and neck cancer. Furthermore, data on the reference range of cervical lymph nodes, based on cadaveric studies, are derived from the non-Asian population,[11] and to date, the literature is sparse with regard to the reference range of cervical lymph node counts in Indian population. When compared to the available western data on the cervical lymph node counts,[11],[15] we had slightly lower counts which could be attributed to racial factors and possibly low body mass index (BMI) in our patients, in view of their high alcohol consumption, smoking, and tobacco chewing habits. The previous studies have reported low BMI in oral cancers patients, which were associated with alcohol consumption and tobacco use.[19],[20

The number of locally advanced GBS-SCC patients with pN0 status in our study was 28% which was lower than that reported by Walvekar *et al*.[1] However, the mean LNY increased significantly with the increase in the number of positive nodes. The immunological response that has been shown by the previous studies [21] could have contributed to the overall increase in the LNY. The ECS of tumor in the lymph nodes was associated with increase in the LNY. Although the contribution of ECS in increasing the LNY in head and neck cancer has not been clearly elucidated, the association of ECS with increase in the number of positive nodes has been shown in patients with breast cancer following axillary clearance, especially in large-sized tumors.[22] The presence of ECS in a lymph node can channelize the passage of tumor cells into surrounding lymphatic vessels, thereby increasing the number of positive nodes and overall LNY.

The delay in surgical treatment over 16 days to 30 days after the diagnosis of oral SCC was associated with an increase in the mean LNY compared to the patients that were treated within 15 days of diagnosis. The possibility of disease progression during the waiting period can be considered as a leading cause of metastatic lymphadenopathy, although it was not confirmed in this study by a second imaging to document a definitive disease progression during waiting period before surgery, as reported by Waaijer *et al*.[23]

The age, sex, and tumor differentiation were not significantly associated with increase in the mean LNY as the distribution of patients with respect to these factors was not uniform. In addition to this, the lack of larger sample size was a drawback of this study. We did not include the BMI as a parameter that can contribute to the variability of LNY. The mean LNY was slightly higher in patients with tumor thickness >1 cm . However, the involvement of skin by the infiltration of tumor and patients with locally advanced SCC of lower GBS presenting with orocutaneous fistula showed a higher LNY. Apart from the locally advanced primary tumor, the inflammatory response resulting from secondary infections in a chronic nonhealing oral ulcer could have triggered the increased LNY. Furthermore, the role of inflammatory response has been shown by studies as key feature in the pathogenesis of oral submucous fibrosis (OSF) that was seen in a majority of our patients presenting with SCC of mandibular GBS.[24] This condition is often associated with trismus, poor oral hygiene, and multiple ulcerations in the oral mucosa. The mean LNY in these patients was significantly higher than the patients with SCC of mandibular GBS presenting without a clinical evidence of OPMD. Thus, the role of inflammatory response in oral tissues secondary to OSF and its associated conditions leading to increased mean LNY cannot be ruled out.

CONCLUSION

In patients with locally advanced SCC of mandibular GBS, the mean LNY was 21.00. The presence of ECS, positive nodes for metastasis of SCC, delay in treatment of more than 15 days following diagnosis of SCC, skin infiltration by the tumor or presence of orocutaneous fistula and association of OPMD, especially OSF were significant factors that contributed to higher LNY. Further studies with larger sample size, incorporating multivariate statistical analysis, are required to validate the findings of this study.

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