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ORIGINAL ARTICLE

# Submandibular Gland in Neck Dissection: Necessary Fatality or Unfortunate Prey?

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**Abstract**
Excision of submandibular gland is currently victim in all neck dissections. In this study we intend to estimate the prevalence of submandibular gland involvement in squamous cell oral carcinomas and identify the factors associated with it. This is a single institutional, retrospective observational study conducted from 22 to 2018 to 28 February 2020. 317 patients were included for analysis as per study criteria. The prevalence of involvement of submandibular gland was 3.8%. Increased risk of submandibular gland involvement was associated with involvement of level-Ib nodes (Odds ratio: 13.6, 2.9–63.3, 95% CI and p = < 0.001) and presence of extra-nodal extension (Odds ratio: 67, 8.4–532, 95% CI and p = < 0.001) and perineurial invasion (Odds ratio: 5, 1.6–16.8 and p = 0.003). In oral cancers, especially early stage carcinoma of buccal mucosa, submandibular gland preservation may be feasible in absence of extra-nodal extension and level-Ib involvement.

**Keywords** Submandibular gland · Neck dissection · Oral cancer · Squamous cell cancer

## Introduction

As per GLOBOCON-2020 data, oral cavity cancers constitute second leading cause of cancers in India with an overall incidence of 10.3% of all the new cases [1]. The standard surgical treatment of oral cancer is removal of the tumor with free margin along with neck dissection. [2]. A landmark study from India has proved that elective neck dissection improves 5-year overall survival by 12.5%, which is basis for current practice of elective neck dissection in oral cancer [3]. Currently, submandibular gland is routinely removed during dissection of level-IB nodes for various reasons : (a) to expedite the optimal clearance of level Ib node (b) to eradicate possibility of intra parenchymal gland metastasis (c) to remove intra-glandular lymph nodes [4]. Submandibular gland is important organ as it produces around 70% of saliva in the unstimulated state, which helps in lubrication of oral cavity thereby allows for swallowing, initiation of digestion and dental hygiene. Removal of submandibular gland has negative impact on salivary secretion [5]. This negative effect is added when resection is combined with adjuvant radiation resulting in future risk of xerostomia and subsequent loss in quality of life [6]. In this study we intend to estimate the prevalence of, and identify factors associated with, submandibular gland involvement in oral cavity squamous cell carcinomas treated at our institute. Further, we have attempted to identify favourable subsite of oral cavity which may be chosen for submandibular gland preservation.

## Methods

This is a single institutional, retrospective observational study. We included all consecutive patients who underwent upfront curative surgery (excision of tumor with simultaneous neck dissection) for biopsy proven oral squamous cell cancers at head and neck surgery department of tertiary care referral cancer centre in North-East India. Patients with recurrent cases, salivary gland neoplasm, history of any neoadjuvant treatment, history of other head and neck malignancy, presence of distant metastasis were excluded. The study period was from 22 to 2018 to 28 February 2020. This study was conducted in accordance with guidelines of scientific and ethical committee of the institute.

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**Table 1** Demographics, procedure and pathological characteristics of the patients (n = 317)

| Median age (years) | 53+/-11.8 |
|---|---|
| **Male:Female ratio** | 2.4:1 |
| **Neck Dissection** | |
| SOHND | 127(40.1%) |
| Extended SOHND | 54(17%) |
| MRND | 133(42%) |
| RND | 3(0.9%) |
| **Submandibular gland involvement** | 12(3.8%) |
| **Pathological T stage** | |
| pT1 | 16(5%) |
| pT2 | 84(26.5%) |
| pT3 | 84(26.5%) |
| pT4 | 133(42%) |
| **Pathological N stage** | |
| pN0 | 194(61.2%) |
| pN1 | 32(10%) |
| pN2a | 7(2.3%) |
| pN2b | 30(9.5%) |
| pN2c | 3(0.9%) |
| pN3b | 51(16.1%) |
| **Nodal level involvement** | |
| Ia | 24(7.6%) |
| Ib | 92(29%) |
| IIa | 47(14.8%) |
| IIb | 41(12.9%) |
| III | 23(7.3%) |
| IV | 5(1.5%) |
| V | 1(0.3%) |
| **Involvement of bone** | |
| No | 214(67.5%) |
| Yes | 103(32.5%) |
| **Extranodal extension** | |
| No | 263(83%) |
| Yes | 54(17%) |
| **Lymphovascular invasion** | |
| No | 315(99.4%) |
| Yes | 20(0.6%) |
| **Perineural invasion** | |
| No | 245(77.3%) |
| Yes | 72(22.7%) |

SOHND- Supra omohyoid neck dissection; ESOHND- Extended supraomohyoid neck dissection; MRND- Modified radical neck dissection; RND- Radical neck dissection

Detailed data pertaining to clinical profile of patients was retrieved from hospital records, electronic database and was analysed. Data extracted included parameters like demography, clinical history, histopathology report and details of treatment undertaken.

A consistent treatment strategy was followed during the entire study period. Evaluation of patients included detailed history, physical examination and standard blood investigations. Laryngoscopy, upper gastrointestinal endoscopy and biopsy was done for all patients. Contrast enhanced computerised tomography(CT) or magnetic resonance imaging(MRI) was done depending on subsite involved. Pulmonary metastasis was assessed with non contrast CT Scan. PET [positron emission tomography] scan was done wherever indicated. Staging was done according to eighth edition AJCC/UICC manual.

All the patients underwent wide excision of primary tumor with at least 1 cm three dimensional margin along with simultaneous neck dissection. Comprehensive neck dissection was done for node positive cases and selective neck dissection was done for node negative cases. Submandibular gland was removed in all cases during level Ib clearance. The specimen were handed to the pathology department for histopathologic examination.

The primary objective of this study was to estimate the prevalence of involvement of submandibular gland in oral cavity cancers and secondary objectives were to analyse factors associated with its involvement and to identify favourable subsite of oral cavity which may be chosen for submandibular gland preservation.

### Statistical Analysis

Data were collected from hospital records and computer based online hospital reporting system. The statistical analysis was performed using statistical package for the social sciences(SPSS) version 21. Mean and percentages were used for descriptive statistics. Association between categorical variables was assessed using chi-square test and risk was calculated using binary logistic regression. T-test was used to find out mean difference for continuous variables subject to following normality. P value less than 0.05 was considered statistically significant at 95% confidence interval.

## Results

A total of 317 patients new included in the study. Mean age was 53 ± 11.8 years. There were 224 males and 93 females with male to female ratio of 2.4. Table 1 shows summary of clinico-pathological characteristics.

Majority of patients were carcinoma buccal mucosa (116/317). 133(42%) patients underwent comprehensive neck dissection and 127(40.1%) patients underwent supraomohyoid neck dissection. 133 patients had pT4a (pathological) comprising nearly 42% of the study population. 61.2% of patients had pathological N0 stage while 16.1% of patients had pN3b stage. Level-Ib nodal involvement was present in 92(29%) patients. Peri-neural invasion was present in 72(22.7%) and extra-nodal extension was present in 54(17%) of patients.

**Table 2** Association between various factors and submandibular gland involvement ($n = 317$)

| | Submandibular gland involvement Yes | No | Odds Ratio | P value |
|---|---|---|---|---|
| **Subsite** | 0 | 1 | | 0.88 |
| Upper lip | 0 | 10 | | |
| Lower lip | 7 | 109 | | |
| Buccal mucosa | 0 | 5 | | |
| Angle of mouth | 0 | 11 | | |
| Upper GBS | 1 | 64 | | |
| Lower GBS | 1 | 10 | | |
| Floor of mouth | 2 | 47 | | |
| Tongue | 0 | 4 | | |
| Hard palate | 1 | 16 | | |
| RMT | | | | |
| **Type of procedure** | 1 | 116 | | |
| SOHND | 2 | 45 | | |
| ESOHND | 9 | 142 | | |
| MRND | 0 | 2 | | |
| RND | | | | |
| **pT stage** | 2 | 98 | - | 0.25 |
| pT1-T2 | 10 | 207 | 2.36 | |
| pT3-T4 | | | | |
| **pN stage** | 1 | 225 | - | < 0.001 |
| pN0-N1 | 11 | 80 | 30.9 | |
| pN2-N3 | | | | |
| **Level Ib involvement** | 10(10.9%) | 82 | 13.6 | < 0.001 |
| **Yes** | 2(0.9%) | (89.1%) | (2.6–63.3) | |
| **No** | | 223 (99.15) | | |
| **Extra-nodal extension** | 11 (20.4%) | 43 | 67 | < 0.001 |
| **Yes** | 1 (0.4%) | (79.6%) | (8.4–532) | |
| **No** | | 262 (99.6%) | | |
| **Peri neural invasion** | 7 (9.7% | 65 | 5 | 0.003 |
| **Yes** | 5 (2%) | (90.3%) | (1.6–16.8) | |
| **No** | | 240 (98%) | | |
| **Lympho vascular invasion** | 0 (0%) | 2 | | 0.778 |
| **Yes** | 12 (3.8%) | (100%) | | |
| **No** | | 303 (96.2%) | | |
| **Bone involvement** | 3 (2.9% | 100 | 0.68 | 0.57 |
| **Yes** | 9 (4.2%) | (97.1%) | | |
| **No** | | 205 (95.8%) | | |
| **Differentiation** | 11 (3.8%) | 276 | | 0.884 |
| **Well differentiated** | 1 (4.2%) | (96.2%) | | |
| **Moderate differentiated** | 0(0%) | 23 (95.8%) | | |
| **Poor differentiation** | | 6 (100%) | | |
| **Mean DOI** | 12 | - | | 0.43 |
| **> 1.1 cm** | - | 305 | | |
| **</=0.97** | | | | |

GBS- ginigivo buccal sulcus; RMT- retromolar trigone; SOHND- supraomohyoid neck dissection; ESOHND- extended supraomohyoid neck dissection; MRND- modified radical neck dissection; RND- radical neck dissection; p- pathological stage; T-Tumor stage; N-nodal stage; DOI- depth of invasion

A total of 12 patients revealed submandibular gland involvement. The prevalence of involvement of submandibular gland was 3.8%. Table 2 depicts association between various factors and submandibular gland involvement. The gland involvement was present in only 7 out of 116 patients with carcinoma buccal mucosa and all of them had pathological N3b nodal status in ipsilateral level Ib suggesting possible direct extension to gland from adjacent node. Out of 11 patients with floor of mouth disease, one patient had gland involvement suggesting possibility of direct extension from the primary.

2 patients (2%) with pathological T1-T2 had involvement of gland whereas gland involvement was present in 10 patients (4.6%) with pT3-T4 stage. Among patients with pN2-N3, 12.1% of patients had involvement of gland with an odds ratio of 30.9 (3.9 to 243.5, 95% C.I and $p = < 0.01$).

Metastatic disease to level-Ib nodal level increased the risk of submandibular gland involvement with an odds ratio of 13.6(2.9–63.3, 95% C.I and $p = < 0.01$). Presence of extra-nodal extension was associated with highest risk of gland involvement with an odds ratio of 67(8.4 to 532, 95% CI and $p = < 0.001$). When there was peri-neural invasion around 7(9.7%) of patients had submandibular gland involvement (odds ratio: 5, 1.6 to 16.8, 95% CI and $p = 0.003$). The mean depth of invasion in patients with submandibular gland involvement was > 1.17 cm.

Patients with positive level-Ib lymph nodes, extra nodal extension and peri-neural invasion were significant risk factors for involvement of submandibular gland in oral squamous cell carcinomas.

## Discussion

The cumulative risk of oral cavity cancers in India is 1 in 103 as per cancer statistics 2020 [7]. In North-East part of India due to rampant use of smokeless tobacco, there is increase in oral cancer related morbidity and mortality [8]. Our institute is a tertiary referral cancer centre for North-East India.

About half of patients with oral squamous cell carcinomas present with neck node metastasis. Currently, elective neck dissection in standard of care in oral squamous cell cancer in lieu of improving overall survival and disease free survival [3]. Based on the characteristics of histopathology report, decision regarding need for adjuvant treatment is taken [9]. Neck dissection has evolved from radical to modified radical to functional with aim of improving quality of life and minimising morbidity [10]. In literature, submandibular gland involvement in oral cavity cancer varies between 0 and 5% [11]. Still, it is prey of all neck dissections.

Submandibular gland is content of submandibular triangle which consists of level Ib lymph nodes as well. According to Rouviere, lymph nodes in level-Ib region are divided into five groups into pre-glandular, pre-vascular, post-vascular, post-glandular and intra-glandular [12]. Di Nardo described sixth group of deep lymph nodes from his cadaveric studies [13]. Presence of intra glandular lymph nodes are debatable because lymphatic drainage develops after encapsulation of submandibular gland. Proposed mechanisms for submandibular gland involvement include, direct extension by primary tumor or adjacent node, adjacent lymph node, extension through Wharton's duct or hematogenous metastasis. Direct invasion accounts for more than 90% of the cases [14].

Submandibular gland accounts for 70% of unstimulated salivary flow. Saliva has many functions like buffering oral pH, maintaining oral and dental hygiene, digestion, lubrication and anti microbial properties. Removal of submandibular gland leads to decreased salivary secretion [5] and increased risk of xerostomia [15]. All these consequences may affect quality of life of patients by disrupting mastication, speech and taste. Besides, excision of gland also harbours risk of damaging marginal mandibular nerve, hypoglossal nerve and lingual nerve resulting in functional and cosmetic defects [16]. Literature reveals that involvement of submandibular gland is uncommon, none of them show involvement of more than 4.6% [17]. Despite such low incidence, submandibular gland preservation has not been included in any nomenclature. In many cases, we need to do bilateral neck dissection for tumors approaching or crossing midline where we end up sacrificing both the submandibular glands. Chen et al. reported that submandibular gland preservation should be pondered in contralateral neck dissection during bilateral neck dissection [18]. Previous studies have shown feasibility of submandibular gland preservation while dissection of level-IB nodal level [4]. Involvement of deep group of lymph nodes is rare, hence gland mobilisation is not required especially in early cancers [19].

Prevalence of submandibular gland involvement in present study was 3.8%. Majority of our patients were with pathological T4a status with around 61.2% of pathological N0 status. Advanced T stage had higher risk of gland involvement with an odds ratio of 2.36. When compared to pathological N0 patients, pN3b involvement had statistically significant higher risk of gland involvement with odds ratio of 30.9[3.9–243.5]. Most common site was buccal mucosa (116 patients) but submandibular gland involvement was seen only in seven patients and all of them had pathological N3b nodal status in ipsilateral level Ib suggesting possible direct extension to gland from adjacent node. Metastasis to level-Ib node level with extra nodal extension had significant risk of gland involvement. Out of 11 patients of floor of mouth, one patient had involvement of gland suggesting possible direct extension from the tumor. The submandibular gland has a capsule which is a barrier for tumor invasion, oncologically it is safe to dissect only the capsule with surrounding lymph nodes especially in early oral cancer, unless there are adherent nodes or nodes with extracapsular extension [20].

The perineural invasion (PNI) has been considered as an independent poor prognostic marker in oral cancer but its association with respect to submandibular gland involvement is deficient in literature [21]. In the present study, amongst the high risk histopathological factors like lymph-vascular invasion (LVI), peri neural invasion (PNI), grade of differentiation, depth of invasion, only presence of peri-neural invasion revealed increased risk of gland involvement.

Chen et al. studied that there was similar disease free survival and overall survival in tongue and buccal carcinomas with and without submandibular gland invasion [22]. Du et al. [23] reported that there was no statistically significant difference in the 5-year loco-regional control rates (84% versus 73%, p-value 0.239) and 5-year diseases specific survival (88% versus 84%, p-value 0.524) in floor of mouth cancer with or without submandibular gland preservation. They highlighted that submandibular gland can be preserved without affecting oncological outcomes. In many floor of mouth cancer cases, however, resection of primary may involve removal of Wharton's duct, hence, preservation in that scenario might be a problem.

The limitations of present study is that it is retrospective. Also, the present study doesn't take into account the actual mechanism of submandibular gland involvement. Oncological outcomes and quality of life implication in removing submandibular gland versus preservation is not addressed in the present study. Pros of the study were that high risk histopathological factors have been studied for association with gland involvement. We have attempted to identify favourable subsite of oral cavity cancer that may be chosen for submandibular gland preservation. In the present study, overall involvement of submandibular gland was low even in advanced T stages. More than T stage of the tumor, extra nodal extension of level Ib node (pN3b) was important factor for submandibular gland involvement. The submandibular gland may be preserved in in cT1-T2N0 oral cavity cancer. Buccal mucosa subsite is anatomically away from the gland and duct. We propose that early stage carcinoma of buccal mucosa may be ideal for preservation of submandibular gland. Our results might be useful for planning future prospective studies. Studies on correlation of preoperative clinical and / or radiological parameters with submandibular gland involvement would be more helpful in deciding if sparing of the gland can be done.

## Conclusion

Submandibular gland is a functional organ and its routine casualty in every neck dissection needs to be revisited. In our study submandibular gland involvement was only 3.8%. Despite such low involvement of gland, it's unfortunate to always become the victim. Presence of extranodal extension of Ib node and perineurial invasion were the important factors for involvement of submandibular gland. Early buccal mucosa cancer may be preferred site for considering preservation of gland.

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## Declarations

**Conflict of Interest** The authors declare that they have no conflict of interest.

**Ethical Approval** Ethical approval was taken from the Institution Ethics Committee. All procedures were in accordance with the ethical standards of the institution.

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