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Incidence of Submandibular Gland Involvement in Oral Cancer Patients with Positive Lymph Nodes: Experience at a Tertiary Cancer Centre in South India

Vasantha Dhara, MDS, Rajani Bejjihalli, MDS, Nadimul Hoda♦, MDS, Sabitha Kortikere, MDS, Subhabrata Ghosh, MDS, Vinitha Annavarjula, MDS

Oral Oncology, Kidwai Memorial Institute of Oncology, Bangalore, India

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Abstract

Background: Routine excision of submandibular gland along with level Ib lymph nodes is carried out as a part of standard neck dissections. The current study aimed to evaluate the incidence of submandibular gland involvement in oral squamous cell carcinoma cases undergoing neck dissections with clinically positive nodes.

Method: We carried out a retrospective observational experiment. The records of 520 patients diagnosed with oral cavity squamous cell carcinoma, who underwent neck dissection, were retrospectively reviewed. We recorded the incidence of submandibular gland involvement by the primary tumour.

Results: Metastasis to level 1 lymph nodes was found in 35.6% of the patients. The involvement of submandibular gland in our study sample was 0.96%.

Conclusion: Recent literature has recommended sparing of the submandibular gland in certain cases; that is, because its removal causes postoperative xerostomia with exaggeration due to radiotherapy, which is considered morbid, based on various anatomical models. However, this finding is controversial. Our study suggested submandibular gland sparing neck dissections in all subsites, except for tongue, anterior alveolus, and floor of mouth tumours.

Keywords: Submandibular gland, Oral cancer, Neck dissection, Xerostomia

Introduction

Oral squamous cell carcinoma (OSCC) includes a vast proportion of oral neoplasms worldwide. Its presentation is usually accompanied by metastasis to the cervical lymph nodes. Crile first performed and established neck dissection for oral cancer patients in 1906.[1] Neck dissection has been shown to be oncologically beneficial even in patients without evidence of cervical lymph node metastasis as an elective neck dissection procedure over the therapeutic neck dissection. This essential procedure has undergone several modifications over the past decades in order to obtain better

♦Corresponding Author:
Nadimul Hoda, MDS
Oral Oncology, Kidwai Memorial Institute of Oncology, Bangalore, India
Tel: +918197127702
Email: drnadimulkmio@gmail.com

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understanding of regional metastasis. This has led surgeons to choose more conservative and functional procedures over radical and aggressive dissection. The anatomic levels of I, II, and III with extensions to levels IV and V are generally involved in the dissection of oral cavity cancers. The submandibular triangle constitutes the submandibular gland and the corresponding lymph nodes. The lymph nodes in this triangle essentially serve as the first echelon station for metastasis from oral cancer.

Apart from the preservation of standard structures, viz. spinal accessory nerve, internal jugular vein, and sternocleidomastoid muscle, as described by Bocca, the dissection of submandibular gland in removal of level 1B has been sought after.[2] A vital consideration in removing the submandibular gland (SMG) during neck dissection, particularly when done bilaterally, is the potential adverse impact on salivary flow. Resection of the SMG in oral cancer patients leads to symptomatic xerostomia affecting the quality of life. The incidence of xerostomia in head and neck cancer patients who have received radiotherapy is generally reported to be between 94 and 100%.[3,4] Understanding the anatomic relationship between the lymph nodes and the submandibular gland has highlighted the possibility of sparing of the salivary gland in routine neck dissections of certain cases.

We conducted this study to examine and ascertain the incidence of the involvement of submandibular salivary gland in oral cancer patients who underwent surgical treatment with clinically positive nodes.

Materials and Methods

A retrospective observational study was carried out. In this retrospective study, we included the data records of oral SCC patients with clinically positive lymph nodes who underwent curative wide excision of the primary tumor and simultaneous neck dissection at Kidwai Cancer Centre between January 1, 2016, and December 31, 2018. The research study was retrospectively conducted exclusively from data records. Thus, the present work was waived off by the Ethical Committee of the Institutional Review Board of Kidwai Memorial Institute of Oncology (ethics code: KMIO/IEC/2016-21/3214). The exclusion

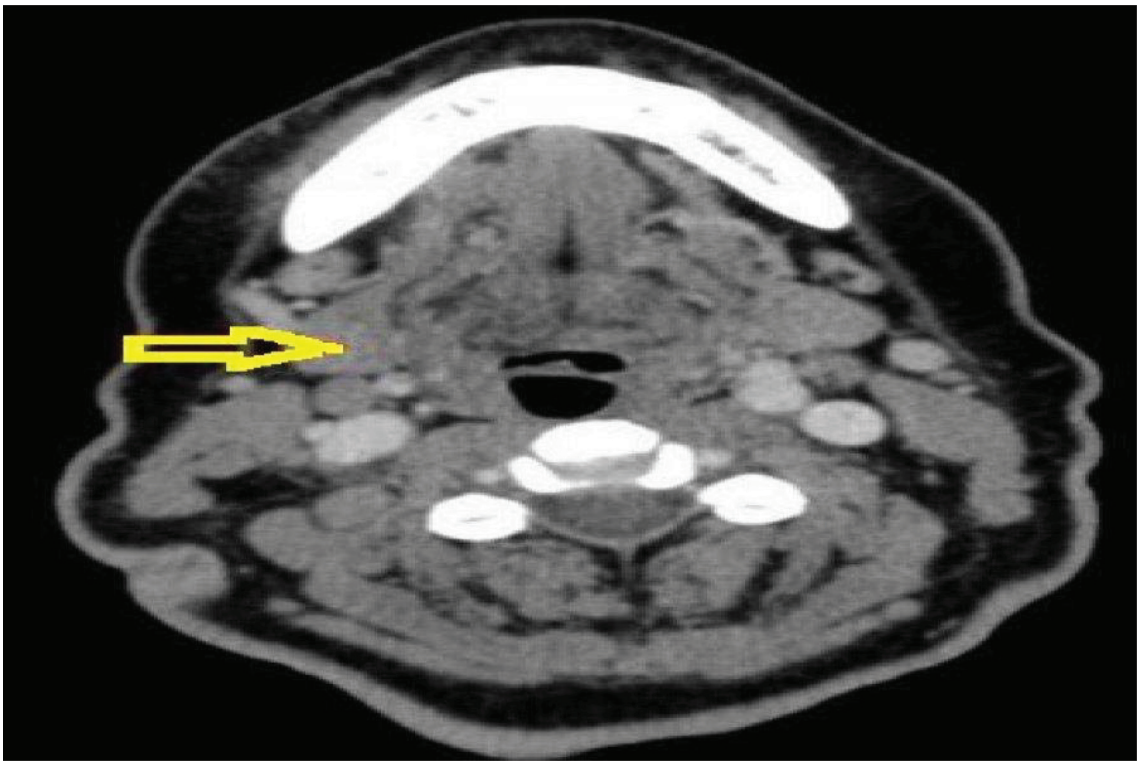

Figure 1. This computed tomography section shows suspected involvement of submandibular gland with primary tumour.

criteria included the records of patients with synchronous or metachronous multiple primary malignancies, distant metastases, recurrent carcinoma, along with those treated by preoperative radiotherapy or chemotherapy. The medical records and pathologic reports, the data including the age at diagnosis, sex, location of primary site, TNM staging, grade, and status of cervical lymph node metastasis and involvement of submandibular gland were retrospectively reviewed.

At our institution, the patients with histopathologically proven squamous cell carcinoma of oral cavity, with palpable nodes or with radiologically suspicious cervical lymph nodes are generally treated by primary surgical resection and neck dissection. Preoperative staging with contrast enhanced computed tomography (CT) scans is obtained in all patients (Figure 1). The extent of neck dissection includes a minimum of levels I, II, and III, with submandibular gland resection undertaken as part of level I dissection in all cases. Bilateral neck dissection is performed in case of tumours involving the anterior FOM or approaching or crossing the midline. Lower nodal levels are considered depending on the tumour site, size, and nodal involvement. In our

Table 1. Characteristics of the subjects' records

Gender	
Male	322
Female	198
Median age	38-68 years
Sites	
Lower gingivobuccal sulcus	202
Buccal mucosa	104
Tongue	85
Floor of the mouth	38
Lip	34
Upper gingivobuccal sulcus	26
Retromolar trigone	21
Palate	10
Tumour stage	
T1	52
T2	104
T3	174
T4	190
Nodal stage	
N1	384
N2	136
Extent of neck dissection	
Unilateral	446
Bilateral	74

T: Tumour; N: Node

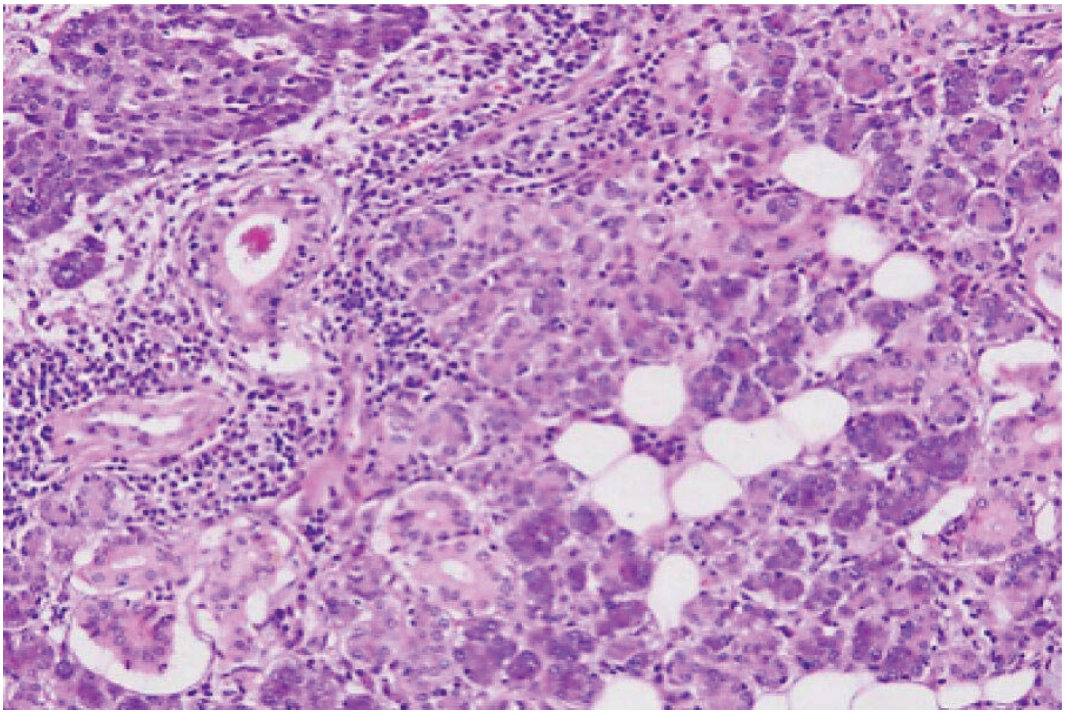

Figure 2. This figure shows histopathological slide (H&E; 100×) view of squamous cell carcinoma invading submandibular gland.

Table 2. Association of tumour characteristics with submandibular gland involvement

Parameter	Submandibular gland involvement (*P* value)
Tumour location	0.048
Tumour stage	0.768

P < 0.05 was considered to be statistically significant

experiment, the extracted specimen of neck dissection was first divided according to each neck level by the surgeon in the operating room. Afterwards, it was taken for pathologic examination. The histopathological examination had been recorded in their charts as per the AJCC (American Joint Committee on Cancer) staging manual for cancer staging analysis.

Tumour location, clinical and pathological T and N stages, and extension of a tumour to the floor of mouth were investigated concerning their relevance to submandibular gland involvement from the records. This was an observational retrospective study of patients' records and was exempted from institutional review board approval.

Results

Records of a total 520 patients (322 males and 198 females) with positive neck lymph nodes were undertaken in the study. Their median age was 38-68 years. The most common primary site was lower gingivobuccal sulcus (n = 202), followed by buccal mucosa (n = 104), tongue (n = 85), floor of mouth (n = 38), upper gingivobuccal sulcus (n = 26), palate (n = 10), lip (n = 34), and retromolar trigone (n=21). Table 1 summarizes the demographic characteristics of the study subjects' records. Their tumour stage and node stage according to the histopathological examination were T1 (n = 52), T2 (n = 104), T3 (n = 174), T4 (n = 190), N1 (n = 384), and N2 (n = 136). Among the 520 study subjects, 446 underwent curative wide excision of the primary carcinoma with ipsilateral neck dissection, while 74 underwent curative wide excision of primary carcinoma with bilateral neck dissection. Totally, 594 submandibular glands were resected. No lymph nodes were detected in any SMGs in the records of the subjects. Five of the study subjects, three with floor of mouth lesion (T3, T4a, and T4a) and two with tongue lesions with floor of mouth extension (T3,T4a), had involvement of the gland; thus, the involvement rate in our study sample was 0.96% (5/520) (Figure 2). T stage (Pearson chi-square test, $P = 0.768$) was not a risk factor for submandibular gland involvement, whereas the location of the tumour (Fischer test, $P = 0.048$) had a significant relationship with it considering floor of mouth and tongue (Table 2). The submandibular gland involvement in these patients was by direct spread from the primary carcinoma (Figure 1). There was no significant association between N stage and involvement of SMG ($P = 0.95$). Metastasis to level 1 lymph nodes was found in 185/520 (35.6%) study subjects. In 14 cases, we observed a metastatic level IB lymph node in close proximity to the submandibular salivary gland; meanwhile, light microscopic examination of the specimen did not show invasion of its parenchyma. Among the 185 study subjects, eight had extranodal extension with respect to level IB lymph nodes, but there was no invasion of the gland parenchyma. In two subjects, the fibrous tissue around the gland was involved by extranodal extension from a positive level 1B lymph node.

Discussion

In our study, the rate of SMG involvement was a mere 0.96%. This finding is consistent with the results of prior studies, in which the involvement rate of the SMG in oral carcinoma cases has ranged from 0% to 5.5%.[5,6,7] It is well acknowledged that the submandibular gland is remarkably different from the parotid gland, in a way that it does not encompass a rich network of lymphovascular structures and intraglandular lymph nodes; in addition, it has a thick capsule. Hence, it lowers the probability of lymphatic spread to the gland itself.[8,9,10] The literature suggests that primary submandibular gland

invasion is the most common form of involvement, especially for floor of mouth tumours, which was also noted in our study.[11] In the majority of cases, tumour invasion of submandibular gland was found to be associated with tumours primarily located in or extending to the floor of mouth or mandible, or with an advanced T stage.

The primary treatment for the majority of cases of oral SCC is removal of the primary tumor, followed by selective neck dissection of levels I to III/IV.[12] The submandibular gland is typically removed during this surgery considering three factors: (1) for possible SMG invasion, (2) to aid level IB dissection, (3) to resect level IB lymph nodes.[5] These findings point towards a submandibular gland sparing neck dissection in oral SCC cases with low risk. Xerostomia, as a consequence of radiotherapy, was reported by Jean Bergonie in 1911. In addition, it has been considered that radiation doses as low as 35 Gy can permanently damage the secretory action of the salivary gland.[13] SMGs are responsible for an estimated 70% of unstimulated salivary flow and removal of one submandibular gland can trigger xerostomia which can lead to dental caries, mucositis, difficulties in mastication, swallowing, impaired nutrition, and other complications impairing the quality of life.[14,15] Thus, routine excision of the submandibular gland during level I dissection causes a significant decrease in unstimulated saliva production, which is further worsened by adjuvant radiotherapy.[16,17]

The pre-glandular, pre-vascular, retrovascular, retroglandular, intra-capsular, and deep submandibular groups of lymph nodes constitute the level I nodal basin.[18] Three possible routes of submandibular gland tumoural involvement may be due to the following factors: an anatomic proximity, lymphatic spread, and haematogenous spread. In a study by Junquera et al., submandibular gland involvement in patients with primary cancer of the floor of mouth was evaluated. They concluded that with the peri-glandular (pre-glandular and retroglandular) metastasis rate was 31.7%, while no submandibular gland involvement was detected.[19] Studies supporting submandibular gland sparing neck dissections are based on the embryologic concept that the lymphatic system develops after the submandibular gland has been encapsulated; therefore, lymph nodes and lymphatic channels do not get entrapped within the parenchyma of the gland and are thus distinct.[20,21] Accordingly, the ideology of submandibular gland sparing neck dissection has both anatomic and embryological basis.

In a paper by Dhiwakar et al.,[22] patients undergoing neck dissections were prospectively studied. Sublevel IB dissection was performed by three sequential surgical steps sparing the submandibular gland. They demonstrated that complete removal of lymph nodes located in the submandibular triangle is possible without removal of the gland per se, and that direct invasion of the submandibular gland is unlikely due to the lack of parenchymal lymph nodes within the gland.[22] Based on this finding, specific surgical techniques could be designed so as to preserve the submandibular gland when performing neck level I dissection. Seikaly et al. developed a surgical technique, in which the transfer of the contralateral submandibular gland to the submental area was done. The long-term outcomes were investigated, which indicated that the technique was significantly conducive to preventing xerostomia, in addition to there being no disease recurrences on the side of the transferred gland or in the submental space.[23]

Currently, there is no documentation or evidence of an uninvolved submandibular gland causing tumour recurrence or decreased survival rate when preserved during neck dissection. An oncological peril of the gland preservation, specifically for floor of mouth carcinomas, is the inability to exclude the possibility of involvement due to spread of cancer along Wharton's duct.[24] A study by Lanzer et al. concluded that preserving the submandibular gland for oral cavity and oropharyngeal cancers is advantageous; nonetheless, it is not valid for floor of the mouth and tongue cancers, which are associated with a higher rate of locoregional recurrences.[25] Our retrospective study supported the key findings in

literature of low rate of submandibular gland involvement in oral cancers and the higher probability of such occurrence in floor of the mouth tumours.

Conclusion

The results obtained herein revealed that the rate of SMG involvement is extremely low and that involvement primarily occurs through direct extension from the primary tumor, especially in cases of cancers in the floor of mouth and tongue. Thus, it could be suggested that it is oncologically safe to preserve the SMG during selective neck dissection of patients. SMG preservation has a positive effect on the post-treatment quality of life in operated patients by reducing the risk of xerostomia.

Conflict of Interest

None declared.

References

1. Crile G. Landmark article Dec 1, 1906: Excision of cancer of the head and neck. With special reference to the plan of dissection based on one hundred and thirty-two operations. By George Crile. *JAMA*. 1987;258(22):3286-93. doi: 10.1001/jama.258.22.3286.
2. Bocca E, Pignataro O. A conservation technique in radical neck dissection. *Ann Otol Rhinol Laryngol.* 1967;76(5):975-87. doi: 10.1177/000348946707600508.
3. Ramirez-Amador V, Silverman S Jr, Mayer P, Tyler M, Quivey J. Candidal colonization and oral candidiasis in patients undergoing oral and pharyngeal radiation therapy. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 1997;84(2):149-53. doi: 10.1016/s1079-2104(97)90061-5.
4. Kies MS, Haraf DJ, Rosen F, Stenson K, List M, Brockstein B, et al. Concomitant infusional paclitaxel and fluorouracil, oral hydroxyurea, and hyperfractionated radiation for locally advanced squamous head and neck cancer. *J Clin Oncol.* 2001;19(7):1961-9. doi: 10.1200/JCO.2001.19.7.1961.
5. Basaran B, Ulusan M, Orhan KS, Gunes S, Suoglu Y. Is it necessary to remove submandibular glands in squamous cell carcinomas of the oral cavity? *Acta Otorhinolaryngol Ital.* 2013;33(2):88-92.
6. Malik A, Nair S, Nair D, Chaturvedi P. A prospective study to evaluate the pattern of lymphatic metastasis in relation to submandibular gland in the patients with carcinoma of the oral cavity. *Eur J Cancer.* 2016;38(11):1703-7.
7. Dundar Y, Mandle Q, Raza SN, Lin HS, Cramer J, Hotaling JM. Submandibular gland invasion by oral cavity cancers: A systematic review. *Otolaryngol Head Neck Surg.* 2019;161(2):227-34. doi:10.1177/0194599819838475.
8. Razfar A, Walvekar RR, Melkane A, Johnson JT, Myers EN. Incidence and patterns of regional metastasis in early oral squamous cell cancers: feasibility of submandibular gland preservation. *Head Neck.* 2009;31(12):1619-23. doi:10.1002/hed.21129.
9. Kruse A, Grätz KW. Evaluation of metastases in the submandibular gland in head and neck malignancy. *J Craniofac Surg.* 2009;20(6):2024-7. doi:10.1097/SCS.0b013e3181be87a3.
10. Spiegel JH, Brys AK, Bhakti A, Singer MI. Metastasis to the submandibular gland in head and neck carcinomas. *Head Neck.* 2004;26(12):1064-8.
11. Cakir Cetin A, Dogan E, Ozay H, Kumus O, Erdag TK, Karabay N, et al. Submandibular gland invasion and feasibility of gland-sparing neck dissection in oral cavity carcinoma. *J Laryngol Otol.* 2018;132(5):446-51. doi: 10.1017/S0022215118000592.
12. Chen TC, Lo WC, Ko JY, Lou PJ, Yang TL, Wang CP. Rare involvement of submandibular gland by oral squamous cell carcinoma. *Head Neck.* 2009;31(7):877-81. doi:10.1002/hed.21039.
13. Hughes PJ, Scott PM, Kew J, Cheung DM, Leung SF, Ahuja AT, et al. Dysphagia in treated nasopharyngeal cancer. *Head Neck.* 2000;22(4):393-7.
14. Cunning DM, Lipke N, Wax MK. Significance of unilateral submandibular gland excision on salivary flow in noncancer patients. *Laryngoscope.* 1998;108(6):812-5.
15. Bruce SD. Radiation-induced xerostomia: how dry is your patient? *Clin J Oncol Nurs.* 2004;8(1):61-7. doi:10.1188/04.CJON.61-67.
16. Jaguar GC, Lima EN, Kowalski LP, Pellizon AC, Carvalho AL, Alves FA. Impact of submandibular gland excision on salivary gland function in head and neck cancer patients. *Oral Oncol.* 2010;46(5):349-54.
17. Jacob RF, Weber RS, King GE. Whole salivary flow rates following submandibular gland resection. *Head Neck.* 1996;18(3):242-7.
18. DiNardo LJ. Lymphatics of the submandibular space: an anatomic, clinical, and pathologic study with applications to floor-of-mouth carcinoma. *Laryngoscope.* 1998;108(2):206-14. doi:10.1097/00005537-199802000-00009.
19. Junquera L, Albertos J, Ascani G, Baladrón J, Vicente J. Involvement of the submandibular region in epidermoid carcinoma of the mouth floor. Prospective study of 31 cases [in Italian]. *Minerva Stomatol.* 1999;49 (11):521-5.
20. Guney E, Yigitbasi OG. Functional surgical approach

to the level 1 for staging early carcinoma of the lower lip. *Otolaryngol Head Neck Surg.* 2004;131(4):503-8.
21. Truffert P. Le cou: anatomie topographique. Les apone´vroses, les loges. Paris: Arnette; 1922.
22. Dhiwakar M, Ronen O, Malone J, Rao K, Bell S, Phillips R, et al. Feasibility of submandibular gland preservation in neck dissection: A prospective anatomic-pathologic study. *Head Neck.* 2011;33(5): 603-9. doi: 10.1002/hed.21499.
23. Seikaly H, Jha N, Harris JR, Barnaby P, Liu R, Williams D, et al. Long-term outcomes of submandibular gland transfer for prevention of postradiation xerostomia. *Arch Otolaryngol Head Neck Surg.* 2004;130(8):956-61. doi: 10.1001/archotol.130.8.956.
24. Fives C, Feeley L, Sadadcharam M, O'Leary G, Sheahan P. Incidence of intraglandular lymph nodes within submandibular gland, and involvement by floor of mouth cancer. *Eur Arch Otorhinolaryngol.* 2017; 274(1):461-6. doi: 10.1007/s00405-016-4205-0.
25. Lanzer M, Gander T, Lubbers HT, Bredell M, Reinisch S. Preservation of ipsilateral submandibular gland is ill advised in cancer of the floor of the mouth or tongue. *Laryngoscope.* 2014;124:2070-4.