

Clinicopathological study of involvement of the submandibular gland in oral squamous cell carcinoma

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Abstract

Our purpose was to provide a pathological basis for preservation of the submandibular glands during neck dissection for oral squamous cell carcinoma (SCC) by investigating whether intraglandular lymph nodes exist in submandibular glands, and the modes of involvement of submandibular glands in oral SCC. We studied the records of 95 patients with oral SCC (other than that in the floor of the mouth) treated at our hospital from January 2017 to June 2018. The specimens of submandibular glands discarded after neck dissection were analysed, and serially sectioned. Sections 5 µm thick were obtained at 0.5 mm intervals and stained with haematoxylin and eosin for examination under light microscopy. A total of 116 specimens were obtained from the 95 patients, and about 5000 slides were evaluated. No intraglandular lymph nodes were detected in the submandibular glands. In the subgroup of patients whose primary tumours had extended into the floor of the mouth, four submandibular glands were involved by direct spread of the primary tumour. In the subgroup with metastases to level Ib lymph nodes, four submandibular glands were involved by extranodal extension from the metastatic nodes. No intraglandular lymph nodes or micrometastases were detected. We conclude that no intraglandular lymph nodes are present in submandibular glands, which may be involved by direct extension of the primary carcinoma or metastatic cervical lymph nodes with extranodal extension. Preservation of the submandibular glands during neck dissection seems to be feasible and safe in selected patients with oral SCC.

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Introduction

Oral squamous cell carcinoma (SCC) is the most common carcinoma in the head and neck,¹ and neck dissection is an important part of its primary surgical treatment.² More than 100 years ago Crile recommended radical neck dissection as standard practice for treatment of SCC in the head and neck.³

Since then, other techniques (such as modified and selective neck dissection) have been developed in an attempt to avoid the complications associated with radical neck dissections.^{4,5} However, whichever technique is used, the submandibular gland is invariably sacrificed,⁶ and these account for 65% of the saliva that is secreted in the resting state.^{7,8} Saliva is essential for various oral functions,^{9,10} and any reduction will have an adverse impact on the patient's health and quality of life. Excision of even one submandibular gland has been shown to result in subjective xerostomia.¹¹

The need for removal of a submandibular gland during neck dissection for patients with oral SCC remains

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controversial.¹² Two issues need to be clarified, and the first is whether lymph nodes exist within submandibular glands. Although some anatomical studies have shown that they do not,^{13,14} Chen et al reported intraglandular lymph node metastases in patients with oral SCC,¹⁵ so it is possible that there are small lymph nodes or micrometastases that might not be detected by conventional sectioning techniques.

The second issue is the incidence and mode of involvement of the submandibular glands in oral SCC. Several research workers have reported that involvement is rare, and so it may be oncologically safe to preserve the gland during neck dissection.^{16–18} However, most of the reported studies were retrospective and, in the few cases where submandibular glands were seen to be involved, the mode at different stages of disease was not analysed. In addition, the studies that did report intraglandular lymph node metastases did not report their histopathological features.

The aims of this study were to use the step-serial sectioning technique to establish whether intraglandular lymph nodes are present in the submandibular glands, and to ascertain the mode of involvement of the glands at different stages of oral SCC. The findings will help surgeons to decide if preservation of the submandibular glands is feasible and safe during neck dissection in patients with oral SCC.

Material and methods

The study comprised patients with biopsy-confirmed oral SCC who had extended resection of the primary tumour with simultaneous neck dissection (other than primary SCC of the floor of mouth) from January 2017 to June 2018. Patients who required preoperative radiotherapy or chemotherapy and those with a history of malignant tumour or resection of an ipsilateral submandibular gland were excluded.

The surgical specimens of submandibular gland were carefully orientated and fixed in 10% formalin before being cut into pieces (about 5 mm thick, 1 cm long, and 1 cm wide) for embedding in paraffin. Sections 5 µm thick were obtained at 0.5 mm intervals and stained with haematoxylin and eosin (H & E).

All slides were first evaluated by one author and then sent to the chief pathologist for confirmation of the diagnosis. Pathological stages of the tumour and nodes were decided according to the American Joint Committee on Cancer (AJCC) 8th edition criteria.¹⁹ Diameter of the tumour, its depth of invasion, and extranodal extension of invaded lymph nodes were recorded.

This study was approved by the Institutional Review Board of Peking University School of Stomatology and was organised in accordance with the Helsinki Declaration. The need for informed consent was waived because the study was based on analysis of discarded surgical specimens.

Statistical analysis

Descriptive statistics were used for analysis, the median being given for continuous variables because the data were not normally distributed. The number was given for categorical variables. For statistical analysis we used IBM SPSS Statistics, (version 20.0, IBM Corp).

Results

A total of 95 patients were studied, and their personal and clinical details are given in [Table 1](#).

Seventy-four of the 95 patients had unilateral, and the remaining 21 had bilateral, neck dissection. A total of 116 submandibular glands were resected, and about 5000 slides stained with H & E were evaluated.

The diameter of the primary carcinoma (measured in 90 patients) ranged from 0.9 cm to 6.0 cm (median 2.5 cm), and in five patients it could not be measured because it was situated in the central mandible.

Depth of invasion (measured in 74 patients) ranged from 0.1 cm to 4.0 cm (median 1.0 cm) and in 21 patients it could not be measured because the bone was involved.

The number of the lymph nodes in level Ib in each patient (measured in 95 patients) ranged from 2 - 5 (mean 2.8), but we found no deep submandibular nodes.

Table 1
Personal and clinical details of patients.

Variable	No.
Sex:	
Male	58
Female	37
Alcohol:	
No	60
Yes	35
Tobacco:	
No	65
Yes	30
Site:	
Anterior tongue	46
lower gingiva	19
Buccal mucosa	11
Upper gingiva	9
Central mandible	5
Hard palate	4
Retromolar trigone	1
Tumour stage:	
pT ₁	8
pT ₂	32
pT ₃	25
pT ₄	6
pT _x	24
Nodal stage:	
pN ₀	39
pN ₁	16
pN ₂	27
pN ₃	13

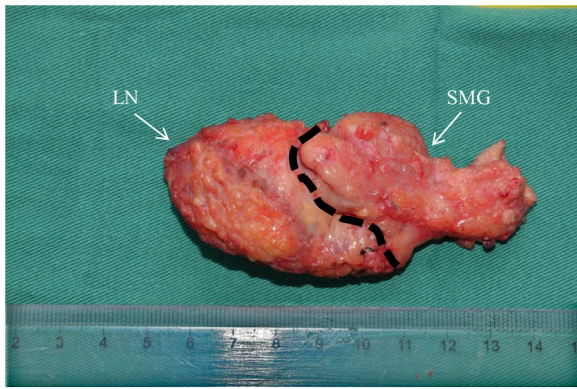


Fig. 1. Photograph showing a lymph node adhering to the submandibular gland.

Involvement of the submandibular gland in patients with and without invasion of the floor of the mouth

Lymph nodes were adherent to the submandibular glands in four patients (Fig. 1); the remaining 91 patients were divided into two groups - those in whom the floor of the mouth was clear (n = 87) and those in whom it was involved with tumour (n = 4).

Among the 87 patients with no involvement, 72 had unilateral, and 15 bilateral, neck dissections. A total of 102 submandibular glands were resected, and about 4000 H & E-stained slides were evaluated. No submandibular gland was involved in this group.

Among the four patients with involvement, one had unilateral, and three bilateral, neck dissections. Seven submandibular glands were resected and about 400 H & E-stained slides were evaluated. Four submandibular glands were involved by direct spread of the primary tumour (Fig. 2).

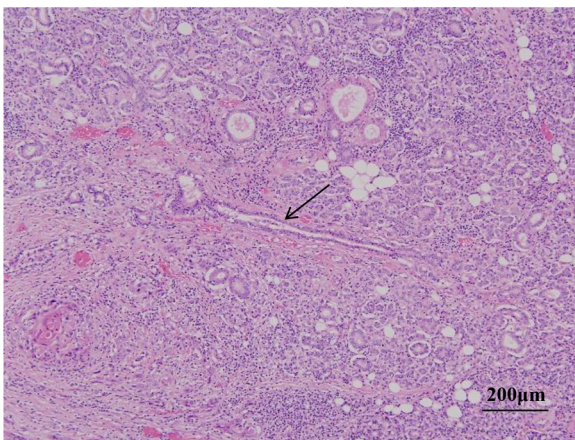


Fig. 2. Slides show involvement of the submandibular gland by extension of the primary tumour to the floor of mouth (haematoxylin and eosin stain).

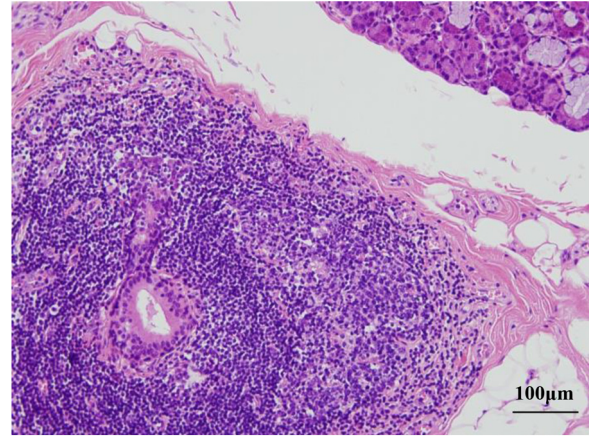


Fig. 3. Lymphoid follicle and germinal centre in the parenchyma of submandibular glands (haematoxylin and eosin stain).

Involvement of the submandibular gland in patients whose cervical lymph nodes were affected in other ways

After excluding four patients in whom the floor of the mouth was involved, the remaining 91 were divided into five groups: those with clear cervical lymph nodes (n = 39), those with metastases in level Ib lymph nodes but no capsular invasion (n = 27), those with extranodal extension to level Ib lymph nodes (n = 4), those with metastases to other lymph nodes (n = 33), and those with extranodal extension from other lymph nodes (n = 9).

Among the 39 patients with pathologically-confirmed clear cervical nodes, 36 had unilateral, and three bilateral, neck dissections. Forty-two submandibular glands were resected, and about 2100 H & E-stained slides were evaluated. No submandibular gland was involved in this group, and no intraglandular lymph nodes were detected. However, lymphoid follicles and germinal centres were detected in the parenchyma of two submandibular glands (Fig. 3).

Among the 27 patients with intranodal metastases in level Ib lymph nodes but no capsular invasion, 20 had unilateral, and seven bilateral, neck dissections. A total of 34 submandibular glands were resected, and about 1600 H & E-stained slides were evaluated. No submandibular glands were involved in this group, and no intraglandular lymph nodes were detected.

Among the four patients with extranodal extension to level Ib lymph nodes, one had unilateral, and three bilateral, neck dissections. Seven submandibular glands were resected, and about 300 H & E-stained slides were evaluated. In four patients the submandibular glands were involved by extranodal extension of metastatic carcinoma. In one patient only the capsule of the submandibular gland was involved (Fig. 4), whereas in the other three the glandular parenchyma was affected (Fig. 5). No micrometastatic foci were found other than in the involved part of the gland.

Among the 33 patients with intranodal metastases in lymph nodes at other levels, 24 had unilateral, and nine

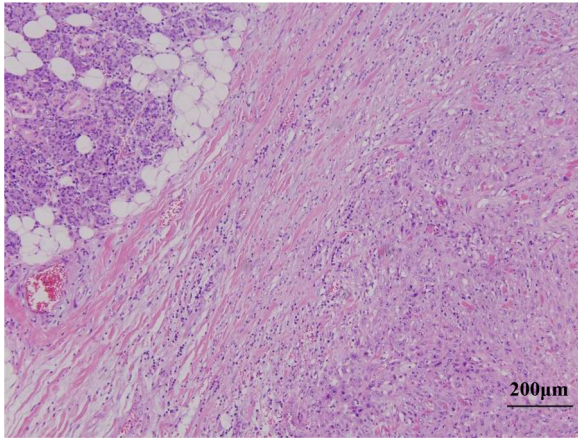


Fig. 4. Submandibular glands in the subgroup of extranodal extension in level Ib. The capsule of the submandibular gland was involved (haematoxylin and eosin).

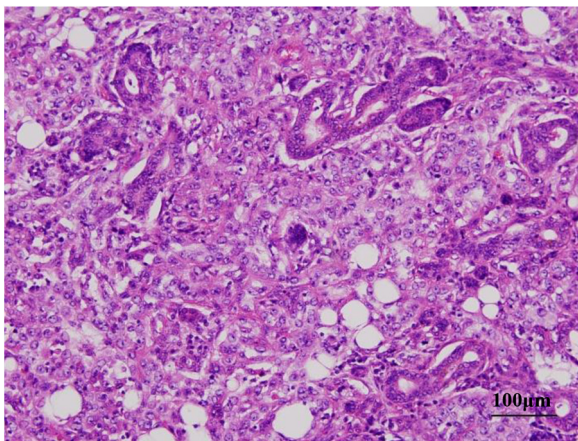


Fig. 5. Submandibular glands in the subgroup of extranodal extension in level Ib. The parenchyma of the submandibular gland was involved (haematoxylin and eosin).

bilateral, neck dissections. Forty-two submandibular glands were resected, and about 2500 H & E-stained slides were evaluated. No submandibular gland was involved.

Among the nine patients with extranodal extension in lymph nodes at other levels, six had unilateral, and three bilateral, neck dissections. Twelve submandibular glands were resected, and about 500 H & E-stained slides were evaluated. No submandibular gland was involved.

Discussion

With improved understanding of the distribution of cervical lymph node metastases in oral SCC, neck dissection evolved to become more selective.²⁰ Earlier, the submandibular gland was routinely excised during neck dissection. However, it is a functional organ²¹ and a major contributor to salivary flow at rest, so excision can have an important adverse impact on oral health and function.²⁰ It is therefore necessary to confirm

the safety of preservation of the submandibular glands during neck dissection in oral SCC.

There is still no consensus about whether an intraglandular lymph node exists in the submandibular glands.¹³ In 1998, in an anatomical study of 41 cadavers that were examined by the traditional sectioning technique, DiNardo found no intraglandular lymph nodes in the submandibular glands.¹³ However, there have been some reports of intraglandular lymph node metastases in the glands of patients with oral SCC.^{15,18} The cervical lymph node might be small, with a diameter of only 1 mm,²² and therefore step-serial sectioning would be required to establish its presence. In the present study about 5000 serial sections at 0.5 mm intervals were obtained from 116 glands, but no intraglandular lymph nodes were detected.

The submandibular glands can be involved by extension of the primary tumour. In a retrospective study of 177 patients with oral SCC, Fives et al showed that involvement of the submandibular glands was by direct spread of the primary tumour in the floor of the mouth.²³ We found that in the subgroup of patients with extension of the primary tumour to the floor of mouth, four glands were involved by direct spread. It should be noted that Wharton's ducts are usually sacrificed during radical resection of oral SCC that arises from, or involves, the floor of the mouth, and therefore preservation of the glands during neck dissection is not indicated. We found no involvement of submandibular glands in patients with primary tumours in other locations, or without invasion of the floor of the mouth. Proximity to the primary tumour, therefore, seems to be responsible for involvement of the glands.

It is not clear how the possibility of involvement of submandibular glands changes with the condition of the cervical lymph nodes. According to Kruse and Graz the glands should be excised in patients with head and neck cancer and invaded level I lymph nodes.¹⁸ We divided patients into five subgroups according to the condition of the cervical lymph nodes and analysed involvement of the submandibular glands. Only four patients in the subgroup with extranodal extension to level Ib lymph nodes had involvement of the glands, and in all cases it was by direct extension from the metastatic node. No micrometastatic foci were found at any distance from the involved part of the glands. In the other four subgroups, the glands were not involved. In the subgroup of patients with extranodal extension in other levels, we found no involvement of the submandibular glands, probably because of the distance between the metastatic lymph nodes and the glands. It seems therefore that the submandibular glands are involved by direct spread of metastatic lymph nodes with extranodal extension and not through the lymphatics.

Although we did not detect any deep submandibular nodes in our study, this group of lymph nodes has been described in another study.¹³ Under these circumstances, it would be necessary for surgeons to take more time to clear out the deep submandibular nodes, and in theory this contributes to the preservation of the glands. However, in our

clinical experience it is feasible for experienced surgeons to clear out the deep submandibular nodes. The potential complications need further follow-up study to validate.

Postoperative radiotherapy is commonly used as adjuvant treatment in patients with advanced oral SCC—either extensive primary carcinoma or multiple cervical metastases, and this damages the gland and affects function. For patients with advanced disease, therefore, preservation of the glands is not indicated. Frozen section biopsy is usually used for evaluation of metastatic lymph nodes during the operation.²⁴ If the biopsy specimen shows invasion of level Ib lymph nodes or even extranodal extension, the submandibular glands will not be preserved.

Conclusions

In summary, this clinicopathological study with step-serial sectioning and histopathological examination confirms that intraglandular lymph nodes are not present in the submandibular glands. In patients with oral SCC the glands may be involved by direct extension of the primary carcinoma from the floor of the mouth or by spread from metastatic cervical lymph nodes. Preservation of the submandibular glands during neck dissection therefore seems to be a feasible and safe option for selected patients with oral SCC.

Conflict of interest

We have no conflicts of interest.

Ethics statement/confirmation of patients' permission

This study was approved by the Institutional Review Board of Peking University School of Stomatology and was done in accordance with the Helsinki Declaration. The need for informed consent was waived because we used discarded specimens in the study.

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References

- Hu YJ, Chen J, Zhong WS, et al. Trend Analysis of betel nut-associated oral cancer and health burden in China. *Chin J Dent Res* 2017;**20**:69–78.

- Omura K. Current status of oral cancer treatment strategies: surgical treatments for oral squamous cell carcinoma. *Int J Clin Oncol* 2014;**19**:423–30.
- 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**:3286–93.
- Bocca E, Pignataro A. A conservation technique in radical neck dissection. *Ann Otol Rhinol Laryngol* 1967;**76**:975–87.
- Ferlito A, Rinaldo A, Silver CE, et al. Neck dissection: then and now. *Auris Nasus Larynx* 2006;**33**:365–74.
- Kowalski LP, Sanabria A. Elective neck dissection in oral carcinoma: a critical review of the evidence. *Acta Otorhinolaryngol Ital* 2007;**27**:113–7.
- Humphrey SP, Williamson RT. A review of saliva: normal composition, flow, and function. *J Prosthet Dent* 2001;**85**:162–9.
- Schneyer LH. Source of resting total mixed saliva of man. *J Appl Physiol* 1956;**9**:79–81.
- Moss SJ. Clinical implications of recent advances in salivary research. *J Esthet Dent* 1995;**7**:197–203.
- Mandel ID. The functions of saliva. *J Dent Res* 1987;**66 Spec No**:623–7.
- Cunning DM, Lipke N, Wax MK. Significance of unilateral submandibular gland excision on salivary flow in noncancer patients. *Laryngoscope* 1998;**108**:812–5.
- Okoturo EM, Trivedi NP, Kekatpure V, et al. A retrospective evaluation of submandibular gland involvement in oral cavity cancers: a case for gland preservation. *Int J Oral Maxillofac Surg* 2012;**41**:1383–6.
- DiNardo LJ. Lymphatics of the submandibular space: an anatomic, clinical, and pathologic study with applications to floor-of-mouth carcinoma. *Laryngoscope* 1998;**108**:206–14.
- Malik A, Joshi P, Mishra A, et al. Prospective study of the pattern of lymphatic metastasis in relation to the submandibular gland in patients with carcinoma of the oral cavity. *Head Neck* 2016;**38**:1703–7.
- Chen TC, Lo WC, Ko JY, et al. Rare involvement of submandibular gland by oral squamous cell carcinoma. *Head Neck* 2009;**31**:877–81.
- Dhiwakar M, Ronen O, Malone J, et al. Feasibility of submandibular gland preservation in neck dissection: a prospective anatomic-pathologic study. *Head Neck* 2011;**33**:603–9.
- Spiegel JH, Brys AK, Bhakti A, et al. Metastasis to the submandibular gland in head and neck carcinomas. *Head Neck* 2004;**26**:1064–8.
- Kruse A, Grätz KW. Evaluation of metastases in the submandibular gland in head and neck malignancy. *J Craniofac Surg* 2009;**20**:2024–7.
- Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol* 2010;**17**:1471–4.
- Razfar A, Walvekar RR, Melkane A, et al. Incidence and patterns of regional metastasis in early oral squamous cell cancers: feasibility of submandibular gland preservation. *Head Neck* 2009;**31**:1619–23.
- Chen TC, Lou PJ, Ko JY, et al. Feasibility of preservation of the submandibular gland during neck dissection in patients with early-stage oral cancer. *Ann Surg Oncol* 2011;**18**:497–504.
- Burusapat C, Jarungroongruangchai W, Charoenpitakchai M. Prognostic factors of cervical node status in head and neck squamous cell carcinoma. *World J Surg Oncol* 2015;**13**:51.
- Fives C, Feeley L, Sadadcharam M, et al. Incidence of intraglandular lymph nodes within submandibular gland, and involvement by floor of mouth cancer. *Eur Arch Otorhinolaryngol* 2017;**274**:461–6.
- Tschopp L, Nuyens M, Stauffer E, et al. The value of frozen section analysis of the sentinel lymph node in clinically N0 squamous cell carcinoma of the oral cavity and oropharynx. *Otolaryngol Head Neck Surg* 2005;**132**:99–102.