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Original Article

Involvement of the submandibular gland in oral squamous cell carcinoma patients with positive lymph nodes

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ABSTRACT

Background: No consensus exists about submandibular glands (SMGs) involvement in oral squamous cell carcinoma (OSCC) patients with cervical lymph node metastasis. We aimed to investigate the prevalence of SMG involvement in OSCC patients with positive lymph nodes.
Methods: Retrospective analysis of data of 302 study subjects with positive lymph nodes in OSCC operated between January 2002 and December 2012.
Results: Only 1/302 (0.3%) study subject had SMG involvement. The mode of spread was by direct extension of the primary carcinoma. Extracapsular spread of level IB lymph nodes was seen in 12/302 (4%) patients. Only one of these patients had involvement of the fibrous tissue around the SMG.
Conclusion: SMG involvement is very rare in OSCC patients with cervical lymph node metastasis. Preservation of the ipsilateral SMG during neck dissection might be oncologically safe when involvement by direct spread is unlikely.

1. Introduction

Oral squamous cell carcinoma (OSCC) constitutes a large proportion of oral and maxillofacial malignant tumors worldwide [1,2]. It is usually accompanied by cervical lymph node metastasis [3]. Neck dissection has been standard treatment for oral cancer patients ever since Crile first performed this surgery in 1906 [4]. Neck dissection has been shown to be oncologically beneficial even in patients without evidence of cervical lymph node metastasis [5,6]. Crile advocated that the cellular tissue of the neck be removed en bloc, along with the internal jugular vein, the spinal accessory nerve, the digastric, stylohyoid, sternocleidomastoid muscles, and the submandibular gland (SMG) [7]. However, this radical neck dissection is associated with a high complication rate [8]. In 1967 Bocca advocated a more conservative approach, with preservation of important structures such as spinal accessory nerve, internal jugular vein, and the sternocleidomastoid muscle [9]. He suggested that this approach would preserve cervical tissues and reduce the risk of complications such as the shoulder syndrome.

Neck dissection has undergone several modifications over the past decades as a result of improved understanding of the distribution of regional metastasis, and surgeons are increasingly preferring more selective and functional procedures over radical dissection. However, the SMG is invariably sacrificed [7] One reason for resection of the SMG is that it is a component of level IB in the neck, and surgeons worry that level IB lymph nodes may not be extirpated totally unless the SMG is also removed [10].

Salivary secretion from the SMG is important for normal function of the oral cavity. SMG salivary secretion at rest is much more than that of other salivary glands [11]. Resection of the SMG in oral cancer patients might result in symptomatic xerostomia even if adjuvant radiotherapy (ART) is not administered [12]. Lack of unstimulated saliva causes subjective xerostomia, which can impair the quality of life of patients [13].

Only a few researches focused on whether it is oncologically safe to preserve the ipsilateral SMG in OSCC patients with positive lymph nodes. We hypothesized that if the metastatic lymph nodes in OSCC are not in close proximity with the SMG it may be safe to preserve the SMG during neck dissection. This study was performed to investigate the prevalence of SMG involvement in OSCC patients with positive lymph nodes and to evaluate the feasibility of preservation of the SMG during neck dissection.

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2. Materials and Methods

OSCC patients with histopathologically positive lymph nodes who underwent curative wide excision of the primary tumor and simultaneous neck dissection at the Peking University School of Stomatology between January 1, 2002, and December 31, 2012, were included in this retrospective study. We searched the charts and pathological records by computer in the Department of Oral Pathology. Data were collected on gender, age, primary site, alcohol and/or tobacco consumption, extent of neck dissection, TNM stage (according to the criteria of the American Joint Committee on Cancer (2002), [12] histopathological features of SMG, and condition of cervical lymph nodes. Study subjects with synchronous or metachronous multiple primary malignancies, recurrent carcinoma, distant metastases, and those treated by preoperative radiotherapy or chemotherapy were excluded. All the H&E slides were evaluated by one author and confirmed by one chief pathologist under microscopy.

This study was approved by the Institutional Review Board of Peking University School of Stomatology and was conducted in accordance with the Heslinki Declaration of 1975 as revised in 1983. The need for informed consent was waived in view of the retrospective nature of the study.

2.1. Statistical analysis

The variable of involvement rate of the submandibular gland in oral squamous cell carcinoma subjects with positive lymph nodes was expressed as percentage. The variables of T stage and N stage of the study subjects were also analyzed. SPSS software, version 20.0 (IBM Inc., Armonk, NY, USA) was used for statistical analysis.

3. Results

A total 302 patients (188 males and 114 females) with positive neck lymph nodes were enrolled. The median age was 57 years (range, 16–86 years). The commonest primary site was the tongue ($n = 124$; 41.1%), followed by the lower gingiva ($n = 58$; 19.2%), floor of mouth ($n = 38$; 12.6%), buccal mucosa ($n = 36$; 11.9%), upper gingiva ($n = 36$; 11.9%), hard palate ($n = 8$; 2.6%), and central mandible ($n = 2$; 0.7%). Table 1 summarizes the demographic characteristics of the study subjects. The tumor stage and node stage of study subjects in histopathological were T_1 ($n = 36$), T_2 ($n = 130$), T_3 ($n = 28$), T_4 ($n = 108$), N_1 ($n = 127$), N_2 ($n = 175$).

Among the 302 study subjects, 249(82.5%) underwent curative wide excision of the primary carcinoma and simultaneous ipsilateral neck dissection, while 53 (17.5%) study subjects underwent curative wide excision of primary carcinoma and simultaneous bilateral neck dissection. Totally, 355 submandibular glands were resected. No intraglandular lymph nodes were detected in any SMGs in the study subjects.

Table 1
Characteristics of the study population.

Variable	No. of Patients	%
Gender		
Male	188	62.3
Female	114	37.7
Alcohol		
No	176	58.3
Yes	126	41.7
Tabacco		
No	144	47.7
Yes	158	52.3
Site		
Tongue	124	41.1
Lower gingiva	58	19.2
Floor of mouth	38	12.6
Buccal	36	11.9
Upper gingiva	36	11.9
Hard palate	8	2.6
Mandibular	2	0.7

Only one of the study subjects—a patient with stage 4 disease and primary tumor in the floor of the mouth—had involvement of the SMG; thus the involvement rate in our sample was 0.3% (1/302). The SMG involvment in this patient was by direct spread from the primary carcinoma (Fig. 1A and B). Microscopic examination of hematoxylin and eosin (H&E)–stained specimens did not reveal micrometastasis in any study subjects.

Metastasis to level 1 lymph nodes was found in 189/302 (62.6%) study subjects, 3 of whom had metastasis to contralateral level I lymph nodes. In one study subject, a metastatic level IB lymph node was found in close proximity to the SMG, but light microscopic examination of resected specimen did not show invasion of SMG parenchyma (Fig. 2A); the fibrous capsule around the SMG was however thicker than normal (Fig. 2B). Among the 189 study subjects, 12 had extranodal extension to level IB lymph nodes, but there was no invasion of SMG parenchyma. In one study subject, the fibrous tissue around the SMG was involved by extranodal extension from a positive level 1B lymph node, but the SMG parenchyma was not invaded (Fig. 3A and B).

4. Discussion

The primary aim of this study was to determine the prevalence of SMG involvement in OSCC patients with positive lymph nodes. In our sample of 302 OSCC study subjects the involvement rate was only 0.3%. This was consistent with the results of previous studies, which the involvement rate of the SMG in OSCC has ranged from 0% to 5.5% [11,14]. Okoturo et al. found that the ipsilateral SMG was

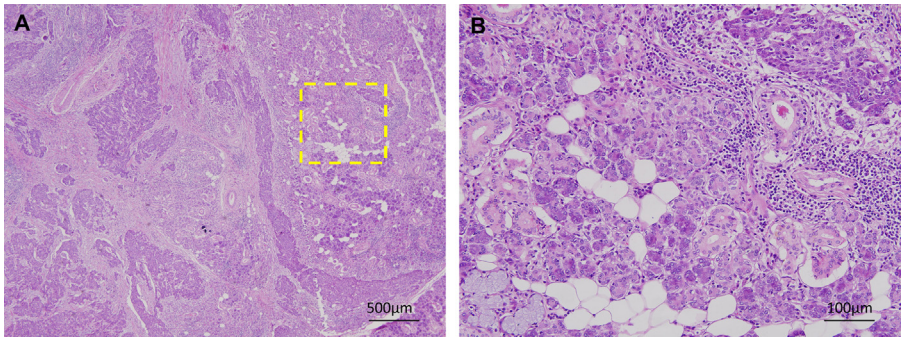

Fig. 1. The submandibular gland was involved by squmous cell carcinoma of floor of mouth. (A) H&E-stained specimen under a 4× objective. (B) Enlarged image of the boxed region in (A).

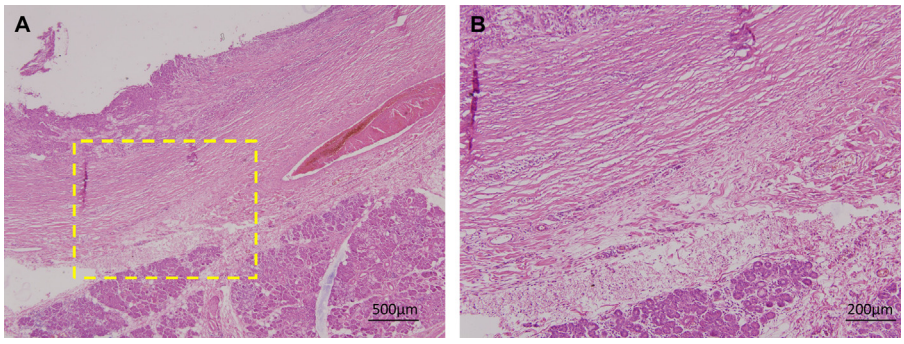

Fig. 2. No involvement of parenchyma of the submandibular gland in a patient with metastatic lymph node in level IB. (A) H&E-stained specimen under a 4× objective. (B) Enlarged image of the boxed region in (A).

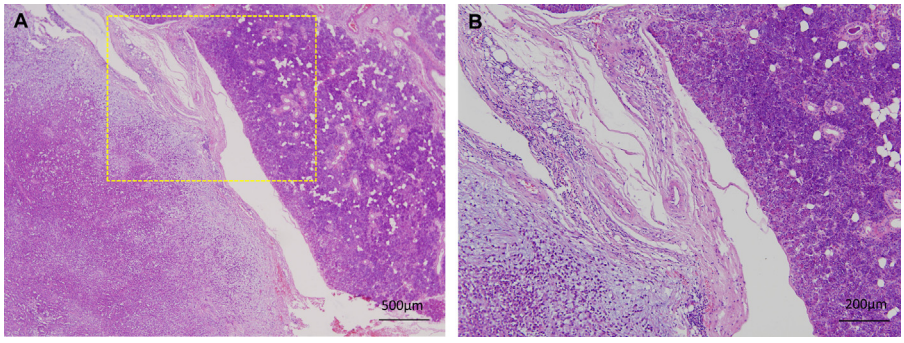

Fig. 3. Fibrous tissue around the submandibular gland was involved by the extracapsular spread of the positive lymph node in level IB (H&E). (B) Enlarged image of the boxed region in (A).

involved by direct infiltration and not by metastases [15]. However, SMGs might be involved in OSCC by four modes: direct spread from the primary carcinoma, direct extranodal extension from positive level IB lymph nodes, metastases to intraglandular lymph nodes, and carcinoma growing along Wharton's duct [16–18]. Kruse et al. proposed that the SMGs should be excised in OSCC patients when there were high risk of occult metastases at level I [19]. Panda et al. thought that the SMGs might be involved by extranodal extension from level IB lymph nodes [18]. Among the 13 study subjects in our samples with extranodal extension from positive level IB lymph nodes, 1 study subject had carcinoma infiltration of the fibrosis tissue around the SMG. With continued progress of cancer, it was possible that the parenchyma of the SMG might have been ultimately involved. In this patient the fibrous capsule around the SMG was thicker than in the normal condition, probably due to an immune response to the invasion by the carcinoma.

In OSCC patients undergoing bilateral neck dissection it may be more meaningful to consider the preservation of SMG [20], because there was still no effective method to fully restore saliva flow after resection of the SMGs [21,22]. Preservation of cancer-free SMG during neck dissection is being increasingly considered by surgeons as the only way to avoid the complications associated with xerostomia (e.g., severe dental caries) [23]. Some researches showed that SMG metastasis was rare in early-stage oral cancer, and so preservation of the SMG during neck dissection was a feasible option [24–26].

There was controversy about whether lymph vessels or lymph nodes exist in the SMGs [10,27]. Rosti et al. stated that unlike the parotid glands the SMGs were devoid of lymph nodes or lymph vessels [28]. In a prospective anatomic-pathologic study in 2010, Dhiwakar et al. found no subcapsular or intraparenchymal lymph nodes in the SMGs [20]. These findings were consistent with the embryologic concept that the encapsulation of the SMG occurred before the development of the lymphatic system, and so it was impossible that lymph node or lymphatic vessels could be contained in the SMGs [20,29,30]. However, Chen et al. detected one case, which the SMG was involved by intraglandular lymph node metastasis in a retrospective study included 383 cases [17]. Given that they did not provide any H&E images as evidence, we still had no idea about the histological structure of intra-glandular lymph nodes [17]. In our study no intraglandular lymph nodes were detected in the 355 resected SMGs. However, we only performed routine microscopic examination of H&E-stained slices; more rigorous techniques, such as examination after serial section, may have been more informative.

In a retrospective study of 168 patients with oral and oropharyngeal cancer, Lanzer et al. examined the rationality of preserving the SMG during neck dissection [23]. The SMG was preserved in 21(31.8%) of 66 patients with carcinoma in the floor of mouth or the tongue, and in 34 (33.3%) of 102 patients with carcinoma at a site other than floor of the mouth or the tongue. They found that overall survival and recurrence-free survival were similar between patients who did and did not undergo SMG preservation. However, the location of the primary carcinoma was related to prognosis in patients with preservation of SMG. Lymph node recurrence–free survival decreased in 28.5% (6/21) of patients with carcinoma in floor of the mouth or the tongue if the SMG was preserved. Excision of the SMG did not influence lymph node recurrence-free survival in the patients with carcinoma at a site other than the floor of the mouth or the tongue; only 3 patients (3/34, 8.8%) in whom the SMG was preserved developed lymph node recurrence in this group. On the basis of their results, Lanzer et al. proposed that preservation of SMG was not advisable for patients with squamous cell carcinoma of tissues closest to the

SMG (e.g., floor of mouth or tongue). In our opinion, squamous cell carcinoma of the floor of mouth was not an indication for preservation of SMG because the Wharton's duct was usually sacrificed during excision of the primary carcinoma. However, in early cases of tongue carcinoma preservation of the SMG should be considered unless there was carcinoma extension to tissues in the floor of the mouth.

This study has certain limitations. First, this was a retrospective study of patients form a single institution. Second, we did not have follow-up/survival data and so cannot answer the question on how SMG preservation affects prognosis. Third, we could not perform serial section of SMG limited by retrospective study.

5. Conclusions

Involvement of the ipsilateral SMG was very rare in OSCC patients even when there were positive lymph nodes in level IB. It might be oncologically safe to preserve the SMG during neck dissection in patients in whom involvement by direct extension of carcinoma is unlikely.

Disclosure of interest

The authors declare that they have no competing interest.

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