Head and neck

Is it necessary to remove submandibular glands in squamous cell carcinomas of the oral cavity?

È necessaria l'asportazione chirurgica delle ghiandole sottomandibolari nel carcinoma squamoso del cavo orale?

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SUMMARY

The aim of this study was to determine the frequency and the mechanism of submandibular gland (SMG) involvement in oral cavity squamous cell carcinomas (OCSCC), and to discuss the necessity of extirpation of the gland. The authors investigated and analyzed the retrospective charts of 236 patients who underwent surgery for OCSCC over a 10-year period and the pathology reports of 294 neck dissections with SMG removal. SMG involvement was evident in 13 cases (4%). Eight cases were due to direct invasion, which was the most common mechanism. Four cases had infiltration from a metastatic periglandular lymphadenopathy, and in 1 case, metastatic disease was confirmed. The tongue and floor of the mouth were the most frequent primary sites associated with SMG involvement. The study found no bilateral cases, and in 135 SMG specimens benign pathologies were detected. Involvement of the SMG in OCSCC is not frequent. It is appropriate to preserve the gland unless the primary tumour or metastatic regional lymphadenopathy is adherent to the gland.

KEY WORDS: Submandibular gland • Oral cavity • Neck dissection • Squamous cell carcinoma • Xerostomia

RIASSUNTO

Scopo del presente lavoro è di determinare la frequenza e il meccanismo patologico con cui le ghiandole sottomandibolari vengono interessate nel carcinoma squamoso del cavo orale e di discutere la necessità di asportazione chirurgica di tali strutture. Nel nostro studio retrospettivo sono state analizzate le cartelle cliniche di 236 pazienti sottoposti ad intervento chirurgico per carcinoma squamoso del cavo orale in un periodo di 10 anni ed in particolare i riscontri istopatologici di 294 interventi di svuotamento latero-cervicale comprensivo con asportazione della ghiandola sottomandibolare. Il coinvolgimento patologico delle ghiandole sottomandibolari risultava evidente in 13 casi (4%). In otto di questi era determinato da infiltrazione diretta, il più comune tra i meccanismi possibili. In quattro casi derivava invece da metastasi linfonodali perighiandolari. Solo in un caso si riscontrava malattia metastatica franca. Le sedi primitive associate più frequentemente ad interessamento delle ghiandole sottomandibolari risultavano essere la lingua e il pavimento orale. Non è stato riscontrato alcun caso di coinvolgimento ghiandolare bilaterale. Nei restanti 135 interventi il tessuto ghiandolare prelevato è risultato non interessato dalla malattia. Concludendo il coinvolgimento secondario delle ghiandole sottomandibolari nel carcinoma squamoso del cavo orale non è un'evenienza frequente, di conseguenza preservare tali strutture è consigliabile. Fanno eccezione tutti i casi in cui la malattia primitiva o l'eventuale metastasi linfonodale loco-regionale sia contigua alla ghiandola.

PAROLE CHIAVE: *Ghiandole sottomandibolari • Cavo orale • Svuotamento latero-cervicale • Carcinoma squamoso • Xerostomia*

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Introduction

Squamous cell carcinoma of the oral cavity is one of the most common tumours of the head and neck region [1]. Current surgical treatment includes wide surgical excision of the primary lesion with appropriate neck dissection. Neck metastases are most frequently observed in levels 1-2-3, but rarely in level-4 [2]. The submandibular glands are located in level-1b where rich lymphatic tissues surround them. Lymphatic metastases are common to this area, especially in floor of mouth (FOM) and tongue cancers. According to Rouviere, there are 5 lymph node groups in this region: preglandular, prevascular, retrovascular, retroglandular and intracapsular [2]. DiNardo added the "deep submandibular node" to this group [3]. Among these, the perivascular nodes (comprising prevascular and retrovascular nodes) are the most important because they are the primary afferent draining nodes of the oral cavity. Perivascular node involvement in FOM and tongue cancers is seen in about 5-7% of cases [4].

Although tumour metastasis to the gland is uncommon, SMGs are frequently excised as a part of neck dissection because of their proximity to the primary lesion and af-

ferent lymph nodes. However, the SMG is not a tissue without function; it secretes the majority of unstimulated saliva, especially during the night [5]. Saliva has many functions such as lubrication, buffering, immune defence, tooth enamel remineralisation and aiding mastication. Excision of submandibular glands may lead to xerostomia, which causes serious discomfort and a variety of problems in the oral cavity. Preservation of at least one gland will prevent these complications [6]; however, there is no consensus about the preservation of the submandibular glands in oral cavity tumours [7].

Herein, we investigated the rate of involvement and mechanism of submandibular glands in oral cavity tumours, and discuss the controversy about preservation of the SMGs.

Materials and methods

The current study retrospectively reviewed the medical and pathologic charts of 236 patients who underwent surgery for OCSCC at the Istanbul University Medical Faculty between the years 2000 and 2010. Patients were staged according to the American Joint Committee on Cancer (AJCC) 2002 staging guidelines [8]. Inclusion criteria were histopathologically confirmed squamous cell carcinoma of the oral cavity and surgery as the primary treatment modality, consisting of resection of the primary lesion with additional neck dissection, including at least one submandibular gland. Patients with tumour histology other than squamous cell carcinoma or with a history of previous head and neck radiotherapy were excluded.

Results

The study included 236 patients. The mean age at presentation was 57 years (range: 23-83 years) and the sample included 157 males and 79 females. Surgery in 58 of the patients (24.6%) involved bilateral neck dissection with bilateral SMG excision, while in the remaining 178 patients (75.4%) one-sided neck dissection with unilateral SMG excision was performed. Consequently, 236 patients and 294 submandibular glands were included in the study. Table I shows the distribution of primary tumour sites.

Tumour involvement of the SMG was observed in 13 patients (5.5%) (Table II). Of these, 8 were due to direct invasion of the primary lesion (3 tongue tumours with T3N2b, T3N1, T4N3 lesions, 4 FOM tumours with T3N0, T4N0, T4N2b, T4N1 lesions and one lip tumour with a T4N1 lesion). Four glands displayed invasion through the metastatic periglandular lymph node (2 tongue tumours with T2N0 and T2N2a lesions, one FOM tumour with a T4N2b lesion and one buccal mucosa tumour with a T4N2b lesion). Metastasis to the SMG was observed in only one patient whose primary lesion was a T2N0 tongue carcinoma. In 66 early staged patients (stage 1&2), only 2 cases involvement of the SMG were observed (3%). In advanced stages (stage 3&4), of the 170 patients, 11 had SMG involvement (6.5%). In addition, the highest probability of SMG involvement was in FOM tumours (13.9%); the ratio of tongue tumours was lower (2.5%). As expected, SMG involvement was mostly due to the invasion of primary tumours due to their proximity. In advanced tongue tumours, invasion via FOM, SMG was seen in 3 cases. In addition, direct invasion was detected in 1 case of advanced stage lower lip carcinoma.

Most of the cases with SMG involvement were N+ and locally advanced (Table III). Contralateral SMG involvement was observed in only 1 case, which was due to invasion through a metastatic periglandular lymph node. There was no bilateral SMG involvement.

In 135 SMG specimens, benign pathologies such as fibrosis, ductal ectasy, chronic sialoadenitis and Warthin's tumour (2 cases) were found.

Discussion

Saliva has many functions. It assists speech, mastication and swallowing by way of lubrication. Bicarbonate in saliva makes it slightly alkaline, which is important in buffering acidic bacterial enzymes, and it plays an important role in tooth integrity by helping mineralization. Its antimicrobial activity comes from IgA, lactoferrin and other enzymes. Amylase starts digestion of carbohydrates in the mouth. Saliva is also important in taste because it transports food particles to the taste buds. SMGs secrete most of the unstimulated, resting saliva (70-80%) and are responsible for most of the protective functions of saliva.

Xerostomia is defined as the perception of dry mouth. In the case of decreased saliva, patients have trouble in speaking, swallowing, chewing and tasting. The frequency of dental caries and infections such as oral candidiasis increase [10]. Ultimately, decreased feeding and weight loss appear, which interrupts concomitant cancer treatment. Xerostomia also has psychological effects; patients do not want to talk with other people, and avoid smiling due to their dental status [11]. They cannot eat what they would like, and the quality of life significantly decreases.

In advanced oral cavity tumours, radiation therapy (RT) is often an adjuvant treatment that damages salivary glands and aggravates xerostomia. Parotid glands, which have an affinity to damage by RT, are affected rapidly and irreversibly. Mucous glands are less sensitive. Many changes in salivary glands at 60 Gy are reversible, but beyond this, permanent damage occurs [12]. RT decreases salivary volume and pH, and changes its composition [13]. Decreased taste bud stimulation causes decreased stimulation of salivary secretion, which results in aggravation of the problem. One important complication of xerostomia is osteoradionecrosis due to plaques, gingivitis and periodontitis in the absence of salivary protection [14]. When the submandibular glands are excised, these processes occur more rapidly and patients may cease RT. With the use

of intensity-modulated radiation therapy (IMRT), the frequency of xerostomia decreases and preservation of the SMGs during surgery becomes more important.

In oral cavity tumours, SMGs are excised for two reasons: for dissection of lymph nodes in level 1b and for SMG invasion. SMG involvement in oral cavity tumours ranges between 0.6 and 4.5% (Table V) in the literature and has 3 mechanisms. The first and most frequent (66-100%) is direct invasion by the tumour (Table V). In the current series, direct invasion by the tumour was also the most frequent mechanism (61%). The important point is that the overall SMG direct invasion rate in the series ranged between 0.6 and 3%, which indicates that direct invasion was an inessential reason for SMG removal. The results (2.7%) were also consistent with literature reports. As expected, FOM (9%) and tongue (2%) tumours directly invaded SMGs most frequently (Tables II-IV).

The second mechanism is through metastatic lymph nodes in the region, which accounts for 0-1.5% of cases in the literature (Table V). Although metastasis to level 1b is frequent, metastatic lymph nodes do not invade the gland. In Junquera's investigation, with tumours of the FOM from 31 patients the incidence of ipsilateral level-1 metastasis was 31.7%; however, there were no cases of SMG invasion through

Table I. Distribution of primary tumours and clinical T stages with cumulative percentages.

		T stage			
Primary site	**No. of cases Total (%)**	**T1 (%)**	**T2, (%)**	**T3, (%)**	**T4, (%)**
Tongue	108 (45.7)	18 (16.7)	53 (49.1)	20 (18.5)	17 (15.7)
Floor of Mouth	33 (13.9)	3 (9.1)	10 (30.3)	4 (12.1)	16 (48.5)
Buccal mucosa	24 (10.1)	1 (4.2)	8 (33.3)	6 (25)	9 (37.5)
Retromolar Trigone (RMT)	21 (8.8)	3 (14.3)	3 (14.3)	0	15 (71.4)
Alveolar Ridge	16 (6.7)	1 (6.3)	0	1 (6.3)	14 (87.5)
Lip	12 (5)	2 (16.7)	6 (50)	1 (8.3)	3 (25)
Palate	22 (9.3)	2 (9.1)	7 (31.8)	4 (18.2)	9 (40.9)

Table II. Distribution of cases with SMG involvement according to clinical T stage.

Tumour site	**Patients (n)**	**Direct SMG invasion (n)**	**Invasion through metastatic LN (n)**	**Metastasis to SMG (n)**	**Total SMG involvement(n)**
Tongue	108	3 *(T3,T3,T4)*	2 *(T2,T2)*	1 *(T2)*	6 (4.2%)
FOM	33	4 *(T3,T4,T4,T4)*	1 *(T4)*	0	5 (11.3%)
Buccal mucosa	24	-	1 *(T4)*	-	1 (3.7%)
Palate	22	-	-	-	0
RMT	21	-	-	-	0
AR	16	-	-	-	0
Lip	12	1 *(T4)*	0	0	1 (7.6%)
Total	236	8	4	1	13 (4.4%)

(LN: Lymph-node, n: number, FOM: floor of mouth, AR: Alveolar ridge, RMT: Retromolar trigon, SMG: Submandibular gland)

Table III. TNM classification and staging of cases with SMG involvement.

T	**SMG involvement (n)**	**N**	**SMG involvement (n)**	**Stage**	**SMG involvement (n)**
T1	-	N0	2	1	-
T2	5	N1	4	2	2
T3	1	N2	4	3	2
T4	7	N3	3	4	9

(SMG: Submandibular gland)

Table IV. Literature review of SMG involvement according to site of primary tumour in the oral cavity. (Number of submandibular glands involved/number of patients excised).

Author	**Tongue**	**FOM**	**Tongue Base**	**RMT**	**Alveolar Ridge/ Gingiva**	**Palate**	**Buccal**	**Lip**	**Posterior pharynx**	**Other**
Siegel [16]	†2/54	5/25	0/15	0/11	‡2/11	0/6	0/6	0/5	0/2	*0/15
Chen [17]	0/121	3/17	-	0/22	2/20	0/14	5/143	0/5	-	-
Razfar [25]	0/58	1/36	-	0/16	0/7	0/5	0/9	-	-	0/1
Byeon [26]	0/132	1/35	-	1/10	0/9	-	0/14	0/1	-	-
Our series	6/108	5/33	-	0/21	0/16	0/22	1/24	1/12	-	-

(FOM: Floor of mouth, RMT: Retromolar trigon)

**tonsillary fossa, 12 cases involve multiple structures, †One case involves both FOM and tongue, ‡ One case involves both FOM and Alveolar ridge*

this path [15]. It is likely that the capsule of the gland and the free spaces in the region direct the tumour to tissues adjacent to the SMGs. It seems reasonable to preserve SMGs because tumours due to metastatic lymphadenopathy (LAP) in the region seldom infiltrate the glands.

Table V. Literature review of SMG involvement according to mechanism.

Author	Total SMG	+ SMG	Mechanism of SMG involvement (n)		
			Tumour invasion	Invasion by metastatic LAP	Metastasis to SMG
Siegel [16]	196	9	6	3	-
Chen [17]	383	7	5	1	1
Razfar [22]	153	1	1	-	-
Byeon [23]	316	2	2	-	-
Our series	294	13	8	4	1

(n: number of SMG, +: SMG involvement, LAP: lymphadenopathy, SMG: Submandibular gland)

The third and most discussed mechanism is metastasis through intraglandular lymphoid tissue [2 3 16]. There are very few reports that accept this possibility [2 3]. Chen reported one case of metastasis to the SMG [17]. Vaidya reported two cases, one of which was a tongue tumour, while the other was a palate tumour in a patient who had undergone radiotherapy 9 years earlier [18]. It is interesting that both of these cases were N0. Oncologically, intraglandular nodes seem to be silent and unaffected by most tumours of the region. Conversely, metastatic disease in the SMGs more often involves haematogenous mechanisms, especially in cancers of the breast, lung and genitourinary system [19].

Among the OCSCC series, only one case of bilateral SMG involvement was seen [17]. There was no bilateral SMG involvement in this study. It is not rational to excise both glands for an OCSCC. The authors strongly recommended preserving at least one SMG in light of this data**.** There is no data about the prognostic significance of SMG involvement in OCSCC. Clark investigated sublingual gland invasion in oral cavity cancers and did not find any differences in disease-specific survival (DSS), loco regional control or distant metastasis rates [20].

Decisions regarding the excision of SMGs must be entirely based on the proximity of the primary tumour to the gland [21]. As seen in our study, in early stages and except for FOM tumours, involvement of the SMG in oral cavity tumours is very rare [22 23]. Because the gland has a unique structure and because its capsule displays resistance against tumour invasion, oncologically, it is enough to dissect only the capsule of the gland with the surrounding lymph nodes. It is better to strive to preserve the glands unless there are adherent pathologic lymph nodes or very close metastatic or primary tumors [24]. Instead of preoperative planned gland resection, the decision to excise the SMG must be determined during the operation with the help of inspection and frozen sections. One must take into account that xerostomia is a very important complication that may decrease the quality of life and lead to cessation of treatment. Surgeons should try to modify and develop techniques to protect SMGs in the treatment of oral cavity tumours. More research is warranted to investigate the effects of SMG preservation on survival and loco regional control of disease.

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