

# The preservation and application of the submandibular gland in oral squamous cell carcinoma (STROBE)

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## Abstract

This prospective study aimed to investigate metastases of oral squamous cell carcinoma (OSCC) to cervical lymph nodes and submandibular glands and to analyze the safety and feasibility of preserving and using submandibular glandular flaps to repair postoperative OSCC defects.

Overall, 330 patients with OSCC who met the inclusion criteria were enrolled in the study from January 2014 to July 2018. OSCC metastasis to cervical lymph nodes and submandibular glands was investigated using intraoperative frozen section and postoperative pathological observation. Fifteen patients who underwent repair of postoperative OSCC defects with submandibular glandular flaps were monitored for postoperative wound healing, complications, pathology, and appearance satisfaction and were followed up long term.

Among the 330 patients with OSCC, the most common type was tongue cancer (138/330); 204 patients were node negative and 126 were node positive. Of 363 samples of the submandibular gland, 7 were metastatic with stage IV lesion, 5 were directly invaded by the primary tumor, and 2 were metastatic with extranodal extension in level Ib. None of the submandibular gland samples showed intraglandular hematogenous and nodal metastases. The repair of OSCC defects with submandibular glandular flaps was successful in all 15 patients, including 11 males and 4 females, with an age range of 19–74 years and a mean of 51 years. Of 15 patients, some had complications with heart and cerebrovascular diseases, diabetes, or chronic respiratory disease. All the submandibular glandular flaps survived postoperatively without any complications, and the mucosification on the surface was adequate. Follow-ups (median duration: 14 months) revealed the satisfactory recovery of shape and function without any local recurrences or distant metastases.

Direct invasion is the main form of OSCC metastasis to the submandibular gland, while hematogenous and nodal metastases are uncommon. Preservation of the submandibular gland is oncologically safe. Thus, repair of postoperative OSCC defects with submandibular gland flaps is a feasible and promising procedure.

**Abbreviations:** DIPT = direct invasion of primary tumors, IGLN = intraglandular lymph node, OSCC = Oral squamous cell carcinoma, PGLN = periglandular lymph nodes.

**Keywords:** lymph node dissection, lymphatic metastasis, oral cancer, reconstruction, submandibular gland

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## 1. Introduction

Oral cancer, a common head and neck malignancy, has several common pathological types, among which squamous cell carcinoma is the most prevalent. Each year, there are approximately 300,000 new cases and 130,000 deaths associated with oral cancer worldwide.<sup>[1]</sup> The use of tobacco and areca nut is the most important high risk factor for oral cancer, followed by diet, lifestyle, and genetic factors.<sup>[2]</sup> Developing countries, including China's rural areas, India, and Pakistan, have a high incidence of oral cancer.<sup>[3]</sup> The treatment of oral cancer is generally surgical resection combined with chemotherapy or other remedies. Lymph node or distant metastases are important factors affecting prognosis. In addition to primary tumor excision, neck dissection is an indispensable part of oral cancer surgery.<sup>[4]</sup> In past clinical practice, the excision of the submandibular gland together with the involved lymph nodes in the level Ib region resulted in submandibular gland function loss and xerostomia, thereby affecting patients' quality of life.<sup>[5]</sup> However, in recent years, scholars have proposed that the preservation of the submandibular gland is feasible during neck dissection because metastasis of head and neck tumors to submandibular glands is rare, and the preservation of non-invaded submandibular glands does not lead

to tumor recurrence or metastases.<sup>[6]</sup> Some studies have even indicated that the preservation of the submandibular gland in head and neck tumors of stages T1-T2 and N0 can improve oncological safety and postoperative quality of life of patients.<sup>[7,8]</sup>

To confirm the safety of preserving and using submandibular gland in oral cancer, we conducted a multicenter prospective study on patients with oral squamous cell carcinoma (OSCC). These patients underwent primary tumor excision and neck dissection involving resection of their submandibular glands and lymph nodes in the regions of levels Ia and Ib. The involvement of lymph nodes and submandibular glands was investigated. Suitable patients received postoperative defect repair with submandibular glandular flaps and were followed up to assess flap survival and postoperative recurrence.

## 2. Methods

### 2.1. Ethics statement

The Ethical Committee of the Tumor Hospital of Ganzhou Review Board approved the study protocol (20130102), and the study was conducted according to the principles of the Declaration of Helsinki on research involving human subjects. Each patient provided written informed consent to participate after the details of the study was explained.

### 2.2. Clinical data

**2.2.1. Subjects.** Overall, 330 patients with OSCC were enrolled from Ganzhou Cancer Hospital, the First Affiliated Hospital of Gannan Medical College and the First Hospital in Qiqihar City, China from January 2014 to July 2018. All patients underwent primary tumor excision, selective or modified radical neck dissection (including the resection of submandibular glands), and postoperative pathological examination. The inclusion criteria were as follows:

1. squamous cell carcinoma confirmed by pathology;
2. complete imaging data (computed tomography or magnetic resonance imaging) for primary tumors and cervical lymph nodes; and
3. ) patient tolerance of primary tumor neck dissection.

The exclusion criteria were as follows:

1. history of surgery or radiotherapy in the neck;
2. submandibular gland diseases;
3. distant metastasis; and
4. vital organs with lesions and inability to tolerate surgery.

The tumor–node–metastasis cancer staging was performed according to Cancer Staging Manual (American Joint Commission on Cancer, 2010 edition).

### 2.2.2. Procedures

**2.2.2.1. Clinical data collection.** Complete preoperative imaging and clinical data were collected and relationships between the primary tumor, submandibular triangle lymph nodes, and submandibular glands were analyzed. Morphology and signs of invasion or metastasis were observed and the clinical stage was determined. During surgery, isolated cervical tissues were placed according to the anatomical positions immediately after the neck dissection. Lymph nodes in levels I-IV were isolated based on preoperative images and intraoperative observation. Level I was divided into Ia and Ib, and level Ib was further divided into

the submandibular gland, periglandular lymph nodes (PGLN), and adipose tissue. All samples were sent for pathological examination.

**2.2.2.2. Literature data collection.** Related literature was searched on PubMed using the keywords “submandibular gland, metastasis, oral, malignancy”. The data were summarized and analyzed.

**2.2.2.3. Surgical method.** Inclusion criteria for the repair of postoperative OSCC defects with submandibular glandular flaps were as follows:

1. age >17 years;
2. oral cancer confirmed by pathology;
3. preoperative images and intraoperative frozen sections indicating no positive nodes or extracapsular invasion in level Ib;
4. Karnofsky score  $\geq 80$ ;
5. expected survival > 1 year; and
6. voluntary signing of the informed consent form.

Exclusion criteria were

1. invasion or presence of other lesions on the submandibular gland;
2. history of surgery or radiotherapy in the neck;
3. distant metastasis; and
4. vital organs with lesions and inability to tolerate surgery.

The surgical method used was the same as described in formal literature.<sup>[9]</sup>

**2.2.2.4. Postoperative observational indicators.** Postoperative wound healing; complications; pathology of infraorbital, submandibular, and cervical lymph nodes; recovery of appearance; occlusal relationship; effects on breath, pronunciation, swallow, gape, and occlusal relationship; and recurrences of the primary tumor and cervical nodal involvement were observed.

### 2.3. Statistical methods

IBM SPSS Statistics 20.0 was used. Count data were analyzed by Chi-Squared test.  $P < .05$  was considered statistically significant.

## 3. Results

Of the 330 patients with oral carcinoma who were included in the study, all had the pathological confirmation of squamous cell carcinoma, including 131 females and 199 males, with the mean age of 54.8 years (range: 24–72 years). Unilateral neck dissection was performed in 297 patients, and bilateral neck dissection was performed in 33 patients. A total of 363 submandibular gland samples were collected, including tongue cancer (138 cases, 41.8%), buccal mucosal cancer (45 cases, 13.6%), gingival cancer (57 cases, 17.3%), carcinoma of the floor of mouth (69 cases, 20.9%), and carcinoma of the hard palate (21 cases, 6.36%). Rare oral cancer types were not included in the study. In this study, stage T1 (111 cases, 33.6%) was the most common, followed by T2 (108 cases, 32.6%), T3 (66 cases, 19.9%), and T4 (45 cases, 13.7%). Postoperative pathology confirmed 204 node-negative and 126 node-positive cases (Tables 1 and 2). Submandibular gland invasion was confirmed in 7 cases, including 5 cases of direct invasion and 2 cases of level Ib

**Table 1**  
Infringement and metastasis of submandibular gland in oral cancer.

Site	No.	N stage	T stage	No. of +SMG	Mode of aggression/Staging
Oral tongue	138	N0	96	2	DIPT =1(T4aN1M0) PGLN=1(T4aN2M0)
		N1	33		
		N2	9		
Buccal mucosa	45	N0	24	2	DIPT =1(T4aN2M0) PGLN=1(T4aN2M0)
		N1	9		
		N2	12		
Gingiva	57	N0	33	1	DIPT=1(T4aN1M0)
		N1	9		
		N2	15		
Floor of mouth	69	N0	30	1	DIPT=1(T4aN1M0)
		N1	21		
		N2	18		
Hard palate	21	N0	12	1	DIPT=1(T4aN2M0)
		N1	7		
		N2	2		
Total	330			7	DIPT =5 PGLN=2

DIPT = direct invasion of primary tumors, IGLN = Intraglandular lymph node, PGLN = periglandular lymph nodes, SMG = submandibular gland.

extranodal extension through the capsule. All 7 cases were stage T4. Submandibular gland involvement was related to the invasion of the primary lesion, and the difference was statistically significant ( $P < .001$ ).

Submandibular gland involvement has 3 types: direct invasion of primary tumors (DIPTs) to the glandular parenchyma, involvement of level Ib PGLN, and intraglandular lymph node (IGLN) metastasis. A literature search of PubMed was performed using the keywords “submandibular gland, metastasis, oral, malignancy”. The summary and analysis of the data indicate that of 2875 submandibular gland samples from 2750 patients with oral and oropharyngeal cancer, 59 (2.05%) were involved, including 44 samples of DIPT, 13 of PGLN, and 2 of IGLN reported only by Basaran (Table 3).

**Table 2**  
Clinical factor predicting submandibular gland invasion.

Variables	n	Positive submandibular gland	P value
Age			NS
≤45 y	107	3 (2.80%)	
>45 y	223	4 (1.79%)	
Sex			NS
Male	199	5 (2.51%)	
Female	131	2 (1.53%)	
T classification			$P < .001$
T1	111 (33.6%)	0 (0.00%)	
T2	108 (32.8%)	0 (0.00%)	
T3	66 (19.9%)	0 (0.00%)	
T4	45 (13.7%)	7 (15.56%)	
N classification			$P < .001$
N0	204 (62%)	0 (0.00%)	
N1	72 (22%)	3 (4.17%)	
N2	54 (16%)	4 (5.41%)	

Additionally, based on our preliminary study, we expanded the indications and conducted the repair of postoperative defects of oral cancer with submandibular gland flaps in 15 patients, including 10 patients with tongue cancer, 2 with gingival cancer, 3 with carcinoma of the floor of mouth. One patient was stage I, 5 were stage II, 7 were stage III, and 2 were stage Va. The mean age was 51 years (range: 19–64 years) and the median follow-up time was 14 months. After the surgery, there were no deaths; all the flaps survived without complications or pain in the submandibular gland, and the glandular surface was well mucosalized, and all the surgical incisions healed in first stage. A total of 43 lymph nodes were cleared in the level Ib region of the 15 patients, where no metastasis was found in the intraoperative frozen section and postoperative paraffin section. The lymph nodes from other cervical regions were also not metastatic. All 15 patients were followed up for 5 to 27 months (follow-up rate: 100%). Long-term cosmesis and function (speech and swallowing) were exceptional good and the results indicated no local recurrence in the submandibular gland flap-repaired area, 2 new cases of distant metastases, and no deaths (Table 4). In 1 of the cases, we used submental island pedicled flap combined with submandibular gland flap to repair defects of gingival site and partial mandible. The SMG became mucosalized in 3 to 4 weeks and the patient appeared normal, including the extent to which the mouth opened (Fig. 1A-F).

#### 4. Discussion

For patients with early-stage oral cavity cancers, the recommended initial options are resection of the primary tumor or definitive. In general, many patients undergo either ipsilateral or bilateral neck dissection, which is guided by tumor thickness. Lymph node metastasis is one of the most important factors that affects the prognosis of oral cancer. Thus, when the primary tumor is resected, nodal metastasis must be addressed to improve

**Table 3**  
**Analysis of literatures concerned on SMG involvement by metastasis from squamous cell carcinoma sorted by year of publication.**

Authors	No.of patients/No.of SMG	No. of +SMG	Mode of SMG involvement
Junquera et al (2000) <sup>[10]</sup>	31/31	0 (0.00%)	0
Spiegel et al (2004) <sup>[11]</sup>	169/196	9 (4.59%)	DIPT = 6 PGLN = 3
Razfar et al (2009) <sup>[12]</sup>	261/253	1 (0.39%)	DIPT = 1
Byeon et al (2009) <sup>[13]</sup>	201/316	2 (0.63%)	DIPT = 2
Chen et al (2010) <sup>[14]</sup>	383/383	7 (1.83%)	DIPT = 5 PGLN = 1 IGLN = 1
Ebrahim et al (2011) <sup>[8]</sup>	107/107	1 (0.93%)	DIPT = 1
Naidu et al (2011) <sup>[15]</sup>	69/69	0 (0.00%)	0
Okoturo et al (2012) <sup>[7]</sup>	194/229	3 (1.31%)	DIPT = 3
Kruse et al (2009) <sup>[16]</sup>	171/171	6 (3.51%)	DIPT = 5 PGLN = 1
Basaran et al (2013) <sup>[17]</sup>	236/294	13 (4.42%)	DIPT = 8 PGLN = 4 IGLN = 1
Howard et al (2014) <sup>[18]</sup>	253/157	4 (2.55%)	DIPT = 4
Ashfaq et al (2014) <sup>[19]</sup>	110/110	2 (1.82%)	DIPT = 2
Malgond et al (2015) <sup>[20]</sup>	94/98	3 (3.06%)	DIPT = 2 PGLN = 1
Panda et al (2015) <sup>[21]</sup>	204/163	6 (3.68%)	DIPT = 4 PGLN = 2
Gaurav et al (2016) <sup>[22]</sup>	112/115	0 (0.00%)	0
Cakir et al (2018) <sup>[6]</sup>	155/183	2 (1.09%)	DIPT = 1 PGLN = 1
Total	2750/2875	59 (2.05%)	DIPT=44 PGLN = 13 IGLN = 2

DIPT = direct invasion of primary tumors, IGLN = Intraglandular lymph node, PGLN = periglandular lymph nodes, SMG = submandibular gland.

the cure rate. The submandibular gland is located in the submandibular triangle, which is frequently excised during neck dissection. Since functional preservation in oral and maxillofacial surgery has its obvious advantages, submandibular gland preservation has become a hot research topic. Metastases to the submandibular glands are mostly hematogenous, originating from tumors outside the head and neck, such as breast cancer, renal cancer, lung cancer, and leiomyosarcoma, while primary tumors in the head and neck seldom invade the submandibular gland.<sup>[23,24]</sup>

It is widely believed that the rarity of submandibular gland metastasis is related to the absence of abundant lymphatic vascular structure and IGLN network, which is significantly different from the parotid gland. In OSCC, invasion of the submandibular gland caused by level Ib periglandular nodal metastasis is observed in 0.3% to 1.7% of cases.<sup>[17]</sup> In the retrospective review by Ebrahim et al, only 8% of 107 neck

dissection cases had level Ib involvement, among which only 1 case was caused by direct invasion of the submandibular gland.<sup>[8]</sup> Naidu TK et al reported that only 2 out of 69 patients with OSCC had submandibular glandular metastases, which resulted from the direct invasion of the primary tumors.<sup>[15]</sup> Cheng et al analyzed 7 cases of submandibular gland metastasis, where 5 cases were caused by direct invasion of primary lesions, 1 case by level Ib nodal invasion, and 1 case by intraglandular nodal involvement.<sup>[14]</sup> In the cases of submandibular gland metastasis, all primary tumors were staged T4 ( $P < .0003$ ), and all regional nodal stages were beyond N2b ( $P < .0001$ ). No metastasis to submandibular gland was seen in stages T1-T3 or N0-N2a. The rate of submandibular glandular involvement was 6.67% in stage T4 and 8.22% in stages N2b-N3.<sup>[10]</sup> In summary, metastases to submandibular gland are uncommon, most of which are caused by direct invasion. In this study, although 38% of the 330 enrolled patients had regional nodal metastasis, there was no

**Table 4**  
**Clinical and personal details of patients.**

Case No	Sex/age (years)	Site	Diagnosis	Complications	TNM/Stage	Follow-up (Months)
1	M/19	Lateral border of tongue	Squamous	None	T2N0M0,II	27
2	M/63	Lateral border of tongue	Squamous	Hypertension	T2N1M0,III	11
3	F/48	Floor of mouth	Squamous	Diabetes mellitus	T2N0M0,II	5
4	M/69	Lateral border of tongue	Squamous	Hypertension. Diabetes mellitus	T3N1M0,II	14
5	M/45	Lateral border of tongue	Squamous	None	T1N1M0,III	24
6	M/39	Lateral border of tongue	Squamous	None	T2N1M0,III	23
7	F/42	Floor of mouth	Squamous	Diabetes mellitus	T2N0M0,II	15
8	M/27	Lateral border of tongue	Squamous	None	T1N0M0,I	9
9	M/40	Lateral border of tongue	Squamous	Diabetes mellitus	T1N1M0,III	11
10	M/53	Floor of mouth	Squamous	Hypertension.	T2N0M0,II	14
11	F/74	Lateral border of tongue	Squamous	Cerebral infarction	T4N2M0,IVa	15
12	F/70	Gingiva	Squamous	Cerebral infarction Heart disease	T3N1M0,III	7
13	M/67	Lateral border of tongue	Squamous	Hypertension Diabetes mellitus	T2N2M0,IVa	8
14	M/52	Gingiva	Squamous	None	T2N1M0,III	15
15	M/57	Lateral border of tongue	Squamous	Chronic bronchitis	T2N1M0,III	15





**Figure 1.** (A) Prime lesion of gingival; (B) Submental island pedicled flap and submandibular gland flap were performed; (C, D) Repaired defects of gingival site and partial mandible defects; (E) One Week after surgery. (F) Four weeks after surgery, submandibular gland is completely mucosalized. White arrow: Submental island pedicled flap. Black arrow: submandibular gland flap.

statistical significance in the relationship between submandibular gland involvement and cervical nodal metastasis. Only 7 cases had metastatic submandibular glands, caused mainly by direct invasion of primary lesions or periglandular nodes. In addition, literature review showed tumor involvement in 2.05% of 2875 submandibular gland samples, including 2 cases of intraglandular nodal metastases and 57 cases of invasion of primary lesions or periglandular nodal extension through the capsule.

Submandibular gland metastasis is related to the presence of intraglandular nodes, but whether the intraglandular nodes exist or not is still controversial. Liu et al investigated Submandibular gland from 210 corpses and did not detect any visible lymph nodes in.<sup>[25]</sup> Zhao et al observed and analyzed head and neck specimens from 57 adults and histologically examined sequential slices of the submandibular glands from 6 neonates, which showed no IGLNs.<sup>[26]</sup> In a prospective study by Dhiwakar et al, submandibular glands from 30 samples of neck dissection were sliced into specimens with a thickness of 3 mm, in which no intraglandular nodes or metastatic tumors were detected.<sup>[27]</sup> Jin

et al reported that intraglandular nodes existed in 9% of submandibular glands and proposed that the intraglandular nodes might only collect lymph produced by submandibular gland or a very small region, which was based on 2 considerations:

1. for submandibular glands in the submandibular triangle, extracapsular lymphadenitis is much more common than intraglandular lymphadenitis; and
2. metastasis of oral and maxillofacial cancer to submandibular glands is very rare. In the 363 submandibular gland samples we studied, no apparent intraglandular nodes were present. Therefore, the probability of submandibular gland involvement caused by nodal metastasis is low, almost negligible.

Due to the low probability of submandibular glandular metastasis in oral cancer, submandibular gland preservation is oncologically safe. Additionally, the submandibular gland has a rich blood supply, which is advantageous in the repair of postoperative defects in oral and parapharyngeal tumors. The

blood supply of the submandibular flap is derived from the facial artery, and most of its venous blood passes through the vein accompanying the facial artery and finally flows into the anterior facial vein.<sup>[28]</sup> The submandibular gland has a large twist angle, so it can be used in the reconstruction of defects in the floor of the mouth, retromolar triangle, lateral pharyngeal wall, and ventral part of the tongue. Mozolewski for the first time used submandibular glandular flaps in the reconstruction of the hypopharynx.<sup>[29]</sup> According to Mashrah, the submaxillary gland flap is a fascial flap, with favorable long-term outcome in repairing defects of oral non-squamous cell carcinoma; no hair is transferred to the mouth with the flap, which is superior to the submental island flap.<sup>[30]</sup> In a previous study, we used submandibular gland flaps to repair the postoperative defects in elderly patients with early-stage oral and oropharynx cancer and achieved satisfactory results in terms of submandibular gland flap survival, functional recovery, and aesthetic outcome, without tumor recurrence in or metastasis to a submandibular gland in the subsequent 28-month follow-up.<sup>[9]</sup> Based on these results, we applied submandibular gland flaps to repair defects in patients with stages 2 and 3 oral cancer but without the metastases to periglandular nodes and adipose tissue, which were confirmed by intraoperative frozen section. These patients received adjuvant radiotherapy or chemotherapy postoperatively, and the average 14.2-month follow-up showed no tumor recurrence in the submandibular gland flaps.

The submandibular glandular flaps has the potential for epithelialization. The process of epithelialization takes 3 to 6 weeks, subject to flap size, local factors, and systemic condition. The flap matches the color of surrounding mucosa, with minimal injury to the donor area. It can be harvested from the submandibular incision, which is concealed in the neck wrinkles. In addition, the flap is located in the same surgical area as the defect sites. This flap also has some shortcomings. Its blood supply is not as good as the pectoralis muscle flap or other free flaps, as the blood comes from the glandular branch of the facial artery. Therefore, more attention should be paid to the process of harvesting and handling the flap. The capsule should also be taken out during flap harvest to avoid vascular damage.

Our multicenter prospective study and literature review confirmed the oncological safety of preserving the submandibular gland in oral cancer. The repair of postoperative large defects with submandibular gland flaps has also achieved a satisfactory clinical outcome, especially in elderly and frail patients, because it greatly reduces surgical time and injury, blood loss, and hospital stay. However, the application of the submandibular gland flap requires a thorough understanding of indications and intraoperative details to increase the survival and safety of the flap. At present, the number of cases is still small; further research on the application of submandibular glandular flaps is expected to provide options for the repair of varied defects.

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## References

- [1] André Lopes C, Inês Nobuko N, Califano JA, et al. Trends in incidence and prognosis for head and neck cancer in the United States: a site-specific analysis of the SEER database. *Int J Cancer* 2005;114:806–16.
- [2] Stefano P, Crispian S. Determinants of oral cancer at the national level: just a question of smoking and alcohol drinking prevalence? *Odontology* 2010;98:144–52.
- [3] Marianna DCC, Lydia V, Marta GY, et al. Oral cavity cancer in developed and in developing countries: population-based incidence. *China J Oral Maxillofac Surg* 2010;32:357–67.
- [4] Susumu S, Masahito T, Keisuke S, et al. Impact of lymph node metastasis on the pattern of failure and survival in oral carcinomas. *Am J Surg* 2003;185:278–84.
- [5] Jaguar GC, Lima E, Kowalski LP. Impact of submandibular gland excision on salivary gland function in head and neck cancer patients. *Oral Oncol* 2010;46:349–54.
- [6] Cakir AC, Dogan E, Ozay H, et al. Submandibular gland invasion and feasibility of gland-sparing neck dissection in oral cavity carcinoma. *J Laryngol Otol* 2018;1–6.
- [7] 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.
- [8] Ebrahim AK, Looock JW, Afrogheh A, et al. Is it oncologically safe to leave the ipsilateral submandibular gland during neck dissection for head and neck squamous cell carcinoma? *J Laryngol Otol* 2011;125:837–40.
- [9] Zhang X, Liu F, Lan X, et al. Combined submandibular gland flap and sternocleidomastoid musculocutaneous flap for postoperative reconstruction in older aged patients with oral cavity and oropharyngeal cancers. *World J Surg Oncol* 2014;12:1–9.
- [10] Junquera L, Albertos JM, Ascani G, et al. Involvement of the submandibular region in epidermoid carcinoma of the mouth floor. Prospective study of 31 cases. *Minerva Stomatol* 2000;49:521.
- [11] Spiegel JH, Brys AK, Bhakti A, et al. Metastasis to the submandibular gland in head and neck carcinomas. *Head Neck* 2004;26:1064.
- [12] Ali R, Walvekar RR, Antoine M, 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.
- [13] Hyung Kwon B, Young Chang L, Bon Seok K, et al. Metastasis to the submandibular gland in oral cavity squamous cell carcinomas: pathologic analysis. *Acta Otol* 2009;129:96.
- [14] Tseng-Cheng C, Wu-Chia L, Jenq-Yuh K, et al. Rare involvement of submandibular gland by oral squamous cell carcinoma. *Head Neck* 2010;31:877–81.
- [15] Naidu TK, Naidoo SK, Ramdial PK. Oral cavity squamous cell carcinoma metastasis to the submandibular gland. *J Laryngol Otol* 2012;126:279–84.
- [16] Kruse A, Grätz KW. Evaluation of metastases in the submandibular gland in head and neck malignancy. *J Craniofac Surg* 2009;20:2024–7.
- [17] Basaran B, Ulasan M, Orhan KS, et al. Is it necessary to remove submandibular glands in squamous cell carcinomas of the oral cavity? *Acta Otorhinolaryngol Ital* 2013;33:88–92.
- [18] Howard BE, Hinni ML, Nagel TH, et al. Submandibular gland preservation during concurrent neck dissection and transoral surgery for oropharyngeal squamous cell carcinoma. *Otolaryngol Head Neck Surg* 2014;150:587–93.
- [19] Kamran A, Muhammed A, Attique A, et al. Submandibular gland involvement in early stage oral cavity carcinomas: can the gland be left behind? *J Coll Phy Surg–PakV* 24 2014;565.
- [20] Malgonde MS, Manoj K. Practicability of submandibular gland in squamous cell carcinomas of oral cavity. *Indian J Otolaryngol Head Neck Surg* 2015;67:138–40.

- [21] Panda NK, Patro SK, Bakshi J, et al. Metastasis to submandibular glands in oral cavity cancers: can we preserve the gland safely? *Auris Nasus Larynx* 2015;42:322–5.
- [22] Agarwal G, Nagpure PS, Chavan SS. Questionable necessity for removing submandibular gland in neck dissection in squamous cell carcinoma of oral cavity. *Indian J Otolaryngol Head Neck Surg* 2016;68:314–6.
- [23] Vessecchia G, Palma S, Giardini R. Submandibular gland metastasis of breast carcinoma: a case report and review of the literature. *Virchows Arch* 1995;427:349–51.
- [24] Sánchez AJ, Burgos , Papi M, et al. Metastasis in submandibular gland from a leiomyosarcoma of the uterus. *Acta Otorrinolaringológica España* 2002;53:67–70.
- [25] Liu M, Zhong S, Tao Y, et al. Morphology of submandibular lymph nodes. *Chin J Anat* 1981;375–8.
- [26] Zhao S, Chen G, Wang Y. Anatomical study of submandibular lymph nodes. *Chin J Clin Anat* 2002;20:444–6.
- [27] 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.
- [28] Sieg P, Geerling G, Kosmehl H, Domarus V. Microvascular submandibular gland transfer for severe cases of keratoconjunctivitis sicca. *Plast Reconstr Surg* 2000;106:554–60. discussion 561-552.
- [29] Mozolewski E, Maj P, Kordowski J, et al. Vascular pedicle flap of the thyroid or submandibular gland in the reconstruction following partial laryngectomy. *Otolaryngol Polska Polish Otolaryngol* 1999; 53:387–96.
- [30] Mashrah MA, Zhou SH, Abdelrehem A, et al. Oropharyngeal reconstruction with a pedicled submandibular gland flap. *Br J Oral Maxillofac Surg* 2016;54:388–93.