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Research Article

Metastasis to the Submandibular Gland in Patients Presenting with Oral Squamous Cell Carcinoma

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Abstract

Background: Approximately one third of patients undergoing neck dissection procedure that includes gland resection experience xerostomia, particularly nocturnal xerostomia. Metastasis to level 1b lymph nodes in patients presenting with OSCC is considered frequent, however, submandibular gland invasion is rare and preservation of the gland offers multiple benefits.

Objective: The objective is to study the prevalence of submandibular gland involvement in patients presenting with oral squamous cell carcinoma.

Methods: It's a cross sectional analytical study consisting of 90 patients presenting with biopsy proven OSCC. All patients presenting to centers of Dow University of health sciences are included in the study. Data entry and analysis was carried out on SPSS version 21. Results are expressed in frequencies and percentages. Chi squared test was applied to analyze the relationship between submandibular gland involvement and patient's sociodemographic and tumor related variables.

Results: A total of 90 participants were a part of the study. 71.1% were male whereas 28.9% were female. The median age is 48. The most common tumor site among our patients is buccal mucosa (63.3%). The depth of invasion ranged from 0.2cm to 5cm (median 0.95cm) with round 55.6% patients presenting with depth of invasion <1cm. Majority of the patients (48.9%) presented with stage IVa (AJCC). 71.1% had level 1b negative nodes, whereas 28.9% patients demonstrated positive level 1b nodes. 50% of the patients presented with stage IVa. Number of patients with submandibular gland involvement were 5.

Conclusion: Based on the results of our study, due to rare involvement of submandibular gland, it should be persevered wherever possible and decision to preserve should be based on determinants, such as, primary tumor site, level 1b involvement and depth of invasion.

Keywords: Oral squamous cell carcinoma; Xerostomia; Submandibular gland

Abbreviations

OSCC: Oral Squamous Cell Carcinoma; AJCC: American Joint Committee on Cancer; SMg: Submandibular gland; CI: Confidence Interval; H&E Staining: Hemotoxylin and Eosin Staining.

Background

Approximately 72% of the unstimulated saliva is secreted by submandibular glands and 28% from minor salivary glands [1,2]. These mucin secreting glands are removed on regular basis along with sublevel Ib when selective neck dissection is carried out [3,4]. There are two reasons that justify the gland excision; for dissection of lymph nodes in level 1b and for SMg invasion. SMg involvement in oral cavity tumors is extremely rare and ranges between 0.6 and 4.5% in the literature [5,7]. Regional metastasis is common in floor of the mouth tumors and tongue tumors and makes up about 5-7% [8].

The standard procedure carried out for management of metastatic cervical lymphadenopathy is neck dissection [9]. Approximately one third of patients undergoing neck dissection procedure that includes gland resection experience xerostomia, particularly nocturnal xerostomia [10-12]. Patients experience alteration in taste, chewing and swallowing inconveniency, loss of appetite and weight loss [3]. Secondly, unilateral SMG excision may lead to asymmetric lower inclination of the ipsilateral neck below the mandible. Third, hypoglossal (2.9%) and lingual nerve injury (1.4%) is still at-risk during SMG excision despite attempts to avoid it [13]. This results in swallowing difficulty, dysgeusia, and tongue paresthesia to some degree [14]. Radiotherapy, as a post-surgical treatment further affects the healthy tissues by altering the barrier function of the gland [15]. A radiation dose as little as 35 Gyleads to permanent salivary gland dysfunction [7,16]. These all adversely affect the quality of patient's life [3].

Objective

The objective is to study the prevalence of submandibular gland involvement in patients presenting with oral squamous cell carcinoma.

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Methodology

This is a cross sectional analytical studies consisting of participants presenting to multiple centers of Dow university of health sciences. Using Pass version 11, test for one sample proportion with 95% CI, 80% power of the test, 90 was the calculated sample size. All participants with biopsy proven OSCC and undergoing surgical excision of the lesion along with neck dissection were included in the study through non-probability purposive sampling technique. However, we excluded those patients who were previously treated for OSCC (surgical treatment or radiotherapy).

The submandibular gland sent for biopsy was divided by the pathologist and the fat containing nodes was separated. The tissue sections of level 1b lymph nodes and the submandibular gland were submitted for biopsy.

Apart from the submandibular gland involvement, primary parameters of the tumor including primary site, depth of invasion, tumor staging (AJCC) and level Ib nodal involvement were also recorded.

Data was collected and analyzed using H & N staining. Collected data was entered and analyzed on SPSS, ver.21 and results are reported in percentage& frequency. Chi squared test was applied to analyze the relationship between submandibular gland involvement and patient's gender and tumor related variables.

Results

A total of 90 participants were included in the study. 71.1% were male and 28.9% were female. The median age is 48. The most common tumor site among our patients is buccal mucosa (63.3%), followed by mandible (12.2%), maxilla (11.1%), tongue (8.9%), floor of the mouth (3.3%) and lip (1.1%).The depth of invasion ranged from 0.2cm to 5cm (median 0.95cm) with round 55.6% patients presenting with depth of invasion <1cm. Majority of the patients (48.9%) presented with stage IVa (AJCC), followed by stage III (21.1%), stage II (20%), stage I (8.9%) and stage IVb (1.1%). 71.1% had level 1b negative nodes, whereas 28.9% patients demonstrated positive level 1b nodes. 49% of the patients presented with stage IVa. Number of patients with submandibular gland involvement were 5.

Fisher's exact test was applied to observe the association between submandibular gland involvement and various tumor related variables including, primary site, depth of invasion, tumor stage and level 1b nodal involvement. The results demonstrated significant relation between submandibular gland involvement and primary site of the tumor, depth of invasion and level 1b involvement. However, non- significant association was observed between submandibular gland involvement and gender and tumor stage (Table 1).

Discussion

Tumor seeding to the submandibular gland can take place via three courses: hematogenous, lymphatic and direct extension [1]. Around 66-100% of metastasis occurs by direct invasion by the primary tumor which ranges between 0.6 and 3% [17]. Spread through metastatic cervical lymph nodes constitutes 0-1.5% of cases in the literature [17]. Metastasis to level 1b lymph nodes in patients presenting with OSCC is considered frequent, however, submandibular gland invasion is rare [17].

Table 1: Submandibular gland involvement.

Variables		Involvement 5 (5.6%)	No involvement 85 (94.4%)	P- value
Gender	Males	2	62	0.143[f]
	Females	3	23	
Primary Site	Buccal mucosa	2	55	**0.027[f]**
	Lips	0	1	
	Tongue	0	8	
	Maxilla	0	10	
	Mandible	1	10	
	Floor of the mouth	2	1	
Level Ib involvement	Involvement	4	22	**0.023[f]**
	No involvement	1	63	
Depth of invasion	<10mm	0	50	**0.002[f]**
	10-19 mm	1	23	
	20-29 mm	3	10	
	30-39 m	0	1	
	>40mm	1	1	
Tumor staging	Stage I	0	8	0.595[f]
	Stage II	0	18	
	Stage III	2	17	
	Stage IVa	3	41	
	Stage IVb	0	1	

f=Fisher's Exact Test

Metastasis by hematogenous route occurs more frequently from primaries that do not originate from the head and neck region, which includes breast, genitourinary system and lung [1,7].

Head and neck tumors majorly spread to the parotid gland while tumors originating below the clavicles metastasize to submandibular gland (breast, kidney, and lung) [18]. The fibrous capsule enclosing the submandibular gland offers effectual impediment to the spread of cancer in previously untreated patients. The spread to the glandular parenchyma is seldom observed even though the gland may be compressed by massive metastatic disease [19].

The decision for submandibular gland resection must be made during the surgical procedure on the basis of inspection and frozen sections [17]. However, the reliable modality for detection of metastasis to submandibular gland is ultrasonography [18].

Preservation of submandibular gland offers multiple potential benefits [20]. Hyposalivation which increases the risk of oral infections can be avoided in patients who do not undergo radiotherapy [20,21]. This results in undiminished basal salivary flow that is primarily mucinous, and is responsible for the sensation of mucosal lubrication [20]. Furthermore, basal salivary flow is vital for maintaining good oral hygiene [22]. Secondly, submandibular glands are more responsive to therapeutic agents at minimizing xerostomia both during and after radiation therapy [23]. A number of therapies for xerostomia include medications, acupuncture, synthetic saliva, gustatory stimulus, electrostimulation and autologous saliva storage. Some of these therapies have side effects and none of them have proved to improve patient's quality of life [10,24].

Finally, preserving the gland maintains the external contour of the superior neck region, along with lowering the risk of injury to the lingual and hypoglossal nerves [25].

According to our study, out of 90 patients, 5 patients were positive for submandibular gland involvement. Tumor related variables primary site and depth of invasion were found to have statistically significant association with submandibular gland involvement. Participants presenting with OSCC of buccal mucosa (2/57), mandible (1/11) and floor of the mouth (2/3) demonstrated submandibular gland involvement by tumor cells. This coincides with the results of a study which showed submandibular gland invasion in similar sites including buccal mucosa (5/35), floor of the mouth (5/13) and tongue (11/178) [26]. Another study that was conducted to evaluate the oncological safety to leave the ipsilateral submandibular gland also supports the results of this study in terms of primary site involvement, demonstrating submandibular gland involvement in just one patient out of 107 with buccal mucosa being the primary tumor site [1].

According to a study which evaluated the submandibular gland metastasis in the head and neck cancer, excision of submandibular gland should be done in patients presenting with head and neck cancer and in patients with level I nodes invasion [16]. In the current study, level Ib nodes were positive in 26 patients. However, submandibular gland involvement was observed in only 4 patients. Statistically significant association was also observed between positive level Ib and submandibular gland involvement. This is supported by results of another study which demonstrated only four patients with extra nodal extension to level Ib lymph nodes and had submandibular gland involvement which makes it look like involvement of submandibular gland takes place by direct spread with extra nodal extension and not via lymphatics [27]. A retrospective study evaluated 229 salivary glands and found malignancy in only 3 patients [3]. All these cases were positive for level Ib involvement (3).

As a part of our study depth of invasion was recorded. It ranged from 0.2cm to 5cm with 0.95cm being the median value. This was compared to median value (10.0 cm) reported in another study which was closer to the median reported in our study [27]. Statistical test was applied to test the association between submandibular gland involvement and depth of invasion. A highly significant association was observed between the two variables (p= 0.02).

Around 50% of the participants presented with stage IV tumor. Submandibular gland involvement was observed in all the patients. 2 participants with stage III tumor and 3 participants with stage IV tumor demonstrated submandibular gland involvement. However, a non- significant association was observed between tumor stage and submandibular gland involvement.

Conclusion

Due to rare involvement of submandibular gland in OSCC, conservation of submandibular gland is recommended wherever achievable for reducing complications post-neck dissection. Based on the results of our study, decision to preserve the gland should be based on determinants, such as, primary tumor site, level 1b involvement and depth of invasion. However, regular follow-up is required to comment on the oncological safety.

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