



Implications of Oral Squamous Cell Carcinoma to Submandibular Gland: A Systematic Analysis

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Objective: Submandibular Gland (SG) Located in Level IB Region of Neck. During neck dissection, it is routinely removed along with level IB lymph nodes. Less data is available to represent SMG involvement in oral squamous cell carcinoma (OSCC). Main objectives of systemic Review are to establish the rate, pattern and pathways of SMG involvement in OSCC.

Data Sources: A systematic review of related article were analyzed and articles recognized through PubMed, Scopus, Medline and Cochrane library were studied until November 2019.

Review Methods: Explanatory features of main primary tumours, key management modalities, rate, pattern and pathway of SMG involvement, existence results. If existent were conveyed, subsequent PRISMA guidelines.

Results: The collected information were investigated and produced 259 articles, 19 out of 259 fulfil the inclusion criteria. 2699 patients in that 3235 SMG resections is selected out of 19 articles. Sixty-

four glands (1.97%) had tumour participation. direct SMG infiltration by primary tumour was most common pathway (48 of 64, 1.4%). The subsequent usual method of SMG invasion was from involved peri-glandular lymph nodes (12 of 64, 0.3%). Only 3 resected SMG out of 3235 (0.1%) had metastatic parenchymal involvement from primary tumor.

Conclusion: Scarcity of SMG involvement in OSCC, SMG protection could be practicable in some patients. Decision regarding resection of submandibular glands should be done after visual examination during surgery instead of pre-planned resection. Though, extra analyses is required to assess the function of retained SMGs amongst patients who received postoperative radiotherapy.

Keywords: Submandibular Gland (SMG); Oral Squamous Cell carcinoma (OSCC); tongue; Floor of Mouth (FOM); neck dissection; dry mouth and lymph nodes.

1. INTRODUCTION

Neck dissection is important Procedure for the treatment of head and neck cancer. It is always debatable topic among head and neck oncosurgeon that involved metastatic lymph nodes should be excised in neck Dissection. The initial conceptual method for metastasis involvement of nodes was made by Magnano M [1]; he explained removal of lymph nodes situated inside submandibular triangle for head approach to tongue cancer. In radical neck dissection there is en bloc excision of lymph nodes and tissue around lymph nodes, explained by Carlson ER [2] and CorletteTH [3] and it was dominant surgical process of twentieth century.

Recently conservation of tissue for cosmetic and functional purpose leads to development of more conservative management approaches. Management often includes surgical removal of primary lesion, Proper neck dissection and then radiotherapy. Radiotherapy for head and neck region is associated with illness, in that dry mouth is most common. Description regarding Post Radiation therapy related dry mouth was initially explained by French radiobiologist Ward GE. [4] and Guillaumondegei OM et al. [5] According to them the dose of 40 Gy in region of submandibular gland reduces salivary function drastically. As submandibular glands are more accountable for basal salivary flow [6].

In head and neck area OSCC is common Primary tumors. [7] Surgical management of OSCC include wide Excision of the primary tumors with adequate neck dissection. Metastases is common in levels I-II-III of Neck, but uncommon in level-IV [8]. The submandibular glands lie in level- IB and surrounded by more lymphatic tissues. Metastasis in this area is very common, particularly in floor of mouth (FOM) and tongue cancers. Rouviere, divided the Five lymph node

groups in level- IB area as: 2-perivascular (prevascular, retrovascular), 2- peri glandular (preglandular, retroglandular) and 1 as intracapsular [8]. Chen AM mentioned one more group as "deep submandibular node"(added By DiNardo) [9]. Perivascular node are highly significant as these are main afferent lymph nodes of oral cavity. The Incidents of Perivascular lymph nodes involvement is around 5-7% in FOM and tongue cancers [10].

Even though submandibular glands have less metastasis, in every neck dissection SMGs routinely removed as it is located near to main Primary tumor and draining lymphatic nodes. The important function of SMG is production of large amount of non-stimulated saliva at night time. [11]Important functions of saliva are lubrication, chewing, digestion, buffering, tooth enamel Remineralization and immune defense etc. Removal of submandibular glands causes dry mouth that is associated with discomfort and numerous complications in the oral cavity. Preservation of at least single gland will decrease these problems [12]; as study showed there are no problems in protection of the submandibular glands in oral cavity tumors [13].

2. MATERIALS AND METHODS

2.1 Search Strategy

Articles defining rate, pathway and pattern of Submandibular gland association with OSCC were scientifically recognized with the electronic data base like PubMed, Medline Scopus and Cochrane records. Keywords included "Oral Squamous Cell Carcinoma" "Neck dissection," "submandibular gland", "Dry mouth" and "level I." original research studies published in English languages are reviewed. Total 259 abstracts studied, and 222out of 259articles were excluded from systematic analysis. By considering PRISMA guidelines only37 articles (n = 37) were fulfilled inclusion criteria.

2.2 Selection Criteria

Inclusion criteria were histopathological confirmed cases OSCC and histopathological comments on submandibular gland invasion. Patients excluded from the study are those with neck dissection in which primary tumor was not OSCC, and that data was <5 patients or those patient having history of radiotherapy. Out of 37 reviewed articles, we excluded 18 articles from systemic analysis study; in that 18 articles, they do not have information regarding Submandibular gland association. Remained (n = 19) articles after Exclusion criteria taken into consideration for systematic analysis.

2.3 Data Extraction

We included 19 isolated articles in our databank. Histopathologically proven OSCC those managed by neck dissection, mean age, sex, tumor site, staging of tumor (if present), total number of removed Submandibular gland, number of involved Submandibular glands. Rate, Pathway and Pattern of involvement of gland and survival data of patients (if present). 3 articles do not mention the male and female data and 5 do not mention the mean age of patient. Primary Locations of oral cavity are lips, tongue, alveolar ridge, floor of mouth, retromolar trigone, Gingivobuccal Sulcus, buccal mucosa, palate, and multiple sites /Unknown/others.

3. RESULTS

19 articles available from year 2004 to 2019 were analyzed. Total patients were 2699, and removed submandibular glands were 3235. Gender wise (n = 2152), 68.26% (1469) male and 31.7% (683) female.

Table 1 represents the specificity of 19 studies, comprising patient mean age and sex. Total primary tumor site described (n = 2646), oral tongue (37.94%) were the most common sites, 2nd most were buccal mucosa (20.55%), then other site in decreasing order as FOM (16.32%), and alveolar ridge (11.30%). multiple site involvements of primary tumors (n = 12) and 42 tumors were in various, unknown sites.

Table 2 represents primary tumor sites location for individual study, and shortlisted total occurrence of each site.

Out of the 3235 Submandibular gland extirpations, invasion seen in only 64 (1.97%) glands from OSCC, in that direct extension from OSCC seen in 48 (1.4%). Metastatically involve lymph node infiltration in submandibular gland seen in 12 (0.3%). Direct infiltration from primary tumor was most common seen in decreasingly order as FOM (n = 17), then tongue (n = 9), alveolus (n = 9), buccal mucosa (n = 6), retromolar trigone (n = 1), lip (n = 1), Palate(1), Gingivobuccal complex(1) and multiple sites (n = 2) in decreasing orders. Infiltration by lymph nodes seen most common in tongue (n = 5), then buccal mucosa (n = 3), FOM (n = 2), alveolar ridge (n = 2) in decreasing orders and above both mechanisms of involvements seen in one Submandibular gland. Only 3 resected SMG out of 3235 (0.01%) had metastatic parenchymal involvement in that buccal mucosa (n = 1), tongue (n = 1) and unknown primary lesion site (n = 1).

Table 3 shows the rate and pathway of Submandibular gland involved for each study, and depicts frequency of each invasion mechanism.

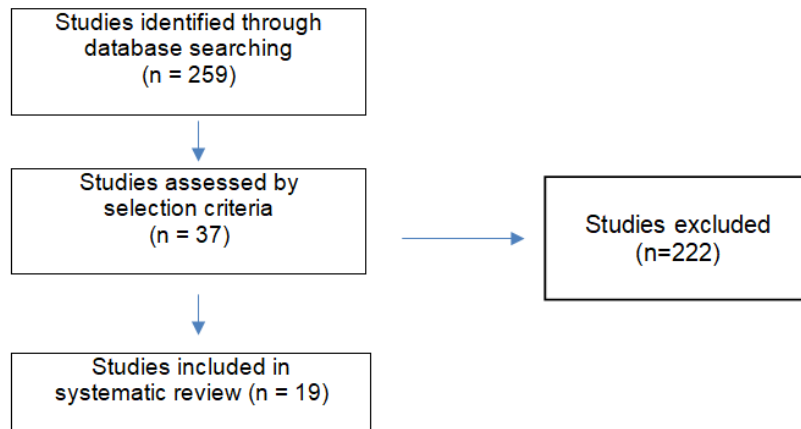


Fig. 1. Flow chart (PRISMA guidelines) representing studies included in systematic analysis

Table 1. Individual study and characteristics of patient

First Author	Year	Patients (n)			Mean age (years)
		Total	Males	Females	
Jeffrey HS [18]	2004	137	—	—	—
ChenAM [9]	2009	342	302	40	50
Hyung KB [17]	2009	201	—	—	—
Astrid K [13]	2009	130	77	53	61.1
Ali RBS [12]	2009	132	76	56	59
Muthuswamy D [25]	2011	20	13	7	56.5
Khader AE [36]	2011	52	—	—	—
Naidu [37]	2012	69	46	23	58
Okoturo [20]	2012	194	120	74	50.61
Basaran [19]	2013	236	157	79	57
Ashfaq [23]	2014	110	78	32	—
Monika SM [26]	2015	94	66	28	51
Naresh KP [27]	2015	157	-	-	49
Gaurav A [16]	2016	112	74	38	—
Akshat M [29]	2016	137	110	27	A(49, 52)
Cakir Cetin [34]	2018	155	92	63	56.9
Eser M [38]	2019	44	33	11	64.55
Zeng W [39]	2019	330	199	131	54.8
Alharbi J [40]	2019	47	26	21	56
Total		2699			
Total with Male &Female		2152	1469	683	
% with Male and Female			68.26%	31.73%	

A-49Neck positive, A-52Neck negative

4. DISCUSSION

Current management of Oral Squamous Cell Carcinoma involves wide local excision of Primary lesion and Proper neck dissection (level I, II, III and IV) including Submandibular resection [14]. The SMG routinely removed by considering 4 main objects: (1) Possible SMG infiltration, (2)

removal of metastatic level IB lymph nodes, (3) to increase fastness of level IB dissection, and (4) for good clearance of level IB [15]. One rare reason of the SMG removal might be to increase access to resection and reconstruction of tumor. This is the initial systematic which reviews systematically to confirm or to describe rates, Pattern and Pathway of SMG invasion in OSCC.

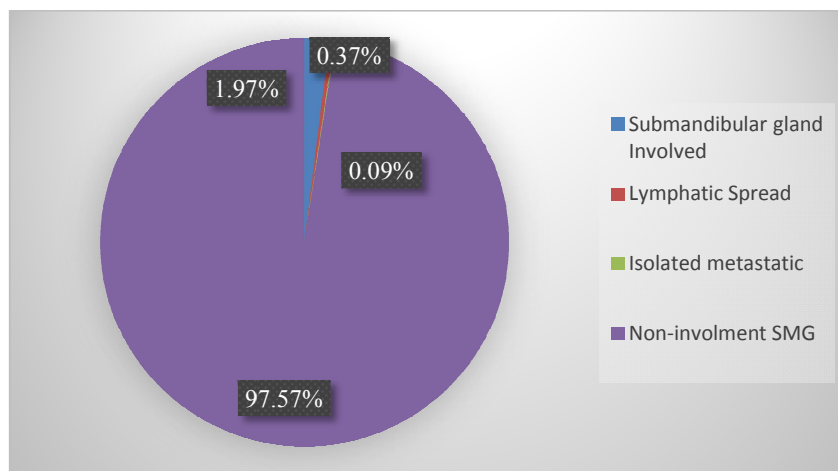


Fig. 2. Distribution of different studies with mechanism of submandibular gland involvement

Table 2. Primary tumor site of individual study

First Author	Lip	FOM	Tongue	Alveolar Ridge	Buccal Mucosa	Palate	RMT	Gingivobuccal sulcus	Multiple Sites/Unknown/other
Jeffrey HS [18]	5	25	54	11	6	6	11		12(Multiple Sites)
Chen AM [9]	5	17	121	20	143	14	22		
Hyung KB [17]	1	35	132	9	14		10		
Astrid K [13]		29	23	42	8	15			
Ali RBS [12]		36	58	7	9	5	16		1(Other)
Muthuswamy D [25]	1	7	8	1	1		1		1(Unknown)
Naidu [37]		22	28	6	6	2	5		
Okoturo [20]		4	51	11	71	18	16	14	10(Other)
Basaran [19]	12	33	108	16	24	22	21		
Ashfaq [23]		23	46	19	15	7			
Monika SM [26]	2	12	34		46				
Naresh KP [27]		32	56	33	36			18	18
Gaurav A [16]	5	3	20	31	35				
Akshat M [29]		58		22	55		2		
Cakir Cetin [34]		25	85	11	20	3	11		
Eser M [38]	33	2	6		3				
Zeng W [39]		69	138	57	45	21			
Alharbi J [40]	1		36	3	7				
Total									
N	65	432	1004	299	544	113	115	32	42
%	2.45	16.32	37.94	11.30	20.55	4.27	4.34	1.20	1.58

Table 3. Rate and Pathway of submandibular glands Invasion of individual study

First author	Submandibular gland resections	Submandibular gland Involved	Direct extension	Lymphatic spread	Isolated metastatic
Jeffrey HS [18]	164	9	6	3	
Chen AM [9]	383	7	5	1	1
Hyung KB [17]	316	2	2	-	-
Astrid K [13]	171	6	5	-	1
Ali RBS [12]	253	1	1	-	-
Muthuswamy D [25]	33	0		-	-
KhaderAE [36]	52	1	1	-	-
Naidu [37]	69	2	2	-	-
Okoturo [20]	229	3	3	-	-
Basaran [19]	294	13	8	4	1
Ashfaq [23]	110	2	2	-	
Monika SM [26]	98	3	2	1	
Naresh KP [27]	163	6	4	1	
Gaurav A [16]	112	0	0	-	-
Akshat M [29]	152	0	-	-	-
Cakir Cetin [33]	183	2	2	-	-
Eser M [38]	61	0	-	-	-
Zeng W [39]	330	7	5	2	-
Alharbi J [40]	62	0	-	-	-
Total					
N	3235	64	48	12	03
%	100	1.97	1.4	0.3	0.09

Remark: Naresh KP - 1 patient has SMG invasion by infiltration by primary tumour and submandibular lymph nodes

Review of 19 articles from last 15 years (2004 to 2019) showed that submandibular gland invasion is not common and not a single study shows rate of involvement of submandibular gland more than 4.6%, many studies recommended that resection of SMG in case of OSCC during selective neck dissection is usually unjustified. It is hypothesized in literature that tough fibrous capsule, no intraglandular lymph tissue and vasculature of SMG are the reason for low probability of invasion [16] and data in literature shows submandibular gland invasion seen mainly from direct infiltration from primary lesion very frequently from FOM, Buccal mucosa and tongue and alveolus, as proximity of this anatomical structure to submandibular Gland, and it is considered that conservation of SMG might have a more risk if main tumor is near to the gland, mostly when concerning the FOM [17].

Highest Quantity of saliva secreted by submandibular gland and physiological Role of Saliva is mastication, taste, tooth surface remineralisation, talking, digestion, and immune defences [18]. The SMG is associated with maximum non-stimulated and some stimulated salivary secretions which is associated with

general salivary secretion (i.e., not related with eating), mainly during sleep [19]. Removal of single SMG in patient is associated with decrease secretion of saliva which causes dryness of mouth, decrease salivary flow has adverse influence on speech, taste, oral hygiene and disturb psychology of patient that affects quality of life [20].

Many studies in literature showed that there is reduced non-stimulated salivary secretion rate after SMG removal for Malignant or Benign Conditions. Nabili V stated showed 22.1% of dry mouth after resection of SMG due to benign disorders [21]. Felix A et al assessed total 80 patients of head and neck tumor and equated quantity salivary flow by scintigraphy earlier and afterward the management (radiation Vs surgery) [22]. The study stated reduced non-stimulated salivary quantity in both management groups with 21% of patients facing dry mouth after surgery. When SMGs removed bilaterally problem of dry mouth is more [23].

Post-surgical radiation is associated with dry mouth. According to Laco J et al, dry mouth is severe when patient had undergone both surgery

and radiotherapy [24]. Subsequently, for patients who clinically does not have metastasis specific to neck nodes and no post-surgical radiation therapy, protection of Both SMG significantly increases patient's quality of life [25]. One concept to decrease problems of dry mouth is to transfer SMG to another anatomical but there are no large studies on SMG transfer so it's better to preserve SM [26]. There is no effective study which shows effect of salivary secretion flow in irradiated SMG and we can do radiotherapy modality by gland sparing (e.g. Intensity modulated radiation therapy) which improves salivary function after the definitive or adjuvant radiotherapy procedures [27].

Generally, SMG removed during Level-I B neck dissection to gain good access to all lymphatics tissue around glands and there is intraglandular group of lymph nodes as described by Maxwell JH in 2013 [28]. But many authors clarify that such group of lymph node normally does not occur or metastasis to this group is not common, which explain lower chances of recurrence to the SMG by direct lymphatic tissue extent [29]. Paleri V et al did histological study of excised SMG and concluded that no lymph node inside the SMG, reason may be delay in embryological formation between lymphatic system and SMG [30]. Ross GL model describes less number of the deep group of nodes in most of the cases [31].

SMG normally Excise to gain access pre-and retro vascular Lymph nodes conversely together called as Perivascular lymph nodes in level I B. these are main lymphatic drainage area and these are small in number but significant occurrence of metastasis in OSCC seen and mainly in Primary lesion of FOM and Tongue [32]. Kowalski LP et al stated comparable low perivascular nodes involvement but metastasis rate to above nodes is more among patient with confirmed level-I metastasis [33]. It is apparent that perivascular nodes excision is vital in level IB neck dissection; though present discussion of concern is whether SMG requires to be valued, maximum head and neck surgeon remove it routinely [34]. According to Shah JP et al Lymph nodes and vessel in region of level IB which are situated in between superficial and the deep layers of neck fascia and it is not only possible but also feasible to preserve SMG with complete removal of all groups of lymph nodes and SMG excision is needless [35]. Khader AE et al showed that preservation of SMG is helpful in OSCC and Oropharyngeal SCC thought it is not

valid in case of tongue and FOM carcinomas, which shows increase rate of loco regional recurrence [36].

According to Eser M et al. while performing level 1b dissection, preservation SMG require good surgical skill and Experience, although there is sufficient reason for the preservation of SMG. Even though it is ideal to maintain SMG without risking oncologic safety, if the lymphatic structures in level 1b cannot be cleared without removal of SMG, SMG subtraction would be a more appropriate approach for oncologic safety [38]. According to Zeng W et al stated that SMG flaps can be use for post-operative defect repair with satisfactory outcome also it decreases time of surgery, injury to tissue, loss of blood and stay in hospital [39]. In addition, Alharbi J et al revealed that SMG preservation in initial stage oral cancer is a valid therapeutic option, unless there is evidence of tumor invasion from Tongue or FOM [40]. A number of related studies were reported [41-44].

Our collected data encourage that invasion of SMG seen with FOM and tongue cancers. More study is required to confirm scientifically, oncologically and from patients safety prospective for preservation of SMG in neck dissections.

Based upon the facts and figures from collected data it is not necessary to remove SMG at time of level IB dissection only for the fear of hidden gland invasion [37]. A prospective analysis will require to evaluate the oncological safety of protecting SMG in throughout level IB dissection, as preservation of SMG in present Surgical scenario might help to prevent problem of dry mouth and increases patients quality of life. Conversely, further decision may be desirable if the main lesion or local metastases are near to Submandibular gland. More study is required to observe the functionality of preserved SMG in post radiation treatment.

Limitation of present meta-analysis is that it depended on reviewing studies. That may contain collection bias interestingly incidence with SMG infiltration, Different pathological criteria and procedures of evaluation for primary tumour involvement in the SMG, no Consideration on etiological factor as in human Papilloma virus or other viruses, and no distinct investigation for primary stage of tumor and N stage of Lymph nodes.

5. CONCLUSION

According to information received from data we can conclude that association of SMG is not common and involvement mainly arises from direct invasion from the primary tumor. above consequences recommend that it might be oncological safe to save SMG in early stages OSCC and No neck involvement , until there is no direct invasion of primary lesion to gland. Saved SMG is helpful to support Quality of Life of patient by decreasing chances of dry mouth, oral Hygiene maintenance. Since metastasis of perivascular lymph nodes in level IB is likely seen in OSCC, more analyses with more number of patients are require to explain survival consequences and loco regional recurrence rates of SMG protection.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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