Rate of Submandibular Gland Involvement in Oral Squamous Cell Carcinoma

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Purpose: Whether the submandibular gland (SMG) can be preserved during neck dissection in the surgical treatment of oral squamous cell carcinoma (OSCC) is controversial. This study investigated the SMG involvement rate and provides a basis for preserving the SMG during neck dissection in appropriate cases of OSCC.

Materials and Methods: A comprehensive systematic review was conducted on the PubMed and MEDLINE, Embase, and Cochrane Library databases for studies on SMG involvement in OSCC published before December 2017 with a data analysis technique. Predictor variables were numbers of patients and resected SMGs, primary site, and tumor, node, and metastasis stage. Outcome variables were the number of involved SMGs and mode of involvement. Other variables, namely first author, publication year, mean age, and condition of neck lymph nodes at level Ib, also were extracted. A random-effects model was used to analyze the rate of SMG involvement in OSCC.

Results: Twelve studies involving 2,126 patients with OSCC who underwent neck dissection were included in the study. Fifty-two SMGs were involved, and the pooled involvement rate was 2% (I^2 = 73%; 95% confidence interval [CI], 1-3). Forty-eight SMGs were involved through direct spread from the primary site or extracapsular spread of positive lymph nodes, and the pooled involvement rate was 1.9% (I^2 = 72%; 95% CI, 0.9-3.1). Except for direct spread, 4 SMGs were involved through the intraglandular lymph node or carcinoma growing along Wharton ducts, and the pooled involvement rate was only 0.1% (I^2 = 0%; 95% CI, 0-0.2).

Conclusions: The rate of SMG involvement in OSCC is very low, and the most common mode of involvement is by direct spread. The SMG might be preserved during neck dissection in OSCC when it is unlikely to be involved through direct spread.

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It has been more than 100 years since George Crile[1] introduced radical neck dissection for the clinical treatment of head and neck cancer. Since then, surgeons have attempted to develop means of modifying radical neck dissection to decrease surgical morbidity, such as functional neck dissection and selective neck dissection.[2] However, the submandibular gland (SMG) is sacrificed as part of level Ib during neck dissection regardless of the type of neck dissection.[3]

The SMG functions not only as an exocrine gland but also as an endocrine gland.[4,5] As 1 of the 3 major salivary glands, SMG secretions account for 60 to 65% of all unstimulated saliva, and saliva plays a very important role in oral health, such as in protecting the oral cavity mucosa, mediation of taste, acting as an acid buffer, and tooth mineralization.[6,7] Unilateral excision of the SMG will decrease the resting saliva flow rate and increase the possibility of subjective xerostomia.[7]

However, is it necessary to remove the SMG during neck dissection in patients with oral cancer? Malik et al[8] carried out a prospective study and showed that, even when metastasis occurred at level Ib, direct metastases to the SMGs were rare in early tongue cancer, and the rate of involvement was 0%. Basaran et al[9] reported the involvement of 13 SMGs in 236 patients with oral cancer, and the rate of involvement was 6%. There is no consensus on the rate of SMG involvement in oral squamous cell carcinoma (OSCC).

The authors hypothesized that if SMG involvement is very rare and the mechanism of involvement is clear in OSCC, then it might be oncologically safe to preserve the SMG during neck dissection in appropriate OSCC cases. The purposes of this study were to evaluate the rate of SMG involvement, the possible mechanism of SMG involvement, and the feasibility of preserving the SMG during neck dissection in OSCC.

Materials and Methods

STUDY DESIGN

To address the purposes listed earlier, a systematic review modeled on the Cochrane Collaboration recommendations was designed and implemented. The review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.[10] The study population was composed of all English-language publications on the topic of SMG involvement in OSCC until December 31, 2017. The search was conducted on the PubMed and MEDLINE, Embase, and Cochrane Library databases. The search terms used with PubMed were (((((metastasis) OR involved) OR involvement)) AND (((submandibular gland) AND (((((oral) OR oral cavity) OR (head and neck)) OR head neck) OR mouth)) AND ((((cancer) OR squamous cell carcinoma) AND neoplasm) AND carcinoma))). Then, the other 2 databases were searched using modified versions of the search string.

DATA COLLECTION

Inclusion Criteria

To be included in the study sample, publications had to satisfy the following conditions. *1)* Variables of interest could be extracted from the original article. Predictor variables were the number of patients, number of resected SMGs, primary site, and tumor, node, and metastasis (TNM) stage. Outcome variables were the number of involved SMGs and mode of involvement. *2)* The diagnosis of SCC was confirmed by histopathology. *3)* The primary site of the lesion was in the oral cavity. *4)* Neck dissection was performed simultaneously with resection of the primary lesion. *5)* Articles were published in English.

Exclusion Criteria

Publications were excluded from this analysis if they met 1 of the following conditions: *1)* the primary lesion site was other than in the oral cavity, such as in the oropharynx, larynx, or hypopharynx; *2)* the study subjects had another malignant oncologic history; *3)* the study subjects had undergone any prior SMG resection; or *4)* the study subjects had received radiotherapy or chemotherapy before the surgery.

Two researchers independently screened the titles and abstracts of the included articles. Then, they read the full articles of the included studies and extracted the data. All discrepancies were resolved by negotiation.

VARIABLES

Primary predictor variables were the number of study subjects and number of resected SMGs. Secondary predictor variables were first author, publication year, country of origin, mean age, primary sites (eg, tongue, floor of the mouth, alveolus, buccal mucosa, lip, or retromolar trigone), TNM stage (pathologic TNM), and the condition of neck lymph nodes at level Ib (eg, positive or negative). Primary outcome variables were the number of pathology-confirmed involved SMGs and the mode or mechanism of involvement.

METHODOLOGIC QUALITY ASSESSMENT

Because these studies were nonrandomized studies, the Newcastle-Ottawa Scale was used to assess the methodologic quality and risk of bias of each eligible study.[11]

The scale contains 3 sections: selection section (4 items), comparability section (1 item), and outcome

section (3 items). The full score is 9 points, which covers the 3 sections. A study with a score higher than 6 is considered high quality, and a score lower than 4 indicates a low-quality study. Two authors independently assessed the quality of each included study and differences were adjudicated by another author.

DATA ANALYSES

Data analyses were performed using Review Manager 5.2 (Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark). The rate of SMG involvement was defined as the common effect size. A meta-analysis was performed by calculating the pooled proportion of the SMG involvement rate. Heterogeneity between studies was assessed using the I^2 statistic (with 95% confidence interval [CI]); an I^2 value greater than 50% indicated marked inter-study heterogeneity.

Potential publication bias was assessed by funnel plots, with the Begg test conducted to estimate the plots' asymmetry using R 5.3 (R Project; https://www.r-project.org/).

Results

Figure 1 shows the flow diagram of the study selection process. Included were 12 studies published from 2004 through December 2017 and involved 2,126 patients with OSCC.[8,9,12-21] Only 1 of the 12 studies was a prospective study[8]; the remaining 11 were retrospective studies. Three studies reported that the SMG specimens had been processed routinely (eg, sectioned for gross inspection and then sectioned to 3- to 5-mm split thickness to be made into slides, which were observed under light microscopy).[16,20,22] The other 9 studies did not report detailed information on gross observations.[8,9,12-15,17,18,21] The included studies were of good quality because all scored higher than 6 on the Newcastle-Ottawa Scale (Table 1).

Table 2 presents the demographic characteristics of each included study. The studies involved 69 to 342 patients. The common primary sites were the tongue, floor of the mouth, buccal mucosa, and alveolus. The largest number of SMGs harvested from neck dissection was 383. Tumor stage ranged from T1 to T4.

Table 3 presents details of the involved SMGs (range, 0 to 13). In total, there were 52 involved SMGs.

There were 4 modes of SMG involvement (Table 4). *1)* For direct spread from the primary site (38 cases), the common primary sites were the floor of the mouth, tongue, and buccal extension to the mandible. *2)* For extracapsular spread from positive lymph nodes at level Ib according to histopathologic examination (9 cases), the common primary sites were the tongue and floor of the mouth. One SMG was involved by direct spread of the primary tumor and extracapsular spread

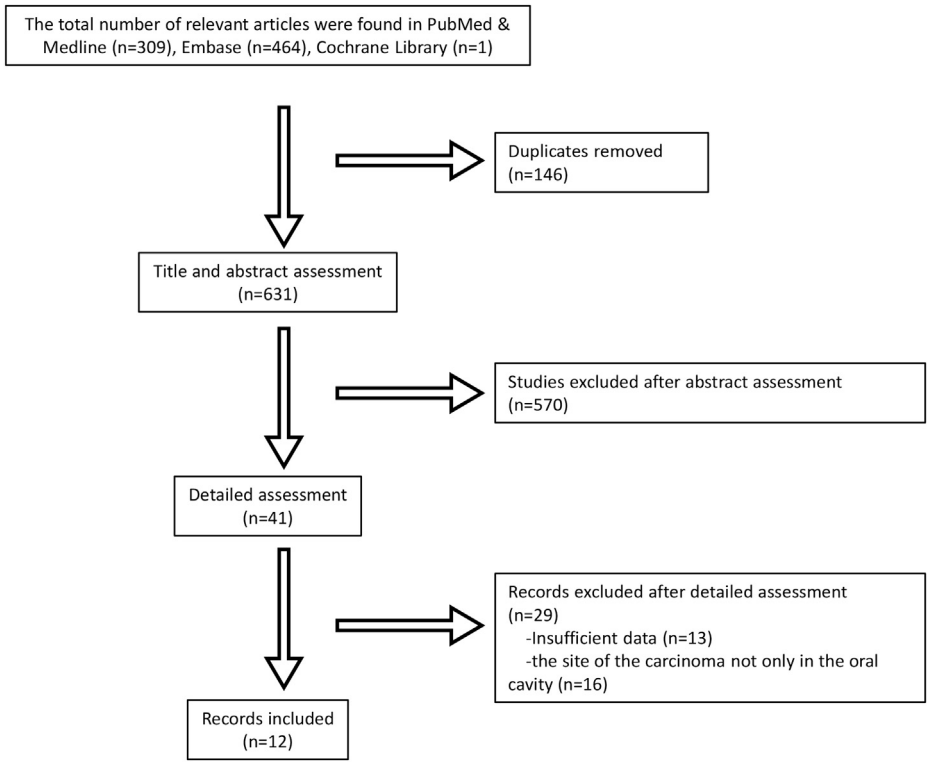

FIGURE 1. Flow diagram of literature search procedure.

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Table 1. METHODOLOGIC QUALITY OF STUDIES INCLUDED IN THE ANALYSIS

			Selection				Comparability		Outcome			
Study	Year	Study Design	1	2	3	4	1	2	1	2	3	Total
Malik et al[8]	2016	Prospective cohort	1	1	1	1	1	0	1	1	1	8
Panda et al[12]	2015	Retrospective cohort	1	1	1	0	1	0	1	1	1	7
Fives et al[13]	2017	Retrospective cohort	1	1	1	1	1	0	1	1	1	8
Ashfaq et al[14]	2014	Retrospective cohort	1	1	0	1	1	0	1	1	1	7
Basaran et al[9]	2013	Retrospective cohort	1	1	1	1	1	0	1	1	1	8
Okoturo et al[15]	2012	Retrospective cohort	1	1	1	0	1	0	1	1	1	7
Naidu et al[16]	2012	Retrospective cohort	1	1	1	1	1	0	1	1	1	8
Razfar et al[17]	2009	Retrospective cohort	1	1	1	0	1	0	1	1	1	7
Kruse and Grätz[18]	2009	Retrospective cohort	1	1	1	1	1	0	1	1	1	8
Chen et al[19]	2009	Retrospective cohort	1	1	1	1	1	0	1	1	1	8
Byeon et al[20]	2009	Retrospective cohort	1	1	1	1	1	0	1	1	1	8
Spiegel et al[21]	2004	Retrospective cohort	1	1	1	1	1	0	1	1	1	8

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Table 2. CLINICOPATHOLOGIC FEATURES OF INCLUDED STUDIES

											Primary Site					
Study	Year	Country	Patients, N	Age (yr), Mean	pT1	pT2	pT3	pT4	pN^+	pIb^+	Tongue	Buccal Mucosa	Alveolus	FOM	Other Oral Site	SMGs, n
Malik et al[8]	2016	India	137	52	35	51	15	36	52	30	58	55	22	0	2	152
Panda et al[12]	2015	India	157	NR	11	30	41	75	NR	NR	56	36	33	NR	32	163
Fives et al[13]	2017	Ireland	176	NR	NR	NR	NR	NR	63	28	67	10	30	51	18	203
Ashfaq et al[14]	2014	Pakistan	99	NR	NR	NR	NR	NR	NR	NR	44	14	19	22	1	NR
Basaran et al[9]	2013	Turkey	236	57	30	87	36	83	NR	NR	108	24	16	33	55	294
Okoturo et al[15]	2012	India	174	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Naidu et al[16]	2012	South Africa	69	58	3	23	20	23	12	NR	28	6	6	22	7	106
Razfar et al[17]	2009	America	253	59	NR	NR	NR	NR	NR	3	NR	NR	NR	NR	NR	261
Kruse and Grätz[18]	2009	Switzerland	130	61	NR	50	NR	NR	71	NR	23	8	57	29	13	171
Chen et al[19]	2009	Taiwan	342	50	NR	NR	NR	90	NR	NR	121	143	20	17	41	383
Byeon et al[20]	2009	Korea	201	56	59	102	17	23	186	NR	132	14	9	35	20	316
Spiegel et al[21]	2004	America	152	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

Abbreviations: FOM, floor of mouth; NR, not reported; SMG, submandibular gland.

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Table 3. DETAILED FEATURES OF INVOLVED SMGS

				Mode of Involvement					Primary Lesion Site						pT			pN				
Study	Year	Country	Involved SMGs, n	Direct Spread	Extracapsular Spread From Ib LN	Direct Spread + Extracapsular Spread From Ib LN	Intraglandular LN	Along Wharton Ducts	Tongue	FOM	Alveolus	Buccal	Lip	Retromolar Trigone	T2	T3	T4	N0	N1	N2	N3	pIb+
Malik et al[8]	2016	India	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Panda et al[12]	2015	India	6	4	1	1	0	0	1	1	3	1	0	0	0	1	5	NR	NR	NR	NR	NR
Fives et al[13]	2017	Ireland	2	1	0	0	0	1	0	2	0	0	0	0	NR	NR	NR	NR	NR	NR	NR	NR
Ashfaq et al[14]	2014	Pakistan	2	2	0	0	0	0	0	1	1	0	0	0	NR	NR	NR	0	0	2	0	NR
Basaran et al[9]	2013	Turkey	13	8	4	0	1	0	6	5	0	1	1	0	3	3	7	4	3	5	1	NR
Okoturo et al[15]	2012	India	2	2	0	0	0	0	1	0	1	0	0	0	0	0	2	0	0	2	0	2
Naidu et al[16]	2012	South Africa	2	2	0	0	0	0	1	1	0	0	0	0	0	0	2	0	0	2	0	NR
Razfar et al[17]	2009	America	1	1	0	0	0	0	0	1	0	0	0	0	NR	NR	NR	NR	NR	NR	NR	NR
Kruse and Grätz	2009	Switzerland	6	5	0	0	1	0	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	6
Chen et al[19]	2009	Taiwan	7	5	1	0	1	0	0	0	1	6	0	0	0	0	7	NR	NR	NR	NR	NR
Byeon et al[20]	2009	Korea	2	2	0	0	0	0	0	1	0	0	0	1	1	0	1	1	1	0	0	0
Spiegel et al[21]	2004	America	9	6	3	0	0	0	1	7	1	0	0	0	NR	NR	NR	NR	NR	NR	NR	NR
Total			52	38	9	1	3	1														

Abbreviations: FOM, floor of mouth; LN, lymph node; NR, not reported; SMG, submandibular gland.

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Table 4. DETAILED FEATURES OF PRIMARY SITES OF INVOLVED SUBMANDIBULAR GLANDS

		Primary Site									
Mode of Involvement	N	Tongue	Lip	Low Alveolus	FOM	Buccal Extension to Mandible	Buccal	Buccal Extension to FOM	Gingival Extension to FOM	Retromolar Trigone	NR
Direct spread	38	5	1	5	16	3	0	1	1	1	5
Extracapsular spread from Ib LN	9	3	0	1	3	0	1	0	1	0	0
Direct spread and extracapsular spread from Ib LN	1	0	0	0	0	0	1	0	0	0	0
Intraglandular LN	3	1	0	0	0	1	1	0	0	0	0
Along Wharton ducts	1	0	0	0	1	0	0	0	0	0	0

Abbreviations: FOM, floor of mouth; LN, lymph node; NR, not reported.

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from lymph nodes in level Ib. *3)* For carcinoma along the Wharton ducts (1 case), the primary site was the floor of the mouth. *4)* For intraglandular lymph node metastasis (3 cases), the primary sites were the tongue (1 case), buccal carcinoma extending to the mandible (1 case), and buccal carcinoma (1 case).

A random-effects model was used to calculate the pooled involvement rate. Pooled analysis showed that the pooled SMG involvement rate was 2% (I^2 = 73%; 95% CI, 1-3; Fig 2), although the I^2 value suggested marked heterogeneity.

A random-effects model also was used to calculate the pooled involvement rate for the mode of direct spread from the primary site and extracapsular spread of the lymph nodes. Pooled analysis showed that the involvement rate was 1.9% (I^2 = 72%; 95% CI, 0.9-3.1; Fig 3).

A random-effects model was used to calculate the pooled involvement rate for the other 2 novel modes (intraglandular lymph node metastasis and along the Wharton ducts). Pooled analysis showed that the involvement rate for these 2 modes was 0.1% (I^2 = 0%; 95% CI, 0-0.2; Fig 4).

Potential publication bias was assessed by funnel plots with the Begg test. The Begg test showed no significant publication bias in the included studies (P = .4929; Fig 5).

Discussion

During the past 100 years, neck dissection has been modified to protect non-lymphatic tissue based on the premise that it does not influence the treatment effect.[23] However, the SMG is routinely sacrificed during neck dissection in OSCC.[24] Is it possible to preserve the SMG during neck dissection in OSCC? The present systematic review showed that the rate of SMG involvement was low (ie, 2%; I^2 = 73%; 95% CI, 1-3). Most

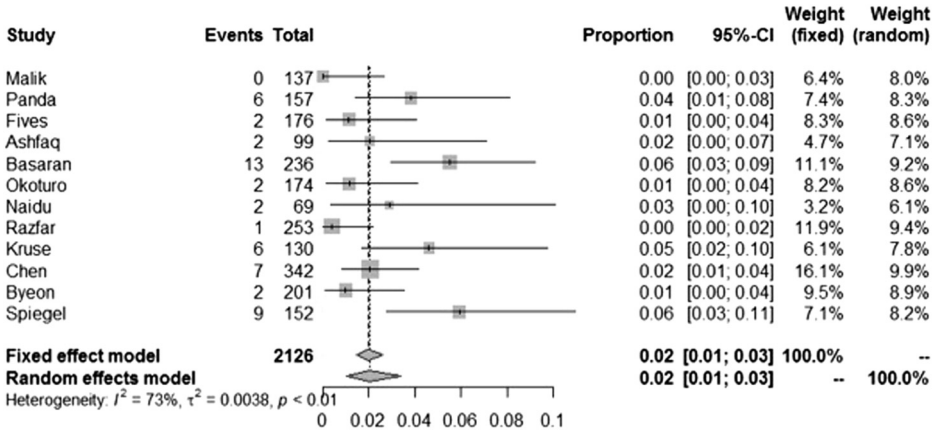

FIGURE 2. Pooled analysis of submandibular gland involvement rate. CI, confidence interval.

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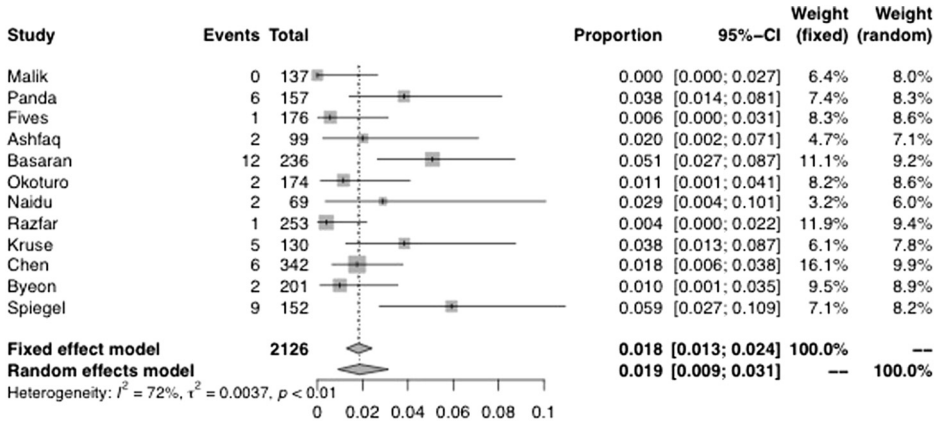

FIGURE 3. Pooled analysis of submandibular gland involvement rate by direct spread from the primary site and extracapsular spread of lymph nodes. CI, confidence interval.

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involved SMGs (92%; 48 of 52) were involved by direct spread from the primary site with or without extracapsular spread of positive lymph nodes. In other words, except for direct spread, the pooled rate of SMG involvement in OSCC was only 0.1% (I^2 = 0%; 95% CI, 0-0.2). These results might provide a basis for preserving the SMG during neck dissection in OSCC.

In the present review, 4 modes of SMG involvement in OSCC were found: *1)* direct spread from the primary site, *2)* direct spread from extracapsular spread of positive lymph nodes, *3)* intraglandular lymph node metastasis, and *4)* along the Wharton ducts.[12,13,19] Seventy-three percent (38 of 52) of involved SMGs were involved by direct spread from the primary site. Most direct spread occurred when the floor of the mouth was involved and occurred in approximately 55% of cases (18 of 33). One study in this series did not report detailed information on the primary sites of 5 involved SMGs.[18] This indicates that SMGs are more likely to be involved when carcinoma infiltrates the floor of the mouth. Preserving the SMG during neck dissection might be more difficult in cancer of the floor of the mouth, because pull-through resection is used as a classic technique for treating cancer of the floor of mouth and of the tongue, which is in close proximity to tissues in the floor of mouth.[25] During pull-through resection, the Wharton ducts are destroyed.[26] Therefore, it is impossible to preserve functional SMGs if the floor of the mouth is involved in OSCC.

In the present analysis, the SMG was involved by direct extracapsular spread of positive lymph nodes in 10 cases. The positive lymph nodes in these cases were at level Ib. Therefore, SMG involvement should be considered when there are clinically positive lymph nodes, especially at level Ib.

Except for direct spread, the present analysis found that 3 SMGs were involved by intraglandular lymph

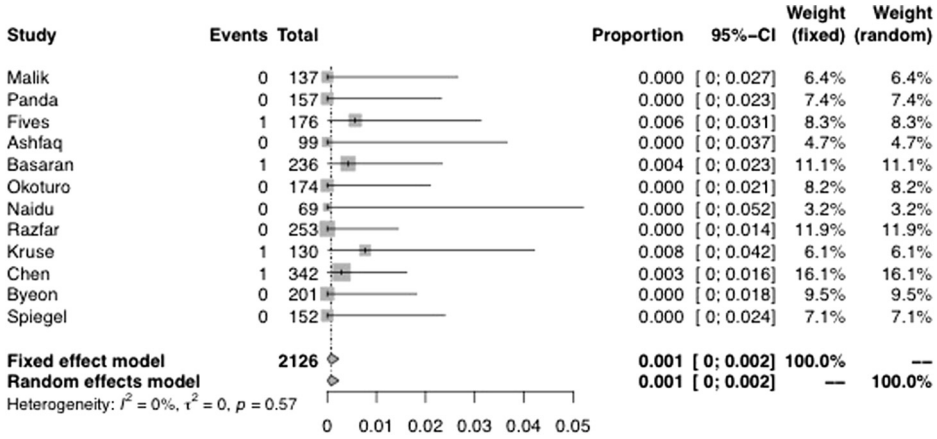

FIGURE 4. Pooled analysis of submandibular gland involvement rate by 2 other modes of involvement (intraglandular lymph node metastasis and along the Wharton duct). CI, confidence interval.

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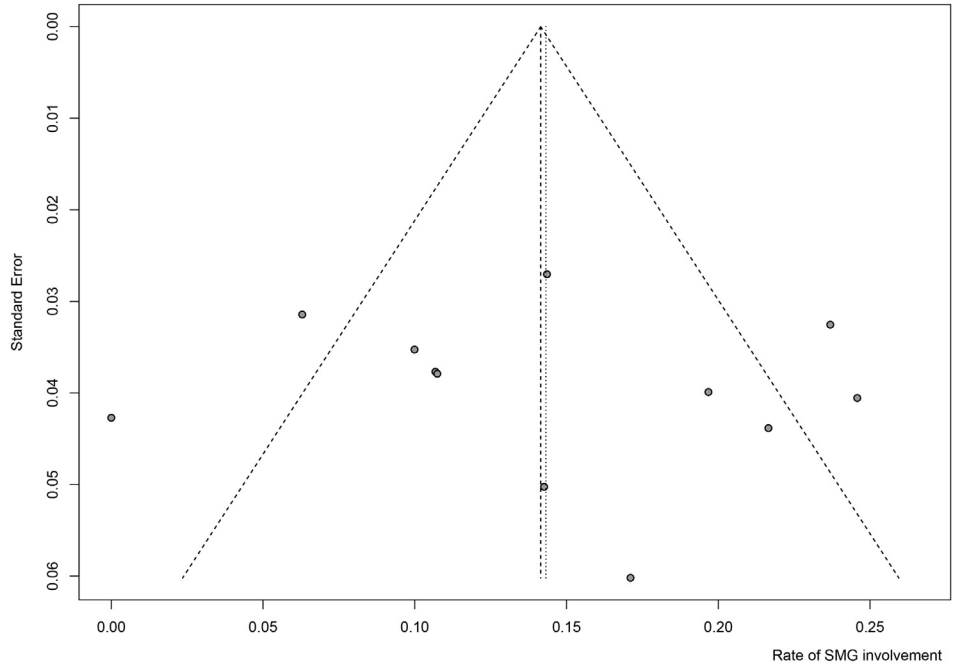

FIGURE 5. Funnel plot for SMG involvement in oral squamous cell carcinoma. SMG, submandibular gland.

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node metastasis and 1 SMG was involved by carcinoma growing along the Wharton ducts. The existence of intraglandular lymph nodes in SMGs is controversial. From most researchers' viewpoints, there are no intraglandular lymph nodes in the SMG.[8,27,28] These 3 studies, which were included in this review, did not provide figures showing slices stained with hematoxylin and eosin or descriptions of the histopathologic appearances of metastatic intraglandular lymph nodes. Therefore, the issue of SMG involvement through intraglandular lymph nodes requires further investigation in studies with precise design. Fives et al[13] found that 1 SMG was infiltrated by carcinoma growing along the Wharton duct in cancer of the floor of mouth. It was a novel mechanism that has never been reported. However, the incidence of these 2 modes is very rare (only 0.1% in this analysis).

The present systematic review had some limitations. First, most (11 of 12) included studies were retrospective and only 1 study was prospective. Some studies did not include complete information of the cases. Second, traditional sectioning was used in all cases rather than serial sectioning, which would have yielded more information. Third, because the authors were restricted by the research data, they could not answer the question of whether SMG preservation in neck dissection would affect OSCC prognosis compared with conventional procedures.

The present systematic review suggests that the rate of SMG involvement in OSCC is very low and that the common mode of involvement is by direct spread. Although the authors report a rare mechanism of metastasis, the exact steps require confirmation. The SMG might be preserved during neck dissection in relatively early-stage OSCC. Further studies with a large case number and more precise scientific design are needed to provide more compelling evidence.

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