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REVIEW ARTICLE

Distant metastasis from oral cavity—correlation between histopathology results and primary site

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Abstract

Objectives Oral cancer is the eighth most common type of cancer worldwide and a significant contributor to the global burden caused by this disease. The principal parameters considered to influence prognosis, and thus treatment selection, are size and location of the primary tumor, as well as assessment of the presence and extent of lymph node and distant metastasis (DM). However, no known report regarding the relationship between the primary site and DM has been presented. For effective treatment selection and good prognosis, the correlation of DM with anatomic site and histopathology results of the primary malignancy is important. In the present study, we performed a systematic review of published reports in an effort to determine the relationship between the anatomic site of various types of oral cavity cancer and DM.

Methods A systematic review of articles published until the end of 2018 was performed using PubMed/MEDLINE.

Results A total of 150 studies were selected for this review. The percentage of all cases reported with DM was 6.3%, ranging from 0.6% to 33.1% in the individual studies. The rate of incidence of tongue occurrence was 9.3%. A frequent DM site was the lungs, with adenoid cystic carcinoma the most commonly involved histopathological factor. Malignant melanoma was most frequent (43.4%) in all histopathology findings, whereas there were no cases with an acinic cell carcinoma or cystadenocarcinoma.

Conclusions We found that the occurrence of DM from the primary site as well as rate of incidence was dependent on histopathological factors.

Keywords Oral · Distant metastases · Malignancy histopathology

Introduction

Oral cancer is the eighth most common cancer worldwide and a significant contributor to the global burden caused by this disease [1], with squamous cell carcinoma (SCC) noted in 90% of diagnosed cases [2]. The staging system of the American Joint Committee on Cancer for oral squamous cell carcinoma, commonly used to determine the extent of disease and predict clinical outcome, is based on primary tumor classification (T), which is assessed as the maximum diameter of the tumor, quantification of nodal metastases (N) according to size, number, and distribution, and the presence of distant metastasis (M) (DM) [3]. However, the American Joint Committee on Cancer revised its staging system for neoplasms in 2016 (eighth edition); thus TNM classification of Malignant Tumors was revised in 2017. Depth of tumor invasion was newly added as factor for T classification of the oral cavity and extra-nodal extension was newly added as a factor for N classification [4].

The presence or absence of lymph node metastasis has often been cited as the most important predictor of outcome [2]; thus several related studies have been presented. Furthermore, size and location of the primary tumor, as well as assessment of the presence and extent of lymph node metastasis, and DM are the principal investigated parameters influencing prognosis and thus treatment selection [5]. While the relationship of DM with various histopathological factors, such as SCC, salivary gland malignancy, and sarcoma,

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has been investigated, no report regarding the relationship between various primary sites of oral cavity cancer and DM has been presented. For effective treatment selection and good prognosis, it is important to understand the correlation of DM with the anatomic site and histopathology findings of the primary malignancy. In the present study, we performed a systematic review of published reports in an effort to determine the relationship between the anatomic site of various types of oral cavity cancer and DM.

Materials and methods

Using the PubMed/MEDLINE service, we performed a systematic search of studies published until the end of 2018 using the following key words: medical heading (Mesh-) terms "oral" OR "gingiva" OR "gingival" OR "tongue" OR "cheek" OR "buccal mucosa" OR "palate" OR "submandibular gland" OR "sublingual gland" OR "mandible" OR "mandibular" OR "maxilla" OR "maxillary" or "lip" AND "distant metastases" OR "distant metastasis".

After obtaining summaries of the studies obtained in that search, we selected relevant articles according to specific criteria, which included publication in English, number of cases of SCC greater than 50, and number of non-SCC cases greater than 10, while the exclusion criteria were case reports, reviews, studies in which the primary tumor was not pathologically confirmed, and studies that showed no relationship between histopathology and DM. Inclusion of salivary glands was permitted, while parotid gland cases were excluded. The initial step for study selection was analysis of the title and abstract, then all studies considered relevant were obtained and analyzed in full. Finally, based on consensus, the final selected articles were analyzed and included in systematization of the present data.

Evaluations

The numbers of overall cases and DM cases were summed for each histopathology type and then the site of occurrence was analyzed in accordance with histopathology results. Relationships between the primary site and DM frequency, between the primary site and DM site, between histopathology results and DM site, and between histopathology results and DM frequency were then examined.

Results

For the present systematic review, 137 studies were selected, while additional 13 articles were selected from review articles and added, for a total 150 used in this study. The pathology results in those study cases are shown in Table 1. Many of the studies included several different results, though we did not classify the histopathology subtype. The most frequent was SCC (104 studies) [6–109], followed by ACC (23 studies) [74, 110–131], malignant melanoma (11 studies) [122, 132–141] and sarcoma (11 studies) [122, 142-151], mucoepidermoid carcinoma (8 studies) [74, 111, 112, 117, 122, 125–127], and adenocarcinoma (7 studies) [74, 111, 112, 117, 122, 126, 152].

Table 1 Distribution of histopathology findings

Histopathology	Number of DM studies included in article	Reference numbers
SCC	104	[6–109]
ACC	23	[74, 110–131]
Malignant melanoma	11	[122, 132–141]
Sarcoma	11	[122, 142–151]
Mucoepidermoid carcinoma	8	[74, 111, 112, 117, 122, 125–127]
Adenocarcinoma	7	[74, 111, 112, 117, 122, 126, 127]
Malignant mixed tumor	5	[74, 112, 117, 125, 126]
Acinic cell carcinoma	3	[74, 111, 112]
Salivary duct carcinoma	3	[74, 127, 153]
Cystadenocarcinoma	2	[112, 125]
Myoepithelial carcinoma	2	[126, 154]
Malignant ameloblastoma	1	[122]
Merkel cell carcinoma	1	[155]
Poorly different carcinoma	1	[125]
Small-cell carcinoma neuroendocrine type	1	[122]

SCC squamous cell carcinoma, *ACC* adenoid cystic carcinoma, *DM* distant metastasis

Table 2 shows the relationship between primary cancer site and DM frequency. The total number of cases was 47, 841 and that of cases with DM was 3013, for a rate of 6.3% of all cases, with a range of 0.6% to 33.1% in the individual studies. An anatomic site was most frequent, followed by the lip and tongue. The 2 most frequent anatomic sites of DM were submandibular (33.1%) and sublingual (31.4%) glands, while the lip had the lowest frequency (0.6%). The rate of incidence of DM related to the tongue was 9.3%.

Table 2 Distribution by anatomic site

Anatomic site	No. of cases	No. of DM cases	Rate of DM
Tongue	2506	232	9.3
Gingiva, not specified	228	28	12.3
Upper gingiva	236	37	15.7
Lower gingiva	241	29	12.0
Maxilla	134	26	19.4
Mandible	137	37	27.0
Cheek	836	104	12.4
Lip	9170	53	0.6
Palate, not specified	92	17	18.5
Hard palate	188	46	24.5
Soft palate	4	1	25.0
Oral floor	674	118	17.5
Submandibular gland	178	59	33.1
Sublingual gland	121	38	31.4
Minor gland	62	14	22.6
Oral cavity, not specified	33,034	2175	6.6
Total	47,841	3014	6.3

DM distant metastasis

All studies did not describe relationship between primary site and DM site, and relationship between histopathology results and DM site. Only 51 articles of all described the distant metastases site [9, 13, 14, 17, 19, 30, 34, 38, 40, 43, 44, 47, 61, 63, 67, 70, 72, 75, 79, 80, 83, 88, 90, 94, 102, 103, 110, 112, 118–120, 122, 123, 125–128, 132, 134–137, 140, 144, 146–150, 154].

Thus Table 3 demonstrates the relationship between primary site and DM site and Table 4 demonstrates the relationship between histopathology results and DM site.

The relationships between the primary and DM sites are presented in Table 3. A site in the lungs (574 of all 1,014sites) was the most frequent, followed by bone, whereas the brain (24 sites) had the lowest frequency. When the tongue was the primary site, the most frequent site of DM was the lungs, followed by bone. Frequent anatomic sites related to lung DM were the tongue, maxilla, cheek, mandible and sublingual gland, while the hard palate as an anatomic site was frequently related to bone metastasis.

Table 4 shows relationships between histopathology results and DM site. ACC metastasis was most frequently

Table 3 Relationship between primary site and DM site

Primary site	No. of cases	No. of DM cases	DM site					
			Lungs	Bone	Brain	Liver	Others (including multiple)	Total
Tongue	553	33	30	3			2	35
Gingiva, not specified	16	1	1			1	2	4
Upper gingiva	174	26	24		1		1	26
Lower gingiva	78	10	8				2	10
Maxilla	86	15	14	6		1	3	24
Mandible	83	22	12	8	1		1	22
Cheek	267	22	14	1	1	2	4	22
Lip	347	10	8	2	1	1	2	14
Palate, not specified	63	8	7		1			8
Hard palate	39	13	10		1		2	13
Soft palate	1	1	1					1
Oral floor	100	11	11		1			12
Submandibular gland	19	3	3				1	4
Sublingual gland	39	12	11				1	12
Oral cavity	7105	647	419	137	17	64	169	806
Total	8970	834	573	157	24	69	190	1013

References [9, 13, 14, 17, 19, 30, 34, 38, 40, 43, 44, 47, 61, 63, 67, 70, 72, 75, 79, 80, 83, 88, 90, 94, 102, 103, 110, 112, 118–120, 122, 123, 125–128, 132, 134–137, 140, 144, 146–150, 154]

Table 4 Relationship between histopathology results and DM site

Histopathology	Number of cases	Number of DM	DM site					
	Overall	Cases	Lungs	Bone	Brain	Liver	Others (including multiple)	Total
SCC	8150	563	385	128	9	39	147	708
ACC	219	57	51	3	4		2	60
Malignant melanoma	382	170	107	12	9	29	35	192
Sarcoma	174	37	26	14	1	1	4	46
Myoepithelial carcinoma	32	2			1		1	2
Adenocarcinoma	5	1	1					1
Mucoepidermoid carcinoma	6	3	3					3
Salivary duct carcinoma	2	1					1	1
Total	8970	834	573	157	24	69	190	1013

DM distant metastasis, *SCC* squamous cell carcinoma, *ACC* adenoid cystic carcinoma

References [9, 13, 14, 17, 19, 30, 34, 38, 40, 43, 44, 47, 61, 63, 67, 70, 72, 75, 79, 80, 83, 88, 90, 94, 102, 103, 110, 112, 118–120, 122, 123, 125–128, 132, 134–137, 140, 144, 146–150, 154]

found in the lungs. The incidence of DM from SCC was relatively low, while metastasis of a malignant melanoma to the liver was frequently noted (29 of 192 sites).

The relationships of histopathology results and DM frequency are presented in Table 5. Malignant melanoma was most frequently noted (43.4%), whereas there were no reports of acinic cell carcinoma or cystadenocarcinoma. Among all histopathological factors, the frequency of SCC (5.3%) was relatively low.

Discussion

Primary sites

Tongue

The most common type of intraoral malignancy was found to be SCC of the tongue and, after excluding lip lesions, that was shown to account for 25–40% of oral carcinoma cases, with DM generally occurring in the lungs or liver [156]. Among the studies examined, the tongue was the most frequently noted anatomic site, though the incidence of DM (9.3%) from the tongue was lower as compared with other anatomic sites. Histopathology findings showed SCC (2,458of 2506cases) most often, followed by ACC (43 of 2506). For ACC, the incidence of DM was 37.2%, which was higher as compared to that of SCC (8.7%). When treating a case of ACC, it might be necessary to perform screening for DM. The most frequent site of DM was the lungs and, though the rate of incidence of low, a lung examination may be necessary in affected patients.

Cheek

Cheek lesions accounted for approximately 10% of all oral SCC cases [156]. In this examination, the cheek was a relatively frequent anatomic site, while the incidence of DM was 12.4%, lower as compared with other anatomic sites. The most common histopathology finding was SCC (786 of 836 cases), followed by ACC (35 of 836). As for the anatomic site of ACC, the frequency of cheek occurrence was higher than that of SCC. In the myoepithelial carcinoma cases, the incidence of DM was 1 of 7 cases and the most frequent site of metastasis was the lungs. Again, the rate of incidence was low, though a lung examination might be necessary.

Oral floor

Oral floor lesions accounted for 15% to 20% of oral SCC occurrence [156]. The incidence of DM was 17.7%, while the most frequent site was the lungs. Compared with the tongue, cheek, DM activity of oral floor was higher.

Gingiva, including upper and lower gingiva

Gingival lesions accounted for approximately 10% of the oral SCC cases [156], with occurrence in the upper more frequent than in the lower gingiva. The most frequent site in both the upper and lower gingiva was lung.

Jaw (maxilla and mandible)

Primary malignant neoplasm of epithelium (i.e. SCC) may raise from any mucosal surface including gingiva. Sarcomas, arising from cells with a mesenchymal lineage are most

Table 5 Relationship between histopathology results and DM frequency

Histopathology	SCC		ACC		Malignant melanoma		Sarcoma	
Primary site	No. of cases	No. of DM cases	No. of cases	No. of DM cases	No. of cases	No. of DM cases	No. of cases	No. of DM cases
Tongue	2458	215	43	16	1	1	2	
Gingiva, not specified	223	28					2	
Upper gingiva	206	20			30	17		
Lower gingiva	193	13	28	6	20	10		
Maxilla			2	2			129	24
Mandible							137	37
Cheek	786	91	35	10	2		5	1
Lip	8995	37	11	4	51	5	1	1
Palate, not specified	1		59	9	17	7		
Hard palate	13	1	137	33	36	12		
Soft palate			3	1				
Oral floor	656	116	14	1	2	1		
Submandibular gland	3	2	133	46				
Sublingual gland			108	36				
Minor gland			35	14				
Oral cavity	31,870	1884	685	128	300	146	49	14
Total	45,404	2407	1293	306	459	199	325	77

Histopathology	Adenocarcinoma		Mucoepidermoid carcinoma		Malignant mixed tumor		Acinic cell carcinoma		Salivary duct carcinoma	
Primary site	No. of cases	No. of DM cases	No. of cases	No. of DM cases	No. of cases	No. of DM cases	No. of cases	No. of DM cases	No. of cases	No. of DM cases
Tongue										
Gingiva, not specified										
Upper gingiva										
Lower gingiva										
Maxilla										
Mandible										
Cheek			1	1						
Lip										
Palate, not specified										
Hard palate					1				1	
Soft palate										
Oral floor										
Submandibular gland	4		11	3	8	2			19	6
Sublingual gland	5	1	2		1		2		2	1
Minor gland	18		6		3					
Oral cavity	21	1	70	1	22		5		1	
Total	48	2	90	5	35	2	7		23	7

Table 5 (continued)

Histopathology	Myoepithelial carcinoma		Cystadenocarcinoma		Others		Total	
Primary site	No. of cases	No. of DM cases	No. of cases	No. of DM cases	No. of cases	No. of DM cases	No. of cases	No. of DM cases
Tongue	2						2506	232
Gingiva, not specified	3						228	28
Upper gingiva							236	37
Lower gingiva							241	29
Maxilla	3						134	26
Mandible							137	37
Cheek	7	1					836	104
Lip					112	6	9170	53
Palate, not specified	15	1					92	17
Hard palate							188	46
Soft palate			1				4	1
Oral floor	1				1		674	118
Submandibular gland							178	59
Sublingual gland	1						121	38
Minor gland							62	14
Oral cavity			9		2	1	33,034	2175
Total	32	2	10		115	7	47,841	3014

DM distant metastasis, *SCC* squamous cell carcinoma, *ACC* adenoid cystic carcinoma

Others: malignant ameloblastoma, merkel cell carcinoma, poorly different carcinoma, small-cell carcinoma neuroendocrine type

common in the mandible and in the posterior regions of both jaws [157]. Thus, jaw (maxilla and mandible) was included in the primary sites.

In cases of the jaw, the incidence of DM in the mandible was greater than that in the maxilla, while the site of metastasis for both was the lungs.

Lip

A lip carcinoma accounted for 25–30% of all oral cancer cases [156]. In the present survey, the lip was the most frequently reported anatomic site. DM from the lip was uncommon (0.6%), though the rate of incidence related to ACC was 36.4% and higher than that for SCC. DM from the lip appeared in the lungs; thus, as in cases of ACC, it might be necessary to perform screening for metastasis there.

Palate (including hard and soft palate)

Lesions of the palate accounted for 10% to 20% of all intraoral lesions [156]. Frequently, the histopathology of DM was shown to be ACC, with metastasis occurring more often from a hard palate as compared to a soft palate tumor. The frequency of malignant melanoma was lower than that of ACC, though the incidence of DM was higher (37.3% vs. 24.2%). A frequent site of metastasis from the hard palate was bone.

Submandibular gland

Histopathology findings showing submandibular gland tumors most often indicated ACC, followed by salivary duct carcinoma, mucoepidermoid carcinoma, malignant mixed tumor, adenocarcinoma and SCC. The incidence rate of DM was high (> 25%) and the site was predominantly the lungs. For cases of malignancy in the submandibular gland, lung screening may be necessary.

Sublingual gland

The histopathology findings of sublingual gland tumors most often indicated ACC, followed by adenocarcinoma, mucoepidermoid carcinoma, salivary duct carcinoma, malignant mixed tumor and myoepithelial carcinoma. Except for ACC, the number of other types of cases was quite low, whereas the incidence of DM was high.

Minor glands

For minor glands, histopathology findings frequently showed ACC, followed by adenocarcinoma, mucoepidermoid carcinoma and malignant mixed tumor. DM from a submandibular, sublingual, or minor gland had high rates of incidence of 33.1%, 31.4% and 22.6%, respectively. Histopathology findings for nearly all salivary gland tumors indicated ACC. For cases of ACC or salivary duct carcinoma, it is recommended to perform an examination of possible DM from the primary tumor.

Histopathology results

SCC

Relative to the incidence of all types of cancer, oral and oropharyngeal SCC cases represented approximately 3% of those occurring in males and 2% of those in females [156]. Ninety percent of the oral cancer tumors were squamous cell carcinoma (SCC [2].

Of 47,841cases reviewed in this study, SCC occurred in 45,404 (94.9%). The primary site was the lip, followed by tongue and cheek. Furthermore, the rate of incidence of DM was 5.3% (2407/45,404), while the frequency of metastasis from the tongue, gingiva, upper gingiva and cheek was approximately10%, while that frequency from the lip was lower and oral floor was higher. Thus, the frequency of DM of SCC was low overall as compared other histopathological factors. The average incidence rate for the tongue, gingival tissue (including upper and lower gingiva) and cheek was 9.9%. Therefore, SCC cases showing DM, excluding occurrence in the lip and oral floor were thought to comprise approximately 10% of all.

The most frequent site of DM was the lungs, followed by bone and liver. Occurrence in the liver was more frequent as compared with other histopathology findings, while the rate of incidence of DM to the lungs was approximately 50%. Thus, it might be necessary to perform lung screening at the initial examination of affected patients.

An SCC arising within the salivary glands is relatively rare, though the submandibular gland is most commonly involved in those cases, while DM is unusual [156]. In this review, we found only 3 of 45,404 SCC cases that occurred in the submandibular gland, the site with the lowest rate of incidence. On the other hand, DM from the submandibular gland was noted in 2 of 3 cases; thus SCC arising within the salivary glands might be prone to DM.

ACC

Approximately 50% to 70% of ACC cases occur in minor salivary glands of the head and neck, chiefly the palate, with distant spreading to the lungs more common than metastasis to regional lymph nodes [156]. In this study, our results showed that the hard palate was most often involved. As for the rate of incidence of DM, the average for ACC was 23.7% (306/1293) which was higher than that for SCC (5.3% (2407/45,404)). The rate of DM from the tongue, lip, submandibular, sublingual, and minor glands, and soft palate was greater than 30%, while the oral floor had a lower frequency. Nearly all metastasis sites were in the lungs. In this review, the number of cases from the lip was very few, though the DM ratio (36.4%) was high as compared to that of SCC (0.4%). When ACC occurs in the lip, it might be necessary to screen for DM.

Malignant melanoma

An oral mucosal melanoma represented only about 0.5% of all oral malignancies, with 80% occurring in the palate, maxillary alveolus, or gingivae [158]. In this study, the most frequent anatomic sites were found to the lip, palate (including hard palate) and gingiva (upper and lower), while the sites of DM were the lungs, liver and bone, with the latter more frequent as compared with the others. The incidence of malignant melanoma was higher than that of SCC in cases of lip occurrence, thus screening for DM from the primary tumor might be necessary in affected patients.

Sarcoma

For the present study, sarcoma included hard tissues and non-osseous tumors. An osteosarcoma is more likely to metastasize to the lungs or brain as compared to regional lymph nodes [156]. We found that the frequency for regional lymph nodes has not been reported; thus there are no data available for examining the relationship with DM. The average incidence rate of DM for sarcoma was 23.7% (77/325), significantly greater than that for SCC (5.3% (2407/45,404)), and screening for metastasis may be necessary in affected patients. In our findings, the most frequent sites of DM were the lungs and bone.

Mucoepidermoid carcinoma

A mucoepidermoid carcinoma accounted for approximately 34% of parotid, 20% of submandibular gland, and 30% of minor salivary gland malignancies [156]. About 53% of mucoepidermoid carcinoma cases show occurrence in the major glands, while 45% occur in the parotid, 7% in the submandibular, and 1% percent in the sublingual glands [159]. The most often involved sites of DM from a mucoepidermoid carcinoma are the lungs, bone and brain [159]. The incidence of DM was 5.6% (5/90), which was the same as that of SCC. As compared with other salivary glands, the incidence of malignancy was low.

Adenocarcinoma

Previous examination showed that approximately 41% of adenocarcinoma occurrence is in minor glands and 59% in major glands [159]. In cases of major gland occurrence, 11% are in the submandibular gland and less than 0.5% in the sublingual gland, while DM was seen in 26% of these cases, with the lungs involved in approximately 50% of those [159]. We noted that the incidence of DM was 4.2% (2/48), which was low as compared with other salivary gland malignancies.

Malignant mixed tumor

Malignant mixed tumor most frequently arises in the parotid gland; but may also originate from the submandibular gland and minor salivary sites, most commonly the palate, occasionally with involvement of the nasopharynx [158]. The metastatic rate varies with each series; up to 70% of patients develop local or distant metastasis [158]. Metastatic sites in oral of frequency are lung bone (especially spine), abdomen and central nervous system [158]. The submandibular gland was involved in 8 of all 35 cases. DM incidence of the submandibular gland was 25% (2/8).

Acinic cell carcinoma

Approximately 80% of acinic cell carcinomas develop in the parotid gland, while the submandibular gland was the site of occurrence in 4% and the intraoral minor gland in 17% of these cases, with DM noted in approximately 15% of the affected patients [156]. Although the number of acinic cell carcinoma cases was quite low, DM was seen in 0% (0/7%), thus metastasis may be rare.

Salivary duct carcinoma

A salivary duct carcinoma is a high-grade malignancy of the major salivary gland. The parotid gland was involved in more than 80% of the cases, while the remainder occurred in the submandibular glands, with lung and bone metastasis often noted [156]. The incidence of DM in these patients was high at 30.4% (7/23) and most frequently in association with a malignant salivary gland tumor, though salivary duct carcinoma had a low rate of frequency among all of the pathological factors. The submandibular gland was involved in 19 of all 23 cases reported.

Myoepithelial carcinoma

The majority of myoepithelial carcinoma occurrence was in major glands, particularly the parotid gland (80%) [158]. The rate of DM was higher as compared to that of the cervical lymph node [159] The incidence of DM was 6.3% (2/32) and that was relatively low as compared with the other pathological factors.

Cystadenocarcinoma

Cystadenocarcinomas accounted for 2% of malignant salivary gland tumors and approximately 60% occurred in major salivary glands [159]. The total number of these cases was 10 and the rate of incidence of DM was 0% (0/10).

DM rate from lip of SCC was relatively low (0.4%), while that of ACC was high (36.4%). DM rate from tongue of SCC was relatively low (8.7%), while that of ACC was high (37.2%). DM rate from oral floor of SCC was relatively high (17.7%), while that of ACC was low (7.1%). But rates of DM spreading from the submandibular gland of almost histopathology were high. Thus it might be that DM would be dependent on histopathology but not on primary site. However, occurrence of DM from submandibular gland might be thought to be high.

Limitations of this study include a lack of consideration of the timing of evaluation of DM, the treatment method used for the primary lesion and patient characteristics. If those were considered, the DM incidence ratios might be different. Although some studies have described methods of DM evaluation, including autopsy, CT and PET results, such descriptions are rare. Thus, methods for evaluating DM are not discussed in the present study.

Conclusion

We found that the occurrence of DM from the primary site and well as rate of incidence was dependent on histopathological factors. The majority of tumors occurring in the tongue and cheek were SCC, with the DM ratio the same at approximately 10%. The rates of DM spreading from the submandibular, sublingual and minor glands were high at 33.1%, 31.4% and 22.6%, respectively.

Compliance with ethical standards

Conflict of interest Our work is free of conflict of interest and has no grant support.

Human and animal rights Human participants and/or animals were not included.

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