



Distribution Pattern and Outcome of Primary Oral Mucosal Melanoma: A Systematic Review

Ilker Burgaz¹, Ma Xiao-kun² and Wang Dian-can²

¹Department of Oral and Maxillofacial Surgery, Dental, Oral and Health Clinic, Istanbul, Turkey

²Department of Oral and Maxillofacial Surgery, Peking University School and Hospital of Stomatology, Beijing, People's Republic of China

Abstract

Background: Primary Oral Mucosal Melanoma (POMM) is an extremely rare malignant tumor with a very poor prognosis. Interestingly, various reports have shown its uneven distribution in the oral cavity and a predominance of POMM in areas of high mechanical stress like maxillary gingiva and hard palate.

Objectives: This systematic review is focused on distribution, clinical significance and the outcome of POMM in the masticatory, lining and specialized mucosa.

Data sources: With the search limited between 01-01-1998 to 11-26-2018, a systematic review of English electronic databases was done with "oral", "mouth", "mucosal", "melanoma" and a combination of these terms. By searching for references and/or bibliographies, a list of selected reviews and studies was prepared. Further, by consulting experts in the field, few more additional studies were identified. All the studies were restricted to humans. Only the studies written in the English language were included.

Data extraction: A data collection table was used to retrieve information regarding patient characteristics, interventions, outcomes, and study design independently by two researchers. Study quality indicators were determined and papers were stratified accordingly. The collected data were analyzed.

Data synthesis: A total of 27 articles met our inclusion criteria. The masticatory mucosa was the most common (87%) site of occurrence of POMM, followed by lining mucosa (11%) and specialized mucosa (2%). The prevalence of POMM was highest on the hard palate followed by gingiva with the ventral tongue being the rarest location.

Limitations: This is a review of uncontrolled studies in which cases with any stage were included, treated with different operators and follow up duration was not uniform. The outcome information was not sufficient to have a conclusion about the prognosis of this disease in each type of mucosa.

Conclusion: We suggest further studies with clear localization and outcome information about each type of mucosa to have a better understanding.

Keywords: Oral; Mucosal; Melanoma; Malignant neoplasm

Introduction

Rationale

Oral Mucosal Melanoma (OMM) is an extremely rare malignant tumor, accounting for 0.2% to 8% of all melanomas in Europe and 0.26% to 0.5% of all malignant neoplasms of the oral cavity [1-4]. The prognosis of OMM is poor despite aggressive treatment, and the 5-year Overall Survival (OS) rate is 6.6% to 40% [4-8]. Surgery has traditionally been the primary treatment modality for OMM. Combined treatment with surgery and biotherapy can significantly improve the prognosis [9]. The etiology of OMM remains unclear but is hardly associated with daylight exposure, just like cutaneous melanoma [10]. There is a predominance of race in OMM. It accounts for <1% of all melanomas in the United States and about 7.5% in Asia [11,12]. The typical age at which it is diagnosed is between the 5th to 7th decades of life [13,14].

Among the mucosal melanoma's almost 55.4% occurs in the head and neck area with almost half occurring in the oral cavity [15,16]. It has a slight male predominance (M/F:1.2) [2]. The distribution of oral melanoma, according to the type of mucosa is 78.1% in masticatory, 14.5% in lining, and 7.2% in specialized mucosa [17].

OPEN ACCESS

*Correspondence:

Wang Dian-Can, Department of Oral and Maxillofacial Surgery, Peking University School and Hospital of Stomatology, 22 South Zhongguancun Avenue, Beijing, 100081, China, E-mail: bjwdc@sina.com

Received Date: 20 Mar 2020

Accepted Date: 07 Apr 2020

Published Date: 09 Apr 2020

Citation:

Burgaz I, Xiao-kun M, Dian-can W. Distribution Pattern and Outcome of Primary Oral Mucosal Melanoma: A Systematic Review. *J Dent Oral Biol*. 2020; 5(2): 1162. ISSN: 2475-5680

Copyright © 2020 Wang Dian-Can. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

POMM is a rare and aggressive disease with poor prognosis. Since OMM is a malignant tumor with poor prognosis, the most ideal management is by prevention and early detection. Many reports have revealed that there is a predominance of OMM in areas of high mechanical stress [18]. The most affected areas are the maxillary gingiva and hard palate.

Objectives

The location of the tumor is an independent prognostic factor for OMM. Tumors that are localized in the oral cavity have a better prognosis than those in the nasopharynx and paranasal sinuses [19]. OMM shows different behaviors in different mucosa types and this affects the survival rate [20]. In this study, we aim to focus on mucosal melanomas that are located primarily in the oral cavity. This is a systematic review of OMM cases describing the incidence and prognosis according to each mucosa type.

Materials and Methods

Protocol and registration

This systematic review was performed on the basis of PRISMA statement and structured on the basis of recommended guidelines [21].

Eligibility criteria

Inclusion criteria were the articles that reported malignant melanoma occurring in the human oral mucosa, randomized controlled trials, case reports (if more than 5 cases), clinical studies, controlled clinical trials, comparative studies, multi-centered studies, observational studies, and reviews written in English. Only the cases of the authors' (if more than 5 cases) were included in the study from review papers. The search limit for studies was between 1st January 1998 to 26th November 2018.

Exclusion criteria were lesions occurring outside the scope of the oral cavity such as soft palate, uvula, nasal cavity, and skin; systematic reviews; multiple sites or metastases; basic research like pathology or genetic loci.

If the tumor location was precise about mucosa type but not apparent about the exact location, it was included in the study and specified in Table 1. However, if the location was not mentioned and the mucosa type was not clear from the text, the studies were excluded. These accounted for more than 15% of the oral mucosa cases. Studies from the same center were analyzed according to their case numbers, distribution and outcome information. Only one study was included from each center.

Information sources and searches

With the search limitation between 1st January 1998 to 26th November 2018, an extensive search was performed in the electronic databases PubMed, Cochrane Library, OVID, EMBASE, Web of Science and Embase, and specific journals on the subject matter that included Melanoma Research, Journal of Clinical Oncology, Oral Oncology, Head and Neck, International Journal of Oral and Maxillofacial Surgery, Journal of Cranio-maxillofacial Surgery and JAMA-Otolaryngology and Laryngoscope.

The search words used were: "oral", "mouth", "mucosal", "melanoma" and a combination of these terms. The searches were limited to humans and only written in the English language. The reference list of the selected studies and review articles was checked for relevant publications. In addition, the experts in the field of head

and neck and oral oncology were also consulted and relevant studies further identified.

Study selection

Two researchers (M.X.K and B.I) independently performed the search and stratification of eligible and ineligible studies. The results were analyzed and any disagreement or confusion was resolved by discussion and consensus. If still, they had some disagreements, other senior authors were consulted for an expert opinion.

Data collection process

The data of publications regarding patient characteristics, outcomes, interventions, and study design were independently searched by two researchers and collected in a table (MS Excel). One researcher extracted the necessary information and data into the table and the second researcher proofread the extracted data. In order to get some missing data in papers, four corresponding authors were contacted but only one of them responded and provided with the intended data. There were fourteen papers from the same centers and the same authors included in the final search. In total, seven publications overlapped the time range with a risk of inclusion of the same patients. As a result, seven publications that were bigger case series and had better outcome information were accepted for review.

Data items

All the information deemed necessary were extracted from the included studies in the data collection table. The elements of the table included:

1. General information about the study and patients' characteristics.
2. Information on intervention and its outcome measures.
3. Conclusion of the study and comments (Datasheet in appendix). We classified each site according to mucosa type, lining, masticatory, and specialized mucosa; the specific location in each group is shown in Table 1.

We made certain assumptions about missing or unclear information in this analysis, which we believe are inevitable in retrospective multicenter studies. These assumptions are as follows: 1) The anatomic location of melanoma; 2) The management of the disease; 3) The intervention and its outcome.

Study quality assessment/risk of bias across the studies:

Since there was no adequate quality assessment tool recommended in the literature, the methodological quality of identified studies was categorized using the following criteria:

- Case number:

Score 1: Studies that have 5 to 49 cases

Score 2: Studies that have 50 to 99 cases

Score 3: Studies that have more than 99 cases

- Outcome:

Score 0: Studies that do not have five-year survival ratio of oral melanoma cases

Score 1: Studies that have five-year survival ratio of oral melanoma cases

- Gender

Score 0: Studies that do not have gender information of oral melanoma cases

Table 1: Study quality assessment/risk of bias across the studies.

Papers	Y	Lining Mucosa							Masticatory Mucosa				Specialized Mucosa			Gender					
		FOM	AM	L/B	R	VT	NS	T	G	HP	NS	T	DT	T	NM	All	SP	L	F	M	OS
Yamada et al. [30]	2017	1		2				3	21	14		35		0		38			14	24	40%
Naganawa et al. [31]	2017							0	5	11		16	2	2		18		1	10	9	57.40%
Smith et al. [32]	2016		1	7	1		2	11	8	4	4	16	1	1	2	28	2		19	11	NA
Breik et al. [33]	2016			1				1	1	4		5		0		6			2	4	33.30%
Kumar et al. [34]	2015		2				2	4		4		4		0		8		1	3	6	NA
Wu et al. [20]	2014			12				12	116	124		240	2	2		254			99	155	30.50%
Sun et al. [9]	2012	2		5				7	34	7		41		0		48	3		15	36	20.70%
De-Andreda et al. [35]	2012			2				2	6	7	5	18		0	2	20			14	8	NA
Guevara-Canales et al. [36]	2012	1		3				4	38	46		84	5	5		93		4	51	46	NA
Shuman et al. [37]	2011				1			1	5	2		7		0		8					38%
Borst and Schwipper [38]	2011			5				5	5		17	22		0		27					NA
Mücke et al. [39]	2009	1		2				3	4	3		7		0		10			4	6	30%
Lourenço et al. [40]	2009						9	9			25	25		0	1	34			17	18	14.20%
Aguas et al. [14]	2009							0			10	10		0		10			5	5	42.80%
McLean et al. [41]	2008							0			8	8		0		8			1	7	37.50%
Bachar et al. [42]	2008			1				1	3	5		8	1	1		10					17%
Meleti et al. [43]	2007			1				1	2	9	1	12	1	1		14			9	5	30%
Chidzonga et al. [44]	2007		1	1				2	2	2	1	5		0		7			5	2	NA
Tanaka et al. [6]	2004							0	7	10	17	34	1	1		35			21	14	21.80%
Garzino-demo et al. [45]	2004							0	4		3	7	2	2	1	9			4	6	NA
NW. Yii et al. [46]	2003		3	1		1		5		10		10		0		15					NA
Rapidis et al. [47]	2003							0	3	2		5		0		5			3	2	0
Prasad et al. [48]	2003	2		5				7	29	15		44		0		51					35%
Umeda et al. [49]	2002			1				1	4	9		13		0		14			9	5	50%
Lopez-Graniel et al. [8]	1999			2				2	1	11		12	1	1		15			9	6	6.60%
Nandapalan et al. [50]	1998	3		4				7	13	26		39	2	2		48	4				NA
Pandey et al. [51]	1999							0	3	3		6		0		6					16.60%
Total		10	7	55	2	1	13	88	314	328	91	733	18	18	6	839			314	375	

Y: Year; T: Total; NS: Not specified or located more than one in the lining mucosa or in the masticatory mucosa; F: Female; M: Male; FOM: Floor of Mouth; AM: Alveolar Mucosa; L/B: Labial and Buccal mucosa; R: Retromolar area; VT: Ventral Tongue; G: Gingiva; HP: Hard palate; DT: Dorsal Tongue; NM: Not mentioned cases or more than one type of mucosa involved; SP: Soft Palate; L: Lip; OS: 5-years survival rate; NA: Not available

Score 1: Studies that have gender information of oral melanoma cases

- Stratification

Score 1: No clear information about all the oral melanoma cases' localization

Score 2: Clear information about all the oral melanoma cases' localization

- Study design

Score 0: No clear information about study design

Score 1: Retrospective studies

Score 2: Prospective studies

Studies that are categorized as grade 1 have a score of 2, 3, or 4. Grade 2 studies have a score of 5, 6, or 7. Grade 3 studies have a score of 8 or 9 (Table 2).

Statistical analysis

The reported outcome measures, study designs, and interventions

Table 2: Quality assessment of studies.

Papers	Year	Case number	Outcome	Gender	Stratification	Study design	Total Score	Grade
Yamada et al. [30]	2017	1	1	1	2	1	6	2
Naganawa et al. [31]	2017	1	1	1	2	1	6	2
Smith et al. [32]	2016	1	0	1	1	1	4	1
Breik et al. [33]	2016	1	1	1	2	1	6	2
Kumar et al. [34]	2015	1	0	1	2	1	5	2
Wu et al. [20]	2014	3	1	1	2	1	8	3
Sun et al. [9]	2012	1	1	1	2	1	6	2
De-Andreda et al. [35]	2012	1	0	1	1	1	4	1
Guevara-Canales et al. [36]	2012	2	0	1	2	1	6	2
Shuman et al. [37]	2011	1	1	0	2	1	5	2
Borst and Schwipper [38]	2011	1	0	0	1	1	3	1
Mücke et al. [39]	2009	1	1	1	2	1	6	2
Lourenço et al. [40]	2009	1	1	1	1	1	5	2
Aguas et al. [14]	2009	1	1	1	1	1	5	2
McLean. et al. [41]	2008	1	1	1	1	1	5	2
Bachar et al. [42]	2008	1	1	0	2	1	5	2
Meleti et al. [43]	2007	1	1	1	1	1	5	2
Chidzonga et al. [44]	2007	1	0	1	1	1	4	1
Tanaka et al. [6]	2004	1	1	1	1	1	5	2
Garzino-demo et al. [45]	2004	1	0	1	1	0	3	1
Yii et al. [46]	2003	1	0	0	2	1	4	1
Rapidis et al. [47]	2003	1	1	1	2	1	6	2
Prasad et al. [48]	2003	2	1	0	2	1	6	2
Umeda et al. [49]	2002	1	1	1	2	1	6	2
Lopez-Graniel et al. [8]	1999	1	1	1	2	1	6	2
Nandapalan et al. [52]	1998	1	0	0	2	1	4	1
Pandey et al. [51]	1999	1	1	0	2	1	5	2

varied significantly according to each study. Therefore, we focused on the results, distribution and demographic data of the studies rather than meta-analysis. Outcome measures were undertaken and the pooled estimates of the survival rate were calculated.

Results

Study selection

We identified 3,394 studies during the initial literature search. A total of 1,769 remained for consideration after duplicate removal. The titles and abstracts of these studies were screened according to the inclusion and exclusion criteria, and 1,499 studies were eliminated because of excluded records. The remaining 270 full-text articles were reviewed completely. Seven articles that were from the same centers were excluded. One article was also excluded that had more than 15% cases where the localization of the tumor of patients was not mentioned. A total of 27 papers with a total of 839 patients met the inclusion criteria and were included in the analysis.

Study characteristics

The gender determination was done for 689 cases with 1.2 male/female ratio. Study and patient characteristics are reported in Table 1. The number of patients enrolled in each study ranged from 5 to 254.

The majority of the POMM cases occurred at masticatory mucosa

(87%). The hard palate was the most common area followed by the gingiva. The lining mucosa (11%) was the second common mucosa type with labial-buccal areas being the most affected site. The specialized mucosa (2%) was the rarest mucosa type.

The five-year survival rate was mentioned in 18 studies and the rate differed from 0% to 57.4%. In addition, Wu et al. [20] reported 5-year survival rate of palate, maxillary gingiva and mandibular gingiva as 30%, 26% and 25% respectively.

Discussion

Summary of evidence

In this systematic review, we scanned and pooled 839 POMM cases and calculated the distribution as 87% in masticatory mucosa, 11% lining mucosa, and 2% specialized mucosa, respectively. We do not have enough information about location-specific or mucosal type-specific gender of the cases. Thus, we concluded that the masticatory mucosa, i.e., hard palate, and gingival mucosa are the main areas attacked by POMM. In the oral cavity, where tongue and floor of mouth were mostly attacked by Oral Squamous Cell Carcinoma (OSCC), soft palate and retromolar area were often involved by malignancy originating from the minor salivary gland. Such a pattern of cancer distribution is very unique and is of great ineluctability when investigating etiopathology, classification, treatment, and outcome of

POMM. It may also be an important clue for detecting POMM early or prophylactic excision of the suspicious lesion.

So far, the etiopathology of POMM remained unknown. The unique distribution of POMM indicates the low possibility of similar risk factors with OSCC, where tobacco, alcohol misuse, betel quid, immunosuppression, and drinking mate are some of the risk factors described. Further, this regional incidence of POMM is not parallel with the regional differences in epithelial melanocyte activity [22]. Therefore, the features of different tissues from different mucosa may play an important role in the tumorigenesis of POMM. Masticatory mucosa has 1.5 to 2.5 times more connective tissue papillae/mm² compared to lining mucosa which gives it more rigidity [23]. Junction of lamina propria to underlying tissues is also different, i.e., in anterior hard palate and gingiva, lamina propria attaches directly to periosteum while in lining mucosa it is attached to the submucosa of connective tissue [24]. The lining mucosa in the basal layer expresses cytokeratin 19 in a higher amount than masticatory mucosa [25]. Specialized mucosa is located at the dorsum of the tongue and composed of the keratinized and nonkeratinized epithelium with filiform, fungi form and circumvallate papillae [24].

The variations in the features of mucosal tissue contribute to the different mucosal functions. Lining mucosa is more capable of distension with reduced capacity to bear frictional forces than masticatory mucosa. The permeability of lining mucosa is greater than masticatory mucosa and skin [26]. The effect of different histological features on melanoma tumorigenesis is not well known. However, there are huge differences in surgical resection between masticatory mucosal and other oral mucosal POMM.

Wide resection is considered as the primary treatment for early disease and systemic is recommended in later stages [27]. The primary aim of POMM is to achieve negative margins during surgery. Generally, resection margins are considered as 1.5 cm to 2 cm of visible or/and palpable normal mucosa for an adequate margin. This safety margin refers to the tumors totally situated in soft tissues. Masticatory mucosa is the layer of soft tissue thinner than 0.5 cm with overlying bony tissue. There is still a lack of information about the safe margins of bony tissue overlaid by cancer infiltrating soft tissue. The POMM cases that are invaded to bone tissues are viewed as late-stage tumors with poor prognosis. Thus, we recommended that POMM should be classified as masticatory and non-masticatory.

We assumed that masticatory and non-masticatory POMM may have different prognosis. However, in this systemic review, the limited information about POMM cases did not enable us to have a conclusion about this assumption. In this review, one study mentioned the five-year survival rates of gingiva and palate for 240 cases. In maxilla 5-year survival rates of POMM specified for masticatory mucosa very close in each localization. This information supports our theory. However, to have a conclusion there is very few studies. Prognosis of the masticatory mucosa for both jaws has different 5-year survival rates. If five-year survival rate is considered, the difference between palate and gingiva is bigger for two jaws (palate 36% to 49%, gingiva 22% to 37%) [28,29]. Prognosis of OMM is also dependent on other factors, so to make a final decision about this theory, the location of the tumor should also be considered.

In the literature, there is limited information about the change in the survival rate of OMM with mucosa type. It was reported that specialized mucosa has a worse prognosis. However, we have limited

information to make a conclusion. Owing to the rarity of POMM, the etiology and nature of this disease are not studied extensively. We believe further studies should be conducted considering the histology of oral mucosa.

Limitations

Our study has several limitations. The majority of the articles in this study were grade 2 according to our quality assessment that is shown in Table 2. Analyses did not mention details about the survival rate and localization of the tumor. In order to have a better understanding of POMM, we suggest reporting the cases with clear localization information and five-year survival rates in each mucosa type.

Conclusion

The survival rate of POMM can be influenced by each mucosa type in the oral cavity. However, only a few studies have sufficient information to draw a conclusion. The etiology and nature of this disease have not been extensively studied. We believe further studies are warranted considering the histology of oral mucosa with the promise of clear outcome information.

References

- Meleti M, Leemans Cr, Mooi WJ, Vescovi P, van der Waal I. Oral malignant melanoma: A review of the literature. *Oral Oncol.* 2007;43(2):116-21.
- Sortino-Rachou AM, Cancela Mde C, Voti L, Curado MP. Primary oral melanoma: Population-based incidence. *Oral Oncol.* 2009;45(3):254-8.
- Meleti M, Leemans CR, Mooi WJ, van der Waal I. Oral malignant melanoma: The Amsterdam experience. *J Oral Maxillofac Surg.* 2007;65(11):2181-6.
- Hicks MJ, Flaitz CM. Oral mucosal melanoma: Epidemiology and pathobiology. *Oral Oncol.* 2000;36(2):152-69.
- McLean N, Tighiouart M, Muller S. Primary mucosal melanoma of the head and neck. Comparison of clinical presentation and histopathologic features of oral and sinonasal melanoma. *Oral Oncol.* 2008;44(11):1039-46.
- Tanaka N, Mimura M, Ogi K, Amagasa T. Primary malignant melanoma of the oral cavity: Assessment of outcome from the clinical records of 35 patients. *Int J Oral Maxillofac Surg.* 2004;33(8):761-5.
- Song H, Wu Y, Ren G, Guo W, Wang L. Prognostic factors of oral mucosal melanoma: Histopathological analysis in a retrospective cohort of 82 cases. *Histopathology.* 2015;67(4):548-56.
- Lopez-Graniell CM, Ochoa-Carrillo FJ, Meneses-Garcia A. Malignant melanoma of the oral cavity: Diagnosis and treatment experience in a Mexican population. *Oral Oncol.* 1999;35(4):425-30.
- Sun CZ, Chen YF, Jiang YE, Hu ZD, Yang AK, Song M. Treatment and prognosis of oral mucosal melanoma. *Oral Oncol.* 2012;48(7):647-52.
- Gu GM, Epstein JB, Morton TH. Intraoral melanoma: Longterm follow-up and implication for dental clinicians. A case report and literature review. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2003;96(4):404-13.
- Chang AE, Karnell LH, Menck HR. The national cancer data base report on cutaneous and noncutaneous melanoma: A summary of 84,836 cases from the past decade. The American College of Surgeons Commission on Cancer and the American Cancer Society. *Cancer.* 1998;83(8):1664-78.
- Umeda M, Shimada K. Primary malignant melanoma of the oral cavity—its histological classification and treatment. *Br J Oral Maxillofac Surg.* 1994;32(1):39-47.
- Lourenco SV, Fernandes JD, Hsieh R, Coutinho-Camillo CM, Bologna S,

- Sangueza M, et al. Head and neck mucosal melanoma: A review. *Am J Dermatopathol*. 2014;36(7):578-87.
14. Aguas SC, Quarracino MC, Lence AN, Lanfranchi-Tizeira HE. Primary melanoma of the oral cavity: Ten cases and review of 177 cases from literature. *Med Oral Patol Oral Cir Bucal*. 2009;14(6):E265-71.
 15. Chang AE, Karnell LH, Menck HR. The national cancer data base report on cutaneous and noncutaneous melanoma: A summary of 84,836 cases from the past decade. The American College of Surgeons Commission on Cancer and the American Cancer Society. *Cancer*. 1998;83(8):1664-78.
 16. Hicks MJ, Flaitz CM. Oral mucosal melanoma: Epidemiology and pathobiology. *Oral Oncol*. 2000;36(2):152-69.
 17. Wushou A, Zhao YJ. The management and site-specific prognostic factors of primary oral mucosal malignant melanoma. *J Craniofac Surg*. 2015;26(2):430-4.
 18. Rambhia PH, Stojanov IJ, Arbesman J. Predominance of oral mucosal melanoma in areas of high mechanical stress. *J Am Acad Dermatol*. 2019;80(4):1133-35.
 19. Jethanamest D, Vila PM, Sikora AG, Morris LG. Predictors of survival in mucosal melanoma of the head and neck. *Ann Surg Oncol*. 2011;18(10):2748-56.
 20. Wu Y, Zhong Y, Li C, Song H, Guo W, Ren G. Neck dissection for oral mucosal melanoma: Caution of nodular lesion. *Oral Oncol*. 2014;50(4):319-24.
 21. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *PLoS Med*. 2009;6(7):e1000100.
 22. Barrett AW, Beynon AD. A histochemical study on the distribution of melanin in human oral epithelium at six regional sites. *Arch Oral Biol*. 1991;36(10):771-4.
 23. Schroeder HE. Differentiation of human oral stratified epithelia. Switzerland: Karger Publishers; 1981.
 24. Winning TA, Townsend GC. Oral mucosal embryology and histology. *Clin Dermatol*. 2000;18(5):499-511.
 25. Su L, Morgan PR, Lane EB. Keratin 14 and 19 expression in normal, dysplastic and malignant oral epithelia. A study using in situ hybridization and immunohistochemistry. *J Oral Pathol Med*. 1996;25(6):293-301.
 26. Lesch CA, Squier CA, Cruchley A, Williams DM, Speight P. The permeability of human oral mucosa and skin to water. *J Dent Res*. 1989;68(9):1345-9.
 27. Pfister DG, Ang KK, Brizel DM, Burtness BA, Busse PM, Caudell JJ, et al. Head and neck cancers, version 2.2013. Featured updates to the NCCN guidelines. *J Natl Compr Canc Netw*. 2013;11(8):917-23.
 28. Wang X, Wu HM, Ren GX, Tang J, Guo W. Primary oral mucosal melanoma: Advocate a wait-and-see policy in the clinically N0 patient. *J Oral Maxillofac Surg*. 2012;70(5):1192-8.
 29. Wu Y, Wang L, Ma X, Guo W, Ren G. The existence of early stage oral mucosal melanoma: A 10-year retrospective analysis of 170 patients in a single institute. *Oral Oncol*. 2018;87:70-6.
 30. Yamada SI, Kurita H, Kamata T, Kirita T, Ueda M, Yamashita T, et al. Clinical investigation of 38 cases of oral mucosal melanoma: A multicentre retrospective analysis in Japan. *Australas J Dermatol*. 2017;58(4):e223-7.
 31. Naganawa K, Koto M, Takagi R, Hasegawa A, Ikawa H, Shimozato K, et al. Long-term outcomes after carbon-ion radiotherapy for oral mucosal malignant melanoma. *J Radiat Res*. 2017;58(4):517-22.
 32. Smith MH, Bhattacharyya I, Cohen DM, Islam NM, Fitzpatrick SG, Montague LJ, et al. Melanoma of the oral cavity: An analysis of 46 new cases with emphasis on clinical and histopathologic characteristics. *Head Neck Pathol*. 2016;10(3):298-305.
 33. Breik O, Sim F, Wong T, Natri A, Iseli TA, Wiesenfeld D. Survival outcomes of mucosal melanoma in the head and neck: Case series and review of current treatment guidelines. *J Oral Maxillofac Surg*. 2016;74(9):1859-71.
 34. Kumar V, Vishnoi JR, Kori CG, Gupta S, Misra S, Akhtar N. Primary malignant melanoma of oral cavity: A tertiary care center experience. *Natl J Maxillofac Surg*. 2015;6(2):167-71.
 35. de-Andrade BA, Toral-Rizo VH, Leon JE, Contreras E, Carlos R, Delgado-Azanero W, et al. Primary oral melanoma: A histopathological and immunohistochemical study of 22 cases of Latin America. *Med Oral Patol Oral Cir Bucal*. 2012;17(3):e383-8.
 36. Guevara-Canales JO, Gutierrez-Morales MM, Sacsquispe-Contreras SJ, Sanchez-Lihon J, Morales-Vadillo R. Malignant melanoma of the oral cavity. Review of the literature and experience in a Peruvian Population. *Med Oral Patol Oral Cir Bucal*. 2012;17(2):e206-11.
 37. Shuman AG, Light E, Olsen SH, Pynnonen MA, Taylor JM, Johnson TM, et al. Mucosal melanoma of the head and neck: Predictors of prognosis. *Arch Otolaryngol Head Neck Surg*. 2011;137(4):331-7.
 38. Borst A, Schwippen V. Primary mucosal malignant melanoma of the head and neck. *Facial Plast Surg*. 2011;27(3):237-42.
 39. Muecke T, Hoelzle F, Kesting MR, Loeffelbein DJ, Robitzky LK, Hohlweg-Majert B, et al. Tumor size and depth in primary malignant melanoma in the oral cavity influences survival. *J Oral Maxillofac Surg*. 2009;67(7):1409-15.
 40. Lourenco SV, A MS, Sotto MN, Bologna SB, Giacomo TB, Buim ME, et al. Primary oral mucosal melanoma: A series of 35 new cases from South America. *Am J Dermatopathol*. 2009;31(4):323-30.
 41. McLean N, Tighiouart M, Muller S. Primary mucosal melanoma of the head and neck. Comparison of clinical presentation and histopathologic features of oral and sinonasal melanoma. *Oral Oncol*. 2008;44(11):1039-46.
 42. Bachar G, Loh KS, O'Sullivan B, Goldstein D, Wood S, Brown D, et al. Mucosal melanomas of the head and neck: Experience of the Princess Margaret Hospital. *Head Neck*. 2008;30(10):1325-31.
 43. Meleti M, Leemans CR, Mooi WJ, van der Waal I. Oral malignant melanoma: The amsterdam experience. *J Oral Maxillofac Surg*. 2007;65(11):2181-6.
 44. Chidzonga MM, Mahomva L, Marimo C, Makunike-Mutasa R. Primary malignant melanoma of the oral mucosa. *J Oral Maxillofac Surg*. 2007;65(6):1117-20.
 45. Garzino-Demo P, Fasolis M, Maggiore GM, Pagano M, Berrone S. Oral mucosal melanoma: A series of case reports. *J Craniomaxillofac Surg*. 2004;32(4):251-7.
 46. Yii NW, Eisen T, Nicolson M, A'Hern R, Rhys-Evans P, Archer D, et al. Mucosal malignant melanoma of the head and neck: The Marsden experience over half a century. *Clin Oncol (R Coll Radiol)*. 2003;15(4):199-204.
 47. Rapidis AD, Apostolidis C, Vilos G, Valsamis S. Primary malignant melanoma of the oral mucosa. *J Oral Maxillofac Surg*. 2003;61(10):1132-9.
 48. Prasad ML, Busam KJ, Patel SG, Hoshaw-Woodard S, Shah JP, Huvos AG. Clinicopathologic differences in malignant melanoma arising in oral squamous and sinonasal respiratory mucosa of the upper aerodigestive tract. *Arch Pathol Lab Med*. 2003;127(8):997-1002.
 49. Umeda M, Komatsubara H, Shibuya Y, Yokoo S, Komori T. Premalignant melanocytic dysplasia and malignant melanoma of the oral mucosa. *Oral Oncol*. 2002;38(7):714-22.

50. Nandapalan V, Roland NJ, Helliwell TR, Williams EM, Hamilton JW, Jones AS. Mucosal melanoma of the head and neck. *Clin Otolaryngol Allied Sci.* 1998;23(2):107-16.

51. Pandey M, Abraham EK, Mathew A, Ahamed IM. Primary malignant melanoma of the upper aero-digestive tract. *Int J Oral Maxillofac Surg.* 1999;28(1):45-9.