مجلة جامعة دمشق للعلوم الطبية المجلد: (40) العدد: 1 (2024) الصفحات: (75 – 90)

Oral Malignant Melanoma: A Review of the Literature and case report of Hard Palate Malignant Melanoma

Dr. Rania Othman[1], Dr. Basem Alarsan Alyaseen[2]

[1] (DDS,MSc , PhD),Department of Oral Pathology , Faculty of Dentistry, AlSham Private University. r.a.fod@aspu.edu.sy
[2] (DDS,MSc , PhD),Department of Oral Surgery , Faculty of Dentistry, AlSham Private University.

Abstract:

Oral malignant melanoma (OMM) is a rare malignant lesion of the oral mucosa. Most cases arise on the palate or gingiva. We made A Review of the Literature focused on relevant molecular and clinical advancements for the oral melanoma to describe the updated knowledge relating to main diagnostic, clinical, and therapeutic implications .And report a case of malignant melanoma of the hard palate extending to the buccal gingiva in 59-year-old Female patient, Final diagnosis was done based on clinical features and H&E and immunohistochemistry (for human melanoma black (HMB)-45 and S-100 protein)for incisional biopsy. Maxillectomy and bilateral neck lymph nodes curettage was done, after surgery radiotherapy was administered 38.4 Gray (32 doses – 1.2 Rad per dose -twice a week) over a period of 3 months and supportive immunotherapy was done also and there were no signs or symptoms to any recurrence after 12 months follow up period.

Careful clinical examination of patients with unusual focal pigmented lesions in the oral cavity and early detection by histopathological means of pigmented growth and periodic follow-up of patients are essential for a better prognosis of this lethal entity.

Keywords: Oral Malignant Melanoma, Hard Palate, (Hmb)-45.

Submitted: 28/2/2023 **Accepted: 31/5/2023**

ISSN: 2789-7214 (online)
http://journal.damascusuniversity.edu.sy

الورم الصباغي الفموي الخبيث: مراجعة الأدب الطبي وتقرير لحالة ورم صباغي خبيث في قبة الحنك الصلبة

د. رانيه عثمان[1]، د. باسم العرسان الياسين[2]

[1] قسم النسج والتشريح المرضي الفموي، كلية طب الأسنان، جامعة الشام الخاصّة.
[2] قسم جراحة الوجه والفم والفكين، كلية طب الأسنان، جامعة الشام الخاصّة.

الملخص:

الورم الصباغي الفموي الخبيث ورم نادر الحدوث في المخاطية الفموية. تنشأ معظم الحالات في قبة الحنك أو اللّثة. في هذا البحث تمّ إجراء مراجعة للأدب الطبي ركزت على التطورات الجزيئية والسريرية المرتبطة بتشخيص ومعالجة الورم الصباغي الفموي. كما تمّ تسجيل حالة لورم صباغي خبيث في قبة الحنك ممتد لمنطقة اللّثة الخديّة عند مريضة بعمر 59 سنة، تمّ إجراء التشخيص النهائي بناء على الملامح السريرية والخزعة الاستقصائية التي تمّ تلوينها بالتلوين التقليدي الهيماتوكسلين & ايوزين والتلوين المناعي الكيميا نسيجي(45-(HMB)-S-100). تم استئصال الفك العلوي كاملاً وتجريف العقد اللمفاوية في العنق وتُبعت بمعالجة شعاعية بمعدل38.4 غراي (32 جرعة – 1.2 راد لكل جرعة – مرتين بالاسبوع خلال فترة 3 أشهر)، كما أعطيت المريضة معالجة مناعيّة داعمة. وتمّت مراقبة الحالة لمدّة 12 شهر لم تظهر فيها أيّ أعراض للنكس.

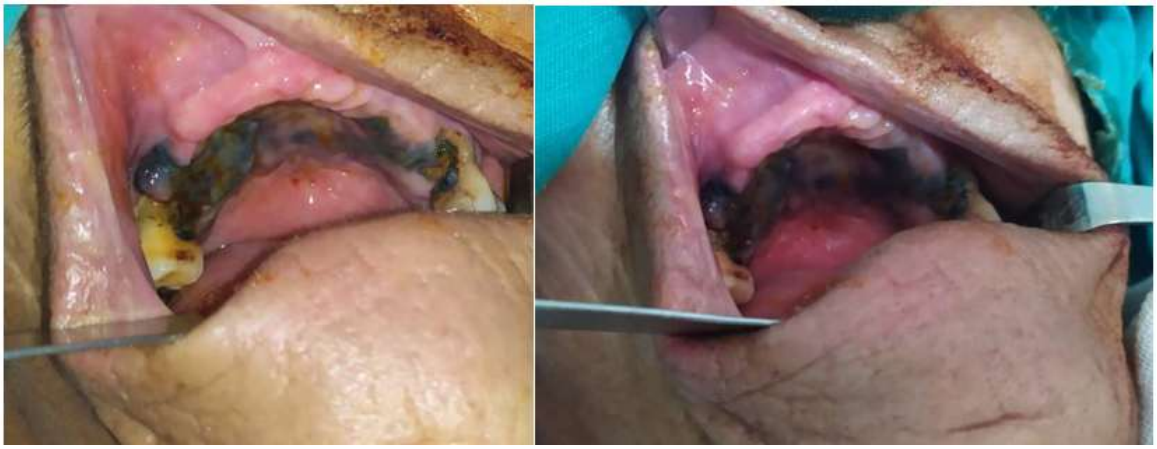
إنّ الفحص السريري الدقيق للمرضى الذين لديهم آفات مصطبغة موضعيّة في الحفرة الفموية واستخدام الطرق المناعيّة النسيجيّة للآفات المصطبغة والمتابعة طويلة الأمد للمرضى هي عوامل أساسيّة لتحسين إنذار الورم الذي قد يكون مميت.

الكلمات المفتاحية: الورم الصباغي الفموي الخبيث، قبة الحنك، 45-(HMB).

CASE Presentation: A 59-year-old Female patient reported with a chief complaint of swelling in the posterior region of hard palate with black pigmentation diffuse on palatal mucosa.

The patient observed swelling and bleeding during brushing. In intraoral clinical examination, a solitary, sessile, and pigmented overgrowth mass was present on the right posterior hard palate with irregular periphery extending to the buccal gingiva adjacent first and second molar tooth and extended to the left part of the hard palate.(Figure 1). Extraoral examination revealed no significant findings and hematological value was normal. Comparing the patient's complaint, with the history and clinical examination a differential diagnosis of melanosis, mucosal nevus, melanotic macule and melanoacanthoma was attained. An incisional biopsy was taken and sent for histopathological diagnosis. The hematoxylin- and eosin-stained sections showed overlying keratinized stratified squamous epithelium showing acanthosis and ulceration with tumoral invasion composed of sheets and masses of large proliferated atypical melanocytes. These malignant cells show significant cellular and nuclear pleomorphism, hyperchromatic nuclei, prominent nucleoli and increased mitotic activity was evident. Cells showing intra-cytoplasmic melanin pigmentation were few in number (Figure 2-a). Immunohistochemical studies exhibited that the tumor cells were positive for human melanoma black (HMB)-45 and S-100 protein (Figure 2-b, 2-c).Therefore, suspecting a malignant melanoma. CT images showed that the tumour extended to hard palate bone superficially. Maxillectomy and bilateral neck lymph nodes curettage was done (Figure 3, 4). The excisional biopsy was consist of maxillary bone measuring 6*5 cm containing 4 teeth present firm mass of 6 cm appeared white with brownish-black area, and had irregular borders. Surgical maxillofacial prosthetic was made and fitted during the surgery (Figure 5) and replaced by another one (with Soft Edges) 21 days after the surgical treatment.

After surgery radiotherapy was administered 38.4 Gray (32 doses – 1.2 Rad per dose -twice a week) over a period of 3 months followed by 5 doses (2 Rad per dose - with an interval of two days) after 3 months. And supportive immunotherapy (pembrolizumab 25mg/ml) was done also. The patient was followed up for 6, 12 months, and there were no signs or symptoms to any recurrence (Figure 6).



(Figure 1): pigmented overgrowth mass was present on the right posterior hard palate.

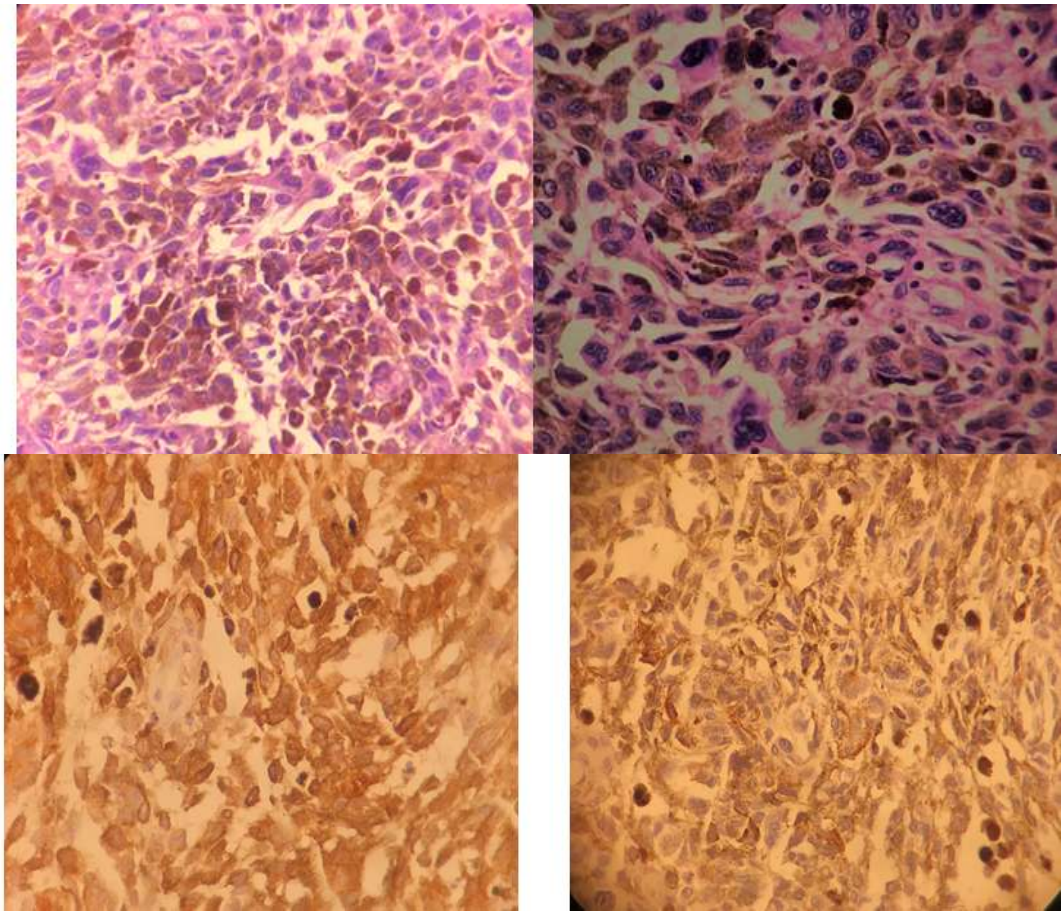


Figure (2): ;(a) Histologic sections showing spindle and plump cells with round, ovoid, or elongated nuclei and intracytoplasmic melanin pigmentation (4× and 40×). (b) Immunohistochemical staining for (HMB)-45, (c) Immunohistochemical staining for S-100 sections showed strongly positive

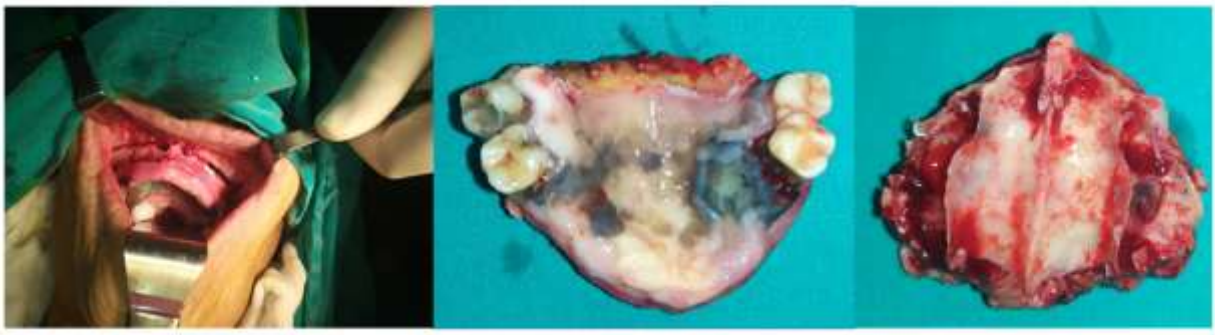


Figure (3): Resection of tumor mass and involved bone.

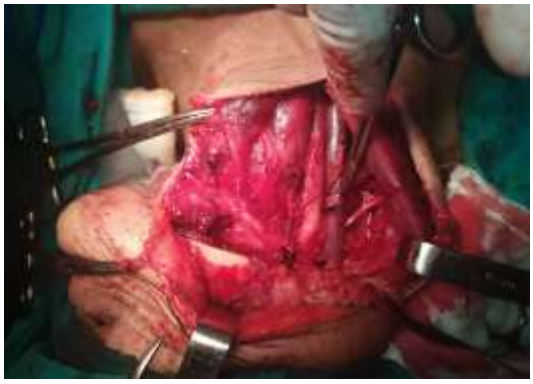
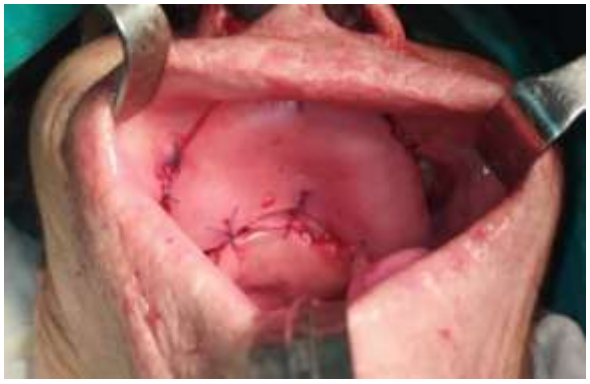
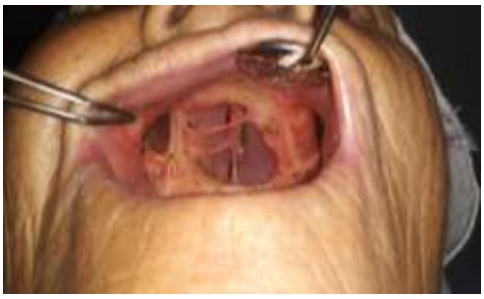


Figure (4): bilateral curettage of neck metastatic lymph nodes



Figure(5): The site of the tumor immediately after surgery- Surgical maxillofacial



Figure(7): 6 months after surgery

Discussion:

The oral cavity is a common site for pigmented lesions, most of them benign ,Oral melanoma is extremely rare and accounts for less than 1% of all melanomas (Ardekian *et al.* 2000) (Athey, Sutton, and Tekeli 2006) and 1.6% of all head and neck malignancies.

Melanoma arising from the neural crest cells. During embryologic development, melanocytes migrate from the neural crest into the epithelial lining of the skin and in the developed skin, they reside primarily in the basal epithelial layer. Because the oral cavity develops from an ectodermal depression or invagination, the epithelial lining of the oral mucosa, similar to skin, normally contains melanocytes in its basal layer (Ardekian *et al*. 2000) which can evolve into melanoma as in the skin.

Primary OMM is a rare neoplasm of unknown etiology. The possible risk factors can be exposure to sunlight, betel quid chewing, cigarette smoking, alcohol consumption, denture irritation (Vinuta *et al.* 2014).Primary oral melanomas are believed to arise either de novo (30% of cases) or from nevi and preexisting pigmented areas (Shah and Jain 2006).

In our case, all histories were negative. Our case arose de novo as the patient has a negative history of naevus. Oral mucosal melanoma is predominantly localized in the region of the hard palate and maxillary alveolus (Chugh *et al.* 2021) (Neville *et al.* 2015). In our case the patient had pigmented overgrowth mass was present on the right posterior hard palate with irregular periphery extending to the buccal gingiva. The average age of patients with mucosal melanoma was range of 50–70 years(Singh, Zwane, and Shangase 2015) (Singh *et al.* 2019) (Wang *et al.* 2015) (Baderca *et al.* 2014) (Smith *et al.* 2016),with higher prevalence among men

(Pour 2008). The probable reason for the higher prevalence of OMM in males might be due to alcohol and tobacco consumption and smoking. Furthermore, studies should also focus on correlation between habits (smoking and alcohol consumption). OMM can occur at any age, the average being 54 years but is less common in people below 30 years,

In Our case Patient is female in 59 years, Late clinical manifestations, slow progression of the disease are the probable reasons for late diagnosis and high incidence of Oral malignant melanoma in advancing age (Mohan *et al.* 2013) (Padhye and D'souza 2011).Surgical excision is the mainstay of treatment for OMM (Naganawa *et al.* 2017). The prognosis for OMM is extremely poor with the 5-year appears to be related to difficulty in achieving wide resection and a tendency for early metastasis. Younger patients have better survival than older patients do, and patients with amelanotic OMM have a particularly poor prognosis. Maxillectomy and bilateral neck lymph nodes curettage was done in our case, as Mohan et al recommended For the palate, maxillectomy with 3–5 cm margins (Mohan *et al.* 2013).Radiotherapy was administered 38.4 Gray (32 doses – 1.2 Rad per dose -twice a week) over a period of 3 months , Even though melanoma is not very radiosensitive, patients in early melanomas have had good response to radiation therapy, and it is beneficial in cases with positive surgical margins or a strong likelihood of local or regional recurrence (Mohan et al. 2013) (Lee, Baek, et al. 2017).Supportive immunotherapy was done also. And the patient followed up for 6, 12 months without any recurrence.

Despite the rarity of the disease, melanoma is the most important pigmented lesion in the oral cavity because of its deadly nature and most, if not all, oral biopsies of pigmented lesions are aimed at excluding malignant melanoma. It is well known that early diagnosis and treatment of melanoma can reduce mortality rate. Age, gender, race, tumor site, stage of disease and treatment are different factors that influence the survival of Oral malignant melanoma patients.

Introduction:

Melanoma is a malignant tumor that arises from epidermal melanocytes. It is a highly aggressive tumor of melanin -producing cells called melanocytes derived from the neural crest cells in the basal layer of the epithelium(Singh, Zwane, and Shangase 2015) (Santeufemia *et al.* 2023) and is most commonly occurs on skin and rarely in the mucosal surfaces (Santeufemia *et al.* 2023) (Tas and Keskin 2013). Malignant melanoma was first described by Weber in 1859. It was recognized as a distinct clinical entity and named as "melanotic sarcoma" by Lucke in 1869 (Shakya, Ongole, and Sumanth 2009). According to the National Cancer Database Report on cutaneous and non-ecutaneous melanoma, 91.2% of all melanomas arise on the skin , mucosal (1.3%), Almost 25% of cutaneous melanomas arise in the head and neck area (Neville *et al.* 2016)

Mucosal melanomas are uncommon, presenting an aggressive clinical behavior much more than cutaneous and a poor prognosis (Santeufemia *et al.* 2023) (Romano et al. 2018) (Nenclares *et al.* 2020). Approximately 50% of all mucosal melanomas are located in the head and neck region (Santeufemia *et al.* 2023) (Breik *et al.* 2016) (de Paulo *et al.* 2015) (Adisa, Olawole, and Sigbeku 2012).

primary oral melanoma accounting for only 0.26% of all oral cavity cancers (Neville et al. 2016) and less than 1% of all melanomas (Singh, Zwane, and Shangase 2015) (de Paulo et al. 2015) (Mohan et al. 2013)In the fourth edition of the World Health Organization Classification of Tumors of the Head and Neck, oral and sinonasal mucosal melanomas are recognized as distinct entities. Oral malignant melanoma (OMM) is the second most common site of occurrence of mucosal melanoma in the head and neck (Williams 2017)

Etiological (Risk factors): Mucosal melanoma has been shown to be significantly different from cutaneous melanoma with regard to its pathogenesis and epidemiologic/clinical characteristics. However, it is documented that melanocytes migrate to both the ectodermal and endodermal mucosa in OMM.Mucosal melanoma is distinguished by the presence of distinct molecular features, most notably

DNA structural changes and mutation signatures (Newell *et al.* 2019) (Sharma 2012).Many genes are implicated in the development of melanoma, including CDKN2A (p16), CDK4 (chromosome 12q15), RB I, CDKN2A (p19), PTEN/MMAC I and ras. They play an important role in both sporadic and hereditarymelanomas (Sivapathasundharam 2016).The RAS/MEK/ERK mitogen-activated protein kinase (MAPK) and PI3K/AKT/PTEN/mTOR pathways were identified through genetic profiling of oral melanomas (Nenclares *et al.* 2020).These two pathways can be activated by activating C-KIT, which regulates the activity of MITF (microphthalmia-associated transcription factor), a transcription factor important for melanogenesis and melanocyte function. (Nenclares *et al.* 2020). Recent research has revealed the expression of BAP1 (BRCA1-associated protein, a BReast CAncer gene) in OMM patients (Song *et al.* 2017).few studies have reported that BRAF mutation/expression was involved in the pathogenesis of OMM (Schaefer, Satzger, and Gutzmer 2017).Recent study show that SF3B1 and KIT, have a higher mutation rate in oral melanoma (Nassar and Tan 2020).UV light appears to play a negligible role in mucosal melanoma carcinogenesis, according to genomic studies. Despite their suggested role as etiologic factors, there is no clear evidence to support the pathogenic role of chemical carcinogens or viruses (Zhou *et al.* 2019) (Elder *et al.* 2020) (Chacón *et al.* 2020).literature has reported that alcohol consumption, tobacco use, cigarette smoking and denture irritation may play a significant role in the occurrence of OMM (Mohan *et al.* 2013) (Ali *et al.* 2015).

OMM is believed to arise de novo from apparently normal mucosa(30% cases) (Gupta *et al.* 2013) or from pigmented nevi, pre-existing pigmented areas (Patel *et al.* 2018), Hutchinson's premalignant lentigo (Warszawik-Hendzel *et al.* 2014) (Sharma 2012) (Santeufemia *et al.* 2023).However, it needs to be mentioned that about one-third of melanomas have had a history of benign pigmented lesions for months and even years before malignant transformation (Patel *et al.* 2018) (Santeufemia *et al.* 2023).Most OMMs appear to arise de novo and are diagnosed at an advanced stage, with a minimum staging of stage III, according to National Comprehensive Cancer Network (NCCN) Guidelines and American Joint Committee on Cancer (AJCC). (Pfister *et al.* 2012; Edge and Compton 2010)

Clinical features: Oral malignant melanoma is considered to be a rare malignancy. It is highly aggressive, with the potential to metastasize and invade surrounding tissues. The early stages of OMM often manifest asymptomatically, which may contribute to its delayed detection, poor prognosis, and low survival rates.(Lee, Lee, *et al.* 2017) . Pain, bleeding and ulceration occur at advanced stages of Oral malignant melanoma (Mihajlovic *et al.* 2012). It is often described as a uniformly pigmented black or brown lesion. But sometimes several shades co-exist: black, brown, gray, pink and red. The lesions are irregular in outline. Sometimes, they are multiple. The elemental lesion may be a flat macula, a low elevated plaque or a soft nodule. These clinical aspects can be present at the same time (Williams 2017) (Garzino-Demo *et al.* 2004). Pigmented mucosal melanoma can be diagnosed clini¬cally following visual signs of melanoma (A-B-C-D-E): A-Asymmetry, B-Border irregularity, C-Color varia¬tion, D-Diameter (> 6mm) or Dark, and E-Evolving in size, shape, color or elevation of the lesion(Ohnishi *et al.* 2015).

In Other side Oral malignant melanoma classified into 5 types: I-pigmented nodular type, II-non-pigmented nodular type, III-pigmented macular type, IV-pigmented mixed type, and V-non-pigmented mixed type (Ohnishi *et al.* 2015) (Pour 2008). 10% of oral melanomas are nonpigmented called amelanotic melanoma and immunohistochemistry can be helpful to confirm the diagnosis of these cases (Williams 2017) (Chidzonga *et al.* 2007) Although lesions in the mouth usually are easily visualized, particularly if pigmented, most cases of OM are in advanced stages when diag¬nosed.The average age of patients with mucosal melanoma was range of 50–70 years(Singh, Zwane, and Shangase 2015) (Singh *et al.* 2019) (Wang *et al.* 2015) (Baderca *et al.* 2014) (Smith *et al.* 2016),with higher prevalence among men (Pour 2008) , the male to

female ratio of 1:0.78. (Singh *et al.* 2019). Sortino-Rachou *et al.* reported highest male (54.54%) and female (45.45%) prevalence (Sortino-Rachou *et al.* 2009), In contrast, Smith *et al.* (62.50%) (Smith *et al.* 2016)and Umeda *et al.* (66.66%) (Umeda *et al.* 2008) reported a high prevalence of OMM in women. Whereas in a some study sex predilection was not observed in OMM patients.(Lee, Lee, *et al.* 2017) (Kim *et al.* 2010). few studies showed the prevalence of OMM both in children as well as in young adults (Wu *et al.* 2014) (Smith *et al.* 2016) (Jing *et al.* 2015). Late clinical manifestations, slow progression of the disease and patients with the history of radiation or chemotherapy for other carcinomas are the probable reasons for late diagnosis and high incidence of OMM in advancing age (Mohan *et al.* 2013) (Padhye and D'souza 2011).The frequency of OMM was high among Indians, Africans, Americans, Japanese, Caucasians and Chinese due to increased melanin pigmentation in the oral mucosa (Lee, Lee, *et al*. 2017) (Wu *et al.* 2014). All oral mucosa sites can be affected by OMM.

Palate was the most common site with an overall prevalence of 32%–40% (Singh, Zwane, and Shangase 2015) (Williams 2017) (Singh *et al.* 2019) (Umeda *et al.* 2008) (Ahmadi-Motamayel, Falsafi, and Baghaei 2013),and maxillary gingiva (16%) (Williams 2017) (Pour 2008) (Ahmadi-Motamayel, Falsafi, and Baghaei 2013) (Jethanamest *et al.* 2011) (Santeufemia *et al.* 2023), other oral sites are mandible, tongue, buccal mucosa and upper and lower lip , floor of the mouth (Pour 2008).Few studies reported gingiva as the most commonly affected tumor site in OMM patients (Lee, Lee, *et al*. 2017) (Sun *et al.* 2012). It was reported that anterior regions of the mouth were extensively pigmented than the posterior regions; therefore, buccal/labial regions are intensely pigmented than the palatal/lingual surfaces(Feller *et al.* 2014).while Literature has reported that lip was the least possible site for the incidence of OMM (Jing *et al.* 2015) , The least incidence of melanoma in the lip region might be due to the absence of melanocytes (Jethanamest *et al.* 2011).Oral malignant melanoma has a higher tendency to metastasize to other underlying tissues distant metastasis which is supported by the intralesional blood vessels or lymphatics as compared to other malignancies of the oral cavity (Sharma 2012) (Shah, Huvos, and Strong 1977). Other than palate and gingiva, mandible, maxilla, tongue and buccal mucosa are the most prominent sites for metastatic melanoma (Elomrani *et al.* 2013). Metastases to regional lymph nodes and distant spread to bone are encountered in end-stage patients. Lymph nodes, central nervous system, lungs, and liver are also common regions for metastasis (Pour 2007) (Santeufemia *et al.* 2023).

Histological Features: In oral mucosa, melanocytes are located along the basal layer of the epithelium.Oral malignant melanoma characterized by the proliferation of atypical melanocytes at the epithelial-connective tissue interface, associated with upward migration into the epithelium and by invasion of the underlying connective tissues(Kumar *et al.* 2012).

These malignant cells show significant cellular and nuclear pleomorphism, hyperchromatic nuclei, prominent nucleoli and detectable mitotic activities (Pour 2008).It is formed by epi¬thelioid, spindle, plasmacytoid or a mixture of these cells arranged in solid,alveolar and pagetoid pattern(de-Andrade *et al.* 2012). Since histological aspect is nonpathognomonic, and 10% of the melanomas are amelanotic, the diagnosis becomes a heavy task.So Immunohistochemistry is strongly indicated. Melanocytes markers commonly used are protein S100, melan-A, tyrosinase, HMB45 (Williams 2017) (de Castro *et al.* 2017).S-100 and HMB-45 are more frequently expressed than Melan-A in primary oral melanomas and these markers are helpful to confirm the diagnosis(de-Andrade *et al.* 2012).PRAME (PReferentially expressed Antigen in MElanoma) have diagnostic and some prognostic utility in diagnosis of cutaneous and oral melanoma(Hovander *et al.* 2022).

Differential diagnosis: The diagnosis of OMM often remains difficult. The differential diagnoses should include benign, malignant and exogenous pigmented lesions(Sharma 2012). Differential diagnosis includes oral melanotic macule, smoking-associated melanosis, medication-induced melanosis (antimalarial drugs and minocycline), melanoplakia, pituitary-based Cushing's syndrome,

postinflammatory pigmentation, melanoacanthoma, melanocytic nevi of the oral mucosa, blue nevi, nevi of Spitz, Addison's disease, Peutz-Jeghers syndrome(Sharma 2012) (Gupta *et al.* 2013), amalgam tattoo, Kaposi's sarcoma, physiologic pigmentation, pigmentation related to the use of heavy metals, and many other conditions sharing some macroscopic characteristics (Gupta *et al.* 2013).

Treatment: Owing to low incidence rate and poor prognosis of Oral malignant melanoma The treatment of choice is surgical excision with safety margins (Naganawa *et al.* 2017) (Umeda *et al.* 2008).

The margins should be at least 1.5 cm for the lesion in head and neck melanoma(Lee, Lee, *et al.* 2017) (Umeda et al. 2008) or 2.5 cm for melanomas larger than 3 cm in diameter. (Lee, Lee, *et al.* 2017). Unfortunatelyelective neck dissections did not improve survival(Haimowitz *et al*. 2023). For the palate, maxillectomy with 3–5 cm margins is recommended (Mohan *et al.* 2013) .To meet this requirement, it is necessary to extend the excision to the soft palate, the tonsillar pillar, and into the pterygomaxillary space. But, the proximity of vital structures makes this objective difficult. No consensus exists so far (Umeda *et al.* 2008). Many patients with early-stage lesions are cured by surgery alone. However, adjuvant radiation therapy can be considered. (Sivapathasundharam 2016) (Lee, Lee, *et al.* 2017).Even though melanoma is not very radiosensitive, patients in early melanomas have had good response to radiation therapy, and it is beneficial in cases with positive surgical margins or a strong likelihood of local or regional recurrence (Mohan *et al.* 2013) (Lee, Baek, *et al.* 2017). Immunotherapy (with interferon-alpha) can be considered too. For patients with distant metastasis vemurafenib and ipilimumab are two novel treatments but agents such as high-dose interleukin-2, dacarbazine, imatinib and paclitaxel have also been tried. the recent developments in genotype directed and immunotherapy have led to prolonged survival of patients (Sivapathasundharam 2016) (Lee, Lee, *et al.* 2017). Recent data from mucosal melanoma show that combination immune therapy has a higher probability of response than chemotherapy. (Nenclares *et al.* 2020)

Targeted therapy: Identification of mutations or genetic alterations is critical because these could be potential therapeutic targets. In oral melanoma, a few cytogenetic and molecular genetic features have been shown to have a strong prognostic value. According to some studies, C-KIT mutation and a high Ki67 score are independent predictors of survival in patients with oral melanoma.(Nenclares *et al.* 2020).New research suggests that systemic adjuvant therapy with immune checkpoint inhibitors or targeted therapies may play a role after complete resection of high-risk (stages III and IV) melanoma, regardless of primary location (Nenclares *et al.* 2020).

In patients with chemotherapy-naive mucosal melanoma, the combination of anti-PD-1 and a VEGFR inhibitor (axitinib) demonstrated promising antitumor activity (Sheng *et al.* 2019).Furthermore, small-scale studies show that targeted therapy is effective against oral melanoma with c-KIT mutations, with a reasonable probability of response (Nenclares *et al.* 2020).

Prognosis: Melanoma is a major health problem. When discovered early and fully excised, melanoma is curable. However, once metastatic disease develops, treatment options are limited and survival is generally measured in months (Shakya, Ongole, and Sumanth 2009). OMM is an aggressive lesion, they have a poorer prognosis than cutaneous melanoma (Sivapathasundharam 2016).(Nisi *et al.* 2022).Anatomical site is prognostic indicator, which correlates significantly with the overall survival rate of OMM patients. Wang *et al* reported that the overall median survival rate among OMM patients with different tumor sites were 51, 40 and 43 months for gingiva, hard palate and other sites, respectively. The higher survival rate in gingiva-affected OMM patients might be due to its easy prognosis (Wang *et al.* 2015). Poor prognosis of melanoma is known fact. It is reported that 79% of the patients die within 5 years from the point of diagnosis(Shah and Vyas 2010). The overall 5-year survival rate is ~6.6%–40% (Naganawa *et al.* 2017) (Lee, Baek, *et al.* 2017).Hence, clinical tumor-node-metastasis staging in association with histopathological

microstaging is an advantageous factor in the prognosis of OM

Stage I: The presence of primary tumor (T N M)

Level I: Pure in situ melanoma with either absence of invasion or in situ melanoma with "microinvasion"

Level II: Involvement of the lamina propria

Level III: Invasion into the deep skeletal tissue (skeletal muscle, bone or cartilage).

Stage II: Metastasis of tumor to regional lymph nodes (T N M)

Stage III: Metastasis of tumor to distant sites (T N M). (Sivapathasundharam 2016)

In situ lesions of melanoma are curable completely by excision. Five years' survival rate holds good for 95% of the patients with lesions <1 mm thickness and without ulcerations. The survival rates for lesions with metastasis is very poor (Shah and Vyas 2010).

Patients with stage III melanoma (involvement of regional lymph nodes) have a 5-year survival of approximately 50% (Shakya, Ongole, and Sumanth 2009). lymph node involvement was associated with worse overall survival (Haimowitz *et al.* 2023).The development of new therapies, advances in surgical interventions, and the addition of individualized adjuvant treatment decisions , a more recent decade of diagnosis may have contributed to improving the 5-year survival rates over those of the previous several decades(Lee, Lee, *et al.* 2017). clinical staging at presentation has been affirmed as the most important predictive factor determining outcome (Williams 2017) (Shen *et al.* 2011).

Conclusion:Oral malignant melanoma is a rare tumor of the oral cavity it is renowned for its poor prognosis .So, any suspected melatonin lesion should undergo histological analysis to diagnose OMM in its early stages .Dentists should keep the possibility of malignant melanoma in mind during any differential diagnosis of a pigmented lesion. .OMM screenings in routine examinations may be beneficial in improving its prognosis.

References:

1. Adisa, AO, WO Olawole, and OF Sigbeku. 2012. 'Oral amelanotic melanoma', *Annals of Ibadan postgraduate medicine*, 10: 6-8.
2. Ahmadi-Motamayel, Fatemeh, Parisa Falsafi, and Fahimeh Baghaei. 2013. 'Report of a rare and aggressive case of oral malignant melanoma', *Oral and maxillofacial surgery*, 17: 47-51.
3. Ali, Elneel Ahmed Mohamed, Musadak Ali Karrar, Abeer Abdalla El-Siddig, and Azza Zulfu. 2015. 'Oral malignant melanoma: a rare case with unusual clinical presentation', *Pan African Medical Journal*, 22.
4. Ardekian, Leon, Daren J Rosen, Micha Peled, Adi Rachmiel, Eli E Machtei, Imad Abu el Naaj, and Dov Laufer. 2000. 'Primary gingival malignant melanoma. Report of 3 cases', *Journal of periodontology*, 71: 117-20.
5. Athey, Elizabeth Mary, David N Sutton, and Kamel M Tekeli. 2006. 'Malignant mucosal melanoma of the right maxillary sinus: a case report', *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology*, 102: e20-e22.
6. Baderca, Flavia, Dana Vincze, Nicolae Balica, and Caius Solovan. 2014. 'Mucosal melanomas in the elderly: challenging cases and review of the literature', *Clinical interventions in aging*, 9: 929.
7. Breik, Omar, Felix Sim, Tim Wong, Alf Nastri, Tim A Iseli, and David Wiesenfeld. 2016. 'Survival outcomes of mucosal melanoma in the head and neck: case series and review of current treatment guidelines', *Journal of Oral and Maxillofacial Surgery*, 74: 1859-71.
8. Chacón, Matías, Yanina Pfluger, Martín Angel, Federico Waisberg, and Diego Enrico. 2020. 'Uncommon subtypes of malignant melanomas: A review based on clinical and molecular perspectives', *Cancers*, 12: 2362.
9. Chidzonga, Midion Mapfumo, Leonard Mahomva, Clemence Marimo, and Rudo Makunike-Mutasa. 2007. 'Primary malignant melanoma of the oral mucosa', *Journal of Oral and Maxillofacial Surgery*, 65: 1117-20.
10. Chugh, Ankita, Yogesh Mittal, Shruti Khatana, Aditi Mishra, Shilajit Bhattacharya, and Jyotsna Nigam. 2021. 'Primary Oral Mucosal Melanoma: A Case Series', *Journal of Maxillofacial and Oral Surgery*: 1-7.
11. de-Andrade, Bruno A B, Víctor H Toral-Rizo, Jorge E León, Elisa Contreras, Román Carlos, Wilson Delgado-Azañero, Adalberto Mosqueda-Taylor, and Oslei P de-Almeida. 2012. 'Primary oral melanoma: a histopathological and immunohistochemical study of 22 cases of Latin America', *Medicina Oral, Patologia Oral y Cirugia Bucal*, 17: e383.
12. de Castro, Mayara Santos, Bruno Saulo de Assis Reis, Denismar Alves Nogueira, Marina Lara de Carli, João Adolfo Costa Hanemann, Alessandro Antônio Costa Pereira, Oslei Paes de Almeida, and Felipe Fornias Sperandio. 2017. 'Primary oral melanoma: A clinicopathologic review and case presentation', *Quintessence International*, 48.
13. de Paulo, Luiz Fernando Barbosa, João Paulo Silva Servato, Roberta Rezende Rosa, Maiolino Thomaz Fonseca Oliveira, Paulo Rogério de Faria, Sindeval José da Silva, Sergio Vitorino Cardoso, and Adriano Mota Loyola. 2015. 'Primary amelanotic mucosal melanoma of the oronasal region: report of two new cases and literature review', *Oral and maxillofacial surgery*, 19: 333-39.
14. Edge, Stephen B, and Carolyn C Compton. 2010. 'The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM', *Annals of surgical oncology*, 17: 1471-74.
15. Elder, David E, Boris C Bastian, Ian A Cree, Daniela Massi, and Richard A Scolyer. 2020. 'The 2018 World Health Organization classification of cutaneous, mucosal, and uveal melanoma: detailed analysis of 9 distinct subtypes defined by their evolutionary pathway', *Archives of pathology & laboratory medicine*, 144: 500-22.

16. Elomrani, F, H Mouzount, I Ouziane, R Khmamouch, A Boukir, M ElKabous, S Boutayeb, H Mrabti, B Elkhannoussi, and H Errihani. 2013. 'Melanoma of the oral cavity: About two cases and review of literature'.
17. Feller, Liviu, Aubrey Masilana, Razia AG Khammissa, Mario Altini, Yusuf Jadwat, and Johan Lemmer. 2014. 'Melanin: the biophysiology of oral melanocytes and physiological oral pigmentation', *Head & face medicine*, 10: 8.
18. Garzino-Demo, Paolo, Massimo Fasolis, Gian Marco La Terra Maggiore, Marco Pagano, and Sid Berrone. 2004. 'Oral mucosal melanoma: a series of case reports', *Journal of Cranio-Maxillofacial Surgery*, 32: 251-57.
19. Gupta, Manish, Manas Gupta, Avanti Aggarwal, Ravish Ahuja, Abhishek Pachauri, and Prince Kumar. 2013. 'Significance of early detection of oral malignant melanoma: some reasonable facts', *Clinical Cancer Investigation Journal*, 2: 178.
20. Haimowitz, Sean, David A Cohen, Aatin Dhanda, Kendyl Barron, Roman Povolotskiy, and Dylan Roden. 2023. 'Mucosal Melanoma of the Oral Cavity: What is the Role of Elective Neck Dissection?', *The Laryngoscope*, 133: 317-26.
21. Hovander, Daniel, Joshua Allen, Dolphine Oda, and Ata S Moshiri. 2022. 'PRAME immunohistochemistry is useful in the diagnosis of oral malignant melanoma', *Oral Oncology*, 124: 105500.
22. Jethanamest, Daniel, Peter M Vila, Andrew G Sikora, and Luc GT Morris. 2011. 'Predictors of survival in mucosal melanoma of the head and neck', *Annals of surgical oncology*, 18: 2748-56.
23. Jing, Guangping, Yunteng Wu, Hao Song, Guoxin Ren, Runxiang Wang, and Wei Guo. 2015. 'Primary malignant melanoma of the lip: A report of 48 cases', *Journal of Oral and Maxillofacial Surgery*, 73: 2232-40.
24. Kim, Hyo Song, Eun Kyoung Kim, Hyun Jung Jun, Sung Yong Oh, Keon Woo Park, Do Hyoung Lim, Soon Il Lee, Jung Han Kim, Kyoung Mee Kim, and Dae Ho Lee. 2010. 'Noncutaneous malignant melanoma: a prognostic model from a retrospective multicenter study', *Bmc Cancer*, 10: 167.
25. Kumar, Ajay, Ruchi Bindal, Devi C Shetty, and Harkanwal P Singh. 2012. 'Primary oral malignant melanoma: Clinicopathological series of four cases', *Dental Research Journal*, 9: 338.
26. Lee, GilJoon, Chung-Hwan Baek, Na Yeon Choi, and Man Ki Chung. 2017. 'The prognostic role of the surgical approach and adjuvant therapy in operable mucosal melanoma of the head and neck', *Clinical and experimental otorhinolaryngology*, 10: 97.
27. Lee, Robert J, Serena A Lee, Thomas Lin, Kevin K Lee, and Russell E Christensen. 2017. 'Determining the epidemiologic, outcome, and prognostic factors of oral malignant melanoma by using the Surveillance, Epidemiology, and End Results database', *The Journal of the American Dental Association*, 148: 288-97.
28. Mihajlovic, Marija, Slobodan Vlajkovic, Predrag Jovanovic, and Vladisav Stefanovic. 2012. 'Primary mucosal melanomas: a comprehensive review', *International journal of clinical and experimental pathology*, 5: 739.
29. Mohan, Muralee, Vihang Y Sukhadia, Deepak Pai, and Smitha Bhat. 2013. 'Oral malignant melanoma: systematic review of literature and report of two cases', *Oral surgery, oral medicine, oral pathology and oral radiology*, 116: e247-e54.
30. Naganawa, Kensuke, Masashi Koto, Ryo Takagi, Azusa Hasegawa, Hiroaki Ikawa, Kazuo Shimozato, Tadashi Kamada, Yoshitaka Okamoto, and Organizing Committee for the Working Group for Head-and-Neck Cancer. 2017. 'Long-term outcomes after carbon-ion radiotherapy for oral mucosal malignant melanoma', *Journal of radiation research*, 58: 517-22.

31. Nassar, Kelsey W, and Aik Choon Tan. 2020. "The mutational landscape of mucosal melanoma." In *Seminars in cancer biology*, 139-48. Elsevier.
32. Nenclares, Pablo, Derfel Ap Dafydd, Izhar Bagwan, Donna Begg, Cyrus Kerawala, Emma King, Ken Lingley, Vinidh Paleri, Gillian Paterson, and Miranda Payne. 2020. 'Head and neck mucosal melanoma: the United Kingdom national guidelines', *European Journal of Cancer*, 138: 11-18.
33. Neville, Brad W, Douglas D Damm, Carl M Allen, and Angela C Chi. 2015. *Oral and maxillofacial pathology* (Elsevier Health Sciences).
34. Neville, BW, DD Damm, AC Chi, and CM Allen. 2016. "Oral and maxillofacial pathology. Canada." In.: Elsevier Health Sciences.
35. Newell, Felicity, Yan Kong, James S Wilmott, Peter A Johansson, Peter M Ferguson, Chuanliang Cui, Zhongwu Li, Stephen H Kazakoff, Hazel Burke, and Tristan J Dodds. 2019. 'Whole-genome landscape of mucosal melanoma reveals diverse drivers and therapeutic targets', *Nature communications*, 10: 3163.
36. Nisi, Marco, Rossana Izzetti, Stefano Gennai, Angela Pucci, Chiara Lenzi, and Filippo Graziani. 2022. 'Oral Mucosal Melanoma', *Journal of Craniofacial Surgery*, 33: 830-34.
37. Ohnishi, Yuichi, Masahiro Watanabe, Tomoko Fujii, Noriko Sunada, Hitoshi Yoshimoto, Hirohito Kubo, Masahiro Wato, and Kenji Kakudo. 2015. 'A rare case of amelanotic malignant melanoma in the oral region: Clinical investigation and immunohistochemical study', *Oncology letters*, 10: 3761-64.
38. Padhye, Ashvini, and Jovita D'souza. 2011. 'Oral malignant melanoma: A silent killer?', *Journal of Indian Society of Periodontology*, 15: 425.
39. Patel, Paras B, John M Wright, David R Kang, and Yi-Shing Lisa Cheng. 2018. 'Longitudinal clinicopathologic data of the progression of oral mucosal melanoma—report of 2 cases and literature review', *Oral surgery, oral medicine, oral pathology and oral radiology*, 126: e21-e30.
40. Pfister, David G, Kie-Kian Ang, David M Brizel, Barbara Burtness, Anthony J Cmelak, A Dimitrios Colevas, Frank Dunphy, David W Eisele, Jill Gilbert, and Maura L Gillison. 2012. 'Mucosal melanoma of the head and neck', *Journal of the National Comprehensive Cancer Network*, 10: 320-38.
41. Pour, MS Hashemi. 2007. 'Malignant melanoma of the oral cavity', *Frontiers in Dentistry*: 44-51.
42. ———. 2008. 'Malignant melanoma of the oral cavity: a review of literature', *Indian Journal of Dental Research*, 19: 47.
43. Romano, Antonio, Giorgio Iaconetta, Antonio Pansini, Massimo Mascolo, Miriam Cieri, Vincenzo Abbate, Giovanni Salzano, Giovanni Dell'Aversana Orabona, and Luigi Califano. 2018. 'Sinonasal mucosal melanoma extended to nose bridge: a one-time reconstruction treatment report', *Oral and Maxillofacial Surgery Cases*, 4: 1-5.
44. Santeufemia, Davide Adriano, Giuseppe Palmieri, Gianmaria Miolo, Maria Colombino, Maria Grazia Doro, Laura Frogheri, Panagiotis Paliogiannis, Giampiero Capobianco, Massimo Madonia, and Antonio Cossu. 2023. 'Current Trends in Mucosal Melanomas: An Overview', *Cancers*, 15: 1356.
45. Schaefer, Tim, Imke Satzger, and Ralf Gutzmer. 2017. 'Clinics, prognosis and new therapeutic options in patients with mucosal melanoma: A retrospective analysis of 75 patients', *Medicine*, 96.
46. Shah, Hetal, and Zankhana Vyas. 2010. 'Malignant melanoma: A case report', *Journal of Advanced Oral Research*, 1: 59-62.
47. Shah, J, and M Jain. 2006. 'Malignant melanoma of the oral cavity: Report of two cases', *Journal of Oral and Maxillofacial Pathology*, 10: 24.
48. Shah, Jatin P, Andrew G Huvos, and Elliot W Strong. 1977. 'Mucosal melanomas of the head and neck', *The American Journal of Surgery*, 134: 531-35.

49. Shakya, Shrijana, Ravikiran Ongole, and KN Sumanth. 2009. 'Intra-oral amelanotic malignant melanoma: Report of a case and review of literature', *Journal of Nepal Dental Association*, 10: 49-52.
50. Sharma, Neeraj. 2012. 'Primary oral malignant melanoma: Two case reports and review of literature', *Case reports in dentistry*, 2012.
51. Shen, Zheng-Yu, Wei Liu, Zhe-Xuan Bao, Zeng-Tong Zhou, and Li-Zhen Wang. 2011. 'Oral melanotic macule and primary oral malignant melanoma: epidemiology, location involved, and clinical implications', *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology*, 112: e21-e25.
52. Sheng, Xinan, Xieqiao Yan, Zhihong Chi, Lu Si, Chuanliang Cui, Bixia Tang, Siming Li, Lili Mao, Bin Lian, and Xuan Wang. 2019. 'Axitinib in combination with toripalimab, a humanized immunoglobulin G4 monoclonal antibody against programmed cell death-1, in patients with metastatic mucosal melanoma: an open-label phase IB trial', *Journal of Clinical Oncology*, 37: 2987.
53. Singh, Diksha, Pragya Pandey, Manish Kumar Singh, and Shailesh Kudva. 2019. 'Prevalence of malignant melanoma in anatomical sites of the oral cavity: A meta-analysis', *Journal of oral and maxillofacial pathology: JOMFP*, 23: 129.
54. Singh, S, NB Zwane, and SL Shangase. 2015. 'Oral medicine case book 70: Oral malignant melanoma', *South African Dental Journal*, 70: 216-19.
55. Sivapathasundharam, B. 2016. *Shafer's Textbook of Oral Pathology-E Book* (Elsevier India).
56. Smith, Molly Housley, Indraneel Bhattacharyya, Donald M Cohen, Nadim M Islam, Sarah G Fitzpatrick, Lindsay J Montague, Douglas D Damm, and Craig B Fowler. 2016. 'Melanoma of the oral cavity: an analysis of 46 new cases with emphasis on clinical and histopathologic characteristics', *Head and neck pathology*, 10: 298-305.
57. Song, Hao, Lizhen Wang, Jiong Lyu, Yunteng Wu, Wei Guo, and Guoxin Ren. 2017. 'Loss of nuclear BAP1 expression is associated with poor prognosis in oral mucosal melanoma', *Oncotarget*, 8: 29080.
58. Sortino-Rachou, Ana Maria, Marianna de Camargo Cancela, Lydia Voti, and Maria Paula Curado. 2009. 'Primary oral melanoma: population-based incidence', *Oral oncology*, 45: 254-58.
59. Sun, Chuan-Zheng, Yan-Feng Chen, Yu-E Jiang, Ze-Dong Hu, An-Kui Yang, and Ming Song. 2012. 'Treatment and prognosis of oral mucosal melanoma', *Oral oncology*, 48: 647-52.
60. Tas, Faruk, and Serkan Keskin. 2013. 'Mucosal melanoma in the head and neck region: different clinical features and same outcome to cutaneous melanoma', *ISRN dermatology*, 2013.
61. Umeda, Masahiro, Hideki Komatsubara, Takashi Shigeta, Yasutaka Ojima, Tsutomu Minamikawa, Yasuyuki Shibuya, Satoshi Yokoo, and Takahide Komori. 2008. 'Treatment and prognosis of malignant melanoma of the oral cavity: preoperative surgical procedure increases risk of distant metastasis', *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology*, 106: 51-57.
62. Vinuta, Hegde, Venkatesh G Naikmasur, Krishna N Burde, Dhirendra G Sirur, and Hallikeri Kaveri. 2014. 'Oral malignant melanoma of the mandibular gingiva–a case report', *International Journal of Medical Research & Health Sciences*, 3: 726-30.
63. Wang, R, G Jing, J Lv, H Song, C Li, X Wang, W Xia, Y Wu, G Ren, and W Guo. 2015. 'Interferon-α-2b as an adjuvant therapy prolongs survival of patients with previously resected oral muscosal melanoma', *Genet Mol Res*, 14: 11944-54.
64. Warszawik-Hendzel, Olga, Monika Słowińska, Małgorzata Olszewska, and Lidia Rudnicka. 2014. 'Melanoma of the oral cavity: pathogenesis, dermoscopy, clinical features, staging and management', *Journal of dermatological case reports*, 8: 60.

65. Williams, Michelle D. 2017. 'Update from the 4th edition of the World Health Organization classification of head and neck tumours: mucosal melanomas', *Head and neck pathology*, 11: 110-17.
66. Wu, Yunteng, Yi Zhong, Chaojun Li, Hao Song, Wei Guo, and Guoxin Ren. 2014. 'Neck dissection for oral mucosal melanoma: caution of nodular lesion', *Oral oncology*, 50: 319-24.
67. Zhou, Rong, Chaoji Shi, Wenjie Tao, Jiang Li, Jing Wu, Yong Han, Guizhu Yang, Ziyue Gu, Shengming Xu, and Yujue Wang. 2019. 'Analysis of Mucosal Melanoma Whole-Genome Landscapes Reveals Clinically Relevant Genomic AberrationsIdentifying Clinically Relevant Genomic Aberrations in MMs', *Clinical Cancer Research*, 25: 3548-60.