Pigmented lesions of the oral and head and neck mucosa, including malignant melanoma

A clinicopathological study
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Chapter 1.

Introduction and aim of the study.
Chapter 1

Introduction

Pigmented lesions of the oral mucosa

Human oral and head and neck mucosa is not uniformly coloured and several degrees of chromatic variegation may be observed in physiological and pathological conditions \(^{1-6}\). The term "pigmentations of the oral and head and neck mucosa" may be applied to a wide range of entities caused by the accumulation of one or more pigments and featuring a change in colour of tissues \(^{1-5, \ 7}\). Pigments associated with mucosal discoloration can be subclassified into endogenous (e.g. melanin and blood-related pigments) and exogenous (e.g. metals and drug-related pigments). Melanin-associated lesions represent the most common pigmentations and include benign entities as well as mucosal melanoma, an extremely aggressive neoplasm \(^{1-7}\).

With the exception of several studies on sinonasal, pharyngeal and conjunctival melanomas \(^{8-36}\), most of the analyses on pigmented lesions of the head and neck mucosa reported in the literature are focused on the oral cavity \(^{1-6, \ 37-71}\). Benign melanin-associated pigmentations of the oral mucosa include racial pigmentation, melanotic macules, oral melanocytic naevi (OMNs), melanoacanthoma, post-inflammatory pigmentations and so-called "smoker's melanosis" \(^{1-6, \ 37-71}\). Several systemic diseases such as Peutz-Jeghers and Laugier-Hunziker syndromes as well as the Addison's disease are also characterized by the presence of benign melanin-associated lesions of the oral and perioral tissues \(^{72-77}\).

Non-melanin associated pigmentations may be caused by blood-related (bilirubin and biliverdin), iron-containing (ferritin and hemosiderin) and metal pigments \(^{1-6, \ 78-82}\). Among these, amalgam pigmentation ("amalgam tattoo") represent the most frequently described \(^{78-82}\). Several drugs have been reported to induce mucosal discoloration through direct deposition on oral surfaces, local accumulation after systemic absorption, stimulation of melanin-related pathways and bacterial metabolism \(^{1-6}\).
Clinical and histopathological diagnosis of pigmented lesions of the oral and head and neck mucosa may be challenging. No reliable criteria exist for the clinical differentiation between mucosal melanoma and a number of other pigmented lesions such as melanotic macules, OMNs or amalgam tattoos\(^{1-6}\). With the exception of oral malignant melanoma (OMM), all pigmented primary lesions in the oral cavity are benign and treatment usually is required only when discomfort is present\(^{1-6}\).

**Head and neck mucosal melanoma**

Head and neck mucosal melanomas (HNMMs) are rated among the most malignant tumours of the human body with a 5-year survival rate for nasal, pharyngeal, oral and sinus melanomas of respectively 30.9, 13.3, 12.3 and less than 5.0 percent\(^{8-36}\).

The incidence of HNMM is approximately four per 10 million population per year in the United States and this malignancy accounts for 8-15% of all head and neck neoplasms, including cutaneous melanoma\(^{6, 8-10, 83, 84}\).

With regard to the subgroup of OMM, it has been reported that it accounts for 0.5% of all oral malignancies and that its incidence is slightly higher among the Japanese population\(^{83-86}\).

Etiology and pathogenesis of HNMM are essentially unknown\(^{8-36, 83-86}\). On the base of epidemiological data some authors hypothesized a possible influence of formaldehyde exposure\(^{27}\). The close anatomic proximity of the commonly affected head and neck mucosal sites (nasal cavity and paranasal sinuses and the palate) may lead to the hypothesis that the pathogenesis of these tumours is related to some abnormality during the embryogenesis of this region\(^{29}\).

It has been reported that almost one third of OMMs are preceded for months or years by pigmented lesions but the nature of such precursors has never been clarified\(^{83, 86}\). Since OMNs and OMM share similar epidemiologic features such as the frequent localization on the hard palate, it may be hypothesized that a particular histotype of OMN represents a potentially malignant precursor\(^{46}\).
However, no data on the potential malignant transformation rate of OMNs are available as they are for the melanocytic nevi of the skin\textsuperscript{54, 57}.

The clinical manifestations of HNMM are extremely heterogeneous. Painful black or brown nodules in the oral cavity and dark polypoid masses in the nasal and paranasal sinus cavities are the most commonly clinical features reported. Other unspecific signs consist of ulceration and bleeding. Few HNMM are non-pigmented (amelanotic melanomas)\textsuperscript{8-36, 83-86}.

From the histopathologic point of view, malignant melanoma cells show a wide range of shapes including spindle, clear cell and epithelioid ones. A distinction between “\textit{in situ}” melanomas, melanomas with an invasive pattern and melanoma with a combined pattern has been proposed for OMMs\textsuperscript{87}. Useful immunohistochemical markers include S-100 protein and HMB-45\textsuperscript{8-36, 83-86}.

The TNM clinical staging system for HNMM recognizes three stages: Stage I, primary tumor present only (T any N0 M0); Stage II, tumor metastatic to regional lymph nodes (T any N1 M0); Stage III, tumor metastatic to distant sites (T any N any M1)\textsuperscript{21, 23}.

Therapy of HNMM is commonly based on surgical excision of the primary tumour, supplemented by radiotherapy, with chemotherapy and immunotherapy serving as adjuncts\textsuperscript{8-36, 83-86}.

Recurrent melanoma may manifest itself up to 10-15 years after primary therapy and distant metastases to the lungs, brain, liver, or bones are frequently observed\textsuperscript{8-36, 83-86}.
Aim of the study

The aim of the present thesis is to report the clinical and pathological features of a number of pigmented lesions of the oral mucosa particularly with regard to malignant melanoma.

A clinicopathological review of the recent literature on oral pigmented lesions, with emphasis on the main diagnostic features, including the use of immunohistochemical markers is presented in chapter 2. After an overview on embryology and histology of oral mucosal melanocytes, we analyze the oral pigmented lesions describing the epidemiological, clinical, histopathological and therapeutical aspects of a number of oral pigmented lesions. A flow-chart for diagnosis and some recommendations for the management are included.

The current knowledge on OMM is critically reviewed in chapter 3. Etiology, clinical and histological features, diagnostic aspects, terminology and classification, staging systems, prognostic factors and survival are extensively discussed. A section of the paper is dedicated to the analysis of the differences between excisional and incisional biopsies in terms of spreading of malignant cells. The role of surgery, including the policy with regard to the neck and the role of primary and postoperative radiotherapy are also reviewed.

The experience with 14 patients with a histopathological diagnosis of OMM and treated at the Department of Oral and Maxillofacial Surgery/Oral Pathology of the VU University medical center (VUmc) in Amsterdam between 1978 and 2005 is presented in chapter 4.

The exceptional finding of pseudoepitheliomatous hyperplasia (PEH) in malignant melanoma of the palate in a 46-year-old female patient is reported in detail in chapter 5. A discussion on the possible histogenesis of PEH is also included.

A case of melanotic pigmentation of the palatal minor salivary glands is reported in detail in chapter 6. Four years later the patient developed a malignant melanoma at the junction of the hard and the soft palate. A discussion on the
presumptive potentially malignant nature of the salivary glands pigmented lesion is included.

The role of oral melanocytic naevi as markers for oral malignant melanoma development is discussed in chapter 7. The paper reports an epidemiological and pathological evaluation on 119 cases of OMNs registered in the nationwide Registry of Pathology (PALGA) in the Netherlands in the period 1980-2005.

The experience with a group of 42 patients with a primary HNMM referred to the VU University medical center (VUmc) in Amsterdam, the Netherlands, and to the Academic Hospital of Parma University, Italy, in the last 30 years, is reported in chapter 8. The emphasis of the study was on the role of surgery and post-operative radiotherapy.
References


Introduction and aim of the study


Chapter 2.

Pigmented lesions of the oral mucosa and perioral tissues: A flow-chart for the diagnosis and some recommendations for the management.

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Chapter 2

Abstract

The term “pigmentation of the oral mucosa” is applied to a wide range of lesions or conditions featuring a change of colour of oral tissues. Lesions not associated with an accumulation of pigment (e.g. Fordyce’s spots) are usually not classified as pigmented lesions.

Two groups of pigmented lesions of the oral mucosa are recognized: 1) melanin-associated lesions, including racial pigmentations, melanotic macules, melanocytic naevi and malignant melanoma; 2) non-melanin-associated (e.g. blood-related pigmentations, metallic pigmentations) lesions.

This paper presents a clinicopathological review of the recent literature with emphasis on the main diagnostic features, including the use of immunohistochemical markers. A flow-chart is added that may help the clinician in the diagnosis and management of these lesions.
1. Introduction

Human oral mucosa is not uniformly colored and several degrees of chromatic variegation may be observed in physiologic and pathologic conditions \(^1-^5\). Oral subsites are characterised by different structural colors, depending on degree of keratinization, numbers and melanogenic activity of melanocytes, vascularization and type of submucosal tissue (muscle, bone, cartilage). The physiologic color of the oral mucosa thus ranges from white to red-purple in white-skinned people, while an evenly black to brown color of gingiva and buccal mucosa and the lips, are characteristic of black-skinned people \(^1-^5\).

In this review, two groups of pigmented lesions are discussed: melanotic lesions, and lesions caused by other pigments. After an overview of oral histology and physiology of melanocytes, a flow-chart will be presented that may help the clinician in the diagnostic process (Figure 1).
Figure 1. Diagnosis and management of pigmented lesions.

* Palate and gingiva are considered subsite at risk for OMM development.
** In case of multiple or diffuse pigmentation(s) further examination for underlying diseases or syndromes (e.g. Addison’s, Peutz-Jeghers syndrome, etc.) may be considered.
2. Melanin-associated pigmented lesions of the oral cavity

2.1. Oral mucosal melanocytes: histology and physiology

Melanocytes were first identified in the oral epithelium by Becker in 1927; a few years later they were isolated from samples of gingival tissue by Laidlaw and Cahn. During early intrauterine life, precursors of melanocytes, melanoblasts, migrate from the neural crest to the epidermis and the hair follicles, becoming differentiated dendritic cells. The head and neck region represents the first part of the body where melanocytes appear after approximately 10 weeks of gestation.

Melanocytes are located in the basal epithelial layer of squamous mucous membranes and do not contact each other. They are regularly interspersed between the basal keratinocytes. Melanocytic dendrites reach a number of keratinocytes in the close vicinity, and through these dendrites, melanin is transported and transmitted to these epithelial cells. An age related increase of oral melanocytes has been observed.

The normal melanocytes of the oral mucosa have a small, round nucleus and a small amount of a clear cytoplasm, with slender dendrites extending between adjacent keratinocytes. Melanocytes are devoid of desmosomes or attachment plates. Melanin-containing electron-dense vesicles, so called melanosomes, are formed within the cytoplasm and transported along the dendrites.

The use of 3, 4 dihydroxyphenylalanine (DOPA), a substrate for tyrosinase, represents the most specific histochemical method for labeling melanocytes. Other methods include argentaffinic melanin-labeling techniques such as the Masson-Fontana staining. Inactive oral mucosal melanocytes, lacking melanin and melanin precursors, may not stain with this method.

Immunohistochemically, the S100 antigen is by far the most common marker used. S100 staining appears to be stronger in melanocytes lacking pigment. Another commonly used marker is HMB-45, a monoclonal antibody directed against a melanosomal glycoprotein. HMB-45 is not expressed by melanocytes that lack all melanogenic activity.
Chapter 2

The main biochemical function of the mature melanocyte is a process called melanogenesis through which the cell produces and delivers melanin pigment. Eumelanin (brown-black melanin) causes a brown-black color of the skin, hair and eye, while pheomelanin has a reddish color. Neuromelanin, found in some nerve cells, is an unrelated substance.

Various stimuli such as trauma, hormonal changes, medication and radiation may result in an increased production of melanin. Melanin functions include absorption of ultraviolet light and scavenging of some cytotoxic compounds.

2.2 Racial Pigmentation (physiologic pigmentation)

No agreement exists in the literature on the definition of “race”, “racial group”, “ethnic group” and “ethnicity”. Furthermore, it has been demonstrated that the strength of the relationship between skin color and ancestry is quite variable. As a matter of fact, the melanin content of the skin does not seem to be strictly related to ancestry, genetically defined by the so-called “ancestry-informative markers” (AIMs). On the basis of a multivariate evaluation, three categories of humans have been defined: whites, blacks and intermediates. Factors considered include skin color in the medial part of the arm, color and texture of the hair, and shape of nose and lips.

Oral “racial” pigmentations (ORPs) are usually observed in dark-skinned populations. In a study on 1300 children, ORPs were identified in 13.5%. Pigmentations are usually diffuse and bilateral even though a variety of patterns have been observed. Color ranges from light dark to brown. Gingiva, with the exclusion of the marginal border, and buccal mucosa are the most commonly involved sites (Figure 2). Other sites include lips, palate and tongue. Racial pigmentations are innocuous and treatment is only for aesthetic reasons.
2.3 Melanotic macules

Melanotic macules of the oral cavity are relatively common lesions, caused by an increased production and deposition of melanin within the basal cell layer, the lamina propria, or both \(^1-^3\).

In the largest series from one source, Buchner \textit{et al.} reported that melanotic macules of the lips and oral cavity represented 86.1% (665 cases) in a group of 773 cases of solitary melanocytic lesions and the 0.7% in a group of nearly 90,000 biopsies from oral cavity and perioral tissues \(^2^0\). Of these, 207 were located on the lips and 458 involved various subsites of the oral mucosa. The vermillion border and the gingiva were the most commonly affected subsites (60%). In another review, Kaugars \textit{et al.} reported a prevalence of 0.4% among 86,202 biopsies from the oral cavity. Labial lesions almost exclusively affect the lower lip, while gingival melanotic macules are more frequently localized in the anterior part of the maxilla. Black patients are more likely to have involvement of the buccal mucosa \(^2^1\). The female to male ratio is almost 2:1 and the highest incidence is reported during the fifth decade \(^2^0,\, ^2^1\).

Controversy exists on the pathogenetic mechanism that leads to the development of melanotic macules and it is not clear if they represent a physiologic or a reactive process \(^1\). Some authors reported a positive family history and a genetic predisposition has been hypothesized \(^2^2\).
Melanotic macules are usually single, well-circumscribed blue or brown-to-black lesions homogeneously colored, and less than 1 cm in diameter \(^1, 3\). Intraoral lesions tend to be larger than those located on the lips \(^1\). Unlike ephelides, melanotic macules do not darken after exposure to sun radiation \(^2, 3\). Dermatoscopy may show a structureless pattern, characterized by a diffuse brown black pigmentation, seldom irregularly distributed, without pigment network or globules and/or streaks \(^24\).

The diagnosis is usually made on clinical grounds alone \(^1\).

From the histopathologic point of view there is absence of rete ridge elongation and lack of prominent melanocytic activity \(^1-3\). Pigmentation is usually most marked at the tips of the rete ridges and melanophages can also be observed in the upper part of lamina propria \(^2, 22\). There is lack of atypia of melanocytes and HMB-45 immunoreactivity is typically lacking \(^1, 3, 20, 21, 25\). When melanin pigment is observed in the epithelium of a clinically non-pigmented lesion, the term "focal melanosis" has been used by some \(^26\).

### 2.4 Lentigines and ephelides

The term lentigo (plural : lentigines) indicates a well-defined hyperpigmented lesion of the skin with an increased number of melanocytes arranged as solitary units along the epithelial-mesenchymal junction, without formation of nests \(^27\).

Lentigines are subdivided in simple lentigines and solar lentigines, the latter being associated with epithelial hyperplasia, which generally takes the form of rete ridge elongation. Melanocytic hyperplasia is minimal in solar lentigines.

Lentigo simplex is a lesion histologically characterized by more obvious melanocytic hyperplasia, together with increased melanin formation \(^27\). No clear data on epidemiology are available in white skinned population while lentigo simplex has been reported to be the most frequent pigmented lesion in acral sites of darkly pigmented races. Pathogenesis is most likely related to developmental or intrinsic defects in melanocytes homeostasis. Clinical features of lentigo simplex include light to dark brown pigmentation, usually sharply
Oral pigmented lesions

Lesions can be single or multiple, the latter situation being associated with a number of rare syndromes.

Different from lentigo simplex, solar lentigines (synonyms sun-induced freckles, lentigo senilis) are ultraviolet (UV)-induced pigmented lesions. Epidemiology shows an increased incidence among the general population over 60 years of age.

Ephelides (freckles) are small (less than 1 cm) red or light-to dark-brown macules localized on sunexposed areas of the body. They typically affect white-skinned individuals, are multiple, and uniform in color and regular in outline, although confluence leads to irregularly shaped larger patches. Ephelides may appear at any age but most frequently occur in childhood. They wax and wane with the degree of solar exposure, being most conspicuous in the summer months.

No data exist on the prevalence of intraoral lentigines and ephelides; they mainly affect the vermilion border of the lips or the perioral tissues.

2.5 Melanocytic Naevi

Oral melanocytic naevi (OMNs) are benign tumors of melanocytes. Approximately 500 cases have been reported in the English literature; no systematically assembled data on their frequency are available. A recent report from the Netherlands revealed an annual incidence of excised OMNs of 4.35 cases per 10 million population per year.

The etiology and pathogenesis of OMNs are poorly understood even though, as for their cutaneous counterpart, oncogenic mutations of genes coding for components of the RAS signaling pathways may play a role.

Regarding morphogenesis, the melanocytic proliferation can be divided into three phases: 1) proliferation of benign neoplastic melanocytes along the epithelial-mesenchymal junction (junctional naevus); 2) migration of these cells into the mesenchymal compartment (compound naevi); and 3) loss of the junctional component of the naevus, so that all remaining nevomelanocytes are
located within the subepithelial compartment (subepithelial naevi) \(^{12, 27, 31}\) (Figure 4). These steps correspond to the histologic variants of OMNs \(^{29}\). Less common naevus subtypes include blue naevus (Figures 5 and 6), combined naevus and Spitz naevus \(^{32-36}\).

![Figure 4. Histopathological features of subepithelial naevus. All nevomelanocytes are confined within the subepithelial compartment (H&E stain; orig. magn. x50).](image)

**Figure 4.** Histopathological features of subepithelial naevus. All nevomelanocytes are confined within the subepithelial compartment (H&E stain; orig. magn. x50).

![Figure 5. Blue naevus of the palate.](image)

**Figure 5.** Blue naevus of the palate.

![Figure 6. Histopathological features of a blue naevus. Spindle-shaped nevomelanocytes (Schmorl stain: orig. magn x 150).](image)

**Figure 6.** Histopathological features of a blue naevus. Spindle-shaped nevomelanocytes (Schmorl stain: orig. magn x 150).

In the histopathological evaluation, the additional use of immunohistochemical stains may be required, such as the melanocytic markers Melan A, HMB45 and
Oral pigmented lesions

microphthalmia transcription factor (mitf). In melanin pigment laden cells, additional markers, e.g. CD68, a marker for macrophages, may be helpful in identifying the nature of such cells. Such a procedure may be particularly helpful in arriving at a correct diagnosis of a blue naevus.

Congenital melanocytic naevi are present at birth, while those developing after birth are referred to as acquired naevi. Probably, most melanocytic naevi of the oral mucosa are acquired, even though some cases of congenital naevi have been reported. Sizes range from 0.1 to, rarely, 3.0 cm. OMNs typically are well circumscribed round or oval macules or papules, but polypoid larger lesions have been reported as well. OMNs have been reported to occur in a multiple fashion. Elevated acquired naevi are usually lightly pigmented, while flatter lesions tend to be more darkly pigmented. Colors vary from brown to blue, bluish-gray, or black; generally an individual lesion has a similar color throughout. Rare non-pigmented naevi are on record. The hard palate, buccal mucosa and gingiva are most commonly affected.

Despite a strong epidemiological correlation between OMNs and OMMs with regard to age, gender predisposition and oral subsites, there is no proof that naevi of the oral mucosa are markers of the development of malignant melanoma.

2.6 Melanoacanthoma

The term melanoacanthoma has been used to describe a rare, benign mixed lesion of keratinocytes and pigmented-laden dendritic melanocytes. Oral melanoacanthoma is thought to have a reactive nature and usually regresses spontaneously or after incomplete removal, such as incisional biopsy. Approximately 40 cases of oral melanoacanthoma have been reported. Differently from its cutaneous counterpart, oral lesions occur almost exclusively in Blacks, affect a much younger population, develop rapidly and generally have a flat surface. The buccal mucosa is the most frequently affected subsite.
Chapter 2

2.7 Tobacco-associated melanin pigmentation (smoker's melanosis)

Smoking has been found to cause diffuse oral melanin pigmentation in European and Asian population [49-52]. It has been reported in 21.5% of smokers and the intensity of the pigmentation is related to the number of cigarettes consumed [51]. Some authors noticed a significant increase in gingival melanosis of children with parents who smoke [53]. Smoker's melanosis seems to be directly related to a stimulant effect of substances in smoke on melanocytes. In parallel to a model accepted for the skin, some authors hypothesized that melanin may play a role in detoxification of polycyclic amines nicotine and benzopyrene [49, 50].

Subsites involved are mainly gingiva, hard palate, buccal and commissural mucosa, inferior surface of the tongue and lip mucosa (Figure 7). Smoker's melanosis is usually black-brown [49-52].

From a histologic point of view, increased melanin is found in the basal layer of the epithelium, and there may be melanophages in the subjacent connective tissue. No melanin is detected in the upper part of the epithelium [54]. Smoker's melanosis does not require treatment and disappearance has been reported after cessation of the smoking habit [1, 49].

Figure 7. Smoker's melanosis of the lower lip.
2.8 Malignant Melanoma

Oral malignant melanoma (OMM) is an aggressive tumor of melanocytes, accounting for 0.5% of all oral malignancies. The neoplasm is more common in Japan and Africa than in Western countries. The etiology of OMM is unknown. Tobacco use and chronic mechanical irritation resulting from ill-fitting dentures have been mentioned as possible risk factors. Most OMMs arise de novo, from apparently normal mucosa, but about 30% are preceded by oral pigmentations for several months or even years.

The initial symptom and sign of OMM is the emergence of a mass lesion, which is usually pigmented. OMM may be uniformly brown or black, or may show variation of color, with black, brown, grey, purple and red shades, or depigmentations. Satellite foci occasionally surround the primary tumor. In amelanotic melanomas, pigmentation is absent (Figure 8). The most frequently affected oral sites are the palate and the maxillary gingiva.

OMMs probably originate from junctional melanocytes; in its first phase of development, the cells are restricted to the epithelial compartment: in situ melanoma. Subsequently, melanoma cells invade the underlying tissues.
Melanoma cells show a wide range of shapes, including spindle, plasmacytoid, and epithelioid ones. Clear cell change is occasionally seen. OMM is not subdivided into the classical cutaneous melanoma categories, which include superficial spreading melanoma (SSM), nodular melanoma (NM) and acral lentiginous melanoma (ALM). There is, however, often some similarity to ALM and NM. The histological microstaging system of Clark, used in cutaneous melanoma, can not be applied to oral mucosa because of the lack of histologic landmarks analogous to papillary and reticular dermis. Tumor thickness does not appear to be associated with prognosis. The TNM clinical staging system for OMM recognizes three stages: Stage I, primary tumor present only (T any N0 M0); Stage II, tumor metastatic to regional lymph nodes (T any N1 M0); Stage III, tumor metastatic to distant sites (T any N any M1). In different series, the actuarial-5 year overall survival rate for head and neck mucosal melanoma ranges from 21% to 40% and for OMM it is 15%, with a median survival of 25 months. Gingival melanoma has a better 5-year survival rate than the palatal one, with a longer median survival period (46 months vs. 22 months). Recurrent melanoma may manifest itself up to 10-15 years after primary therapy. Distant metastases often affect the lungs, brain, liver, or bones.

3. Systemic disorders associated with the presence of oral pigmented melanocytic lesions

3.1 Peutz-Jeghers and other familial hamartoma syndromes

The Peutz-Jeghers syndrome (PJS) consists of mucocutaneous macules, intestinal hamartomatous polyposis and increased risk of carcinomas of the gastro-intestinal tract, pancreas, breast and thyroid. The disease is associated with germline mutations in the LKB1/STK11 gene, located on the short arm of chromosome.
Oral pigmented lesions

Black-to-brown spots of less than 1 mm in size are typically localized on the lower lip and in the perioral area (Figure 9). Intraoral, intranasal, conjunctival and rectal pigmented lesions as well as spots localized on the acral surfaces may also be present.1-3,68

The oral lesions are benign and histologically characterized by an increase in melanin in the basal layer, without an obviously increased number of melanocytes.1,2 A fading or a disappearance of the spots is usually observed in older age 70. Interestingly, perioral lesions tend to persist.1

So-called “PTEN hamartoma tumor syndromes” (PHTS), characterized by mutations in the tumor suppressor gene PTEN (phosphatase and tensin homologue deleted on chromosome 10) include several rare diseases such as the Ruvalcaba-Myhre-Smith and the Cowden syndrome.68 Perioral lentigines have occasionally been reported in these.2

Figure 9. Perioral involvement in Peutz-Jegher’s syndrome.

3.2 Addison’s disease and other endocrine disorders

Primary hypoadrenalism caused by autoimmune disease, infection or malignancy, also referred to as Addison’s disease, is characterized by deficient production of hormones of the adrenal cortex, leading to increased production
of adrenocorticotropic hormone (ACTH) \textsuperscript{71}. This may result in a diffuse dark pigmentation of the skin and the oral mucosa \textsuperscript{2,72}. Other signs and symptoms of Addison's disease include anorexia, nausea and postural hypotension.

Lips, gingival, buccal mucosa, hard palate and tongue are usually involved (Figure 10). Pigmented lesions may be diffuse or localised and usually precede skin manifestations \textsuperscript{2,3}.

Diffuse or discrete pigmentation of the lips and oral mucosa are sometimes observed in monostotic and polyostotic fibrous dysplasia (McCune-Albright syndrome), hyperthyroidism and Nelson's syndrome \textsuperscript{2}.

Treatment of pigmented lesions of the oral mucosa associated with a systemic disorder is usually not required unless discomfort is present. The disappearance of oral lesions may follow the treatment of the underlying condition.

Figure 10. Oral Manifestation of Addison's disease (Courtesy of dr. J.van Hooff, The Netherlands).

\textbf{3.3 Other conditions}

Oral melanocytic pigmentation have been reported in patients with Laugier-Hunziker syndrome (idiopathic lenticular mucocutaneous pigmentation) and
with Carney complex (spotty skin pigmentation, myxomas and endocrine overactivity) \(^2,73\)–\(^77\).

HIV infection has been associated with multiple, usually well-circumscribed melanotic macules localized on the buccal and palatal mucosa, gingiva and lips \(^5\). However, the association may be only coincidental. The histopathological appearance is similar to classical melanotic macules. It remains unclear whether such pigmentations are caused by the virus, by therapy, or other factors \(^1,2,78\).

Chronic inflammatory conditions such as oral lichen planus, pemphigus, pemphigoid or chronic periodontal disease are sometimes associated with deposition of melanin within the connective tissue resulting in a darkening of the mucosal area \(^1,4\). These phenomenon is mostly observed in dark-skinned individuals \(^3\). Fixed drug reaction after administration with cotrymazole, tetracycline, colchicine, ketoconazole has also been associated with post-inflammationary hyperpigmentation \(^3,79\). It is debatable if these reactions only depend on melanin.

The presence of lesions resembling melanotic macules of the palate in patients with lung diseases, including cancer, has also been reported, but there is lack of evidence on a true association \(^80\).

Melanin production and stimulation may sometimes also follow surgical procedures \(^4\).

### 4. Non-melanin-associated pigmented lesions of the oral cavity

#### 4.1 Lesions caused by endogenous pigments (blood-related pigmentations)

Extravasations of blood in hematomas, petechiae, purpurae and ecchymoses may cause pigmentation \(^3,81\) as a result of accumulation and degradation of
haemoglobin to bilirubin and biliverdin. Color of the lesions depend on length of time from trauma and may range from red to black. Typical traumatic events in the oral cavity possible associated with blood extravasations and hyperpigmentation include biting, traumas with eating and iatrogenic procedures.

Patients with haemochromatosis (“bronze diabetes”) frequently display bluish-grey pigmentation of the hard palate, gingival and buccal mucosa (Figure 11). The pigmentation is caused by deposition of iron containing pigments (ferritin and hemosiderin) within the skin and mucous membranes. Similarly, a diffuse black-brown pigmentation, most commonly in the junction between the hard and soft palate, may be observed in patients with beta-thalassemia.

![Figure 11. Palatal pigmentation in a patient with hemochromatosis. (Courtesy of dr. J.G.N. Swart, The Netherlands).](image)

4.2 Lesions caused by exogenous pigments (metallic pigmention)
4.2.1 Amalgam pigmentation (amalgam tattoo)

Accidental displacement of metal particles in oral soft tissues during restorative dental procedures using amalgam may result in amalgam pigmentation, the
so-called “amalgam tattoo” \(^{1-5}\). Terms such as focal argyrosis or oral localized argyria should be avoided, since not only silver, but also mercury and tin are contained in the amalgam alloy. Despite the high prevalence of these lesions among the general population, little information is available in the dental literature. Buchner and Hansen identified 268 (1.3 %) amalgam tattoos among 20,731 specimens from the oral cavity \(^{82}\). The etiology of amalgam tattoos can be iatrogenic or traumatic. Metal particles may over time leach in the soft oral tissues, resulting in the discoloration. Buchner and Hansen and Owens et al. listed several iatrogenic and traumatic modalities through which amalgam may be introduced in the oral tissues: condensation of the material in abraded mucosa during routine amalgam restorative work; introduction of the material within the lacerated mucosa during removal of amalgam fillings or crowns and bridges; introduction of broken pieces into a socket or the periosteum during extraction of teeth; introduction of metal particles in a surgical wound during root canal treatment with a retrograde amalgam filling \(^{82, 83}\).

Amalgam tattoos usually range from 0.1 up to (rarely) 2 cm in size and can be solitary or multiple. Colors reported are blue, grey or black with a spectrum of variegation depending on the depth of metal within tissues. Gingiva and alveolar mucosa are the subsites most frequently involved. In alveolar edentulous ridges, amalgam tattoos can also be associated with restored antagonistic teeth (Figure 12). The diagnosis is based on clinical findings and the relationship with present or removed amalgam restorations.
Radiographic features may show localized radiopacities. Biopsy is indicated only when suspicion of OMM can not be ruled out on clinical grounds alone. Histopathologic investigation reveals amalgam particles dispersed in the connective tissue and sometimes in the walls of vessels. These particles may also line the basement membrane of the surface epithelium. Brownish granules within phagocytic cells and fibroblasts cytoplasm can also be observed.

A spreading of these pigmented lesions mediated by local migration of phagocytic cells containing metal has also been described.

Histopathologic examination of an amalgam tattoo is usually diagnostic because of the size and shape of the metal particles and the way they are spread in the tissue. However, in rare cases, one may need additional stains. The common melanin and iron stains are often not sufficient for differentiating between metal particles and melanin pigment. Instead, immunohistochemical markers such as HMB-45 and Melan A are more suitable for this purpose.

When dealing with metal pigmentation, one may be able to identify the type of metal(s) by using electron-probe micro-analysis.

There is no indication for complete removal of an amalgam tattoo.
Accidentally or voluntary introduction of other foreign particles include graphite from pencil tips, tattoo inks and chronic contact with charcoal toothpaste and vegetables, such as Juglans regia, Cola Nitida and Catha Edulis 1, 2, 86.

4.2.2 Heavy metals
Systemically absorbed metals may induce discoloration of the oral mucosa, caused by peripheral metal accumulation. These conditions were frequent in the past as result of occupational exposures to certain drugs. Arsenic, lead, bismuth, mercury, silver and gold are the metals most frequently involved 1-5. Bismuth was typically used for the treatment of syphilis and its administration was associated with diffuse oral pigmentation and formation of a blue-black line at the marginal gingival 1. A characteristic feature of plumbism (lead poisoning) is the so-called “Burtonian line”, a grey linear area of discoloration below the gingival margin 1, 3, 4 (Figure 13). Silver (argyria) and gold (chrysiasis) may produce slate-grey oral pigmentation and purple gingival discoloration, respectively 2.

Heavy metal intoxication can be associated with a wide range of systemic signs and symptoms 1, 3.

Figure 13. Oral manifestation of lead poisoning (“Burtonian line”).
5. Drugs associated with pigmented lesions of the oral cavity (excluding heavy metal containing drugs)

Many non-heavy metal containing drugs can induce discoloration of oral tissues. Direct deposition on oral surfaces, local accumulation after systemic absorption, stimulation of melaninrelated pathways, bacterial metabolism, alone or in combination, may result in oral pigmentations. The most commonly reported drugs are listed in table 1.

Table 1. Drugs potentially associated with oral pigmentations. (Ref. 2 and 3)

<table>
<thead>
<tr>
<th>Drug</th>
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<tr>
<td>Nicotine</td>
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<td>Heroin</td>
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<tr>
<td>Busulfan</td>
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<tr>
<td>Doxorubicin</td>
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<tr>
<td>5-Fluorouracil</td>
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<td>Anthracyline</td>
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<td>Quinidine</td>
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<td>Minocycline</td>
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<tr>
<td>Bleomycin</td>
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<tr>
<td>Cyclophosphamide</td>
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<tr>
<td>Antimalarials</td>
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<tr>
<td>Phenothiazines</td>
</tr>
<tr>
<td>Oral contraceptives</td>
</tr>
<tr>
<td>Zidovudine (AZT)</td>
</tr>
<tr>
<td>Ketoconazole</td>
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<tr>
<td>Clofazimine</td>
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<tr>
<td>Tetracyclines</td>
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<tr>
<td>Premarin</td>
</tr>
<tr>
<td>Clofazimine</td>
</tr>
<tr>
<td>Chlorhexidine</td>
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<tr>
<td>Carotene</td>
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</table>
6. Discussion and proposal of a flow-chart

Diagnosis of pigmented lesions of the oral cavity and perioral tissues is challenging. Even though epidemiology may be of some help in orientating the clinician and even though some lesions may confidently be diagnosed on clinical grounds alone, such a diagnosis remains “provisional”. Definitive diagnosis usually requires histopathological evaluation. Occasionally, immunohistochemical stains such as melanocyte marker HMB-45 and macrophage marker CD68 may be required to arrive at a correct diagnosis.

With the exception of OMM, all pigmented primary lesions in the oral cavity are benign and treatment usually is required only when discomfort is present. No reliable criteria exist for the clinical differentiation between OMM and a number of other pigmented lesions such as melanotic macules, oral melanocytic naevi or amalgam tattoos.

The so-called ABCD checklist (“Asymmetry”, “Border” irregularities, “Color” variegation and “Diameter” > 6mm) that is commonly used to aid in the identification of cutaneous melanoma may be of some help in the clinical diagnosis of oral melanoma. Rapidly growing pigmented lesions should always be biopsied.

Location on the palate increases the rate of suspicion of melanoma and usually requires a biopsy or long-term follow-up. When located on the gingiva, the main differential diagnosis is between amalgam tattoo and melanoma. In case of the slightest doubt a biopsy should be taken.

In figure 1 a flow-chart is depicted that may help the clinician in the diagnostic pathway of pigmented lesions of the oral cavity. When history allows to classify a lesion as melanocytic, a subclassification should be made, according to the clinical suspicion of malignancy (ABCD checklist, recent history, age and subsite involved). Lesions presenting “no or low suspicion of malignancy” may be confidently diagnosed on clinical grounds alone (e.g. oral manifestations of systemic diseases, physiologic pigmentation, smoker’s melanosis) or may require histopathological evaluation.
Some non-melanocytic lesions such as ethnic tattoos or pigmentation associated with heavy metal poisoning are easily recognized on clinical grounds (e.g. Burtonian line). In other cases such as an bluish discolorations not clearly related to amalgam restorations and/or not showing radiological signs for the presence of metal particles, histopathological evaluation is needed to reach a firm diagnosis.

A biopsy or referral to a specialist for further evaluation is indicated if the history does not allow to distinguish between melanocytic and non-melanocytic lesion.
References


Oral pigmented lesions


Chapter 3.

Oral malignant melanoma: A review of the literature.

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Abstract
Primary oral malignant melanoma (OMM) is a rare neoplasm, accounting for 0.5% of all oral malignancies. The etiology is unknown; tobacco use and chronic irritation may play some role. Clinically, OMM may mimic other pigmented lesions. A biopsy is required in order to establish the diagnosis. The reported risk of malignant cells spreading during invasive procedures and factors such as size of the lesion or anatomical limitations, may influence the diagnostic surgical procedure. Therapy of OMM is commonly based on surgical excision of the primary tumour, supplemented by radiotherapy, with chemotherapy and immunotherapy serving as adjuncts. Prognosis is poor, with a 5-year survival rate of approximately 15%.
1. Introduction

Malignant melanoma is a potentially aggressive tumour of melanocytic origin. The incidence of head and neck mucosal melanomas (HNMM) is approximately four per 10 million population per year in the USA. Only about 1% of all melanomas arise in the oral mucosa and these account for 0.5% of all oral malignancies. The most frequently affected oral sites are the palate and the maxillary gingival. Oral metastasis of melanoma, derived from a primary elsewhere in the body, is extremely rare and will not be discussed here.

The age of reported patients ranges from 20 to 80 years; some authors have reported a male preponderance. The neoplasm is more common in Japan and Africa than in Western countries. Therapy is commonly based on combinations of surgery, radiotherapy and chemotherapy. The prognosis of OMM is poor, with a 5-year survival of about 15%.

The present review is based on a critical analysis of the relevant literature of the past decades.

2. Etiology

The etiology of OMM is essentially unknown. Tobacco use and chronic irritation from ill-fitting dentures have been mentioned as possible risk factors, but the evidence is weak. Ingested and inhaled environmental carcinogens at high internal body temperature may play some role. Most OMMs arise de novo, from apparently normal mucosa, but about 30% are preceded by oral pigmentations for several months or even years. Some of these flat precursor lesions consist of cytologically atypical melanocytes and may in fact constitute the preinvasive macular phase of melanoma. However, in other lesions a preexistent, histologically benign melanocytic proliferation accounts for the pigmentation.

The histological spectrum of benign melanocytic lesions of the oral mucosa is varied, and includes so-called mucosal melanosis, i.e., a junctional proliferation of melanocytes with or without cytological atypia, resulting in a macular
hyperpigmentation, and a variety of melanocytic naevi. The latter comprise junctional, compound and subepithelial naevi as well as a variety of blue and combined naevi, which are proportionally more common than in the skin. Some melanoma-associated antigens become expressed during the transformation process from a benign melanocytic nevus to melanoma; most of these are related to the melanin production process and most are HLA-restricted. p53 protein alterations have been identified in about two-thirds of OMM. A recent study demonstrates that loss of heterozygosity at 12p13 and loss of p27KIP1 protein expression contribute to melanoma progression. Cytogenetic analysis and evaluation of melanocyte-specific gene-1 (MSG-1) appears to be very helpful for understanding the pathogenesis of OMM.

3. Clinical features
The initial symptom and sign of OMM is often swelling, which is usually pigmented. OMM may be uniformly brown or black, or may show variation of colour, with black, brown, grey, purple and red shades, or depigmentations. Satellite foci may surround the primary. In amelanotic melanomas, pigmentation is absent. The tumour surface may be smooth, with an intact overlying mucosa, or may be ulcerated. Other presenting signs and symptoms include bleeding, ill-fitting dentures, pain, increased mobility of teeth and delayed healing of extraction sockets. Regional lymphadenopathy may be present and connotes a poor prognosis.

Tanaka et al. identified five types of OMM on the basis of the clinical appearance: pigmented nodular type, nonpigmented nodular type, pigmented macular type, pigmented mixed type and nonpigmented mixed type.

4. Diagnostic aspects
Oral melanocytic pigmentations can be observed in dark skinned persons (“racial pigmentations”), in Peutz–Jeghers syndrome, in Addison’s disease, and in some patients with pulmonary disease, including lung cancer. The so-
called ABCD checklist (“Asymmetry”, “Border” irregularities, “Colour” variegation and “Diameter” > 6 mm) that is commonly used in the identification process of cutaneous melanoma 24 could also be of some help in the diagnosis of oral melanoma 25. When an oral pigmentation cannot be confidently diagnosed as benign on clinical grounds, a biopsy is mandatory in order to exclude OMM 1, 25, 26.

Greene et al. proposed three criteria for the diagnosis of primary OMM: demonstration of malignant melanoma in the oral mucosa; presence of so-called ‘junctional activity’ (i.e., melanocytes arranged along the basal layer of the surface epithelium) in the lesion; inability to show malignant melanoma at any other primary site 27. However, the presence of ‘junctional activity’ is now known to be an unreliable indicator that the lesion is a primary one, since melanoma metastases may similarly involve the epithelial junction. Delgado et al. proposed a simple clinical method (“rubbing a gauze”) for the diagnosis of OMM but the value of such procedure seems somewhat questionable. 28, 29 In a report by Garzino-Demo et al. cytological examination and brushed samples were negative in all their cases with a proven histological diagnosis of OMM 30. It should be borne in mind that in cutaneous melanoma, fine needle aspiration or exfoliative cytology of primary pigmented lesions is contraindicated. Radiological examination through computed tomography, magnetic resonance imaging or positron emission tomography (PET) could be useful for evaluation of primary tumour and regional or distant metastases. In a study on 10 patients, Goerres et al. found that PET may be suitable for the staging of patients with HNMM 31.

4.1 Excisional versus incisional biopsy

The current guidelines for the surgical management of primary cutaneous melanoma recommend a diagnostic excisional biopsy of the lesion followed by a wide local excision where the diagnosis is proven 32-34. However, in the oral cavity, the size of the lesion or anatomical limitations, particularly the presence
of teeth, may preclude the taking of an excisional biopsy. Younes et al. proposed to take an excisional biopsy with a 1- to 2-mm margin for small lesions in amenable locations, but incisional biopsy, through the thickest or the most suspicious part of the tumour, in case of a large lesion or a location in sites where an excisional procedure would involve extensive and mutilating surgery.25,35.

It has often been suggested that cutting into a malignant neoplasm during an incisional biopsy or other invasive procedure, could result in accidental dissemination of malignant cells within the adjacent tissues (“seeding”) or even in the blood or lymphatic stream, with the subsequent risk of local recurrence, or regional or distant metastasis.36-38. However, in a retrospective study of 265 patients who had an incisional biopsy of cutaneous melanoma and 496 control cases of excisional biopsy, no such correlation was found.26. These findings are in agreement with similar studies by Lederman and Sober39 and by Lees and Briggs40. On the other hand, Rampen et al.41 and Austin et al.35 did find a somewhat reduced survival rate in patients with melanoma who had incisional biopsies.

Some authors have postulated that a stimulation of tumour outgrowth through release of fibroblast growth factor (FGF) during wound healing could result from the surgical procedures, but this hypothesis has not been supported by results from other studies.42.

5. Histologic features

The 1995 WESTOP (Western Society of Teachers of Oral Pathology) Banff Workshop on OMM drew attention to the fact that most OMMs are discovered and biopsied in an advanced stage, which probably contributes to the heterogeneity of microscopic patterns.5.

Like cutaneous melanoma, OMM probably has in many cases an initial phase characterized by radial growth followed by a phase of invasion of the underlying tissues (the so-called ‘vertical growth phase’).
OMMs can be histologically subclassified into: (1) *in situ* melanoma, which is limited to the epithelium and the epithelial–connective tissue interface; (2) melanomas with an invasive pattern, in which the neoplasm extends into the connective tissue; (3) melanomas with a combined pattern of invasive melanoma with *in situ* component. Malignant cells of OMM show a wide range of shapes, including spindle, plasmocytoid, clear cell and epithelioid ones. The surface epithelium may be flattened and there may be ulceration; conversely, some OMMs induce pseudoepitheliomatous hyperplasia of the mucosal epithelium. Shivas and Maclennan described the presence of melanin pigment in the ductal epithelial cells of the underlying salivary glands, using the term “melanogenic metaplasia”.

Usually, OMM can be diagnosed with confidence on H&E-stained sections. If pigment is completely absent immunohistochemical stains are of significant help. Useful markers include S-100 protein, gp100 (HMB-45), Mart-1 (Melan-A).

OMM does not fit well into any of the classical cutaneous melanoma categories like superficial spreading melanoma (SSM), nodular melanoma (NM) and acral lentiginous melanoma (ALM). There is, however, often some similarity to ALM and NM.

The pathology report should include all information necessary for further treatment planning, such as the extent of tumour, tumour spread in relation to underlying and surrounding tissues, and a statement on the completeness of resection. In many centers, some additional information of established or possible prognostic significance will be added: tumor thickness, presence of ulceration and necrosis, tumor mitotic rate (TMR), vascular invasion. Finally, it is advisable to specify cell morphology and tumour tissue architecture.

6. Terminology and classification

The term *atypical melanocytic proliferation* has been used in case of oral melanocytic lesions in which microscopic evaluation does not result in an
unequivocal diagnosis. Atypical melanocytes have been defined as melanocytes with hyperchromatic and angular nuclei, but with infrequent mitotic figures. In some studies this histologic pattern has been called “atypical melanocytic hyperplasia.” However, since the word “hyperplasia” suggests a reactive rather than a neoplastic origin, the term “proliferation” seems to be preferred here.

**Lentigines** are small, round to oval, brown or black macules. In the skin several types of lentigo such as lentigo simplex (LS), and lentigo maligna (LM) are recognized. The term “lentigo” alone has sometimes been used to refer to lentigo simplex. LS is histologically characterized by heavy pigmentation of the basal layer, with increased numbers of basal melanocytes, typically, but not always, associated with elongation of the rete ridges.

LM is a cutaneous lesion occurring in sun-damaged skin, usually in elderly persons, most frequently on the face. Histologically, it consists of a proliferation of atypical melanocytes, in lentiginous patterns, within a flat and atrophic epidermis, and often extending into cutaneous adnexae. LM is generally regarded as the pre-invasive phase of lentigo maligna melanoma (LMM), but it should be realized that only a very few percent of cases, if untreated, will progress to invasive melanoma. LM has also been referred to as *morbus Dubreuilh*, or *Hutchinson’s freckle*. The term LM should not be applied to lesions of the oral mucosa, because of absence of sun damage at that site.

The term *melanoacanthoma* has been used to describe a benign mixed tumor of keratinocytes and pigmented-laden dendritic melanocytes. In contrast to cutaneous melanoacanthoma, oral lesions occur almost exclusively in Blacks, affect a much younger population, develop rapidly and generally have a flat surface. Oral melanoacanthoma is thought to be reactive in nature, and regression is usually observed after elimination of traumatic factors.
7. Staging system

The histological microstaging system of Clark, used in cutaneous melanoma, cannot be applied to oral mucosa because of the lack of histologic landmarks analogous to papillary and reticular dermis.\textsuperscript{50, 56, 57} The 2002 (revised) TNM Melanoma Staging System of the American Joint Committee on Cancer, applying the T-symbol for the thickness and the ulceration status of the tumour, the symbol N for the regional lymph nodes, the symbol M for distant metastases and the serum lactic dehydrogenase (LDH) level,\textsuperscript{58} does not provide specific guidelines for OMM.

A simple TNM clinical staging system for HNMM (including OMM), shown in Table 1, recognizing three stages, has shown to be of prognostic value.\textsuperscript{10, 50, 51, 59} A recent histopathological microstaging for Stage I subclassifies three levels (Table 1)\textsuperscript{50}.

<table>
<thead>
<tr>
<th>Table 1. Clinical Staging System for OMM with histopathological microstaging for Stage I</th>
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<tr>
<td>Stage I: Primary tumour present only (Tany N0M0)</td>
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<tr>
<td>Level I: Pure in situ melanoma without evidence of invasion or in situ melanoma with “microinvasion”</td>
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<tr>
<td>Level II: Invasion up to the lamina propria</td>
</tr>
<tr>
<td>Level III: Deep skeletal tissue invasion into skeletal muscle, bone or cartilage</td>
</tr>
<tr>
<td>Stage II: Tumour metastatic to regional lymph nodes (Tany N1M0)</td>
</tr>
<tr>
<td>Stage III: Tumour metastatic to distant sites (Tany Nany M1)</td>
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8. Treatment

Treatment of OMM is still controversial and there is no consensus regarding the best therapeutical approach \(^6, ^{10}, ^{60}\). Data from several studies indicate radical resection of the primary as the treatment of choice \(^5, ^6, ^{10}, ^{51}, ^{61}, ^{62}\). Surgery could be combined with radiotherapy, chemotherapy or immunotherapy even though the effectiveness of such therapies both as primary or in association with the surgical treatment is mostly unknown.

8.1 The role of surgery, including the policy with regard to the neck

Unlike cutaneous melanoma, where randomized clinical trials have been carried out to establish the optimal width of the tumour-free margins, no guidelines are available for the surgical treatment of OMM. A protocol adopted by Umeda and Shimada \(^63\) refers to the extent of the margins:

1. excision of the primary lesion, preferably using an intraoral approach and involving at least 1.5 cm of healthy tissue.
2. Excision of any lymph node metastases (Stage II).
3. Consider chemotherapy.

Unfortunately, local control is not a strong predictor for survival \(^10\). Many patients with a presumptive radical excision of tumours develop a recurrence \(^5\), which may be explained by the presence of atypical melanocytes in the surgical margins and/or the presence of satellites \(^6\).

Controversy still remains on the issue of prophylactic neck dissection \(^3, ^{64}\). Patients with primary OMM present lymph node metastasis in 25% of cases and this incidence is higher than HNMM at other sites \(^{51}\). According to Tanaka et al.\(^{60}\), neck dissection should be reserved for cases with preoperatively confirmed lymph node metastases and the choice of the neck dissection modality should be guided by the extent and the level of the nodes. There is no proof that elective nodal dissection improves survival. To our knowledge, no data are available on the issue of the sentinel node biopsy or on the use of PET scanning in OMM except from the study of Goerres et al \(^31\).
8.2 The role of primary and postoperative radiotherapy

Most of the studies on the effects of primary radiotherapy have been performed on the entire group of HNMM and specific data on OMM are scarce \(^{51,65}\). In a study on 35 patients with OMM, Tanaka et al. observed a 5-year cumulative survival rate of 35.5\% in the group of patients treated with irradiation alone, while it was 15.4\% for patients treated with surgery \(^{60}\). Postoperative radiotherapy is generally recommended if poor prognostic pathologic features are present, such as multiple positive nodes, or extranodal spread of metastastic melanoma, even though OMMs are regarded as poorly radiosensitive \(^{5,10}\). Apparently, postoperative radiotherapy does not seem to improve the survival rate, even though on this point, no agreement exists in the literature \(^{6,10,51}\). Temam et al. recently found that in a group of 69 patients affected by HNMM, including 19 with primary OMM, postoperative radiotherapy was useful for increasing local control \(^{66}\). Current postoperative radiotherapy for cutaneous melanoma delivers 30 Gy or 24 Gy, e.g., in five fractions of 6 Gy spread over 2.5 weeks or 3 weeks \(^{67,68}\). Other irradiation modalities such as intraoral mould (\(^{60}\)Co, \(^{192}\)Ir, or \(^{198}\)Au), intraoral electron beam or interstitial brachytherapy have also been used \(^{69}\).

8.3 Other therapies

Adjuvant chemotherapy with decarbazine, platinum analogs, nitrosureas, and microtubular toxins have been used for palliative purposes or for therapy of metastatic melanoma, but does not seem to influence survival \(^{6}\). Umeda and Shimada \(^{63}\), suggested dimethyl triazeno imidazole carboxamide (DTIC), nimustine hydrochloride (ACNU) or vincristine (VNC) as drugs of choice for postoperative chemotherapy.

Anticancer therapy using IFN-\(\gamma\) and anti-Fas antibody has shown positive results against OMM cells in an experimental model \(^{70}\).

Systemic immunotherapy has been used as adjuvant or for palliation in the treatment of disseminated disease. Immunotherapy with IL-2 and other
cytokines is not associated with an enhanced survival rate. The definition of the so-called cancer testis antigens (CTAs) expression profile in OMM could lead to the development of a new vaccine-based therapy. Gene therapy is still in an experimental phase.

9. Prognostic factors and survival

From a prognostic point of view, clinical stage at presentation is probably the most important factor in determining outcome. In a study on 230 patients surgically treated for OMM, Liu et al. found that thickness of the tumour, cervical lymph node metastasis, presence or absence of ulceration and the anatomic sites were all independent risk factors. It has been calculated that nodal involvement in OMM reduces the median survival time from 46 to 18 months. Furthermore, a tumour thickness greater than 5 mm, presence of vascular invasion, necrosis, polymorphous tumour cell morphology and the inability to properly resect the lesions with negative margins have been associated with poor survival in patients with primary HNMM.

Despite the improvement of surgical techniques and the introduction of new chemotherapeutic agents, prognosis of this malignancy remains poor. The generally advanced stage of the tumour at initial diagnosis leads to a poorer survival of patients with mucosal melanoma as compared to patients with cutaneous melanoma. and the presence of a vertical growth phase are associated with a reduced median survival rate.

In different series, the actuarial 5-year overall survival rate for HNMM ranges from 21% to 40% and for OMM it is 15% with a median survival of 25 months. Gingival melanoma has a better 5-year survival rate than palatal melanoma, with a longer median survival period (46 months versus 22 months). Recurrences may occur even 10–15 years after primary therapy. Distant metastases to the lungs, brain, liver and bones are frequently observed.
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Chapter 3


Oral malignant melanoma: a review


Chapter 4.


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Abstract

Purpose. To report the clinical, pathological and therapeutical experience with a group of patients with primary oral malignant melanoma (OMM).

Patients. 14 patients (5 males, 9 females, mean age 57.9 years) with histopathological diagnosis of OMM were treated at the Department of Oral and Maxillofacial Surgery/Oral Pathology of the Vrije Universiteit Medical Centrum (VUmc) in Amsterdam between 1978 and 2005. A pigmented, flat or swollen, irregularly bordered lesion of oral mucosa was detected in most patients during the first clinical examination. Pain was the most commonly referred symptom. The palate was the most frequently affected subsite. Following the mucosal melanoma microstaging system all patients staged as stage I (TanyN0M0) could be subclassified as microstage II (invasion up to the lamina propria), except one who was microstaged as III (deep skeletal tissue invasion into skeletal muscle, bone or cartilage). Where possible, surgery has been the treatment of choice. Postoperative radiotherapy, using fractions of 6 Gy twice a week for a total dose of 330 Gy, was given to 3 patients. Three patients were primarily treated with radiotherapy alone.

Results. Five patients developed a local recurrence within a period of 4 to 72 months and 10 patients developed distant metastases within a period of 6 to 78 months. Ten patients died of their disease within an average interval of 40 months, with a range of 12 to 80 months. Of the ten patients who qualified for evaluation of the five-year-survival rate, one was alive with disease and two were alive without evidence of disease, which results in a five-year survival rate of 30%. However, all patients have died of their disease before the end of the ten-year follow-up period.

Conclusions. Our study confirms that OMM is a rare and aggressive malignancy with a low five-year-survival rate. No evidence-based protocol is available for the best therapeutical approach.
1. Introduction

The incidence of head and neck mucosal melanomas (HNMMs) is approximately four per 10 million population per year in the USA. Oral malignant melanomas (OMMs) represent about 1% of all melanomas and approximately the 0.5% of all oral malignancies. The neoplasm is more common in Japan and in some african regions (e.g. Uganda) than in Western countries. The age of reported patients affected by OMM ranges from 20 to 80 years and a male predilection has been observed. OMM mostly affects the palate and the maxillary gingiva. The possible role of chronic trauma (e.g. ill-fitting dentures), tobacco habits or environmental pollution as “promoter” factors has not been established. It is largely unknown if UV light can have some effects on the oral mucosa biology (especially for mouth-breather patients) as it happens for the sun-exposed skin. Combinations of surgery, radiotherapy and chemotherapy for the management of OMM have variously been reported. The prognosis of this malignancy is extremely poor, with a five year survival ranging between 15% and 20%. Metastasis to the oral cavity derived from a primary melanoma elsewhere in the body, is extremely rare. In 1994 we have reported 8 cases of primary OMM treated at the Vrije Universiteit Medical Center (VUmc) in Amsterdam between 1978 and 1993. The present review is based on our experience with six additional patients referred to our institution between 1994 and 2005.

2. Patients and Methods

Clinical and histopathological data from 14 patients with a diagnosis of OMM, referred to the Department of Oral and Maxillofacial Surgery of VUmc in Amsterdam between 1978 and 2005, were included in this study. There were five males and nine females (table 1). The age of the patients ranged from 31 to 91 years (average 57.9 years). At first clinical evaluation, presence of a pigmented, flat or swollen, irregularly bordered lesion of oral mucosa was noticed in 12 out of 14 patients while a non-
pigmented swelling was recorded in two cases (amelanotic melanoma). In three cases, lesions were superficially ulcerated. Colours observed were brown, black or purple. The size ranged from 0.3 to 1.8 cm in diameter. Pain was the most common referred symptom. The palate was the affected subsite in 9 out of 14 patients (64%); in three cases the lesions were localized in the edentulous maxilla; one patient presented involvement of the buccal mucosa and one of the tongue. No reliable information was available about the presence or absence of pre-existing melanotic pigmentations in the oral subsite where OMM developed, except for one patient in whom a benign melanotic pigmented lesions was removed four years previously (patient 12) and another patient who had been irradiated six years before because of a malignant melanoma of the left cheek mucosa (patient 7).

In all patients an incisional biopsy was performed. Immunohistochemical markers such as S-100 protein, gp100 (HMB-45) and Mart-1 (Melan A) were used in case of doubt. Applying the histopathological system used in the WESTOP Banff workshop proceedings on OMMs all but two lesions could be subclassified as in situ lesions with neoplastic activity limited to epithelium or to epithelial-connective tissue interface. Cases 6 and 14 were characterized by tumour extending within the underlying connective tissue. According to the clinical staging system (7, 9) (table 2), patients without regional lymph node metastases were subclassified as stage I (TanyN0M0) (13 patients), while one patient with clinical positive regional lymph nodes was staged as II (TanyN1M0). Following the mucosal melanoma microstaging system after Prasad et al. (10) (table 2) all patients staged as I (TanyN0M0) could be subclassified as microstage II (invasion up to the lamina propria) except patient 6 who was microstaged as III (deep skeletal tissue invasion into skeletal muscle, bone or cartilage).

Ten out of 14 patients received radical surgery without neck dissection as primary treatment. Simultaneous neck dissection was performed in one patient with preoperatively confirmed lymph node involvement. Postoperative
Radiotherapy, using fractions of 6 Gy twice a week for a total dose of 30 Gy, was given to three patients. Three patients were primarily treated with radiotherapy alone.

Disease specific survival rates were recorded after five and ten years, respectively.

Table 1. Relevant clinical features of fourteen patients treated between 1978 and 2005.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (in years)</th>
<th>Gender</th>
<th>Site</th>
<th>TNM + microstaging</th>
<th>Treatment of the primary</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>68</td>
<td>M</td>
<td>Edentulous maxilla</td>
<td>I-II</td>
<td>Radiotherapy</td>
</tr>
<tr>
<td>2</td>
<td>65</td>
<td>M</td>
<td>Palate</td>
<td>I-II</td>
<td>Surgery + radiotherapy</td>
</tr>
<tr>
<td>3</td>
<td>33</td>
<td>F</td>
<td>Palate</td>
<td>I-II</td>
<td>Surgery</td>
</tr>
<tr>
<td>4</td>
<td>46</td>
<td>F</td>
<td>Edentulous maxilla / palate</td>
<td>I-II</td>
<td>Surgery</td>
</tr>
<tr>
<td>5</td>
<td>56</td>
<td>M</td>
<td>Edentulous maxilla</td>
<td>I-II</td>
<td>Surgery</td>
</tr>
<tr>
<td>6</td>
<td>56</td>
<td>F</td>
<td>Palate</td>
<td>I-III</td>
<td>Surgery</td>
</tr>
<tr>
<td>7</td>
<td>91</td>
<td>F</td>
<td>Palate</td>
<td>I-II</td>
<td>Radiotherapy</td>
</tr>
<tr>
<td>8</td>
<td>82</td>
<td>F</td>
<td>Palate</td>
<td>I-II</td>
<td>Surgery</td>
</tr>
<tr>
<td>9</td>
<td>71</td>
<td>M</td>
<td>Palate</td>
<td>I-II</td>
<td>Radiotherapy</td>
</tr>
<tr>
<td>10</td>
<td>61</td>
<td>F</td>
<td>Palate</td>
<td>I-II</td>
<td>Surgery</td>
</tr>
<tr>
<td>11</td>
<td>59</td>
<td>F</td>
<td>Palate</td>
<td>I-II</td>
<td>Surgery</td>
</tr>
<tr>
<td>12</td>
<td>54</td>
<td>M</td>
<td>Palate</td>
<td>I-II</td>
<td>Surgery</td>
</tr>
<tr>
<td>13</td>
<td>38</td>
<td>F</td>
<td>Tongue</td>
<td>I-II</td>
<td>Surgery + radiotherapy</td>
</tr>
<tr>
<td>14</td>
<td>31</td>
<td>F</td>
<td>Buccal mucosa</td>
<td>II</td>
<td>Surgery, including neck dissection + radiotherapy</td>
</tr>
</tbody>
</table>
Chapter 4

Table 2. Clinical staging system for OMM with histopathological microstaging for Stage I 10.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Primary tumour present only (T any N0M0)</td>
</tr>
<tr>
<td>Level I</td>
<td>Pure in situ melanoma without evidence of invasion or in situ melanoma with</td>
</tr>
<tr>
<td></td>
<td>“microinvasion”</td>
</tr>
<tr>
<td>Level II</td>
<td>Invasion up to the lamina propria</td>
</tr>
<tr>
<td>Level III</td>
<td>Deep skeletal tissue invasion into skeletal muscle, bone or cartilage</td>
</tr>
<tr>
<td>II</td>
<td>Tumour metastatic to regional lymph nodes (T any N1M0)</td>
</tr>
<tr>
<td>III</td>
<td>Tumour metastatic to distant sites (T any N any M1)</td>
</tr>
</tbody>
</table>

3. Results

Complete resection of the primary was achieved in 7 out the 11 patients that received surgery as first treatment (table 3).

Five patients developed a local recurrence within periods of 4 to 72 months. None of these recurrent tumours could successfully be treated.

Regional metastases were present in one patient at initial admission, while six patients developed such metastases within periods of 2 to 21 months. Treatment of such regional metastases consisted in most patients of radical neck dissection followed by radiotherapy.

Distant metastatic spread occurred in 10 patients within periods of 6 to 78 months. The most commonly involved sites were the lung, the mediastium, and the liver with rare metastatic spread to the adrenal glands, thyroid glands, pancreas, atrium and the skin. Some of these distant metastases were only disclosed at autopsy. In one patient a lobectomy was performed, unsuccessfully. In one other patient with lung metastases, treatment with dimethyl-triazeno imidazole carboxamide (DTIC) once every four weeks in a dose of 800 mg/m2 was administered. Although there was a good response of the lung lesions, the patient developed a metastasis in one of the adrenal glands and finally died of the disease. Yet two patients were unsuccessfully
treated for distant metastases in the lung and the liver with gammainterferon and interleukin 2.
Of the 11 patients who had at least a follow-up of 12 months and of whom complete follow-up information was available, ten died of their disease within an average interval of 40 months, with a range of 12 to 73 months. Of the ten patients who qualified for the five-year-survival rate, seven had died of their disease, one was alive with disease and two were alive without evidence of disease. The latter 3 patients died of their disease within the ten-years follow-up period.
The follow-up data are summarized in table 3.
4. Discussion

Most of the epidemiologic, histopathologic and clinical features of our patients were in accordance with those reported in the literature. The incidence in females was almost twice as high as in males, which is in contrast with the finding in a few other papers where a higher prevalence was reported in males \(^2,9\). The palate was the most commonly oral subsite involved.
Oral malignant melanoma: the Amsterdam experience

Our experience confirms that the spectrum of clinical manifestations of these rare tumours is extremely heterogeneous. The lesions can be solitary or multiple, flat and/or elevated (fig. 1), usually dark pigmented even though pigmentation can be completely absent (amelanotic melanoma) \(^3\)\(^,\)\(^11\). Borders of lesions are usually irregular and no clear demarcation exists between the tumor and the adjacent tissues. A melanocytic activity, clinically corresponding to a light brown-black pigmentation gradually fading in the surrounding mucosa, can be observed in most patients.

![Figure 1](image1.png)

**Figure 1.** Malignant melanoma of the palate with a mixed flat/elevated clinical appearance.

Satellite foci around the primary may be present as well (fig. 2) giving some support to the theory of “field cancerization” already proposed for other histological types of malignancy \(^12\).

![Figure 2](image2.png)

**Figure 2.** Malignant melanoma of the palate in a 33-year-old woman. Notice the separate pigmented area caudally.
Pain, superficial ulceration and bleeding were additional signs and symptoms recorded in our patients. One out of 14 (7%) of the patients in this series had regional lymph node involvement at the time of diagnosis. Data form the National Cancer Data Base (NCDB) USA, show that 27% of patients with malignant mucosal melanoma of the head and neck develop regional lymphatic metastases during the course of the disease\(^6,13\).

The existence of an “oral potentially malignant melanocytic lesion” has not clearly been defined and little is known about the pathobiological mechanism that leads to the development of OMM\(^14,15\). According to some authors about 30% of OMMs are preceded by oral pigmnetations for several months or even years\(^2,16\). It is interesting to notice that among pigmented lesions of oral cavity, oral nevomelanocytic nevi (OMNs) and OMMs are mostly localized in the palate\(^17\) and this finding may lead to the hypothesis that subtypes of OMNs could represent precursor lesions in the pathogenesis of OMM. Documentation on the presence of a pre-existing melanotic pigmentation in the same subsite where OMM developed was available only for one patient of our series.

From the diagnostic point of view several procedures have been cited in the literature including cytological examination of brushed samples and clinical methods such as “rubbing a gauze”\(^18,19\).

Histopathological examination of an incisional or excisional biopsy still represents the most accurate diagnostic tool. In the guidelines provided for the surgical management of cutaneous melanoma a diagnostic excisional biopsy of the suspected lesion is recommended followed by a wide local excision when the diagnosis is proven.\(^20-22\). In the head and neck region, however, an excisional biopsy with a 1- to 2-mm margin for small lesions in amenable locations, or an incisional biopsy in case of a large lesion or a location in sites where an excisional procedure would involve extensive and mutilating surgery seem to be preferred because of the presence of anatomical limitations\(^23\). In all the cases we faced, an incisional biopsy has been performed since the large
dimensions of the tumor and/or the close relationship to teeth or vital structures, precluded an excisional biopsy.

It should be borne in mind that surgical diagnostic or therapeutical procedures performed on malignant neoplasms could hypothetically increase the risk of malignant cells spreading in the adjacent tissues (so-called “seeding”) or in other parts of the body through the blood or lymphatic stream \(^{24,25}\). Such an iatrogenic dissemination might play a part in the pathogenesis of recurrences or distant metastases. Results from studies by Rampen et al. and Austin et al. \(^{26,27}\) show a somewhat reduced survival rate in patients with melanoma who had incisional biopsies. Conversely, results from a retrospective study on 265 patients who had an incisional biopsy of cutaneous melanoma and 496 control cases of excisional biopsy, did not show such correlation \(^{28}\); other authors seem to support these findings \(^{29,30}\). Five, 6 and 10 patients out of the 14 described in the present series respectively developed recurrences, regional and distant metastases. We are not able to quantify which role the incisional biopsy may have played in the development of metastases since such evaluation would require the measurement of the level of specific OMM markers in the blood stream before and after the biopsy.

The value of the sentinel node biopsy for OMM has not been established. Adjunctive radiological diagnostic methods such as computed tomography, magnetic resonance imaging and positron emission tomography (PET) are sometimes useful. In a study on the all group of head and neck mucosal melanomas (HNMMs) Goerres et al. recently reported that PET scanning may have some value for staging purposes \(^{31}\).

From the histopathological point of view our experience confirms the usefulness of the WESTOP subclassification for uniform reporting and staging \(^3\). The pathology report should also indicate the OMM cellular subtype as well as the presence of atypical findings. Our cases showed a wide range of cellular morphological features such as spindle, plasmacytoid, epithelioid and clear cells. In one of our patients we also observed and recently reported in detail the
an extremely rare histological association between OMM and pseudoepitheliomatous hyperplasia. Presence of melanin pigment in the ductal epithelial cells of the underlying salivary glands was described in another case. This feature has rarely been reported and has previously been named “melanogenic metaplasia.”

Complete excision of the primary tumour, with radiotherapy, chemotherapy or immunotherapy as adjuncts, has been the treatment of choice, although the value of adjuvant treatment has not been established. A 1-2 cm tumour-free margin, generally required and accepted for cutaneous melanoma, can rarely be applied in the oral cavity. Nevertheless, local control does not seem to be a strong predictor for survival and even after a presumptive radical excision of tumours many patients develop a recurrence. Some factors potentially implied in the pathogenesis of recurrence may be related to the stimulation of tissues by growth factors after surgery and to the difficulty of obtaining a complete excision. Thus, despite a presumptive radical surgery of the primary, the microscopic evaluation of the specimen may reveal the presence of atypical melanocytes in the margins. In the present evaluation, a radical excision of the primary was achieved in 7 of the 11 patients treated with surgery. Nevertheless all of them experienced recurrence and/or metastases (table 3). The question as whether the usual poor outcome of this disease should condition the surgical approach remains unanswered.

The policy with regard to the treatment of the neck is still controversial. There is no evidence that prophylactic neck dissection enhances survival rate of patients with OMM. According to Tanaka et al., neck dissection should be reserved for cases with preoperatively confirmed lymph node metastases and the choice of the neck dissection modality should be guided by the extent and the level of the nodes. Six out of fourteen patients (43%) developed regional metastases during the follow-up.
Malignant melanoma has been generally regarded as a poorly radiosensitive malignancy. Data on the possible role of primary and postoperative radiotherapy in the management of OMM are scarce and mostly refer to the entire group of HNMM. In a study on 35 patients affected by OMM primary radiotherapy appeared to be more effective than surgical treatment when the 5-years cumulative survival rates were compared. Postoperative radiotherapy could be of some usefulness especially when prognostic pathologic features are poor (e.g. histopathological evidence of no radical excision or regional lymph node involvement). Teman et al. recently found that postoperative radiotherapy did improve local control in a group of 69 patients affected by HNMM, including 19 patients with primary OMM. In the present report, 3 patients received primary radiotherapy and 3 had postoperative radiotherapy. This small number of patients does not allow to draw statistical conclusions on the effectiveness of radiation in the treatment of OMM. Adjuvant chemotherapy does not seem to influence survival.

Prognosis of this malignancy remains extremely poor. In different series, the actuarial-5 year overall survival rate for HNMM ranges from 21% to 40% and for OMM approximately 15% with a median survival of 25 months. Gingival melanoma seems to have a better 5-year survival rate than palatal melanoma, (46 months vs. 22 months of median survival period). In the present report recurrences developed within a period of 4 to 72 months even though lesions occurring on the same subsite of the primary have been reported after 10-15 years.

The relatively small number of included cases does not allow us to make significant statements about a possible relationship between staging, treatment and prognosis. Early diagnosis might be essential for successful treatment and is perhaps the key factor for improving the prognosis of OMM, but this still has to be proven.
References


Oral malignant melanoma: the Amsterdam experience


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Chapter 5.


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Chapter 5

Abstract

Background: Pseudoepitheliomatous hyperplasia (PEH), a histological mimic of squamous cell carcinoma, is an exuberant reactive epithelial proliferation that may be induced by a variety of infectious, traumatic, inflammatory and neoplastic conditions of the skin and mucous membranes. PEH has been described in association with Spitz nevi and intramucosal nevi but not with oral malignant melanoma.

Methods and results: A case of PEH in malignant melanoma of the palate in a 46-year-old female patient has been described. A search of the English literature did not disclose any previously reported case of such event.

Conclusions: PEH associated with oral malignant melanoma is apparently very rare and most likely originates from the surface epithelium. This is in contrast with PEH in cutaneous melanoma where follicular or eccrine units have been suggested to be the origin.
1. Introduction

Pseudoepitheliomatous hyperplasia (PEH) or pseudocarcinomatous hyperplasia is a reactive proliferation of surface epithelium, occasionally occurring in a variety of infectious, traumatic, inflammatory, and neoplastic conditions of the skin or mucous membranes. Diseases of the skin commonly associated with PEH include mycobacterial, fungal, and parasitic infections as well as chronic irritations and neoplasms. PEH has also been reported at the edges of chronic ulcers after burns or in stasis dermatitis. As stated by Hanly et al., Mott et al., and by Filho, association of PEH with melanoma of the skin has not been documented in detail.

In the oral mucosa, PEH has been described in association with granular cell tumor and pleomorphic adenoma. Dorji et al. and Suzuki et al. described Spitz nevi and intramucosal nevi of the oral cavity associated with PEH but, to the best of our knowledge, no case of oral malignant melanoma (OMM) with PEH has thus far been described.

PEH of the skin is thought to represent a proliferation of squamous epithelium of follicular and eccrine units or the epidermis itself. Considering the absence of the follicular apparatus in the oral cavity, some authors have hypothesized a histogenic origin from minor salivary glands or ectopic sebaceous glands for PEH at this site.

We report a patient with malignant melanoma of the oral cavity with associated PEH.
2. Case report

A 46-year-old woman was referred to the Department of Oral and Maxillofacial Surgery for multiple areas of brown-black flat pigmentation involving the edentulous maxilla, partly located on the palate and partly on the adjacent alveolar ridge (Fig. 1). The patient was otherwise healthy.

A biopsy of the most suspicious area on the anterior part of the palate showed malignant melanoma associated with PEH of the surface epithelium (Figs 2 and 3).

Figure 1. Malignant melanoma involving the palate and the maxillary gingiva.

Figure 2. Histologic features of oral malignant melanoma in association with pseudoepitheliomatous hyperplasia of the overlying epithelium, more or less masking the malignant melanoma cells (H&E ×50; microstage level II).

Figure 3. Pseudoepitheliomatous hyperplasia. Higher magnification (H&E 100).
Clinically, there were no signs of regional or distant metastases. CT scanning of the maxilla did not show destruction of the underlying bone. Further work-up, including CT of the thorax, did not show the presence of metastases. According to the TNM staging system proposed for mucosal melanoma of the head and neck (Stage I: localized disease; Stage II: regional metastases; Stage III distant metastases), the patient was subclassified as Stage I. The histopathological microstaging of Clark, used in cutaneous melanoma, cannot be applied to oral mucosa because of the lack of histologic landmarks analogous to papillary and reticular dermis. A recently proposed microstaging system for Stage I recognizes three levels:

1. Level I: pure in situ melanoma without evidence of invasion or in situ melanoma with microinvasion
2. Level II: invasion up to the lamina propria
3. Level III: deep tissue invasion into skeletal muscle, bone, or cartilage

The present case has been microstaged level II. Treatment consisted of a maxillectomy. The defect was temporarily closed with a prosthesis. Two years later, a second malignant melanoma, most likely a second primary, was observed on the right cheek mucosa. This lesion was surgically removed as well. Two months later, a lymph node metastasis developed on the right side of the neck. Radical neck dissection with post-operative radiotherapy was performed. A few months later, local and regional recurrence was noticed. In addition, metastases were detected in the mediastinum, the lungs, and in the liver. The patient was treated with dimethyl triazino imidazole carboxamide chemotherapy once every 4 weeks in a dose of 800 mg/m². A total of 15 courses of chemotherapy were administered. Clinically, there was a partial response, but 6 months later a metastasis was diagnosed in one of the adrenal glands, the patient refused additional treatment, and died 1 year later.
3. Discussion
The distinction between malignant melanoma with PEH and pigmented squamous cell carcinoma (SCC) can be difficult on routine hematoxylin–eosin sections. Histologically, PEH is characterized by irregular cords and nests of epithelial cells, extending into the underlying connective tissue. The irregular contour of nests and strands, hyperkeratosis and papillomatosis, and the presence of occasional squamous pearls and of mitotic activity may lead to an erroneous diagnosis of SCC 1, 2. The identification of the underlying disorder (e.g. granular cell tumor) and the absence of nuclear atypia, abnormal mitotic figures, or individual dyskeratotic keratinocytes are the key features that characterize PEH 2, 3.

In the present case, the presence of both melanocytic and keratinocytic cells could also lead to the misdiagnosis of a tumor with biphenotypic characteristics such as OMM associated with SCC or pigmented SCC. However, the atypical cells of pigmented SCC show strong positivity for cytokeratin and are S-100 negative 16. Our case was characterized by positivity with S-100 but not to cytokeratin, indicative of malignant melanoma associated with PEH.

The origin of PEH in oral mucosa is unclear. Where for the skin a stimulated proliferation of squamous epithelium within follicular and eccrine units has been hypothesized, the same theory cannot be applied to the oral mucosa, because of the lack on non-hair-bearing squamous-lined mucosae of the follicular apparatus 3, 6, 10, 11. Even if a role of the so-called Fordyce’s spots (ectopic sebaceous glands) could be postulated, we would stress the fact that some oral lesions typically associated with PEH (e.g. granular cell tumor) usually develop within oral sites in which these glands are uncommon (e.g., dorsal surface of the tongue). Some authors have also suggested a histogenic origin from minor salivary glands for PEH in this site, but there is no consensus in the literature 3.

Several growth factors (EGF, TGF-α, TGF-β, bFGF, and PDF) and interleukins (IL-1, IL-6, IL-7, IL-8, IL-10, and IL-12) expressed by in vitro melanoma could provide the proliferative stimulus to the epithelial cells 17. Some authors have
emphasized the possible role of the epidermal growth factor receptor in the molecular pathogenesis of melanoma-associated PEH, but results from different studies are inconclusive. Although we cannot provide definitive proof of the structure giving rise to the PEH, we feel that its presence along much of the surface epithelium, in the absence of underlying salivary gland tissue, and as illustrated in Figs 2 and 3, is most compatible with an origin from the surface epithelium itself. In conclusion, although some studies on the rare association between cutaneous melanoma and PEH have been reported in the English literature, we were not able to find such as association for OMM. The present case report documents this intriguing feature of PEH in association with OMM.
Chapter 5

References


Chapter 6.

Melanotic pigmentation of palatal salivary glands; Report of an unusual case.

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Submitted

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Abstract

Presence of melanin pigment within the epithelial cells of minor salivary glands ("melanotic pigmentation") is an exceptionally rare finding and to the best of our knowledge only one documented case, in association with a malignant melanoma, has been described.

In the present paper, a case of melanotic pigmentation of the palatal minor salivary glands is reported. Four years later the patient developed a malignant melanoma at the junction of the hard and the soft palate.
1. Introduction

Melanocytes are embryologically derived from the neural crest and are generally thought not to be constituents of normal salivary tissue \(^1,2\). However, Takeda documented the presence of pigmented cells, most likely melanocytes, in 1.8% of 445 specimens from autopsies and biopsies of human minor salivary glands \(^3\). Melanin-containing cells have also been observed within salivary gland tumours as well as in minor salivary glands adjacent to oral malignant melanoma (OMM) \(^2,4,5\). Phagocytosis and transfer of melanin from melanocytes to other cells types are the two possible explanations for the presence of melanin pigment within the cytoplasm of non-melanogenic cells.

The present case reports the finding of melanotic pigmentation of the ductal cells of minor salivary glands of the palate in the presence of melanosis in the overlying mucosal epithelium and the subsequent development of an OMM, four years later. A review of the English literature disclosed only one somewhat similar case \(^5\).

2. Case report

A 50-year-old man was referred to the Department of Oral and Maxillofacial Surgery/Oral Pathology of the Free University Medical Centrum in Amsterdam because of a pigmented lesion in the oral cavity. Intraoral evaluation showed the presence of a flat, irregularly-shaped, not uniformly pigmented lesion localized on the left side of the hard palate. The lesion was predominantly brown-black, measured approximately 1.5 cm and was surrounded by several minor brownish pigmements (Figure 1). Symptoms were absent and no palpable regional lymph nodes could be detected in the neck. The medical history was essentially negative. The patient did not use any medication. He did not smoke and drank approximately one glass of wine per day.
Under the tentative clinical diagnosis of melanotic macule an excisional biopsy was performed, that included the underlying periosteum. The defect was covered with a skin graft. Histopathological evaluation showed the presence of melanin pigment in the basal layer of the mucosal epithelium. There were no distinct signs of melanocytic atypia. In one of the underlying salivary gland lobules several pigmented epithelial cells were observed in the interlobular and excretory ductal cells. Morphology and architectural pattern resembled those of normal epithelial duct cells with the exception for the presence of intracytoplasmic pigment, staining positive for melanin (Figures 2 and 3).
Figure 2. Presence of melanin pigment within the ductal epithelium of a minor salivary gland in the margin of the surgical specimen (H&E stain; x 50).

Figure 3. Presence of melanin pigment within the ductal epithelium of a minor salivary gland.(H&E stain; x 100).
Follow-up visits were scheduled twice a year. After four years, a white-yellowish soft tissue mass, surrounded by pigmentation, was noticed in the midline at the junction of the hard and the soft palate (Figure 4). An incisional biopsy was performed and histopathological evaluation revealed the presence of a truly invasive malignant melanoma. Further work-up, including a CT-thorax, did not show the presence of regional or distant metastases, resulting in Stage I, according to Patel et al. Treatment consisted of a partial maxillectomy. The surgical margins were free in all directions and there was no bone invasion. One year later there was a local recurrence and at the same time a pancreatic metastasis was detected. The patient died one year thereafter.

![Image](image.png)

**Figure 4.** Oral malignant melanoma developed four years after the diagnosis of possible neoplastic melanocytic proliferation with extension of melanin into the salivary ductal cells.

### 3. Discussion

OMM is a rare and aggressive neoplasm of melanocytic origin, accounting for about 1% of all oral malignancies. Approximately one third of OMMs are
preceeded for months or years by a melanotic macule but the histopathologic nature of such entity is still poorly understood. Oral melanocytic naevi (OMNs) and OMM display similar epidemiological features such as age at occurrence and the frequent involvement of the palate. However, in the present case there has been no evidence of a pre-existing melanocytic nevus.

Presence of melanin pigment within the epithelial cells of minor salivary glands is an exceptional finding. The biological mechanism underlying this phenomenon is unknown although several hypotheses have been put forward. Shivas and Maclellan excluded the concept of a phagocytic property of the salivary gland cells leading to the ingestion of melanin produced in melanocytes elsewhere. Instead, They interpreted their finding as melanogenic metaplasia of mucous cells. In the case of a pigmented mucoepidermoid carcinoma of minor salivary glands of the palate, Sekine et al. speculated about the possible presence of a “migration factor” from cancer cells to pre-existing melanocytes acting as a stimulating factor for melanin production, being delivered to the adjacent cells. In another report of a pigmented pleomorphic adenoma and a pigmented mucoepidermoid carcinoma, Takeda et al. stated that quiescent melanocytes of salivary glands can be activated under certain conditions such as the presence of neoplastic changes. Azzopardi et al. investigated melanin pigmentation in breast carcinomas and also mentioned the possible existence of a cancer cell-related factor stimulating the adjacent melanocytes. Sakaki et al. reported seven cases of “melanotic oncocytic metaplasia” of the nasopharynx, hypothesizing a neuropeptidergic stimulation of the melanocytes and a deposition of melanin within the metaplastic oncocytes. A possible stimulating influence of tobacco smoke on melanocytes was also mentioned by these authors. The phenomenon of melanocytic colonization of neoplasms, reported for malignancies on other sites, may probably occur also in salivary glands tumours.

Takeda et al. identified pigmented cells, most likely melanocytes, in only 1.8% of 455 specimens from minor salivary glands. These cells were located in the
periductal and periacinar fibrous tissue close to the epithelial surface. They displayed a concentric-circular arrangement and were gathered in groups or presented as single cells not connected to epithelial cells \(^3\). In another series, pigmented cells were observed in the interlobular duct of the parotid gland of only one out of 400 cases \(^{14}\). In the present case, we were not able to demonstrate the presence of melanocytes around the pigmented duct cells. On the basis of the present knowledge we have no convincing hypothesis to explain the presence of melanin pigment within the salivary gland ductal cells. Most likely there has been a transfer of the melanin produced by epithelial melanocytes into the ductal cells of the underlying salivary glands. The concept of “melanogenic metaplasia” as being proposed by Shivas and McLennan \(^{5}\) is an interesting one. However, until now there is no scientific evidence to support such concept.
Melanotic pigmentation of minor salivary gland

References


Chapter 7.

Melanocytic nevi of the oral mucosa – No evidence of increased risk of oral malignant melanoma: An analysis of 119 cases.

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Abstract

Pigmented nevi of the oral mucosa are rare benign melanocytic tumours. Epidemiological data are scanty, and the etiology and pathogenesis of these lesions are poorly understood. Reports are mainly based on isolated cases or a relatively small series of cases. Some reviews have drawn attention to the frequent localization of these lesions on the hard palate, the site of preference for oral malignant melanoma (OMM). However, as yet, there is no direct proof that oral melanocytic nevi (OMNs) constitute precursor lesions of OMM. 119 cases of OMNs, registered at the nationwide Registry of Pathology (PALGA) in The Netherlands during the period 1980–2005, have been evaluated. Subepithelial OMNs were the most commonly recorded lesions (96 cases), followed by blue (10 cases), compound (7 cases) and junctional OMNs (5 cases). Only one case of a combined nevus was recorded. None of the patients developed OMM during a mean follow-up period of 8.6 years.

We present an analysis of this series of cases, together with a review of the literature. The findings of the present evaluation do not give support for the hypothesis of OMN being a marker for an increased risk of future development of OMM.
1. Introduction

Oral melanocytic nevi (OMNs) are benign tumours of melanocytes, the pigment producing cells found in the skin and in juxtacutaneous mucous membranes, including the oral mucosa. While cutaneous melanocytic nevi of young adult Caucasians number in the dozens, OMNs are rare, and their etiology and pathogenesis are poorly understood. A Medline database search disclosed approximately 120 articles on OMNs published between 1965 and 2005, most of these being reports of isolated cases or small series of cases. In a review of the literature of 2004, Buchner et al. identified a total number of less than 300 reported OMNs, to which they added a further 91 cases.

The prevalence and incidence of OMNs have not been studied systematically. In Buchner's study from northern California, OMNs represented 0.1% of about 90,000 biopsies accessed at the Oral and Maxillofacial Pathology Laboratory during a 19-year period. The reported female to male ratio was approximately 1.5:1. There was no racial preference. Age at diagnosis ranged from 3 to 85 years.

Regarding etiology and pathogenesis, most studies have focused on cutaneous lesions. It is now clear that melanocytic naevi constitute benign neoplasms of cutaneous melanocytes, which frequently harbour oncogenic BRAF or, less commonly, NRAS or HRAS mutations. Probably, oncogenic mutations drive the initial hyperproliferation that results in the formation of the naevus, while a subsequent growth-arrest response with the features of oncogene-induced cellular senescence accounts for the cessation of further growth.

Different from normal melanocytes which are regularly interspersed as single cells among basal keratinocytes, forming the so-called “epidermal-melanin unit”, nevomelanocytes tend to cluster in compact so-called theques.

In view of the many histologic similarities, it seems plausible that the pathogenesis of OMNs is similar to that of the cutaneous lesions. Regarding morphogenesis, the melanocytic proliferation can be divided into three phases: (1) proliferation of benign neoplastic melanocytes along the submucosal--
mucosal junction (junctional nevus); (2) migration of these cells to the underlying mesenchymal tissue (compound nevi); and (3) loss of the junctional component of the naevus, so that all remaining nevomelanocytes are located within the subepithelial compartment (subepithelial nevi)\(^1\). Congenital melanocytic nevi are present at birth, while those developing after birth are referred to as acquired nevi\(^2\). Probably, most melanocytic nevi of the oral mucosa are acquired\(^5\). Reported size have ranged from 0.1 to, rarely, 3.0 cm\(^4\). OMNs typically are well circumscribed round or oval macules, although slightly raised papules, and polypoid larger lesions have been reported as well\(^1\). OMNs have been reported to occur multiple\(^3\). Elevated acquired nevi are usually lightly pigmented, while flatter lesions tend to be more darkly pigmented\(^1\). Colours vary from brown to blue, bluish-gray, or black; generally an individual lesion has a similar colour throughout\(^1\). Rare non-pigmented nevi are on record\(^3\). The hard palate, buccal mucosa and gingiva are most commonly affected\(^3\). No data in the literature are available regarding presence of symptoms. OMNs are usually discovered during routine dental examinations. The clinical appearance is not diagnostic, so that a biopsy is usually required to exclude other pigmented lesions such as melanotic macula, amalgam tattoo and, most importantly, malignant melanoma\(^3\).

Similarly to their cutaneous counterpart, OMNs are classified in five types: (1) junctional; (2) compound; (3) subepithelial (sometimes referred to as intramucosal); (4) blue and (5) combined\(^5\). In the junctional OMN, nests of nevomelanocytes are arranged along the epithelial–subepithelial junction. Compound and subepithelial nevi are characterized by sheets and cords of nevomelanocytes spreading into the underlying connective tissue. In the subepithelial type the nevus cells are entirely located in the connective tissue compartment,\(^1\) while in the compound nevus, the nevomelanocytes are partly arranged at the epithelial–subepithelial junction and partly in the underlying connective tissue. The blue nevus is characterized by subepithelial proliferation of generally pigmented, elongated, often bipolar, melanocytes,
often accompanied by some stromal fibrotic response and the presence of melanophages. Large, so-called plaque-type blue nevi have occasionally been reported. Another rare variant is the Spitz nevus, a subtype characterized mainly by the large size of the lesional cells. Combined nevi show a combination of a blue nevus with another nevus type, usually a compound nevus.

The aim of the present retrospective analysis is to report the epidemiological and pathologic features as well as the follow-up data of a series of 119 patients with OMNs from the files of the nationwide network and Registry of histo- and cytopathology (PALGA) in The Netherlands in the period between 1980 and 2005. Since 1991 all pathologists in The Netherlands automatically report their diagnoses to that registry. In the period between 1980 and 1991 the participation rate gradually increased from 8% in 1980 to 45% and 96% in 1985 and 1989, respectively. Permission was obtained to retrieve all registered cases of OMNs.

2. Material and methods

Data analyzed in the present retrospective evaluation were obtained from the files of the PALGA Registry of The Netherlands. Criteria adopted for the database search were based on the association of the term “nevus” with “oral mucosa”, “oral cavity”, “mouth” or “alveolar process”. Information on the age and gender, oral subsite, histologic diagnosis, and treatment were obtained. The search disclosed 809 cases recorded between 1st January 1980 and 31st December 2005 (Fig. 1). Of these, 137 lesions could be classified as intraoral; the other cases were located on the lips or the perioral tissues and were excluded from further evaluation. Lesions histologically diagnosed as “melanocytic hyperplasia”, “focal melanosis” or “melanocytic lesion” as well as “white sponge nevus” were excluded from the study. Thus, 119 cases remained for evaluation.
All histopathologic reports were reviewed and OMNs were classified into five groups: junctional, compound, subepithelial, blue nevus and combined nevus according to accepted histologic criteria outlined above [1, 3-5, 10]. Oral subsites were subclassified in seven groups: hard palate, soft palate, gingiva, mucobuccal fold, buccal mucosa, floor of the mouth and tongue.

Follow-up data of the 119 patients were obtained from the PALGA Registry. The length of follow-up varied from 0.5 to 24 years the mean being 8.6 years. Endpoints included the date of 31st December 2005 or a diagnosis of OMM.
3. Results

According to the present evaluation of the period 1991–2005, the annual incidence of excised OMNs in The Netherlands, is 4.35 cases per 10 million population per year.

The relative frequency of the histopathologic types of the 119 OMNs is listed in Table 1. Ninety-six (80.6%) nevi were of the subepithelial type, while blue, compound, junctional and combined nevi accounted for 10 (8.3%), 7 (5.9%), 5 (4.2%) and 1 (0.8%), respectively. The hard palate was the most frequently involved oral subsite (41 cases, 34.4%), followed by the mucobuccal fold (29 cases, 24.3%), the gingiva (27 cases, 22.6%), the buccal mucosa (13 cases, 11%), the soft palate (5 cases, 4.2%), the tongue (2 cases, 1.7%) and the floor of the mouth (2 cases, 1.7%). All OMNs from the gingiva and the soft palate were of the subepithelial type. Eight out 10 (80%) of the common blue nevi were localized in the palate or in the mucobuccal fold, while no such lesions were found in the gingiva.

Table 1. Histopathologic subclassification of 119 OMNs

<table>
<thead>
<tr>
<th>Histopathologic type</th>
<th>Number of cases</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subepithelial</td>
<td>96</td>
<td>80.6</td>
</tr>
<tr>
<td>Junctional</td>
<td>5</td>
<td>4.2</td>
</tr>
<tr>
<td>Compound</td>
<td>7</td>
<td>5.9</td>
</tr>
<tr>
<td>Common blue</td>
<td>10</td>
<td>8.3</td>
</tr>
<tr>
<td>Combined</td>
<td>1</td>
<td>0.8</td>
</tr>
</tbody>
</table>

The gender distribution of OMNs according to histopathologic type and oral subsite involved is presented in Table 2. Age of patients at the time of diagnosis ranged from 5 to 87 years. The age range of patients with subepithelial, compound, junctional and common blue nevi was 5–87 years (mean: 38 years), 16–44 years (mean: 28.7 years), 7–52 years (mean: 28.6 years) and 31–
74 years (mean: 49.1 years), respectively. The only patient with a combined nevus was 38 years of age. In the group of patients younger than 30 years, 15 lesions were located on the hard palate while only four affected the gingiva. Conversely, during the fourth, fifth and sixth decades, the distribution between these subsites was almost the same (hard palate: 22; gingiva: 21). Results from the same evaluation by gender are shown in Table 3.

Table 2. Gender distribution of OMNs.

<table>
<thead>
<tr>
<th>Subsite</th>
<th>Males 47 cases</th>
<th>Females 72 cases</th>
<th>Total 119 cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hard palate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 Subepithelial</td>
<td>16</td>
<td>20</td>
<td>36</td>
</tr>
<tr>
<td>3 Compound</td>
<td></td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>1 Junctional</td>
<td></td>
<td>4 Blue</td>
<td>5</td>
</tr>
<tr>
<td>2 Blue</td>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>1 Combined</td>
<td></td>
<td>6 Blue</td>
<td>7</td>
</tr>
<tr>
<td>Mucobuccal fold</td>
<td>11</td>
<td>16</td>
<td>27</td>
</tr>
<tr>
<td>8 Subepithelial</td>
<td></td>
<td>16 Subepithelial</td>
<td>29</td>
</tr>
<tr>
<td>1 Junctional</td>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>1 Blue</td>
<td></td>
<td>2 Blue</td>
<td>3</td>
</tr>
<tr>
<td>1 Combined</td>
<td></td>
<td>1 Combined</td>
<td>1</td>
</tr>
<tr>
<td>Gingiva</td>
<td>11</td>
<td>14</td>
<td>27</td>
</tr>
<tr>
<td>All subepithelial</td>
<td></td>
<td>14 Subepithelial</td>
<td>27</td>
</tr>
<tr>
<td>1 Compound</td>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>1 Junctional</td>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>1 Blue</td>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>1 Combined</td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Buccal mucosa</td>
<td>6</td>
<td>7</td>
<td>13</td>
</tr>
<tr>
<td>5 Subepithelial</td>
<td></td>
<td>5 Subepithelial</td>
<td>7</td>
</tr>
<tr>
<td>1 Junctional</td>
<td></td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>2 Compound</td>
<td></td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>1 Junctional</td>
<td></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Soft palate</td>
<td>3</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>All subepithelial</td>
<td></td>
<td>All subepithelial</td>
<td>5</td>
</tr>
<tr>
<td>Floor of the mouth</td>
<td></td>
<td>10 Subepithelial</td>
<td>10</td>
</tr>
<tr>
<td>Tongue</td>
<td></td>
<td>1 Blue</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 Blue</td>
<td>1</td>
</tr>
</tbody>
</table>

Lesions are subclassified according to the oral subsite involved. Histological type is also indicated.

Table 3. Age distribution (years) of OMNs according to the histological type.

<table>
<thead>
<tr>
<th>Subsite</th>
<th>0–9</th>
<th>10–19</th>
<th>20–29</th>
<th>30–39</th>
<th>40–49</th>
<th>50–59</th>
<th>60–69</th>
<th>70–79</th>
<th>80–89</th>
<th>All ages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subepithelial</td>
<td>4</td>
<td>7</td>
<td>18</td>
<td>21</td>
<td>29</td>
<td>11</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>96</td>
</tr>
<tr>
<td>Compound</td>
<td></td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7</td>
</tr>
<tr>
<td>Junctional</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Blue</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Combined</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>5</td>
<td>9</td>
<td>22</td>
<td>27</td>
<td>33</td>
<td>14</td>
<td>5</td>
<td>3</td>
<td>1</td>
<td>119</td>
</tr>
</tbody>
</table>
Complete excision of the lesion was performed in 70 cases, while in 49 instances an incisional biopsy was taken. Three out of the 70 excised lesions (4.3%) were reported to have incompletely removed. Presence of melanin pigment was mentioned in 20 cases. Ballooning of lesional melanocytes (presence of copious amounts of finely vacuolated cytoplasm), intrallesional calcification, and mucinous degeneration of nearby minor salivary glands, were observed in three cases each.

In none of the 119 patients concerned, an OMM was registered during the follow-up period.

4. Discussion

The PALGA Registry is rather unique in registering, since 1991, all histopathologic and cytopathologic diagnoses rendered in The Netherlands. For reasons of privacy only data on gender, date of birth and date of diagnosis are made available for research purposes, such as in the present case. The registry does not contain information on the date of death or the cause of death.

Since the oral epithelial lining is considered part of the oral mucosa, the adjective subepithelial rather than intramucosal would seem more appropriate for describing those lesions entirely confined within the connective tissue. At present, melanotic nevi are considered to represent neoplasms rather than malformations, as has been previously thought. Subepithelial OMN is the most common histologic type, followed by blue nevus, compound, junctional and combined nevi. Even though some cases of Spitz nevi and epithelioid or plaque-type variant of blue nevi of the oral cavity have been reported, no such cases were disclosed in the PALGA data base. One case of balloon cell intramucosal-type nevus was encountered. This subtype of nevus, rarely described in the oral cavity, is characterized by nevomelanocytes with copious, finely vacuolated cytoplasm, caused by swelling of abnormal melanosomes, together with the presence of nevomelanocytes of usual appearance and melanophages at the lesional periphery. When comparing
percentages of our study with those from the study of Buchner et al., subepithelial nevi are more frequent in the present series (80.6% vs 55%), while the frequency of blue nevi is lower (8.3% vs 32%)\(^5\).

OMNs were more frequently biopsied in females (F:M = 1.5:1); it is, however, unclear whether this means that OMNs are really more frequent in females. Seven out of 10 blue nevi occurred in women; this contrasts with other studies where a predilection of blue nevi in men has been reported\(^3,8\).

The hard palate is the most common subsite affected by OMNs, followed by mucobuccal fold and gingiva. Involvement of the tongue and the floor of the mouth is exceptional (4 cases out 119, 3.5%). Two out of 4 of lesions at these oral subsites were blue nevi. Our data confirm a distinct predilection of OMNs for the upper part of the oral cavity\(^3,5,14\), a feature that is shared with oral melanoma and differs from that of epithelial neoplasms of the oral mucosa.

In accordance with the literature, our data indicate that junctional and combined nevi are mostly found in young individuals; 75% of the lesions (9 out of 12) were from patients under 40 years of age. Conversely, the peak incidence of diagnosis of subepithelial nevi is in the fifth decade (Fig. 2).

![Figure 2. Distribution of OMNs in relation to age.](image)

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Oral melanocytic naevi

These data support the idea that melanocytic nevi go through a junctional and a compound phase before they become subepithelial. All 10 common blue nevi were found in patients over 30 years of age (Table 4).

Table 4. Age distribution (years) of OMNs according to oral subsite.

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Age distribution (years) of OMNs according to oral subsite</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hard palate</td>
<td>0–9</td>
</tr>
<tr>
<td>Gingiva</td>
<td>1</td>
</tr>
<tr>
<td>Mucobuccal fold</td>
<td>2</td>
</tr>
<tr>
<td>Buccal mucosa</td>
<td>—</td>
</tr>
<tr>
<td>Soft palate</td>
<td>—</td>
</tr>
<tr>
<td>Tongue</td>
<td>—</td>
</tr>
<tr>
<td>Floor of the mouth</td>
<td>—</td>
</tr>
</tbody>
</table>

The present evaluation shows that location of OMNs seems to be significantly related to both age and gender. The reason of the differences of topographical distribution between males and females remains unknown (Fig. 3).

No data on the potential malignant transformation rate of OMNs are available as they are for the cutaneous counterpart. About one third of OMMs are preceded by oral pigmentation for months or even years, but the histologic phenotype of such presumed precursor lesions remains to be reported in detail. The apparently strong correspondence between oral subsites affected either by OMNs and OMMs (hard palate, mucobuccal fold, gingiva) may constitute an indirect argument supporting the idea that some OMNs do progress to OMM. In the present study all oral melanocytic nevi have been excised. Therefore, the question as whether such nevi, if left untreated, may in time transform into a malignant melanoma, remains unanswered. None of the patients developed a malignant melanoma in the oral cavity in an admittedly short mean follow-up period of 8.6 years. Since the PALGA Registry does not contain information about the date of death, the figure of the mean follow-up period may not be completely accurate. Nevertheless, the present evaluation
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does not provide concrete support for the idea that the presence of an oral melanocytic nevus indicates a risk of future development of OMM.
References


Chapter 8.

Head and neck mucosal melanoma. Experience with 42 patients with emphasis on the role of postoperative radiotherapy.

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Submitted

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Abstract

Background. Treatment of head and neck mucosal melanoma (HNMM) remains a challenge. Surgery has traditionally been the main therapeutic approach. The role of postoperative radiotherapy has never been clearly established.

Methods. The experience with a group of 42 patients (16 males; 26 females) with a primary HNMM is reported.

Results. Eleven out of 19 patients (57.9 %) receiving surgery alone developed a regional lymphatic metastasis. For patients receiving postoperative radiotherapy (19 cases), regional metastatic spread occurred in 4 cases (21%). Percentages of local failure were 57.9 % (11/19) and 26.3 % (5/19) for patients treated with surgery alone and for those treated with surgery and radiotherapy, respectively. Distant metastases occurred in 10 out of 19 patients (52.6 %) receiving surgery alone and in 9 out of 19 patients (47.3 %) receiving both therapies.

Conclusions. The present evaluation confirms a poor prognosis for patients with HNMM, independent from the treatment modality.
1. Introduction

Head and neck mucosal melanoma (HNMM) is a rare and aggressive neoplasm of melanocytic origin. This malignancy was firstly described by Weber in 1859 and recognized as a distinct clinical entity, named “melanotic sarcoma” in 1869. HNMM accounts for 8-15% of all head and neck malignancies, including cutaneous melanomas, representing 0.2-10% of all melanomas that may arise in the body. In the National Cancer Database of the USA, only 1.3% out of 84,836 cases of melanoma were proven to be of mucosal origin and 611 (0.7%) of these were located in the head and neck region. In their review, Manolidis and Donald, disclosed a total number of nearly 1000 cases reported in the literature up to 1997.

It has been suggested that the incidence of mucosal melanomas is lower in geographic areas where cutaneous melanomas are more frequently observed. Furthermore, HNMM are apparently more common among Japanese and Ugandan Africans than among Caucasian populations. There is no distinct gender predilection, although a few authors reported a female preponderance in their series. The etiology and pathogenesis are still obscure; this also applies to the role of possible precursor lesions. The clinical manifestations are rather heterogeneous and the histopathologic appearance is sometimes bizarre. HNMMs are rated among the most malignant tumours of the human body with a 5-year survival rate for nasal, pharyngeal, oral and sinus melanomas of 30.9, 13.3, 12.3 and less than 5.0 percent, respectively.

Here we report our experience with a group of 42 patients with a primary HNMM referred to the VU University Medical Center in Amsterdam, the Netherlands, and to the Academic Hospital of Parma University, Italy, during the past 30 years together with a discussion on the role of postoperative radiotherapy.
2. Patients and Methods

Clinical and histopathological data from patients affected by HNMM and referred to the Otolaryngology/Head and Neck Surgery and to the Oral and Maxillofacial Surgery/Oral Pathology departments of the VU University Medical Center in Amsterdam, the Netherlands, and to the Oral and Maxillofacial Surgery department of the Academic Hospital of Parma University, Italy, between 1976 and 2006 were retrieved and analyzed. Patients with a neck lymph node metastasis from cutaneous melanoma or from an unknown primary and patients with a metastasis to the head and neck region from a primary located elsewhere in the body were not included in the study.

Forty-two patients (16 males and 26 females, m:f = 1:1.6) qualified for the evaluation. Age at diagnosis ranged from 31 to 91 years (mean age 63.7 years). The epidemiological data are summarized in table 1.

Table 1. Epidemiological features of 42 patients affected by HNMM.

| Site of primary | Number of cases | Gender | Age (years) | | | |
| | | m | f | m (mean) | f (mean) | total (range and mean) |
| Sinonasal tract | 25 (59.5%) | 10 | 15 | | | |
| Nasal cavity | 18 | 7 | 11 | 67.4 | 66.9 | 37 to 88 mean 67.1 |
| Paranasal sinuses | 5 | 2 | 3 | | | |
| Nasopharynx | 2 | 1 | 1 | | | |
| Oral cavity | 17 (40.5%) | 6 | 11 | 64.3 | 55.8 | 31 to 91 mean 58.8 |
| Total | 42 (100%) | 16 | 26 | 66.2 | 62.2 | 62.7 |
Clinical data included anatomic subsite (nasal cavity and/or paranasal sinuses, nasopharynx, oral cavity and lymph nodes of the neck), signs and symptoms, macroscopic appearance and presence of regional lymph nodes and/or distant metastasis at the time of diagnosis. Twenty-five out of 42 patients (59.5%) were affected by a primary sinonasal mucosal melanoma (SNMM), the remaining 17 cases (40.5%) being diagnosed within the oral cavity.

Where available, additional information such as smoking habits and alcohol intake were collected. Tumour size and presence of neck node metastases were variously evaluated through clinical and radiological examination including CT-scan, MRI and ultrasound. Possible presence of distant metastasis was assessed through chest films, total body CT-scan or bone scintigraphy. All cases were re-staged according to the mucosal melanoma staging system: Stage I primary tumour present only (T any N0 M0); Stage II, tumour metastatic to regional lymph nodes (T any N1 M0) and Stage III tumour metastatic to distant sites (T any N any M1) 21-24.

In all patients an incisional biopsy had been taken and the diagnosis was made on conventional H&E stained sections and, in case of doubt, with the use of immunohistochemical markers (S-100, HMB45, Melan A).

Histopathologic reports from biopsies and surgical specimens as well as surgical reports were reviewed and data regarding melanoma subtype and radicality of the surgical excision were recorded. All patients with stage I disease were microstaged according to the histopathologic staging system for stage I mucosal melanomas 24.

Three out of 42 patients were primarily treated with radiotherapy alone and one patient refused treatment. The remaining 38 patients received surgery with or without post-operative radiotherapy.

One patient received pre-operative radiotherapy. Chemotherapy and immunotherapy were administered in some cases for the treatment of disseminated disease and for palliative purposes.
For 35 patients complete follow-up data were available. The length of follow-up varied from 2 to 80 months, the mean being 27.8 months. Endpoint of data collecting was the date of June 30th, 2006. Kaplan-Meier survival curves were generated and logrank tests were used to evaluate the differences between the overall and disease-specific survival rates. Comparisons of incidence of local and distant metastases as well as local failure were statistically determined through the Fisher’s exact test. A p-value < 0.05 was considered of statistical significance.

2.1 Clinical presentation
Clinical signs and symptoms of patients with SNMM included nasal obstruction, facial swelling, epistaxis and pain. At clinical evaluation, presence of a black-brown polypoid mass invading the nasal cavity, the paranasal sinuses with radiological evidence of bone destruction was often reported. In some cases, the tumour was growing in the nasopharyngeal area and in few cases the lesions were reported as non-pigmented. For patients with OMM, presence of pigmented flat or swollen, often ulcerated lesion accompanied by pain and bleeding were the most frequently reported manifestations. Complete information on smoking habit and alcohol intake were available for 22 out of 42 patients. Of these, 9 were smokers (at least 20 cigarettes/day). Only in 2 patients a positive history of alcohol abuse was recorded.

2.2 Histopathology and microstaging
The differential histopathologic diagnosis based on conventional stained sections (H&E) included a variety of tumours such as poorly differentiated squamous cell carcinoma, lymphoma, esthesioneuroblastoma, rhabdomyosarcoma and unspecific diagnoses like “malignant necrotizing tumour”, “malignant subepithelial tumour” or “poorly differentiated tumour”. In 22 lesions immunohistochemistry was performed; 17 stained positive for S-100
protein and 8 for HMB45. Lesions positively reacting to both markers were 5. Eight out of 42 lesions (19 %; 6 SNMM, 2 OMM) were amelanotic melanomas. Twenty-seven patients (13 SNMM; 14 OMM) and 11 (10 SNMM; 1 OMM) were microstaged as level II and level III respectively, according to the microstaging system for stage I mucosal melanoma (level II: invasion up to the lamina propria and level III deep skeletal tissue invasion into skeletal muscle, bone or cartilage) (Table 2)\textsuperscript{24}.

<table>
<thead>
<tr>
<th>Patients with microstage level II (27 Patients)</th>
<th>Regional metastasis</th>
<th>Local recurrence</th>
<th>Distant metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12 (44.4%)</td>
<td>13 (48.1%)</td>
<td>14 (51.8%)</td>
</tr>
<tr>
<td>Patients with microstage level III (11 Patients)</td>
<td>2 (18.1%)</td>
<td>4 (36.3%)</td>
<td>4 (36.3%)</td>
</tr>
</tbody>
</table>

P value 0.1596 0.7210 0.4848

\textsuperscript{*} Level I: Pure in situ melanoma without evidence of invasion or in situ melanoma with "microinvasion"; not such cases included in the present study

\textsuperscript{24} Level II: Invasion up to the lamina propria

\textsuperscript{24} Level III: Deep skeletal tissue invasion into skeletal muscle, bone or cartilage

No statistically significant differences are observed between microstage levels II and III. However, a decreased incidence of regional and distant metastasis, as well as local failure can be outlined for microstage level III patients.

### 2.3 Treatment of the primary and radicality

Thirty-eight patients underwent surgical excision of the tumour as the treatment of choice. Simultaneous neck dissection was performed in the two patients with preoperatively confirmed lymph node involvement. In 19 cases, additional
postoperative radiotherapy was administered. Three out of 42 patients were treated by radiotherapy alone. One patient refused treatment. Depending on the extension of the primary and the subsite involved, the surgical approach included lateral rhinotomy, nasal septum resection, partial or total maxillectomy, partial glossectomy or a combination of these. Laser treatment was used in one case of SNMM with involvement of the maxillary and sphenoid sinuses in which general conditions of the patient precluded other treatments. Such a treatment was not curative and the patient had a recurrence and died 8 months after therapy.

According to the evaluation of the surgical and the histopathological reports, radicality after excision of the primary was achieved in 23 patients (15 SNMM; 8 OMM). In 11 cases no radicality was obtained (7 SNMM; 4 OMM). For 4 patients the data on radicality were not available.

The most frequently adopted scheme of postoperative radiotherapy consisted of 600 cGy twice a week for a total dose of 3000 cGy.

3. Results

3.1 Local recurrence and metastatic spread

Seventeen out of 42 patients (40.4%; 10 SNMM – 40%; 7 OMM – 41.1%) experienced local failure (development of a recurrence and/or of a second primary) after a period of time ranging between 1 and 72 months (mean 20.4 months; mean SNMM: 10 months; mean OMM: 35.4 months) from the therapy. Recurrences were usually treated by surgery, in some cases followed by radiotherapy.

Fourteen out of 42 patients (33%; 7 SNMM – 28%; 7 OMM – 41.1%) developed regional lymph node metastases during follow-up, in a period ranging between 2 and 39 months (mean 14.2 months: mean SNMM: 13.5 months; mean OMM: 15 months). For patients with SNMM, the involvement of the neck was homolateral in 5 cases, contralateral in one case and bilateral in another. Neck metastases mainly occurred in the submandibular region (5 cases), the others being localized in the submental, subdigastric or infraclavicular areas.
Treatment of these neck metastases mainly consisted of radical neck dissection followed by radiotherapy. Extranodal spread was reported in 2 cases. Twenty-one out of 42 patients (50%; 11 SNMM – 44%, 10 OMM – 58.8%) developed single or multiple distant metastases in a mean period of 21.2 months (ranging between 0 to 78 months; mean SNMM: 16.5 months; mean OMM: 26.4 months). The most commonly involved sites were the lungs (8 patients) and the bone (6 patients). Other sites of distant metastatic spread included brain, liver, breast, pancreas and subcutaneous tissues. Therapy strategies for metastatic disease were mainly based on chemotherapy with dimethyl-triazeno-imidazole carboxamide (DITC), fluorouracil (5-FU) and doxorubicin (L-DOX), immunotherapy with gamma-interferon and interleukin 2, or on a vaccine prepared from the neoplastic cells.

3.2 Follow-up and survival rates; microstaging and prognosis

Overall and disease-specific 2-year and 5-year survival rates were evaluated for patients with SNMM, OMM and for the whole group of patients with HNMM (Table 3; overall and disease-specific 2-year survival rates for OMM = 62.5% and 66.6%; overall and disease-specific 2-year survival rates for SNMM = 38.8% and 53.8%; overall and disease-specific survival rates for HNMM = 50% and 60.7%. Overall and disease-specific 5-year survival rates for OMM = 38.4% and 41.6%; overall and disease-specific 5-year survival rates for SNMM = 0%; overall and disease-specific 5-year survival rates for HNMM = 17.2% and 21.7%). The Kaplan-Meier survival curves show a statistically higher 5-year survival rate for patients affected by OMM as compared to SNMM. (Logrank test : P = 0.0227; 95% CI : 0.1610 to 0.8718). (Figures 1 and 2)
Table 3. Two-year and 5-year overall and disease-specific survival rate for the patients with SNMM, OMM and for the whole group of patients with HNMM.

<table>
<thead>
<tr>
<th>Site of the primary</th>
<th>2-year survival rate</th>
<th>5-year survival rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall</td>
<td>Disease-specific</td>
</tr>
<tr>
<td>SNMM</td>
<td>38.8%</td>
<td>53.8%</td>
</tr>
<tr>
<td>OMM</td>
<td>62.5%</td>
<td>66.6%</td>
</tr>
<tr>
<td>HNMM</td>
<td>50%</td>
<td>60.7%</td>
</tr>
</tbody>
</table>

Figure 1. Overall 5-year survival rate of patients affected by OMM and SNMM.
(Logrank test : P = 0.0227; 95% CI : 0.1610 to 0.8718).
Correlations between histopathological microstaging and occurrence of regional metastasis, local failure and development of distant metastases are shown in Table 2. Histopathologic microstage levels did not significantly correlate with any of the parameters evaluated (P value for regional metastases = 0.1596; P value for local failure = 0.7210; P value for distant metastases = 0.4848), even though a decreased incidence of negative events can be outlined for patients with microstage level III.

The Kaplan-Meier survival curves do not show a difference in the overall and disease-specific 5-year survival rates for patient with microstage level II and III (Logrank test : P1 = 0.2919; 95% CI : 0,1786 to 1,6784. P2 = 0.2254; 95% CI : 0,1037 to 1,8257) (Figures 3 and 4).
Figure 3. Kaplan-Meier estimator for patients with microstage level II and III (overall 5-year survival rate). (Logrank test: P = 0.2919; 95% CI: 0.1786 to 1.6784).

Figure 4. Kaplan-Meier estimator for patients with microstage level II and III (disease-specific 5-year survival rate). (Logrank test: P = 0.2254; 95% CI: 0.1037 to 1.8257).
3.3 Surgery versus surgery + postoperative radiotherapy

Data on the comparison between patients treated with surgery alone or in association with radiotherapy are summarized in Table 4. Eleven out of 19 patients (57.9 %) receiving surgery as only treatment for the primary developed a regional lymphatic metastasis (mean time of occurrence : 14.5 months). On the other hand, in the group of patients receiving postoperative radiotherapy (19 cases) metastatic spread to the lymph nodes of the neck occurred in 4 patients only (21%; mean time of occurrence : 13.75 months) (P = 0.0448).

Table 4. Surgery versus surgery + postoperative radiotherapy.

<table>
<thead>
<tr>
<th>Treatment of the primary</th>
<th>Regional metastasis</th>
<th>Local failure</th>
<th>Distant metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery (19 Patients)</td>
<td>11 (57.9 %)</td>
<td>11 (57.9 %)</td>
<td>10 (52.6 %)</td>
</tr>
<tr>
<td>Surgery + radiotherapy</td>
<td>4 (21 %)</td>
<td>5 (26.3 %)</td>
<td>9 (47.3 %)</td>
</tr>
<tr>
<td>(19 Patients)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A statistically significant difference is observed between patients receiving surgery and patient receiving surgery and postoperative radiotherapy with regard to regional metastasis. A not-statistically significant decreased incidence of regional and distant metastasis, as well as local failure can be outlined for patients treated with postoperative radiotherapy.

Percentages of local failure were 57.9 % (11/19; mean time of occurrence 24.5 months) and 26.3 % (5/19; mean time of occurrence 9.4 months) for patients treated with surgery alone and for those treated with surgery and radiotherapy, respectively (P = 0.0991).

Distant metastases occurred in 10 out of 19 patients (52.6 %; mean time of occurrence 26.3 months) receiving surgery alone and in 9 out of 19 (47.3 %;
mean time of occurrence 15.6 months) patients receiving both therapies (P = 1.000).

A lesser incidence of regional and distant metastasis, as well as local failure was observed for patients treated with surgery and postoperative radiotherapy. The Kaplan-Meier estimator, however, shows a statistically significant better prognosis for patients receiving surgery alone (Logrank tests : P = 0.0028; 95% CI : 0.1162 to 0.6396) (Figures 5 and 6).

Data on stage at diagnosis (including microstage) as well as on radicality of surgery, separately evaluated for the two groups, are reported in tables 5 and 6.

Figure 5. Overall 5-year survival for patients treated by surgery and surgery + postoperative radiotherapy.
“S” = Surgery;
“SR” = Surgery + radiotherapy;
(Logrank test : P = 0.0028; 95% CI : 0.1162 to 0.6396).
Table 5. Relationship between treatment and stage at diagnosis (including microstaging for Stage I*).

<table>
<thead>
<tr>
<th>Treatment of the primary</th>
<th>Stage at diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I-II*</td>
</tr>
<tr>
<td>Surgery (19 Patients)</td>
<td>14 (73.6%)</td>
</tr>
<tr>
<td>Surgery + radiotherapy (19 Patients)</td>
<td>10 (52.63%)</td>
</tr>
</tbody>
</table>

* Level I*: Pure in situ melanoma without evidence of invasion or in situ melanoma with “microinvasion”; not such cases included in the present study; Level II*: Invasion up to the lamina propria; Level III*: Deep skeletal tissue invasion into skeletal muscle, bone or cartilage
Table 6. Relationship between treatment and radicality after the surgical excision of the primary.

<table>
<thead>
<tr>
<th>Treatment of the primary</th>
<th>Radicality after the surgical excision of the primary</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Radical</td>
</tr>
<tr>
<td>Surgery (19 Patients)</td>
<td>14 (73.6%)</td>
</tr>
<tr>
<td>Surgery + radiotherapy (19 Patients)</td>
<td>9 (47.3%)</td>
</tr>
</tbody>
</table>

4. Discussion

Most of the epidemiological and clinical data analyzed in the present study are comparable to those reported in the literature. The peak incidence of HNMM is between the sixth and the seventh decade. In the present series, OMM seems to affect patients younger (mean age 58.8 years) than patients with SNMM (mean age 67.1 years). Women with OMM were significantly younger than men (mean age of 55.8 and 64.3 years respectively). No distinct gender predilection was found.

Nasal obstruction, epistaxis and pain are the most frequently reported symptoms in patients with SNMM. A diagnostic delay, probably mainly related to patients attitudes, ranging between 2 months and 2 years from the appearance of the first symptoms, was recorded in different series. OMM usually presents as a painful pigmented swelling, even though flat lesions or non-pigmented masses are sometimes described (amelanotic melanoma). Both SNMM and OMM are often ulcerated.

The role of tobacco habits and formaldehyde exposure as risk factors for inducing abnormal melanocytic differentiation has been hypothesized by some authors. In the present series, chronic tobacco use was recorded only in a few patients. In contrast to melanoma of the skin, the pathogenesis of HNMM...
seems to be based on genetic mechanisms unrelated to ultraviolet light exposure \(^31\). The close anatomic proximity of the commonly affected head and neck mucosal sites (nasal cavity and paranasal sinuses and the palate) may lead to the hypothesis that the pathogenesis of these tumors is related to some abnormality during the embryogenesis of this region \(^32\).

Approximately one third of OMMs are preceded by localized pigmentation for months or years \(^11\). The nature of such precursor lesions has not been clearly established yet. A recent evaluation on 119 patients with oral melanocytic nevi (OMNs) did not show an increased risk for OMM development \(^15\).

The present experience confirms the rather variable histopathological appearance of HNMM. In many of the cases, a definitive diagnosis could only be obtained with the use of specific markers such as antivimentin, S-100, NKI/C-3 and HMB-45. The histopathologic differential diagnosis mainly included poorly differentiated squamous cell carcinoma, lymphoma and sarcoma. The use of electronic microscopy may provide some help in the demonstration of premelanosomes \(^6\).

Differently from its cutaneous counterpart, where a radical excision can often be achieved, the management of HNMM still represents a challenge. The often late diagnosis, anatomical limitations that preclude the possibility of a radical excision, and probably a more malignant biologic behaviour, negatively influence the success of treatment and the prognosis \(^33, 34\).

The limited size of most reported series and the heterogeneity of data do not enable to assess the effectiveness of the various treatment modalities with regard to variables such as local control, metastatic spread and survival rates \(^35\). Surgery has traditionally been the main therapeutic approach for the treatment of this malignancy \(^35\). The role of postoperative radiotherapy in the management of HNMM has not yet been clearly established and the results of various studies on this subject remain controversial \(^1, 25, 35-37\). Because of the rarity of this neoplasm it will be difficult to perform a randomized-controlled trial for a critical evaluation and comparison of the two treatment modalities. As a
matter of fact, most of the studies in the literature are retrospective analyses performed on small series of patients and these evaluations are biased by the lack of randomized selection criteria, as is the case in the present series. In the present evaluation the number of patients who experienced regional and/or distant metastases as well as a local failure is higher among those who did not receive postoperative radiotherapy. In particular, the percentage of neck lymph node metastases seems to be significantly decreased by the administration of radiotherapy. Surprisingly, the analysis of the overall 5-year survival rate through the Kaplan-Meier estimator, demonstrates a better prognosis for patients treated by surgery without postoperative radiotherapy. This observation holds true when the analysis is separately performed for patients with SNMM and patient with OMM (Figures 5 and 6). These results may probably be explained through the evaluation of data on the radicality after excision of the primary (table 4). In fact, the resection of the tumour was radical for 14 out 19 (76.3%) patients in the group receiving surgery alone. This percentage is significantly decreased in the group of patients treated with post-operative radiotherapy (47.3%; 9 out of 19 patients). Stage at diagnosis (including microstaging) does not seem to be different in the two groups (table 5). These findings are in accordance with some other previously reported studies. Lund et al. did not find any statistical difference of the overall survival rate in a group of 58 patients with SNMM treated with surgery or with surgery and radiotherapy 36. In a retrospective analysis on 48 patients affected by HNMM, Owens et al. showed that the addition of radiotherapy to surgical treatment leads to an improvement of locoregional tumour control 35. Similarly, Temam et al. reported a significant higher local control rate for patients additionally treated with postoperative radiation 25. However, in most of the reported series, local control was not associated with an increased survival rate. An exception is the study by Kingdom and Kaplan who observed an increased survival rate among patients treated with surgery and radiotherapy compared to those treated by surgery alone 38.
The low number of stage II and stage III patients (regional disease and distant metastases, respectively) in the present series does not allow to draw any statistically significant conclusions about the relationship between stage at presentation and prognosis. The observation by Prasad et al. that the histopathological microstage for stage I disease, reflecting tumour progression within the surrounding tissues, is a predictor of survival 24, is not supported by the results of the present study.

The results of the present evaluation confirm a poor prognosis for patients affected by primary HNMM, independent from the treatment modality, being surgery alone or surgery followed by radiotherapy. In particular, the overall 5-year survival rate for the whole group of HNMM of 17.2% seems to be slightly lower compared with those reported in other studies 8, 18, 21, 36, 37, 39-41. A site specific difference was noticed with regard to survival. Patients with OMM seem to have an higher disease-specific 5-year survival rate compared to patients with SNMM (38.4 % and less than 5 percent respectively). It is debatable if this difference depends on factors such as the histopathological microstage for stage I tumour (56.5 % of patients with SNMM had a microstage level III while only 6.6% of patients with OMM had the same microstage level) since such a microstaging system does not seem to correlate with the survival-rate in the present evaluation. However, these results are in contrast with some reports where melanoma arising in the nasal mucosa appears to have a better prognosis 17.
References


Head and neck mucosal melanoma


Chapter 9.

Summary and conclusions
Summary and conclusions

The diagnostic procedure of pigmented lesions of the oral cavity and perioral tissues is a challenging one. Even though epidemiology may be of some help in orientating the clinician and even though some lesions may confidently be diagnosed on clinical grounds alone, such a diagnosis remains “provisional”. A definitive diagnosis usually requires histopathological evaluation. Occasionally, immunohistochemical stains such as melanocyte marker HMB-45 and macrophage marker CD68 may be required to arrive at a correct diagnosis.

The so-called ABCD checklist (“Asymmetry”, “Border” irregularities, “Color” variegation and “Diameter” > 6mm) that is commonly used to aid in the identification of cutaneous melanoma may also be of some help in the clinical diagnosis of oral malignant melanoma (OMM). Rapidly growing pigmented lesions should always be biopsied. Location on the palate increases the rate of suspicion of melanoma and usually requires a biopsy or long-term follow-up.

A critical analysis of the literature on human OMM discloses a lack of thorough knowledge on the etiology and pathogenesis of this malignancy as well as a lack of evidence on the best therapeutical approach. The hypothesis that inhaled environmental carcinogens, including tobacco and formaldehyde, may have some influence in promoting an abnormal melanocytic proliferation is based on few epidemiological observations. Most of the reports do not include data on the presence or absence of exposure to carcinogenetic factors. p53 protein alterations have been identified in about two-thirds of OMM.

Surgical excision is the most frequently reported treatment for OMM. Surgery could be combined with radiotherapy, chemotherapy or immunotherapy even though the effectiveness of such therapies either as primary treatment or in association with surgical treatment is largely unknown.

The Amsterdam experience with 14 patients affected by OMM confirms the extremely malignant and aggressive behaviour of this neoplasm. Five patients developed a local recurrence within a period of 4 to 72 months and 10 patients developed distant metastases within a period of 6 to 78 months. Ten patients
died of their disease within an average interval of 40 months, with a range of 12 to 80 months. Of the ten patients who qualified for evaluation of the five-year survival rate, one was alive with disease and two were alive without evidence of disease, which results in a 30% five-year survival rate. However, all patients have died of their disease before the end of the ten-year follow-up period.

From the histopathological point of view it seems remarkable to report a case of OMM associated with pseudoepitheliomatous hyperplasia (PEH). The presence of both melanocytic and keratinocytic cells could lead to the misdiagnosis of a tumour with biphenotypic characteristics such as OMM associated with squamous cell carcinoma (SCC) or pigmented SCC. The presence of PEH along much of the surface epithelium, in the absence of underlying salivary gland tissue, appears to point at an origin of the PEH from the surface epithelium itself.

In another case, the presence of melanotic pigmentation of the palatal minor salivary glands was documented four years before a diagnosis of an OMM of the palate was established. Presence of melanin pigment within the epithelial cells of minor salivary glands is an exceptional finding and the biological mechanism underlying this phenomenon is unknown. The concept of "melanogenic metaplasia" as being proposed by Shivas and McLennan is an interesting one. However, until now there is no scientific evidence to support such concept. It is questionable whether melanotic pigmentation of the palatal minor salivary glands represents a potentially malignant disease.

Data from the literature show that about 30% of OMM are preceded by mucosal pigmentation for several months or even years. Some of these flat precursor lesions consist of cytologically atypical melanocytes and may in fact constitute the preinvasive macular phase of melanoma.

The apparently strong correspondence between oral subsites affected either by oral melanocytic naevi (OMNs) and OMMs (hard palate, mucobuccal fold, gingiva) may constitute an indirect argument supporting the idea that some OMNs do progress to OMM.
However, the results of our own study do not confirm the hypothesis that the presence of an OMN indicates a risk of future development of OMM. In fact, None of the 119 patients with a diagnosis of OMN developed a malignant melanoma in the oral cavity in a mean follow-up period of 8.6 years.

With regard to the whole group of patients affected by head and neck mucosal melanoma (HNMM), oral malignant melanoma seems to affect patients at a younger age (mean age 58.8 years) than patients with sinonasal mucosal melanoma (SNMM) (mean age 67.1 years). The number of patients who experienced regional and/or distant metastases as well as a local failure was higher among those who did not receive postoperative radiotherapy. In particular, the percentage of neck lymph node metastases seems to be significantly decreased by the administration of radiotherapy. Surprisingly, the analysis of the overall 5-year survival rate through the Kaplan-Meier estimator, showed a better prognosis for patients treated by surgery without postoperative radiotherapy. A similar result was shown when the analysis was separately performed for patients with SNMM and patients with OMM. Because of the retrospective nature and the incompleteness of the clinical records no clear guidelines were provided with regard to the indication for postoperative radiotherapy in the individual patients. A bias of the present evaluation may be represented by the fact that melanomas with an apparently intrinsic worse prognosis (e.g. SNMM) are overrepresented in the group of patients receiving a combined treatment.

Unfortunately, the rarity of this neoplasm makes it rather unrealistic to perform a randomized-controlled trial for a critical evaluation of the role of postoperative radiotherapy.

The observation by Prasad et al. that the histopathological microstage for stage I disease of OMM, reflecting tumour progression within the surrounding tissues, is a predictor of survival, is not supported by the results of the present study. The overall 5-year survival rate for the entire group of HNMM patients of the present series is 17.2%. A site specific difference was noticed with regard to
survival. Patients with OMM seem to have a better disease-specific 5-year survival rate than patients with SNMM.
Chapter 10.

Samenvatting en conclusies
Samenvatting en conclusies

De diagnostiek van gepigmenteerde lesies van de mond en omgevende structuren kan bijzonder lastig zijn. In veel gevallen lijkt het verantwoord om op grond van bijvoorbeeld de leeftijd, de localisatie, de anamnese en het klinische aspect op alleen klinische gronden tot een diagnose te komen, maar in sommige gevallen is toch behoefte aan een meer zekere diagnose met behulp van weefselonderzoek. Het kan daarbij nodig zijn om immuunhistochemische kleuringen toe te passen, zoals de melanocytenmerker HMB-45 en de macrophagenmerker CD68, naast bijvoorbeeld routinematige kleuringen zoals de ijzerkleuring. De in de Engelse literatuur bekende ABCD checklist, waarbij de A staat voor asymmetry, de B voor border irregularities, de C voor verschillen in kleur en de D voor diameter (> 6 mm) die wordt gebruikt bij de diagnostiek van melanomen van de huid is ten dele ook toepasbaar bij het maligne melanoom van het mondslijmvlies. Snel groeiende gepigmenteerde lesies dienen echter altijd te worden gebiopteerd. Localisatie van de pigmentatie op het palatum verhoogt de verdenking op de aanwezigheid van een maligne melanoom of eventueel een voorstadium daarvan en maakt derhalve een biopsie en/of langdurige controle noodzakelijk.

Een kritische analyse van de bestaande literatuur over het orale maligne melanoom laat zien, dat er eigenlijk geen goed inzicht is in de etiologie en de pathogenese van deze kwaadaardige tumor. Bovendien zijn er geen betrouwbare gegevens beschikbaar over de beste manier van behandelen. Ten aanzien van de etiologie wordt door sommigen gesuggereerd, dat schadelijke stoffen uit het milieu carcinogeen kunnen zijn; het gaat daarbij in het bijzonder om tabakrook en formaldehyde. Er zijn echter maar weinig studies van het maligne melanoom van het mondslijmvlies die iets over deze factoren vermelden. Daarnaast wordt in sommige studies melding gemaakt van veranderingen in het p53 gen.

Chirurgische verwijdering is de meest gangbare behandeling van een maligne melanoom van het mondslijmvlies. Chirurgische behandeling kan worden
Samenvatting en conclusies

gecombineerd met bestraling, chemotherapie of immuuntherapie. De effectiviteit van dergelijke aanvullende behandelingen in combinatie met chirurgie of als enkele behandelmodaliteit is nooit met zekerheid aangetoond.

In het onderzoek naar 14 patiënten met maligne melanoom van het mondslijmvlies, gediagnosticeerd in een periode van ruim 30 jaar op de afdelingen mondziekten en kaakchirurgie en keel-, neus- en oorheelkunde van het VU medisch centrum te Amsterdam blijkt duidelijk sprake van het kwaadaardige agressieve karakter van deze tumor. Vijf patiënten ontwikkelden een locaal recidief binnen een periode van 4-72 maanden en tien patiënten ontwikkelden metastasen op afstand, dat wil zeggen buiten het hoofd-halsgebied, binnen een periode van 6 tot 78 maanden. Tien patiënten zijn aan hun ziekte overleden binnen een gemiddeld interval van 40 maanden (spreiding 12-80 maanden).

Van de tien patiënten van wie de 5-jaarsoverleving kon worden nagegaan, bleek er na vijf jaar één in leven te zijn met de ziekte, terwijl twee patiënten in leven waren zonder aanwijzingen voor aanwezigheid van de ziekte. Hoewel het bij kleine getallen niet verantwoord is om de gegevens in percentages uit te drukken, zou het voorgaande betekenen dat er sprake is van een 5-jaarsoverleving van 30%. Alle patiënten zijn uiteindelijk binnen tien jaar aan hun ziekte overleden. De bevinding vanuit de literatuur dat de voorgestelde histopathologische microstadiëring voor stadium I (maligne melanoom van mondslijmvlies, ongeacht de maximale afmeting, maar zonder aanwijzingen voor metastasering) voorspellende waarde heeft voor de overleving, werd niet bevestigd door de resultaten in het huidige onderzoek.

Een ander aspect van het onderzoek betrof onderzoek naar maligne melanomen van andere slijmvliesen in het hoofd-halsgebied, in het bijzonder van de neus- en neusbijholten. Er werd daarbij een vergelijking gemaakt tussen de behandelingsresultaten van patiënten met een maligne melanoom van het mondslijmvlies en die met een maligne melanoom van de neus- en neusbijholte. Opvallend genoeg bleek dat patiënten met een maligne
melanoom van het mondslijmvlies gemiddeld ongeveer tien jaar jonger waren dan de patiënten van de andere groep. De 5-jaarsoverleving was voor patiënten met een maligne melanoom van het mondslijmvlies beter dan voor patiënten met een maligne melanoom elders in het hoofd-halsgebied. Daarbij zij echter opgemerkt, dat het om relatief kleine aantallen patiënten gaat.

Verder bleek dat de kans op locaal recidief en/of regionale en afstandsmetastasering groter was bij patiënten, die niet werden nabestaald. Verrassenderwijs bleek echter de 5-jaarsoverleving voor patiënten die alleen met chirurgie waren behandeld – dus zonder postoperatieve bestraling – beter te zijn dan voor patiënten die werden nabestaald. Gelet op het retrospectieve karakter van het onderzoek en het op sommige plaatsen niet volledig zijn van de patiëntendossiers ten aanzien van de indicatie voor postoperatieve bestraling, kan geen betrouwbare uitspraak worden gedaan over de mogelijke waarde van postoperatieve bestraling bij het orale maligne melanoom. Gelet op de relatieve zeldzaamheid van het maligne melanoom in het hoofd-halsgebied is het niet zonder meer mogelijk een prospectieve studie op dit gebied uit te voeren.

In ons onderzoek hebben wij melding gemaakt van een nogal ongewone casus van een maligne melanoom van het mondslijmvlies waarbij tevens sprake was van pseudo-epitheliomateuze hyperplasie. Er waren in de betreffende casus een aantal argumenten, die het inderdaad het meest waarschijnlijk maakten dat hier sprake was pseudo-epitheliomateuze hyperplasie van het overliggende plaveiselepithel en dat het niet ging om een plaveiselcelcarcinoom met melaninepigmentatie.

Een andere bijzondere casus die in ons onderzoek werd opgenomen, betrof een patiënt met melaninepigmentatie in de kleine speekselklieren van het gehemelte. Bij deze patiënt werd vier jaar later een maligne melanoom op de betreffende plaats gediagnosticeerd. Aanwezigheid van melaninepigment in epitheliaal cellen van kleine speekselklieren is uitzonderlijk en er is geen goede verklaring voor dit fenomeen. In de literatuur wordt wel de term "melanogene
metaplasie” genoemd, maar er is weinig wetenschappelijke ondersteuning voor een dergelijk concept. Verder is de vraag of het aantreffen van melaninepigment in kleine speekselklieren inderdaad als een potentieel kwaadaardig fenomeen moet worden beschouwd.

Uit de literatuur blijkt, dat ongeveer 30% van het maligne melanoom van het mondslijmvlies geassocieerd is of mogelijk jarenlang voorafgegaan is door pigmentatie van het mondslijmvlies. Er kan daarbij sprake zijn van aanwezigheid van atypische melanocyten zonder dat op dat moment de diagnose maligne melanoom kan worden gesteld. De aanwezigheid van dergelijke atypische melanocyten lijkt als een pre-invasief stadium van een maligne melanoom te oeten worden beschouwd.

Een naevus naevocellularis, zoals deze op de huid kan voorkomen, komt een enkele maal ook in de mond voor. De voorkeursplaats van orale naevi komt sterk overeen met die van een maligne melanoom. Het ligt daarom voor de hand om te veronderstellen, dat orale naevi wellicht voorloperlesies zijn van een maligne melanoom van het mondslijmvlies. Uit een landelijk onderzoek, waarbij dankbaar gebruikgemaakt is van het landelijke geautomatiseerde bestand van de pathologen (PALGA) werd echter geen ondersteuning voor deze hypothese gevonden. Geen van de 119 patiënten met een naevus naevocellularis van het mondslijmvlies heeft in een gemiddelde nacontrole periode van 8.6 jaar een maligne melanoom ontwikkeld.
Curriculum Vitae

Pregraduation

- Born in Nardò (Lecce - Italy) 07/12/1977.
- Three-month course of English language at Pitzer College (member of the Claremont Colleges), Los Angeles (CA) in 2001.
- Graduated in dentistry (D.D.S.) at University of Parma (Italy) on 25/02/2002 (after two years of internship at the Oral Pathology and Medicine Department). Full votation (110/110 cum laude). Thesis title : "Epidemiology and clinical manifestations of gingival overgrowth in a group of 121 renal transplant recipients immunosuppressed with cyclosporine".

Postgraduation

- Postgraduated course of Oral Pathology and Medicine at University of Milan (Prof. Antonio Carrassi) in 2003.
- Postgraduated course of Oral Pathology and Medicine at University of Florence (Prof. Giuseppe Ficarra) in 2004.
- Full-time clinical activity at the Oral Pathology and Medicine Department (Prof. Paolo Vescovi) of the University of Parma, from 2002 to 2004.
- Ph.D. student at the Department of Oral and Maxillofacial Surgery/ Oral Pathology of the Free University medical center / ACTA (Prof. Dr. Isaac van der Waal), in Amsterdam from 2004 to 2007.
- Clinical training in Oral Medicine at the Department of Oral Medicine of the University of San Francisco (Prof. Sol Silverman Jr., Prof. Francina Lozada-Nur). October-November 2006
- Member of SIPMO (Italian Society of Oral Medicine and Pathology) since 2002.
- Member of SIOCMF (Italian Society of Oral and Maxillofacial Surgery) since 2002.
- Member of the EAOM (European Association of Oral Medicine) since 2004.
- Member of the SFOPOM (Scandinavian Society of Oral Medicine and Pathology) since 2005
- Currently is “Contract Professor” of “Clinical Stomatology” at the School of Dentistry of the Medical Faculty of the University of Parma.
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Sir Isaac Newton

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