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Chapter

Mucosal Melanoma of the Head and Neck: From Diagnosis to Treatment

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Abstract

Mucosal melanomas of the head and neck are very rare malignancies that present with aggressive behavior and poor prognosis. Usually diagnosed at advanced stages, thus presenting macroscopically as aggressive nodular neoplasms arising from the mucosa; few cases are detected in situ. Tumor staging for mucosal melanoma remains a challenge. Several staging systems have been suggested, including tumor-nodal-metastases (TNM) staging systems, but none are frequently used. There is no clear consensus on the management of head and neck mucosal melanoma, which reflects the rare nature of the disease and complexity of the anatomic site. The late diagnosis, frequently presenting at an advanced stage, denotes the aggressive nature of the disease. Currently, early detection and surgical excision is considered the primary method of treatment. The multidisciplinary team approach can help reduce morbidity and mortality once optimize treatment, reduce costs and minimize adverse events, while maximizing the chances of recovery.

Keywords: mucosal, melanoma, head and neck

1. Introduction

Mucosal melanomas of the head and neck are very rare malignancies that present with aggressive behavior, including frequent local recurrence, and poor prognosis. First described by Weber in 1859 [1] and classified as its own distinct disease by Lucke et al. in 1869 [2], they represent a small fraction of all head and neck melanomas.

Unlike cutaneous melanomas, which incidence is believed to be rising over the years, the incidence of mucosal melanomas seems to remain stable [2]. Its annual incidence rate in Europe was estimated in 1.5 per million, with slight female predominance (1.2 vs. 1.0 per million) and in people aged over of 65 years [3], with median age at diagnosis ranging around 70 years old – developing at more advanced ages when compared to cutaneous melanomas. Significant variation between races is observed, with the Japanese more likely to be affected (8%) when compared to Caucasians [4], especially regarding oral cavity mucosal melanoma, suggesting association of this particular subtype with common hereditary or environmental factors,

still not identified [5]. Mucosal melanomas represent 0.8 to 3.7% of all melanomas, 0.03% of all neoplasms [6] and occur most commonly in the head and neck (55%) [7], mainly in the nasal cavity (lateral wall and septum) and paranasal sinuses (ethmoid and maxillary sinuses) [6], followed by the oral cavity – approximately 80% in the mucosa of the upper jaws (maxillary anterior gingiva), in the keratinizing mucosa of the palate and alveolar gingivae [8] -, pharynx, larynx, and upper esophagus [3, 9].

To date there are no clearly established risk factors for the mucosal melanoma development [5]. Cigarette smoking seems to be a risk factor for the oral tumor, while exposure to formaldehyde has been suggested as risk factor for the sinonasal malignancy. Association with viruses, such as human papilloma viruses, human herpes viruses or polymavirus is unlikely. Although sun radiation is a well-established risk factor for cutaneous melanoma, there is no evidence of its implication in mucosal melanoma pathogenesis, since its common locations preclude exposure to UV light [3].

Another particularity of mucosal melanomas, divergent from the cutaneous ones, is the more hostile behavior and frequent neoplastic dissemination, which results in greater death rate [10]. The mucosal melanoma aggressive clinical course results in very poor prognosis, especially among old male patients, likely due to little understanding of this rare malignancy and delayed detection, given the lack of specific clinical features for diagnosis, a challenging scenario for clinicians and pathologists [4]. Studies made on European cases diagnosed between 2000 and 2007 showed survival rates in 1, 3 and 5 years of 63%, 30% and 20%, respectively, as well as high rates of locoregional recurrence and distant metastasis [3, 11].

Tumor arising from the respiratory mucosa (such as the nasal cavity) have different clinical and pathological features when compared to those involving oral mucosa, as melanomas originating from non-squamous mucosa behave differently than those originating from multilayered squamous mucosa [11], but still they share similar adverse outcomes and prognosis and, therefore, will be discussed further in this chapter [1].

2. Pathology and biology

Melanomas are malignant tumors arising from pigment cells - melanocytes. Tumors can either develop from stem melanocytes with cytogenetic variations or mature melanocytes with secondary cytogenetic alterations due to external stimuli [6]. Precursors of melanocytes migrate from the neural crest to their final destination through embryonic mesenchyme, along specific pathways, most of them ending up in the epidermis and dermis of the skin, while some of them can be found in other locations, such as the mucosal membranes of the respiratory, gastrointestinal, and genitourinary tract [2, 3]. Melanin, the main product of melanocytes, may be missing in rare cases (2 to 8%), resulting in a non-pigmented lesion, referred as amelanotic malignant melanoma [9]. The presence and the function of melanocytes in the mucosa remain unclear. A few studies have supported the hypothesis of anti-oxidative, antimicrobial and immunological functions [3, 6]. In the sinonasal region, melanocytes take part in the metabolization of polycyclic aromatic hydrocarbons, suggesting association between inhaled environmental and immune factors and the development of mucosal melanoma in this particular site [5].

The etiology and pathogenesis of mucosal melanoma of the head and neck is still not fully understood. Whether it is due to preexisting mucosal nevi or racial pigmentation affecting its site, no risk factors have been unequivocally linked to

those features. Despite the common association between cutaneous melanomas and sun exposure, mucosal melanomas are associated with embryology alterations (justifying the close proximity of commonly affected areas), inhaled and ingested carcinogens (e.g. smoking and formaldehyde exposure) and family history. Reports suggest that smoking patients have greater prevalence of pigmented oral lesions due to a hyper-production of melanocytes in the oral mucosa. Furthermore, 33% of oral cavity mucosal melanomas are preceded by pathological oral melanosis - increased number of normal or atypical melanocytes in the basal cell layer of the oral epithelium. Even though, conflicting data suggest oral melanosis should not be considered a pre-cancerous lesion [6]. Molecular studies of mucosal melanoma show several genetic changes in intracellular signaling cascades, which may constitute the distinct pathogenic mechanisms among these malignancies. Genomic hybridization studies have shown varied chromosomal aberrations - gains of 1q, 6p and 8q; gain of function mutations, such as K642E, L576P, D816H and V559A; amplifications of the 4q12 locus [11].

Special attention is addressed to the high incidence of activating mutations in the c-KIT (CD117) oncogene, present in 80% of all primary mucosal melanomas, whereas it seems not to have pathogenic importance in cutaneous melanomas [2, 5, 11]. KIT is a transmembrane tyrosine kinase receptor, expressed on melanocytes, but also on hematopoietic progenitor cells, mast cells, primordial germ cells, and interstitial cells of Cajal. Activating mutations and amplifications generate activation of growth and proliferation pathways, which seem to be important and common in acral and mucosal melanoma, both tumors unrelated to sun exposure [8]. Screening for KIT aberrations may have diagnostic value, given the evidence of a possible pathogenic role of this gene in mucosal melanomas, as well as a possible a therapeutic target in these patients [12]. Therapeutic c-KIT blockade could be useful in the treatment of patients with activating KIT mutation [6]. New drugs, such as imatinib, work on this pathway [8].

Along its signaling pathway, Microphthalmia-associated transcription factor (MITF) is referred to be involved in melanocyte development. The amplification of this gene is found in approximately 15-20% of primary mucosal melanomas. RAS-mitogen activated protein kinase related genes overexpression were found in up to 90% of primary mucosal melanomas [11]. Mutations in B-type Raf gene (proto-oncogene BRaf), present in up to 70% of cutaneous melanomas, have been detected in less than 10% of primary mucosal melanomas [2, 11]. Differently from the Human Papillomavirus (HPV) infection, which leads to p16/INK4a overexpression, loss of p16 expression, CDKN2A mutations, and loss of heterozygosity are observed in up to 50% of primary mucosal melanomas. GNAQ/11 mutations were observed in only 9.5% of the patients, who also presented shorter mean survival when compared to patients with wild type GNAQ/11. Programmed death-ligand 1 (PD-L1) expression seems to occur less frequently in patients with mucosal melanoma, which may lead to believe that mucosal melanomas are less immunogenic due to a lower mutational burden [2]. Primary sinonasal melanomas develop due to distinct genetic abnormalities, that lead to diffuse activation of the PI3K/Akt and RAS-MAPK pathways. These specific genetic pathway alterations, however, are not associated with different prognosis [6].

The key molecular events that trigger the malignancy development and progression is still unknown, which makes it difficult to work on new specific or multimodal treatment for this disease [12]. We can observe that mucosal melanoma is one unique subgroup in a vast emerging molecular classification system of melanoma. The complete understanding of these mechanisms may hopefully lead to a future of more optimized target therapy [11].

3. Diagnosis

Melanomas are malignant tumors arising from pigment cells—melanocytes. Melanocytes in mucosal membranes are distributed to the oral cavity, nasal cavity, paranasal sinuses, esophagus, larynx, vagina, cervix, rectum, and anus [13].

Mucosal melanoma of the head and neck (HNMM) region constitutes 55% of all mucosal melanomas, but <10% of all melanomas of the head and neck region. A majority of these tumors are found in the sinonasal regions (55%), while the rest are located in the oral cavity (25–40%) [13–16]. Mucosal melanomas generally present at a later stage, are more aggressive and carry a worse prognosis regardless of the stage at diagnosis [17–31].

Of all mucosal melanomas, paranasal sinus has the worst prognosis. The best prognosis locations are the nasal and oral cavity [15]. In contrast to cutaneous melanomas, mucosal melanomas more frequently are amelanotic and present in a multifocal fashion [17]. Early detection provides the best chance at survival but is often difficult due to anatomic location [17, 22, 27, 29]. Mucosal melanoma remains a challenge for several reasons: firstly, the clinical diagnosis often occurs relatively late, because it is not usually confirmed before the disease is symptomatic; secondly, traditional aspects of cutaneous melanoma clinical staging may not apply; and thirdly histological diagnosis can be difficult due to its rarity and variable appearance.

3.1 Clinical signs and symptoms

Presenting symptoms of mucosal melanomas differ in relation to the site of origin.

3.1.1 Primary mucosal melanomas of the nose and paranasal sinuses

Sinonasal primary mucosal melanomas (PMM) account for <1% of all melanomas and <5% of all sinonasal tract neoplasms [32].

In the sinonasal tract, early signs and symptoms are similar to those encountered in inflammatory benign conditions and therefore may be overlooked for some time [33].

The tumors can present with non-specific symptoms including nasal obstruction, facial pain, rhinorrhea and epistaxis [34]. In advanced stage primary tumors, symptoms such as diplopia, exophthalmos, ophthalmoplegia, headache, skin infiltration and ulceration, can occur [11].

At endoscopy, MM may present as a polypoid, with strict unilateral involvement in most cases. Lesions may have different degrees of pigmentation, with the possibility of diversely pigmented areas within the same mass. It can assume dark, brown, red, or pale white colors.

Compared with oral melanoma, completely amelanotic tumors are rare but when they do occur are associated with an even worse prognosis because of a more aggressive biology and greater difficulty in diagnosis [33]. Furthermore, multiple lesions (satellite lesions) can be frequently observed, even centimeters away from the main tumor, with spreading occurring along the mucosal/submucosal planes.

Among sinonasal cases, approximately 80% are located in the nasal cavity itself, most commonly the middle and inferior turbinates, lateral nasal wall and nasal septum, while 20% occur in the paranasal sinuses [13, 15, 16].

Concurrent nasal and paranasal lesions are infrequent.

The most frequently involved paranasal sinus is the maxillary sinus followed by the ethmoid, frontal and sphenoid sinuses respectively [11]. Primary lesions of the sphenoid and frontal sinus are exceedingly rare [11, 35].

Most of the patients with melanomas of the nasal cavity (75%) are diagnosed with clinically localized disease. That is the reason why patients with nasal melanoma have a more favorable prognosis when compared with melanoma arising from other head and neck sites. However, melanomas of the paranasal sinuses are usually advanced at presentation. PMMs of the ethmoid and maxillary sinuses have a worse prognosis than those arising from other sites. This is related to the higher T classification and late symptomatology. When occurs infiltration into the orbit, skull base, infratemporal fossa or facial soft tissue, the outcome is very poor [36–39]. At initial diagnosis, lymphatic metastases are present in 10% to 20% of patients with sinonasal PMMs, and <10% of patients have evidence of distant metastases [40]. 40% of cases will develop distant metastases in lungs, brain, bone, and liver, during the course of the disease [41]. Vascular and neural invasion is observed in approximately 40% of patients [42]. Early and repeated recurrences is frequently noticed in malignant melanomas of the nasal cavity and paranal sinuses.

3.1.2 Primary mucosal melanomas of the oral cavity

Primary mucosal melanomas of the oral cavity account for <1% of all melanomas, 0.5% of all oral malignancies, and 40% of all PMMs of the head and neck. The incidence of oral PMMs is higher in Asians, Africans, Hispanics, and Asian Indians [43–45].

Oral primary mucosal melanomas tend to present late as they are usually asymptomatic in the early stages and are often unnoticed by patients [11].

Compared to sinonasal disease, it may be diagnosed earlier due to the greater accessibility for inspection and oral examination.

Oral MM generally presents as a hyperpigmented lesion (**Figures 1** and **2**), with a wide range of colors varying from black, brown, gray to reddish or white. Interestingly, oral lesions may be amelanotic in up to 10–30% of cases; in these patients, diagnosis may be challenging. Amelanotic melanomas may simulate pyogenic granulomas [46, 47].

The tumors can be macular, nodular or plaque-like. Just like cutaneous melanomas, melanoma in the mouth may be asymmetric with irregular borders.

There can also be non-specific symptoms including bleeding, ulceration and pain, which is associated with the vertical growth of the lesion [48].

Macular lesions are flat, and up to one-third of patients have a long history of mucosal pigmentation (melanosis) [49, 50], which is considered the radial growth phase before invasion of underlying tissues (vertical growth phase). Nodular tumors, conversely, have an irregular surface and present as ulcerated, exophytic lesions.

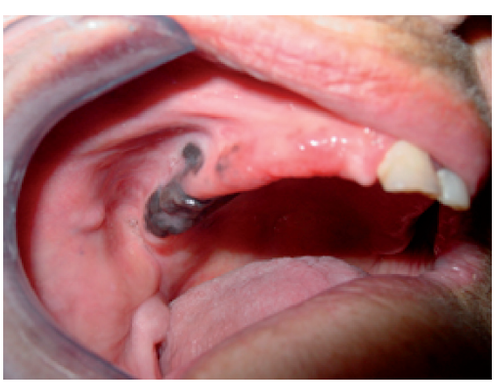


Figure 1.
Aveolar ridge mucosal melanoma.

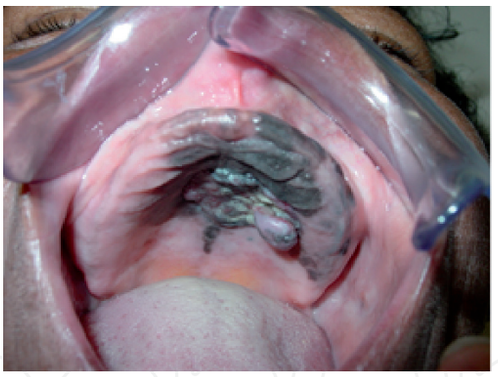


Figure 2.
Hard palate mucosal melanoma.

As with the sinonasal tract, it is also possible to observe satellite lesions in the oral cavity surrounding the primary lesion [49, 51].

The majority of oral melanomas occur in the maxillary alveolar ridge or the hard palate. Such locations favor early invasion of underlying bone, which may account for their poor prognosis. The buccal mucosa, lips, tongue, floor of the mouth, and uvula can also be affected as well [52].

The involvement of other subsites (floor of the mouth and tongue) is not commonly observed.

Tanaka et al. [52] featured oral MM into 5 types: pigmented, nodular type; non-pigmented, nodular type; pigmented, macular type; pigmented, mixed type; non-pigmented, mixed type. This classification was based in patterns of growth and presence of pigmentation.

25% of the patients with oral cavity melanomas present with lymph node metastases. The likelihood of cervical lymph node metastases increases when the tumor thickness is more than 5 mm [53, 54]. Wu et al. [52], on the other hand, found that MMs with a nodular pattern of growth have a higher risk of nodal involvement compared to macular melanomas.

3.1.3 Primary mucosal melanomas of other head and neck sites

Rare cases of laryngeal [55], oropharyngeal [56] and nasopharyngeal [50, 57] MM have been reported; these lesions are extremely rare, with only sixty cases reported in the literature. The tumors are most commonly located in the supraglottic region (62.2%) followed by the vocal cords (37.8%).

Clinical presentation does not generally differ from that typical of other primary tumors, mainly squamous cell carcinomas, arising in the same sites.

The symptoms of laryngeal MM are dysphagia, hoarseness, and painful sore throat [18, 19, 58].

Pharyngeal lesions may cause hemorrhage, dysphagia and/or dyspnea [19].

Symptoms of nasopharyngeal PMMs are similar to sinonasal PMMs; the tumors usually present with epistaxis, nasal obstruction, and obstruction of the Eustachian tube with serous otitis [19].

Notably, the risk of nodal (65.5%) and distant (59.3%) metastases in pharyngo-laryngeal lesions is definitely higher than in other head and neck subsites [4].

As a general rule, the risk of nodal involvement in HNMM at presentation is higher in oral (25-43%) [47] than in sinonasal lesions (<10%) [35, 53].

The high rates of cervical node involvement at presentation is probably related to the size of primary lesions. 61% of nodal involvement occurs in lesions larger than 4 cm. Levels I (68%), II (68%) and III (23%) are the most commonly involved,

whereas the frequency of metastases at levels IV (12%) and V (2%) is much lower [44]. The occurrence of distant metastases at presentation is low (5-10%), with no significant difference between oral and sinonasal lesions [53, 59]. The brain and lungs are the preferential sites of distant localization, whereas multiple organ involvement may be detected in up to one-third of cases [53].

3.2 Histological diagnosis

Head and neck PMMs are usually diagnosed at advanced stages, thus presenting macroscopically as aggressive nodular neoplasms arising from the mucosa; few cases are detected in situ [60]. Histopathological diagnosis is straightforward when the tumor cells are melanin rich. About two thirds of mucosal melanomas contain some intracytoplasmic brown pigment, which has to be confirmed as melanin and can be found in tumor cells or macrophages [61].

The histological features of HNMM can be as diverse as cutaneous melanomas [62], with variable mitotic activity and cell morphology [11]. Approximately 15 to 50% of cases presents with amelanotic lesions [63, 64]; as they can mimic another malignant neoplasms, including squamous cell carcinoma, this diagnosis has been challenging. These tumors frequently have a worse outcome [65, 66].

Histologically, mucosal melanoma is characterized by the proliferation of neoplastic melanocytes with variable phenotypes (epithelioid, spindle, and plasmacytoid cells without maturation and with nuclear changes, appearing as large and hyperchromatic nuclei with prominent nucleoli) that are arranged in a sheet-like, organoid, alveolar, solid, or desmoplastic architecture. They display high mitotic activity and show a pattern of invasion of the submucosa destroying the underlying tissues [67–69].

Tumors with mixed cell phenotypes are more related with vascular invasion and the development of metastasis. The neoplastic proliferation is commonly found along the junction between the epithelial and lamina propria, but this may be difficult to detect in advanced and ulcerated lesions [70].

Molecular studies have tried to find clinical predictors and immunohistochemical biomarkers to improve outcomes and survival rates.

Immunohistochemical stains may help distinguish mucosal melanoma from other malignancies and from cutaneous melanoma.

PMMs variously express S-100 protein and melanocytic markers, including MART-1/Melan-A, tyrosinase, HMB- 45, and MITF. 62 S-100 protein has greater sensitivity, but HMB-45 is probably more specific [42]. The absence or scarcity of melanin makes the diagnosis difficult and immunohistochemical techniques are required. The cells of amelanotic melanomas are positive for S-100 protein Melan-A, HMB-45, MITF and vimentin; and negative for cytokeratin [71].

One study assessed the expression of DNA mismatch repair and looked for the presence of microsatellite instability in HNMM. They showed that the cells had increased expression of mismatch repair proteins and increased microsatellite stability [72]. Besides these classical markers, the diagnostic potential of other molecules has been evaluated in Primary Oral Mucosal Melanoma (POMM), in particular several adhesion molecules. Integrin beta-3 and CD166 expression is correlated with extensive vascular invasion, while lower expression of CD54 is correlated with cell necrosis [73].

The expression of BCL2 in POMM has an important correlation with a longer overall survival [74].

The expression of podoplanin and CD13 in combination with S100 has been useful in the evaluation of lymph vessel and blood vessel invasion. Both markers are related to a poorer prognosis [75].

Programmed cell death ligand 1 (PDL-1) is known as a potent prognostic biomarker in several human tumors. Although this experimental evidence strongly supports the use of monoclonal antibodies targeting immune checkpoint proteins in MM, PDL-1 expression does not seem to be predictive of patient outcome, at least in melanoma [76]. Indeed, although PDL-1 positive tumors achieve a better responses to immunotherapies, PDL-1 negative patients can also have good outcomes.

3.3 Imaging of melanomas of the head and neck

When malignancy is suspected, computed tomography (CT) and magnetic resonance imaging (MRI) are valuable in defining the locoregional extent of the tumor, which is critical in determining resectability. For more accurate evaluation of MM, magnetic resonance imaging (MRI) is the modality of choice. This modality provide more information about the tumor, the localization, its relation to adjacent structures, and expansive or infiltrative characteristics. The analysis of signals in the different sequences is more.

sophisticated than the analysis of CT densities. The MRI signal of mucosal melanoma is influenced by the amount of melanotic pigment and hemorrhage within the lesion.

CT and MRI, when used together, can be complementary and define even better the invasion and destruction of structures of the skull base by soft-tissue masses.

The paramagnetic properties of melanin and of the free radicals produced by the metals ligated to the pigment itself account for a MRI pattern composed of T1 hyperintensity and T2 hypointensity [77].

MM usually manifests radiologically as an aggressive solid tumor with destructive characteristics related to compression or infiltration. The tumor causes bone destruction and invades adjacent soft tissues [13]. Thus, pre-treatment tumor mapping requires definition of tumor relationships with all surrounding anatomic sites and subsites. It is mandatory the accurate evaluation of involvement of intracranial structures and the surrounding vital structures such as cranial nerves or vessels, the anterior cranial fossa, the orbits, the pterygopalatine fossa and the infratemporal fossa.

Tumors arising along the Eustachian tube or in the nasopharynx can spread to the skull base at the foramen lacerum or along the tube to potentially reach the middle ear.

From a surgical point of view, key elements in the preoperative staging of mucosal melanoma of the oral cavity and oropharynx include depth of submucosal invasion, extension across the midline bone invasion and infiltration of deep space of the suprahyoid neck [77]. When the neoplasm reaches important anatomic crossroads, such as the posterior third of the hard palate, the pterygopalatine fossa, and the foramen ovale, perineural growth should be accurately evaluated.

MRI is the standard imaging modality for postoperative surveillance. Micrometastases may be radiologically occult. Because of the high fluorodeoxyglucose avidity of PMMs, FDG-positron emission tomography (PET)/CT may play an important role in the staging of PMM and in selecting the goals of therapy for patients with suspected metastasis or recurrence [78, 79].

3.4 Staging

Tumor staging for mucosal melanoma remains a challenge. Several staging systems have been suggested, including tumor-nodal-metastases (TNM) staging systems, but none are frequently used. TNM staging is only used for head and neck mucosal melanoma [11, 18].

The often concealed locations of mucosal melanoma result in frequent presentations of advanced disease.

In addition, unique to these anatomic locations are vast vascular and lymphatic networks in close proximity to the primary tumor, allowing for diffuse spread, with approximately one third of patients having nodal involvement at diagnosis [17, 21, 22, 24, 25, 29].

While different staging systems are in place for mucosal melanomas of different primary sites, Ballantyne described a three level staging system for classifying mucosal melanomas in 1970, which continues to be largely used:

Stage I: clinically localized disease;
Stage II: regional nodal involvement (cervical lymph node metastases).
Stage III: distant metastatic involvement.

Although its major advantage lies in its simplicity, this classification does not include depth of invasion or local tumor extension. The classification provides limited prognostic information as the majority of patients present with stage I disease [80].

To overcome these limitations, the pattern of tumor invasion has been studied in depth by Prasad et al., who reported that progression of the invasion at the microscopic level is associated with clinical worsening and suggests increased aggression.

They proposed microstaging as a prognostic marker, based on invasion of tissue compartments [81]:

Level I (in situ disease)
Level II (superficially invasive: melanoma invading up to the lamina propria)
Level III (deeply invasive: muscle, bone or cartilage).

The study evidenced a statistically significant difference in disease specific survival rates in levels I (75%), II (52%) and III (23%) respectively. However, this classification system is based on histological findings, the disadvantage is that it can only be used in evaluation of tissues following tumor excision, although invasion noted on pre-treatment imaging can be included.

The American Joint Committee on Cancer (AJCC) staging system for head and neck mucosal melanoma is often utilized, beginning at stage III. This focuses on the extent or size of the primary mucosal tumor using it as a predictor for outcome [82]. Mucosal melanomas are aggressive tumors, therefore T1 and T2 are omitted as are stages I and II.

TNM Clinical Classification:
T – Primary Tumor
TX: Primary tumor cannot be assessed
T0: No evidence of primary tumor
T3: Tumor limited to the epithelium and/or submucosa (mucosal disease)
T4a: Moderately advanced disease involving the deep soft tissue, bone, cartilage, or overlying skin T4b: Tumor invades any of the following: brain, dura, skull base, lower cranial nerves (IX, X, XI, XII), masticator space, carotid artery, prevertebral space, mediastinal structures
N – regional lymph nodes.
NX: regional lymph nodes cannot be assessed
N0: no regional lymph node metastasis
N1: regional lymph node metastasis
M – distant metastasis
M0: no distant metastasis
M1: distant metastasis
Stage Grouping
Stage III: T3 N0 M0
Stage IV A: T4a N0 M0

T3 ou T4a, N1, M0
Stage IV B: T4b, Any N, M0
Stage IV C: Any T, Any N, M1

A staging system should be valid as a prognostic tool to target treatment in terms of overall survival, but this system is not yet identified. At this point, tumor thickness greater than 5 mm, more than 10 mitotic figures per high power fields and/or ulceration has been suggested as independent prognostic factors [11]. To develop a uniform staging system a more thorough understanding of the prognostic factors is required [17]. This could facilitate comparisons of the results of different institutions, and help define the best therapy.

4. Treatment/management

There is no clear consensus on the management of head and neck mucosal melanoma, which reflects the rare nature of the disease and complexity of the anatomic site. The late diagnosis, frequently presenting at an advanced stage, denoting the aggressive nature of the disease. Currently, early detection and surgical excision is considered the primary method of treatment.

4.1 Surgery

Surgical treatment is the "gold standard" [80]. Wide excision with clear margins is the first goal in surgical management, once the complete surgical resection with negative margins significantly improves patient prognosis [83], whereas positive surgical margins have been associated with a higher rate of distant metastases, decreased survival measures, and a significantly higher risk of death compared to patients with negative surgical margins [84–86].

The incision depends on tumor site and size. Due to low rate of regional spread and the lack of effect on survival, elective neck dissection is not recommended. Neck dissection is mandatory only in cases of clinical or radiological positivity neck. Sentinel lymph node biopsy is not usually performed [80, 87, 88].

Surgical excision as a monotherapy should be reserved for patients with small tumors, localized disease and negative margins [89].

For sino-nasal mucosal melanomas, endoscopic techniques or external incision can be used [80, 90, 91]. In cases of oral mucosal tumors, a radical surgical resection with clear margins is the only curative option, and in cases of large masses, maxillectomy or marginal or segmental mandibulectomy is a possibility [11].

For laryngeal or pharyngeal melanomas, for complete resection is necessary total or partial laryngectomy or pharyngectomy [91]. The HNMM can be an aggressive disease and has high recurrences, demanding extensive resection surgery leading to disfigurement [80].

In most cases, complete resection is technically impossible without a destructive or disabling procedure, due to the proximity of the tumor to critical organs, but also because of the acceptable cosmetic result [36, 92], which frequently makes an adjuvant therapy necessary. Supplementary surgery can be executed for patients with recurrent disease and no evidence of distant disease [35, 90].

The National Comprehensive Cancer Network (NCCN, U.S.A.) guidelines emphasize that primary treatment should be surgical for stage III to IVA in the AJCC staging system but state that surgery is not recommended for stages IVB and IVC. These patients should be allocated in clinical trials or offered primary radiation therapy [93].

4.2 Radiotherapy

Radiotherapy (RT) is indicated to control local disease, positive surgical margins, or in case of palliative therapy. The addition of radiotherapy to surgery (adjuvant RT) may reduce the risk loco-regional recurrence without any impact on overall survival and disease-specific survival neither on the risk of distant metastasis [83, 87, 94–98].

According to the NCCN, adjuvant RT is indicated for patients with resected melanoma with high-risk nodal disease with four or more positive lymph nodes, lymph nodes of ≥3 cm and macroscopic extranodal soft tissue extension [93].

There is no clear indication of the appropriate evidence and the best radiation scheme.

Particle-beam therapy has also been used to facilitate the delivery of high doses to the residual tumor while minimizing exposure to the surrounding normal tissues, avoiding severe adverse effect in patients with tumors proximal to critical anatomical structures [99–101].

Primary RT alone has been advocated in patients with non-operable disease or a poor performance status [91].

4.3 Chemotherapy

The role of chemotherapy is minor compared to the biological and immunological systemic therapies [102]. The paucity of association of chemotherapy alone with improve overall survival led to its discontinuation as the election treatment for patients with metastatic mucosal melanoma. Therefore, chemotherapy is nowadays used as an adjuvant therapy in combination with other immunotherapeutic and biological drugs [103, 104].

4.4 Biological treatment

The selective inhibitors of various targeted (targeted therapy) have been approved since 2011 and include the BRAF inhibitors, dabrafenib and vemurafenib, the MEK inhibitors, trametinib and binimetinib and c-KIT inhibitors, which provides an attractive opportunity for developing adjuvant therapies for HNMM, mainly for patients with advanced locoregional or metastatic disease.

Vemurafenib, dabrafenib and trametinib are options for patients with BRAF V600 mutations who have unresectable or metastatic melanoma, mostly in combined therapy [3].

The selective inhibition of c-KIT alteration with, for example, the tyrosine kinase inhibitor, imatinib mesylate, has been revealed significant outcomes in patients with the K642E c-KIT gene mutation [27] whereas dasatinib, showed promising results in clinical trials in patients with L576P c-KIT gene mutation, once the KIT gene is mutated or present in increased numbers in mucosal melanoma [28]. Nilotinib is another selective inhibitor of c-KIT that does not require an active transport mechanism to enter cells [3]. Sadly, target therapy for c-KIT-mutated mucosal melanoma does not attempt the clinical reliability detected with BRAF-targeted treatment in cutaneous melanoma.

In clinical trials vemurafenib, a BRAF kinase inhibitor, has been showed greater efficacy and tolerability when compared to the chemotherapeutic dacarbazine [105, 106], as well as binimetinib, a MEK inhibitor (MEK162), administrated before or after immunotherapy with better overall response, progression-free survival, and disease control [107, 108].

4.5 Immunotherapy

A role for biologic treatment, as well as immunotherapy, has emerged over the last decade. Recent studies suggest that immunotherapy may confer survival benefit to patients with advanced disease.

Multiple prospective and retrospective studies support the use of the monoclonal antibody targeting cytotoxic T-lymphocyte-associated antigen-4 (CTLA4), ipilimumab, a promising immunotherapy [109], and the inhibitor of interactions of ligands PD-L1 and PD-L2 with its receptor, programmed death-1 receptor (PD-1), therefore blocking T-cell activation (anti-PD1 agents), nivolumab and pembrolizumab [110].

Nivolumab has been used as a promisor therapy in clinical trials. In patients with ipilimumab monotherapy-refractory or ipilimumab in combination with BRAF inhibitor-refractory metastatic melanoma, nivolumab showed a higher overall survival rate than standard chemotherapy [110, 111]. Furthermore, nivolumab in combination with ipilimumab has been shown a higher overall response rate then monotherapies [112].

Just like nivolumab, other checkpoint inhibitors, like pembrolizumab, have demonstrated more improvement in progression-free survival, toxicity, and overall survival than ipilimumab [113, 114].

Durvalumab and atezolizumab, other anti-PD-L1 antibody monotherapies, have not been very successful [115], whereas ipilimumab, nivolumab and pembrolizumab are standard options for unresectable or metastatic melanoma and may have potential as adjuvant therapy [3].

5. Prognosis

The prognosis of HNMM is relatively dismal, often due to late diagnosis, with 5-year overall survival rate of 25% [116–121] and higher rates of local recurrence and distant metastases than cutaneous melanomas [10, 122, 123].

Distant metastasis is the most common cause of treatment failure. The most common sites for distant metastases are the lungs, followed by the liver, bones and brain [124].

Local recurrence is frequent and commonly associated to positive surgical margins. Advanced age is associated with decreased survival [59, 83, 98, 124–126]. Present of distant metastases, advanced T-category, ulceration, vascular invasion, deep infiltration and male gender are associated with a poorer prognosis too [8, 97].

The multidisciplinary team approach can help reduce morbidity and mortality once optimize treatment, reduce costs and minimize adverse events, while maximizing the chances of recovery. A collaborative interprofessional team includes surgery, medical oncology, radiation oncology, radiology, nuclear medicine and pathology [127]. A multidisciplinary team workup will provide proper appraisal evidence based decision-making, and the most helpful treatment planning and care.

6. Conclusion

Mucosal melanoma is an exceedingly rare variant of cutaneous melanoma, with aggressive behavior and less favorable prognosis. This could be because of late diagnosis, patients' delay or the obscured anatomic site of origin. Unfortunately, because of its rarity, is poorly described and infrequently studied. Establishing guidelines for the clinical course of mucosal melanoma has been challenging.

The etiology and pathogenesis remain unclear. To date there are no clearly established risk factors for its development.

Primary tumor resection is the best treatment that also provides additional prognostic indicators. The type of surgical approach used is dependent upon the location and extension of the tumor, but the goal is negative margins with minimal cosmetic or functional derangements. Unfortunately, achieving melanoma-free margins is often compromised due to the anatomical complexity of the region and the close proximity of critical anatomic structures. Elective neck dissection is indicated for patients with lymph node metastases, especially in oral mucosal melanomas where there is an increased frequency. Adjuvant external beam radiotherapy is generally advocated with chemotherapy and targeted therapy being used for distant metastatic or unresectable disease.

Systemic treatment with immunotherapy can offer scope for modifying the course of the disease but response rates are lower and clinical research remains a priority. More studies and investigations are necessary to provide enough information and increase the survival rates.

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