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Update on primary head and neck mucosal melanoma

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Abstract

Primary mucosal melanomas (PMMs) of the head and neck are uncommon malignancies that arise mainly in the nasal cavity and paranasal sinuses, followed by the oral cavity. The mainstay of treatment is radical surgical resection followed by adjuvant radiotherapy in selected patients with high-risk features. Multimodality therapy has not been well studied and is not standardized. Adjuvant radiotherapy seems to improve locoregional control but does not improve overall survival (OS). Elective neck dissection is advocated in patients with oral PMM. Systemic therapy should be considered only for patients with metastatic or unresectable locoregional disease. Despite improvements in the field of surgery, radiotherapy, and systemic therapy, patients with

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PMM still face a very unfavorable prognosis (5-year disease-free survival [DFS] <20%) with high rates of locoregional recurrence and distant metastasis. The present review aims to summarize the current state of knowledge on the molecular biology, pathological diagnosis, and management of this disease.

Keywords

head and neck; mucosal melanoma; diagnosis; outcomes; surgery; radiotherapy; chemotherapy; staging system

INTRODUCTION

Most malignant melanomas of the head and neck region — 85% to 90% of them — are cutaneous lesions, most often arising in the skin of the face. Mucosal melanomas are much rarer lesions, which contributes to the fact that they are poorly characterized and incompletely understood.

Primary mucosal melanomas (PMMs) were first described by Weber[1] in 1859 and have since then been considered an uncommon condition. The head and neck region is the most commonly involved site in which PMMs develop.[2]

PMMs of the head and neck account for more than half of all PMMs and involve (in decreasing order of frequency) the nose and paranasal sinuses, oral cavity, pharynx, and larynx.[3–5] Although tumors arising from the respiratory mucosa (such as in the nasal cavity) have different clinicopathologic characteristics than those involving oral mucosa, they share similar adverse prognoses and outcomes.[5] Head and neck PMMs are usually associated with poor clinical outcomes despite aggressive treatments, with 5-year disease-free survival (DFS) rates ranging from 0% to 20% because of poor local and distant control.[6]

The purpose of this review was to present an update on pathobiological and management aspects of head and neck PMMs. Melanomas involving the eye are outside the scope of this review.

EPIDEMIOLOGY

PMM is a rare disease. However, a trend of an increasing incidence during the last several decades is noteworthy.[7] PMMs account for 0.03% of all cancer diagnoses and 0.8% to 3.7% of all melanomas. The USA Cancer Database reported that 1.3% of melanomas were mucosal, of which 55% arose in the head and neck area.[8] These findings are similar to those reported by the Surveillance, Epidemiology, and End Results program between 1973 and 2007.[9]

The nose and paranasal sinuses are the most common sites of origin, followed by the oral cavity.[10] Most series report a similar distribution between men and women.[11] The tumors develop primarily between the fifth and eighth decades of life, with median age of presentation at approximately 60 years, although they may occur in any age group. They are

rare in the first 3 decades of life.[12] Lourenço et al[3] reported a 9-year-old patient affected with PMM of the oral cavity.

The incidence of PMM varies between races. PMMs constitute a greater proportion (8%) of all melanomas in Japanese patients compared with whites (1%); 7.5% of all melanomas in the Japanese arise in the oral cavity versus <1% in whites.[6,13]

ETIOPATHOGENETIC CONSIDERATIONS

PMMs originate from melanocytes that have migrated as neurocristic derivatives in endodermal or ectodermal mucosa.[2,14] It seems that PMMs originating from the respiratory non-squamous mucosa have clinicopathologic differences than those of multilayered squamous mucosa, but share a similar prognosis.[15] Melanocytes are seen in the oral mucosa from 20 weeks of gestation and can be detected even in the salivary gland epithelium (at 23 weeks of gestation).[16] These melanocytes might have antimicrobial and immunological function, such as antigen presentation and cytokine production, but their role requires further clarification.[17]

The pathogenesis of PMM is unknown. Melanoma may be associated with preexisting mucosal nevi, which occur in 0.1% of the population,[8] but no risk factors have been identified that are associated with an increased likelihood of developing PMM.[18,19] There seems to be no relationship between PMMs of the oral cavity and the racial pigmentation affecting that site.

Unlike cutaneous melanomas, PMMs are not associated with sun exposure.[20] It has been suggested that the pathogenesis of these melanomas is linked to embryology because of the close proximity of commonly affected head and neck mucosal sites (lower nasal cavity, and maxillary sinuses, hard palate, and upper gingiva).[21]

Inhaled and ingested carcinogens – particularly products of smoking and formaldehyde – have been implicated in the pathogenesis of sinonasal PMMs, similar to other malignancies of the nasal cavity.[22,23] Two thirds of patients with PMM arising in the pharynx or larynx reported a history of smoking.[24] Factors such as family history and preexisting lesions influence the development of oral PMMs.[13,25]

The malignant transformation of melanocytes occurs through sequential accumulation of genetic and molecular alterations. Although the molecular pathways causing PMMs are still unknown, certain genes and metabolic pathways are known to undergo changes. Recently, some reports indicate that PMMs have several genetic changes in intracellular signaling cascades that may constitute the pathogenetic mechanism of melanoma.[26] The progressive understanding of these molecular mechanisms may hopefully lead to a future of more specific and successful therapies for PMMs. The ideal pathway to be targeted remains to be identified.

Recent data suggests an increased frequency of c-KIT (CD117) aberrations in mucosal melanomas, whereas c-KIT in most types of cutaneous melanomas does not seem to be of pathogenetic importance.[27] The c-KIT overexpression is present in over 80% of PMMs and

somatic mutations are observed in 10% to 30% of cases.[16] Downstream in the c-KIT signaling pathway, microphthalmia-associated transcription factor (MITF) is involved in melanocyte development, and amplification of this gene is found in approximately 15% to 20% of PMMs.[16]

The Genome-Wide Cancer Sequencing Program (the Sanger Institute's Cancer Genome Project) detected frequent mutations of B-type Raf (*BRAF*; proto-oncogene *B-Raf*) in 50% to 70% of cutaneous melanomas.[28] Nearly 90% of reported *BRAF* alterations are oncogenic mutations that lie in the region that encodes the kinase domains, in which valine is replaced by glutamic acid at codon 600 (V600E)[29] and usually occur in melanomas that develop in sites that are chronically sun exposed or have intermittent UV exposure compared with lesions that form in mucosal membranes or unexposed sites. Conversely, *BRAF* mutations in PMMs are uncommon; mutations in this gene have been detected in <10% of PMMs.[16,30]

RAS-mitogen-activated protein kinase pathway alterations, particularly *RAS* somatic mutations and overexpression, were found in 20% and over 90%, respectively, in PMMs.[16]

Alterations in the *CDKN2A* locus, encoding the tumor suppressor protein p16/INK4A, are frequently present in patients with hereditary cutaneous melanoma. The p16/INK4A pathway influences melanomas at sites with less sun exposure.[31] Somatic inactivation of INK4A by point mutation, deletion, or promoter hypermethylation is found in most sporadic melanomas and in 24% to 40% of melanoma-prone families.[28,32] Loss of p16 expression, *CDKN2A* mutations, and loss of heterozygosity are observed in up to 50% of PMMs.[33–36] However, in contrast to cutaneous melanoma, loss of p16 expression is not correlated with worse prognosis in PMM.[37] Human papillomavirus infection leads to altered expression (often overexpression) of p16/INK4A in some human cancers, but this is not a feature of PMM.[38]

It is becoming increasingly evident that melanoma is not one disease, but rather a family of diseases characterized by particular molecular abnormalities. PMM is one such unique subgroup in this emerging molecular classification system of melanoma. This classification system has tremendous implications for the development of new and effective therapies for patients with this disease.

CLINICAL PRESENTATION

Primary mucosal melanomas of the nose and paranasal sinuses

Sinonasal PMMs account for <1% of all melanomas and <5% of all sinonasal tract neoplasms.[39] PMMs of the head and neck occur most frequently in the nasal cavity, where the lateral nasal wall and nasal septum are the most common sites of origin of the sinonasal tract. Melanomas arising from the lateral nasal wall account for almost half of the total.[5] Middle and inferior turbinates and nasal vestibule are other possible sites. The maxillary sinus is the most commonly affected paranasal cavity, followed by the ethmoid (<10%), frontal, and sphenoid sinuses (1%). Concurrent nasal and paranasal lesions are infrequent. The sinonasal PMMs are usually advanced at presentation and the precise site of origin may be difficult to localize.

Clinical symptoms of sinonasal cancer, such as nasal obstruction, facial pain, or persistent rhinorrhea/epistaxis, are nonspecific, often indistinguishable from those of benign sinonasal disease. Proptosis, diplopia, or neurological symptoms appear in more advanced tumor stages.

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. PMMs tend to exhibit low-signal intensity on T2-weighted images and enhancement on precontrast T1-weighted images. MRI is the standard imaging modality for postoperative surveillance. Because of the high fluorodeoxyglucose (FDG) 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.[40,41]

Most of the patients with melanomas of the nasal cavity (75%) are diagnosed with clinically localized disease. However, melanomas of the paranasal sinuses are usually diagnosed at a more advanced stage. This may explain why patients with nasal melanoma have a more favorable prognosis than those with melanoma arising from other head and neck sites. This is probably related to the lower T classification and/or earlier symptomatology of septal/nasal melanomas versus those arising from paranasal sinuses.[5,42,43] PMMs of the ethmoid and maxillary sinuses have a worse prognosis than those arising from other sites; infiltration into the skull base, orbit, or facial soft tissue is associated with a very poor outcome.[44]

Sinonasal PMMs metastasize less frequently to lymph nodes but more frequently to the lungs and brain. 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.[45] An additional 20% can expect to develop nodal metastases during the course of the disease and 40% to 50% will develop distant metastases in the lungs, brain, bone, and liver.[46] Vascular and neural invasion is seen in 40% of cases.[14] Malignant melanomas of the nasal cavity and paranasal sinuses are characterized by early and repeated recurrences.

Stanimirov Rossi et al[47] recently described 2 subtypes of sinonasal PMMs: unilocular and multilocular PMMs. In their reported series, 30% of the cases showed a multilocular distribution pattern, which seems to be associated with an unfavorable DFS compared to its unilocular counterpart.

It is mandatory to rule out the possibility of metastases from melanomas originating in any other parts of the body to the sinonasal tract. The presence of junctional activity or intraepithelial atypical melanocytes in the adjacent mucosa, with or without pagetoid spread, would favor a primary sinonasal tract melanoma, but this may be impossible if the surface epithelium is ulcerated or destroyed.[13,15] A detailed medical history and genetic and molecularly approaches, as discussed above, would be helpful.

The comparative genomic hybridization profiles can help in diagnosing sinonasal PMMs because these tumors have consistent alterations: chromosome 1q is gained in all tumors, and gains of 6p and 8q are present in 93% and 57% of cases, respectively.[48]

Primary mucosal melanomas of the oral cavity

PMMs 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, with an annual incidence of 1.2 cases per 10 million people. The incidence of oral PMMs is higher in Asians, Africans, Hispanics, and Asian Indians. They develop between the ages of 9 and 91 years, and their incidence peaks in the 60s; in general, there is no gender preference.[49–51]

Oral PMMs are asymptomatic in the early stages and are often unnoticed by patients, contributing to their frequent initial diagnosis in advanced stages. A pigmented lesion, sometimes found incidentally during an oral examination, is the presenting symptom in many patients. Other symptoms include pain, bleeding, ulceration, and ill-fitting dentures. The lesion may be macular, plaque-like, or nodular, usually asymmetrical, and in shades of brown, gray, or black. Nonpigmented lesions occur in almost 10% of cases.[52] Satellite lesions may be adjacent to the tumor.

The majority of oral PMMs (80%) occur in the mucosa of the upper maxillary alveolar ridge and 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.

In contrast with the low rate of nodal metastases of sinonasal melanomas, 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]

Primary mucosal melanomas of other head and neck sites

PMMs of the larynx and pharynx are very rare.[55] Most cases (80%) occur in men, who range in age from 35 to 86 years (mean, 61 years). Symptoms are dependent on the subsite that is involved, but the common initial symptom is hoarseness (70% of cases); other symptoms include irritation, sore throat, dysphagia, and a neck mass. The most frequently affected laryngeal region is the supraglottis (60%), followed by the glottis (40%). In the pharynx, melanomas may result in hemorrhage, voice alterations, and breathing and deglutition impairments; these symptoms reflect an advanced stage of the disease. 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.[16] Metastases to the regional lymph nodes are present in up to 65% of cases and to distant sites in 60%.[56]

PATHOLOGY

Head and neck PMMs seem to originate from melanocytes present in the mucosa from the upper aerodigestive tract.[57] The histological features of PMMs may be as polymorphic as in their cutaneous counterpart. 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.[58,59] The detection of in situ components is more difficult in sinonasal mucosa because of the thinness of the surface epithelium and frequent ulceration, as discussed above. In oral PMMs the in situ component may spread along the lining of

salivary ducts, similar to the extension of cutaneous melanomas along adnexae. The prognostic significance of this feature is uncertain, but it may assist in characterizing the tumor as primary.

Histopathological diagnosis is straightforward when the tumor cells are melanin rich. Histologically, melanomas are composed of medium to large size cells that may be polyhedral, round, fusiform, epithelioid, spindle, pleomorphic, microcytic, or a mixture of them. Usually, they show nuclei with one or more eosinophilic nucleoli, which are useful diagnostic clues. Mitotic activity is prominent. A rare balloon cell variant with clear cytoplasm may mimic various types of clear cell tumors, like those arising in salivary glands.[60] Osteocartilaginous differentiation has also been observed.[61] This may reflect the ectomesenchymal potential of neurocristic derivatives. The cells of mucosal melanoma grow in either solid, loosely cohesive, storiform, pseudoalveolar, or organoid patterns.[57] About two thirds of mucosal melanomas contain some intracytoplasmic brown pigment,[57] which has to be confirmed as melanin and can be found in tumor cells or macrophages. Attempts have been made to link particular phenotypes (mixed and undifferentiated) or arrangements (pseudopapillary and sarcomatoid) with tumor aggressiveness, vascular invasion, and metastasis potential, but validation is needed. Amelanotic lesions (between 15% and 50% of cases in some series)[16,60] may present a challenge for the unsuspecting pathologist as the variety of cell phenotypes and arrangements notoriously simulate other malignant tumors.

Once the possibility of malignant melanoma is considered on routine histopathological features, the diagnosis can be easily established with immunohistochemistry. PMMs variously express S-100 protein and melanocytic markers, including MART-1/Melan-A, tyrosinase, HMB-45, and MITF.[62] The use of MITF is not widespread in pathology laboratories. S-100 protein has greater sensitivity, but HMB-45 is probably more specific.[14] The role of CD63 needs to be further explored. A study of a large cohort has shown that no single marker has 100% sensitivity; hence, a panel of markers should be used.[63] There is loss of p16 in 74% of PMMs.[37] When melanin is scarce or is not found, diagnosis may be difficult and immunohistochemical techniques are mandatory. The cells of amelanotic melanomas are negative for cytokeratin and positive for vimentin, S-100 protein Melan-A, and HMB-45, as well as MITF.[62] Currently, there is little to no use for electron microscopy in the diagnosis of PMMs. It may, however, demonstrate premelanosomes and/or melanosomes in tumor cells and could be a valuable research tool.[64]

STAGING

Tumor staging for PMMs remains challenging. In 1970, Ballantyne[65] described a simplified staging system for head and neck PMMs that continues to be a widely utilized scheme. The system classifies the following 3 stages: stage I for localized lesions; stage II for regional dissemination (cervical lymph node metastasis); and stage III for distant metastases. The advantages of this system are its simplicity and that it can be used for all PMMs. However, it takes into account neither the depth of invasion nor local tumor extension. Moreover, this system places too much emphasis on regional spread, which is uncommon in PMMs. Finally, as most patients (75% to 95%) present with localized disease (stage I), it offers limited prognostic information for the majority of patients. To overcome these limitations,

Prasad et al[66] proposed a microstaging system based on the invasion of tissue compartments within the mucosa: level 1 (in situ disease); level 2 (superficially invasive: melanoma invading up to the lamina propria); and level 3 melanomas (deeply invasive: muscle, bone or cartilage). They reported statistically significant differences in the survival rates for levels 1, 2, and 3 (5-year disease-specific survival [DSS] rates of 75%, 52%, and 23%, respectively). Prasad's staging system is histological: the level can only be determined after surgery except when deep tumor invasion is visible on imaging.

PMMs can also be staged according to the American Joint Committee on Cancer (AJCC) criteria that emphasize the extent/size of the primary tumor as a predictor of outcome for the site of origin. Loree et al[42] found that the 5-year overall survival (OS) rate of patients with T1 and T2 PMMs of the head and neck was 32% and for T3 and T4 tumors was 0% ($p = .05$).

The TNM staging system for carcinoma of the nasal cavity and sinuses (carTNM) proposed in 2002 by the AJCC is increasingly used to stage PMMs,[67] and a specific TNM classification for head and neck PMMs (mmTNM) was proposed in 2009, but is infrequently used.[68] The carTNM system seems to be the main staging tool for PMMs of sinonasal origin because it provides an even distribution of the tumor stages and it has a substantial prognostic value in terms of OS and DFS.[69] However, Gal et al[70] have advocated the use of mmTNM. This classification is not dependent on head and neck mucosal origin. Moreover, it respects the oncologic premise that the behavior of PMM is the same regardless of the site of origin. This classification is similar to staging of cutaneous melanoma, in which depth of invasion is more important than invasion of anatomic sites. Michel et al[71] assessed the prognostic value of the 3 staging systems for sinonasal PMMs: the Ballantyne staging system modified by Prasad, the AJCC mmTNM, and the AJCC carTNM. Only carTNM was significantly correlated with OS ($p = .012$) and DFS ($p = .041$). The other 2 classifications were not correlated with survival except for metastatic patients whose OS was lower ($p = .032$). Moreno et al[5] reported a more homogeneous distribution of patients when carTNM was used instead of Ballantyne's clinical staging system. Moreover, tumor size was an excellent predictor for 5-year OS in this series. Thus, carTNM should be the main staging system for patients with PMMs of the sinonasal tract because it shares the same terminology and it reflects the prognosis of these patients.

TREATMENT

Surgery

Complete surgical resection with clear margins is the mainstay of PMM management and may provide the best results, although the therapeutic strategy should be tailored individually according to tumor stage, site, and previous treatment of the patient. Especially for advanced stage tumors, there is a need for more effective and less morbid treatment options. Strategies to improve treatment outcome should focus on local disease control and reducing distant metastasis.

A detailed description of the different potential surgical approaches is beyond the scope of this review. Whenever possible, wide and radical procedures are attempted in order to obtain

negative margins. Intraoperative frozen section analyses of PMMs seem to correlate with final pathology.[72] Because the histopathologically assessed spread is usually greater than the extent of gross disease, and owing to the need to preserve vital structures, free surgical margins may not be achieved in some cases.[73] This results in local control rates <50%.[57] Patients with positive surgical margins have a 21-fold increased risk of dying of the disease.[74] Failure to achieve local control is associated with a markedly increased rate of distant disease (from 14% to 71%) and a significantly decreased OS.[75] Nevertheless, more than 50% of patients achieving local control after surgery (+/− adjuvant radiotherapy) ultimately develop distant metastasis.[2] Thus, although radical surgery offers the best chance for local control, this philosophy must be tempered by the knowledge that local control does not seem to be a strong predictor of enhanced survival.

In patients with recurrent disease and without distant disease, a second surgical procedure is considered as the best option if the tumor can be reasonably resected. However, salvage surgery should not be routinely performed in every patient because insistence on complete removal of the tumor from critical neurovascular structures in all instances could, in some patients, produce a considerable morbidity that would be hardly justified in such an aggressive tumor. Repeated surgery would be capable of salvaging up to 25% of patients who fail locally,[2] but it should be kept in mind that failure to achieve local control is accompanied by the development of distant metastasis in a large majority of patients failing initial resection.[6]

Careful surgical planning is required to avoid significant morbidity and adverse impact on quality of life that is associated with aggressive surgery, especially in the paranasal sinuses. Minimally invasive endoscopic approaches are important recent techniques deserving special attention as they can reduce the likelihood of complications and morbidity because of surgery while maintaining oncologic efficacy.[76] Nicolai et al[77] reported encouraging results based on a series of 17 patients with sinonasal PMM treated exclusively via an endoscopic or cranioendoscopic approach over 10 years. In contrast to the suggestions of some early critics of the endoscopic approach, choosing an endoscopic approach does not exclude radical resection. Moreno et al[5] used an endoscopic-assisted approach in 10 of 58 patients with sinonasal PMMs; patients who had an endoscopic-assisted procedure had a higher 2-year OS when compared with those who had an open procedure (64% vs 36%; $p = .0262$). There may, however, be a selection bias as the approach was more commonly used on patients with localized disease. Thus, radical surgery, including craniofacial resection, represents the gold standard for local control of sinonasal PMMs.

For PMMs of the oral cavity, adequate resection may involve a marginal or segmental mandibulectomy. For PMMs of the larynx and pharynx, a partial pharyngectomy, partial laryngectomy, or total laryngectomy may be needed to remove the tumor adequately.

The unpredictable and aggressive nature of PMMs must be kept in mind when counseling patients whose tumors may require extensive and potentially disfiguring surgery. Although such procedures are often palliative, they frequently represent the only hope for the patient and may result in cure. Moreover, free tissue transfer is a reliable, safe, and effective method for repair of the postsurgical defects.

Elective treatment of the neck is usually not performed, as the incidence of nodal disease at the time of presentation is relatively low, although higher in oral cavity than in sinonasal PMMs, both at initial presentation (25% vs 6%, respectively) and during the course of the disease (42% vs 20%, respectively).[53] Although most authors endorse a conservative approach to the neck,[53,73] Medina et al[78] recommended elective treatment of the neck in patients with oral PMMs. Krengli et al[79] reported a 77% regional recurrence rate for oral PMMs, suggesting a potential advantage for elective neck treatment. The macroscopic appearance of oral PMMs has been found to correlate with the risk of developing regional metastases. Based on this finding, it may be advisable for patients with clinically nodular oral melanomas to undergo prophylactic neck dissection; close follow-up may be acceptable for patients with flattened/macular oral PMMs.[80] Sentinel lymph node biopsy may provide an alternative to identify patients who could benefit from an elective neck dissection. This approach has been successfully used for staging of sinonasal PMMs by some authors.[81,82] Likewise, preoperative PET scanning may be helpful to plan an effective treatment of the neck.[41] However, the role of FDG-PET in this setting requires further clarification. Detailed histopathological assessment of neck dissections would be useful in defining the pN pattern for PMMs of the head and neck and would influence current views on elective treatment.

Radiotherapy

Although malignant melanoma has been traditionally regarded as a radioresistant tumor, a significant intertumor (and intra-tumor) heterogeneity in radioresponsiveness was observed in clinical studies and was also demonstrated in experimental conditions.[83] Not surprisingly, radiotherapy has become widely utilized as part of the treatment algorithm in adjuvant and definitive settings. New radiation techniques, such as intensity-modulated radiation therapy, volumetric-modulated arc therapy, tomotherapy, carbon-ion therapy, neutrons, and proton therapy permit the achievement of superior isodose shaping and sharp dose gradients near the targeted volumes. The greater conformality of these new techniques produces a lower rate of radiation-induced toxicity and increases therapeutic efficiency.[84,85] Liao et al[86] reported high rates of locoregional control achieved with neutrons, despite the presence of gross disease. Nevertheless, survival was limited because of early distant metastases.

Definitive carbon-ion therapy was adopted by Yanagi et al[87] who reported a 5-year local control rate of 84%, with a 5-year OS and DSS of 27% and 40%, respectively. Of note, 85% of the patients who failed at distant sites were free of local disease. This series showed an OS rate higher than those treated with conventional radiotherapy and comparable to those treated with surgery. These authors concluded that carbon-ion therapy is a safe and effective treatment in terms of high local control with acceptable toxicities. Krengli et al[79] reported a series in which definitive radiation with photons, neutrons, or carbon ions was used; local tumor control ranged from 61% to 85% and OS ranged from 15% to 28%. These are comparable to those reported for other therapeutic modalities.[87] Definitive radiotherapy may therefore be a useful and only potentially curative option in cases of unresectable tumors.

Precise indications for adjuvant radiation have yet to be defined and, in most series, it is used only in advanced and recurrent cases.[88] There seems to be agreement regarding its use in cases with positive or close margins, especially as these are a negative prognostic marker.[74]

As the development of a local failure has been suggested as a marker of distant disease, it has been hypothesized that improvements in locoregional control may result in higher survival rates. Adjuvant radiotherapy clearly improves locoregional control but a beneficial effect on OS has not yet been established.[83,88,89] Possibly, postoperative radiotherapy would benefit patients with PMMs arising in difficult locations (especially in paranasal tumors vs oral tumors) where the tumor may be extensive or the margins may be very close.[5] The optimal radiation dose and fractionation regimes are still undetermined, although total doses of more than 54 Gy and hypofractionation may improve local control and OS.[5,90] On the other hand, no superiority of hypofractionated regimens compared to conventional fractionation was observed in other studies, including the postoperative setting.[83]

It seems prudent to consider postoperative radiation for patients with nodal metastases, particularly when metastases are multiple, large in size, and when extranodal extension of tumor can be demonstrated.[91,92] Temam et al[93] reported increased local control rate, from 26% to 62% ($p = .05$), in patients treated with surgery and adjuvant radiotherapy. Distant metastasis DFS was not significantly increased in patients with postoperative radiation ($p = .4$). Owens et al[94] reported that the addition of radiotherapy tended to improve local control ($p = .13$) but did not significantly improve survival ($p = .73$). Krengli et al,[79] Gal et al,[70] and Wu et al[95] reported similar data. They concluded that the addition of radiation increased local and locoregional DFS ($p = .049$ and .015, respectively), but did not have an impact on OS or DSS. As noted above, improved locoregional control has been reported with a total dose greater than 54 Gy ($p = .02$), but this did not affect OS.[5] In contrast, some studies do not support a benefit from adjuvant radiotherapy in PMM.[53,96,97]

Systemic therapy

PMMs of the head and neck are regarded as highly malignant tumors and many patients succumb to distant metastases. Hence, it would be desirable to add effective systemic therapy for patients with advanced and incurable tumors. So far, no systemic therapy regimen has been recognized as effective for metastatic PMM of the head and neck.

Combinations of cytotoxic chemotherapy with a biological, immunomodulatory agent (interferon-α or interleukin-2) have shown higher response rates (as high as 40% to 60%).[98] The advantage is not reflected in an improvement in OS.[99,100] Most of these studies have been performed on patients with metastatic cutaneous melanomas, limiting extrapolation to PMMs. Analyzing data of 616 chemo-naive patients treated with systemic therapy on 8 phase II/III clinical trials, Bedikian et al[101] recognized biochemotherapy as a favorable prognostic factor for long-term survival. Currently, systemic therapy is mainly used in the treatment of disseminated disease and for palliation. Nevertheless, systemic therapy has been considered as adjuvant therapy in high-risk cases.[102] Thus, Bartell et al[98] suggested that biochemotherapy for advanced head and neck PMMs should be considered as a systemic treatment option for patients with metastatic disease, unresectable tumors, or extracapsular spread.

As discussed above, genetic profiling of PMMs have identified a number of frequently altered genes, such as *KIT*, *BRAF*, *N-RAS*, and *GNAQ*, and molecular pathways like PI3K-Akt-mTOR that might be used for targeted therapy with specific antibodies or small

molecule inhibitors.[103] Unlike cutaneous melanoma, PMMs have infrequent *BRAF* mutations and do not seem sensitive to therapies targeting *BRAF*.[30] There is emerging evidence indicating that melanomas with c-KIT alterations of proven functional relevance may respond to c-KIT inhibitors, such as imatinib, sorafenib, dasatinib, or sunitinib.[98,104,105] Some trials investigating the response to imatinib in patients with unresectable melanoma harboring somatic alterations of c-KIT are currently ongoing. In a published phase II study of imatinib in 43 patients with unresectable melanoma harboring mutations or amplification of c-KIT (including 11 patients with PMMs), imatinib was associated with a 23% objective response rate, suggesting a targeted treatment option for molecularly selected patients.[106]

As melanoma can evade the natural protection of the immune system, a number of new agents that enhance cancer immunity have been developed. Ipilimumab, an anti-cytotoxic T-lymphocyte antigen 4, monoclonal antibody, is one such immunomodulatory drug that recently demonstrated improved survival rates for patients with metastatic cutaneous melanoma. However, PMMs typically show a minimal overall response rate to this drug. Postow et al[107] performed a study to assess the efficacy and safety of ipilimumab in PMMs in a group of 33 patients. They observed some responses to ipilimumab, but the overall response rate was low (6%). A recent evaluation of the European Expanded Access Programme for ipilimumab, including 71 patients with pretreated PMMs, demonstrated a 12% response rate and disease control rate of 36%.[108] Further investigation is necessary to clarify the role of ipilimumab and other immune system targets (ie, programmed cell death-1 [PD-1] receptor and programmed death ligand-1 [PD-L1]) in patients with PMM. This area of clinical research is rapidly evolving; of note, the first near-complete and durable response to anti-PD-1 receptor therapy in PMM has recently been reported.[109]

The quest for newly developed targeted therapy faces the challenge to define optimal molecular stratification of patients.[110] Further studies are needed to determine whether cases associated with particular alterations may benefit from specific targeted therapies, and to identify new therapeutic targets for those cases in which no specific alterations have been identified. In addition, longitudinal studies are needed to determine whether these molecular abnormalities have prognostic implications.

PROGNOSIS

Head and neck PMMs continue to be a challenge, as their overall outcome and long-term survival are poor, independent of treatment modality.[111] Table 1[2,5,7,9,49,53,58,59,66,69–71,93,96,97,102,111,112] shows the 5-year DFS and the OS rates for patients with PMM reported in the literature. The 5-year OS is <30% in most series. The major determinant of outcome in PMMs is the extent of the primary tumor (ie, clinical/pathologic staging).[9] As many patients are diagnosed with advanced disease, survival rates in patients with PMM are lower than those of patients with cutaneous melanoma, most of whom are currently diagnosed at an early stage.

Head and neck PMMs behave much more aggressively than their cutaneous counterparts and their prognostic markers have not been fully elucidated. Clinical stage, surgical margin status, tumor thickness greater than 5 mm, and vascular invasion on light microscopy are

considered to be independent predictors of outcome.[53,112] The presence of more than 10 mitotic figures per high-power fields and/or ulceration has been suggested as an independent prognostic factor.[5,109] Amelanotic melanoma has been regarded as a worse prognosis,[11] but the presence or absence of melanin has not been related to DFS or OS in recent series.[49,53,63,88] Distant metastasis is the limiting factor for long-term survival. Recently, Wermker et al[113] evaluated the outcome and value of some prognostic factors in a series of 42 patients with PMM of the head and neck; age above 70 years, occurrence of distant metastasis, and lymphovascular invasion were significantly associated with unfavorable outcome and shorter DSS time. Double immunostaining for S-100 protein/podoplanin and S-100 protein/CD3 may facilitate recognition of lymphovascular invasion, although widespread use of these diagnostic immunohistochemical procedures seems unlikely. Finally, patients with lower Ki67 scores showed better survival than those with higher Ki67 scores[114]; also, high survivin (an inhibitor of apoptosis) scores have correlated significantly with a poor prognosis.[115]

CONCLUSION

PMMs of the head and neck are relatively rare; they are aggressive forms of melanoma for which more effective treatment strategies are needed. The carTNM classifications seem to provide the most reliable prognostic information. Gross tumor resection seems to be the standard of care. However, decisions regarding surgery need to be made in view of the rate of locoregional and distant failure and functional outcome. Endoscopic surgery seems to be suitable when the principles of oncologic surgery with adequate exposure and margins are followed. Neck dissection is indicated in all patients with lymph node metastasis and, because of higher frequency of nodal involvement, elective neck dissection may be considered in patients with oral PMMs. Because of the improvement in therapeutic ratio, adjuvant radiation therapy with new radiation techniques is strongly recommended. Biochemotherapy and targeted therapy are appropriate for patients with unresectable and metastatic disease; its role as adjuvant therapy in patients with extensive locoregional disease has not been defined. For all patients, clinical trial participation, when available, should be strongly encouraged. Genetic profiling, the development of cell and animal models, and the search of “druggable” genetic targets should be explored in an effort at laying the foundations for future targeted and hopefully more effective anticancer therapies for this disease.

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TABLE 1

Five-year disease-free survival and 5-year overall survival reported in the literature.

Authors	No. of patients	5-y DFS (%)	5-y OS (%)	Postoperative radiotherapy (%)
Bridger et al[58]	27	14	43	52
Cheng et al[59]	22		16	41
Dauer et al[49]	61		22	28
Gal et al[70]	304		24	39
Jangard et al[7]	156		20	32
Jethanamest et al[9]	815	32	25	
Koivunen et al[69]	50	48	27	14
Lund et al[96]	115	24	28	51
Manolidis and Donald[2]	14		14	14
Meleti et al[111]	42	22	17	19
Michel et al[71]	19	18	34	42
Moreno et al[5]	58	18	39	57
Narasimhan et al[102]	18		24	56
Patel et al[53]	35		47	
Prasad et al[66]	61	43	31	22
Shuman et al[112]	52	22	38	19
Temam et al[93]	69		20	57
Yii et al[97]	89		23	

Abbreviations: DFS, disease-free survival; OS, overall survival.