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REVIEW ARTICLE

An update on the current management of head and neck mucosal melanoma

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Primary mucosal melanomas of the head and neck are rare and aggressive tumours that arise in the nasal cavity, paranasal sinuses and more rarely in the oral cavity. The current treatment options include radical surgical resection with adjuvant external beam radiotherapy being offered in high-risk patients. Although the latter can improve regional control, it does not reduce overall survival. Elective neck dissection is recommended for nodular oral mucosal melanoma, but its role in the clinically node negative neck is controversial. Systemic therapies including the use of tyrosine kinase inhibitors for tumours with c-KIT mutations are suitable for patients with advanced loco-regional and/or metastatic disease, but current results are variable. Patients with head and neck mucosal melanoma have a poor prognosis due to the high incidence of metastatic disease. This review assesses the latest evidence in the diagnosis and management of primary oral and head and neck mucosal melanoma including details of systemic therapies.
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Introduction

Head and neck primary mucosal melanoma (HNMM) is one of the most aggressive and yet uncommon tumours that arise in this anatomical region. They account for half of all primary mucosal melanomas and most commonly involve the nasal cavity and paranasal sinuses followed by the oral cavity. HNMM account for between 0.2% and 8% of all primary mucosal melanomas arising in Europe and the USA and 0.03% of all cancer diagnoses (1). Most studies demonstrate a similar distribution between males and females (2) and the tumour usually presents in older patients with a mean age of 65 years (1), but a recent epidemiological study looking at HNMM has identified a mean age of 72 years and an age-standardised incidence rate of 1.2 per million person years (3). However, a case in a nine-year-old child has also been reported in the literature (4). There is a significant variation between races with the Japanese more likely to be affected (8%) when compared to Caucasians (5, 6). Unlike cutaneous melanomas, they are not associated with sun exposure (7). HNMM is a challenge to clinicians for several reasons; firstly, clinical diagnosis often occurs relatively late; secondly, clinical staging is different compared to cutaneous melanoma; and thirdly, histological diagnosis is challenging due to its rarity (8).

Presentation

Sinonasal melanomas account for less than 1% of all melanomas, and the majority are found in the lateral nasal wall. They can also occur in the middle and inferior turbinates (9, 10). In the paranasal sinuses, the most common site is the maxillary sinus followed by the ethmoid, frontal and sphenoid sinuses, respectively (11). The tumours can present with non-specific symptoms including nasal obstruction, facial pain and rhinorrhoea (12). In advanced stage primary tumours, symptoms such as diplopia and proptosis can occur (11).

Oral primary mucosal melanomas tend to present late as they are usually asymptomatic in the early stages (11). The tumours can be macular, nodular or plaque-like, and there can also be non-specific symptoms including bleeding, ulceration and pain (Fig. 1). The majority of oral melanomas occur in the maxillary alveolar ridge or the hard palate, but they can also occur in the buccal mucosa, tongue, floor of mouth and lips (13).

Pathology

It has been suggested that HNMM undergoes changes in their genetic and metabolic pathways with intracellular cascades that constitute a potential pathogenetic mechanism of origin (14). There are several differences between mucosal and cutaneous melanomas such as an increased

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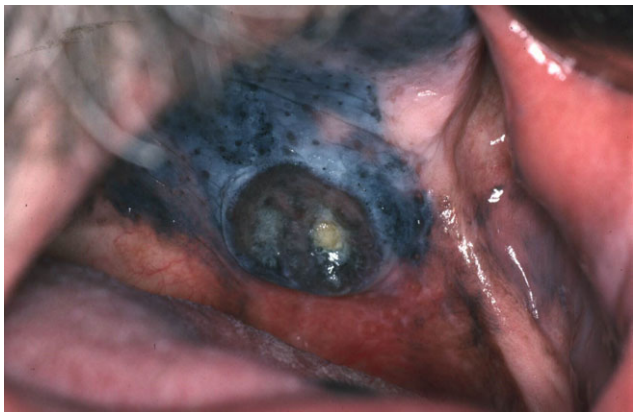

Figure 1 Large ulcerative mucosal melanoma of the soft palate which has spread extensively to involve the hard palate.

frequency of c-KIT mutations in mucosal melanomas (15), which can be found in at least 80% of cases with somatic mutations also occurring in 10–30% of tumours (15). B-type RAF (BRAF) mutations have also been identified in 50–70% of cutaneous melanomas as opposed to less than 10% of mucosal melanomas (16, 17).

The histological features of HNMM can be as diverse as cutaneous melanomas (18). The challenges for clinicians and pathologists are that these tumours are diagnosed at an advanced stage and there is a poor understanding due to its rarity (19, 20). Histological features include medium to large cells that can vary in their morphology and have variable mitotic activity (11). Amelanotic presentations occur in 15–50% of cases (15, 19) causing difficulties in diagnosis as they can mimic other malignancies including squamous cell carcinoma. These tumours tend to have a poorer prognosis (21, 22). The cells are often negative for markers such as cytokeratin but positive for vimentin, S-100 and HMB-45 (23). It has been suggested that the presence of periodic acid-Schiff (PAS) loops and networks could be used to indicate an reduction in overall survival (24). One study (25) 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.

Staging

Tumour staging for HNMM remains a challenge (Table 1). Ballantyne (26) described a three-level staging system for classifying mucosal melanomas in 1970, which continues to be widely used:

Stage I represents localised lesions;

Stage II for regional dissemination (cervical lymph node metastases); and

Stage III for distal metastases.

Although its major advantage lies in its simplicity, this classification does not include depth of invasion or local tumour extension. Regional spread with HNMM is often relatively uncommon and the classification provides limited prognostic information as the majority of patients present with Stage I disease. One histological study suggested a micro-staging system based on invasion of tissue compartments (27):

Table 1 Head and neck mucosal melanoma staging systems

System	*Advantages*	*Disadvantages*
Ballantyne 1970	Simple and widely utilised Suitable for all PMMs	Emphasis on regional spread Does not account for depth of invasion and tumour extension
Prasad 2004	Simple Suitable for all PMMs	Can only be used after surgical resection
TNM 2002	Widely utilised Similar to cutaneous melanoma staging Good reflection of prognosis	Used primarily for sinonasal mucosal melanoma
TNM 2009		Infrequently used May not have a statistically significant prognostic value

Level I (*in situ* disease);

Level II (superficially invasive-to the lamina propria); and

Level III (deeply invasive-bone or cartilage).

The study reported a statistically significant difference in disease-specific survival (DSS) rates in levels I (75%), II (52%) and III (23%), respectively. The disadvantage to this classification system proposed by Prasad et al. (27) is that as it is based on histological findings, it can only be used in assessing tissues following tumour excision, although invasion noted on pre-treatment imaging can be included.

An alternative staging system used is the AJCC (American Joint Committee on Cancer) (28). This focuses on the extent or size of the primary mucosal tumour using it as a predictor for outcome. There is also a TNM system for nasal cavity and paranasal sinus, first proposed in 2002 and used for staging mucosal melanomas and a more specific head and neck version published in 2009 (29). While the 2002 TNM staging system provides an even distribution of tumour stages and has a prognostic value, the more specific 2009 version also allows for assessment of invasion depth.

One study looked at the prognostic value for all three staging systems for sinonasal mucosal melanomas (30), concluding that the 2002 TNM staging system significantly correlated with both overall survival ($P = 0.012$) and disease-free survival ($P = 0.041$). The study found that the other two classification systems did not correlate with survival except in patients with metastatic disease ($P = 0.032$). Moreno et al. reported a more homogeneous distribution of patients when the 2002 TNM staging system was used compared to the 1970 classification proposed by Ballantyne (6). Tumour size was also found to be useful as a reliable predictor for five-year overall survival. A further report supports the results of earlier studies (6, 31) confirming that the TNM system is more able to predict prognosis than the 1970 classification (32).

Management of head and neck mucosal melanoma

Surgery

For effective management of HNMM, complete surgical resection with clear margins is required (33). As might be expected, one study demonstrated that patients who did not

have surgery had a poorer outcome (34). Failure to achieve local control is associated with an increased risk of distant disease and leads to significantly decreased overall survival. However, more than 50% of patients will develop distant metastases despite having good local tumour control (35). For patients with recurrent disease and no evidence of distant disease, further surgery can be performed, helping up to 25% of patients, but there is the risk of distal metastases (5, 36), and it can result in considerable morbidity and potentially reduced quality of life.

For sinonasal mucosal melanomas, endoscopic techniques can be used (36). One study reported a series of 17 patients treated radically by endoscopic surgery (37) and another assessed 10 patients that had endoscopic surgery finding a higher two-year overall survival rate (64%) compared to patients who had an open procedure (36%) (5).

It could be argued that patients having endoscopic surgery might have more localised disease, but the potential advantage of this technique is no increased risk of perioperative death compared to extensive open procedures (38). For oral mucosal tumours, ablative surgery is the only curative option, and this may include maxillectomy if the lesion is located in the upper maxillary alveolar region (the commonest site of presentation), or marginal or segmental mandibulectomy if the tumour is in the floor of mouth, buccal mucosa or tongue (11).

Staging CT to include the chest and liver is important, but in cases where bone involvement is suspected, MRI adds further information when planning resection margins and the likely extent of surgery.

Neck dissection

Elective neck dissection (END) is not usually performed in patients with sinonasal disease, although the incidence of nodal disease is higher in patients with oral cavity mucosal melanoma (13, 39). One study found a neck regional recurrence rate of 77% for oral mucosal melanoma (40). The majority of studies have recommended a conservative approach to neck management is needed but some have suggested routine conservative END, often to include levels I-V.

The clinical features of the primary tumour might help the team to decide about neck management with macular appearing tumours having a lower risk of nodal metastasis than nodular lesions where an END might be advisable (13). This could be a reflection of tumour depth (as with skin melanoma depth predicting prognosis), but further studies are needed. Sentinel lymph node biopsy (SLNB) can be used to help in this regard and has been reported for patients with sinonasal mucosal melanoma (11).

Radiotherapy

External beam radiotherapy (DXT) is being increasingly used to achieve local tumour control in HNMM but its survival benefit is questionable following a meta-analysis of 12 studies and 1593 patients (41). Post-operative neck DXT is suitable for patients with a single metastatic node of 3 cm or larger, two or more positive neck or parotid gland nodes, extra-capsular spread, and in cases with lympho-vascular or peri-neural invasion (42). Some studies advocate the use of simple RT regimens to the primary site where surgery might be difficult.

In a retrospective study of 68 patients (5), 13 patients received palliative RT, 30 received radical DXT and 25 patients had surgery with or without adjuvant DXT. The patients who had radical RT had good local control with a 25% five-year disease-specific survival (43).

It still remains that HNMM is a relatively radiotherapy-resistant tumour. There is also controversy as to the fractionation and dose protocol that should be prescribed. In the majority of studies, conventional fractionation with a dose greater than 50 Gy is used (44). Therapeutic hyper-fractionated radiotherapy (HF-RT) (greater than 3 Gy per treatment fraction) is another technique reported for use in HNMM with one study comparing it to conventional DXT finding that it resulted in better local control and improved disease-specific survival at one and 3 years (73% and 33%) (44). However, complications of HF-RT include mucosal ulceration and major haemorrhage due to the much higher doses given at each treatment (41, 45).

Elective neck DXT irradiation for the management of HNMM in the clinically node negative (cN0) neck is controversial. One comparative analysis study assessing differences between patients who received elective neck DXT or not found no significant differences between the two groups (46). Elective neck DXT might have lower regional relapse rates on comparison, but as overall survival is not significantly improved, it may not be justified (43). Saigal et al. identified that 12% of patients who had post-operative DXT to the primary tumour site only subsequently developed regional nodal metastases (47). For oral cavity melanomas, only one study has reported any benefit from therapeutic neck irradiation in the cN0 neck (39). As there are a lack of studies showing any significant benefit for patients with cN0 disease, the decision to treat should be guided by both the tumour features and clinical judgement, and cases should be discussed at a multidisciplinary team meeting (40, 43).

Systemic therapy (including immunotherapy)

Systemic treatments are being developed for distant metastases from HNMM, but to date, the results have been variable (5, 21, 40, 47). Imatinib, a tyrosine kinase inhibitor, is effective in c-KIT mutations that occur in exon 11, but not exon 17 (48). While over 70% of c-KIT mutations in melanoma occur in exon 11, imatinib is not effective in every case because the mitogen-activated protein kinase (MAPK) cascade can function as an ancillary pathway, thereby preventing cell death (49). A phase 2 trial assessed 43 patients with advanced disease and c-KIT genetic mutations (50). 26% of the patients had mucosal melanoma and were given imatinib. In follow-up at 12 months, tumour regression was identified in 42% of patients and survival rate at 1 year was 51%.

Immunotherapy has also been evaluated in HNMM. Ipilimumab, a monoclonal antibody targeting cytotoxic T lymphocyte-associated antigen-4 (CTLA4) was given to patients with unresectable melanomas in a recent phase 3 trial (51). Mean survival was 10.1 months in patients receiving ipilimumab compared to 6.4 months in those who did not have the drug.

Chemotherapy has limited value, but a possible treatment is a combination of temozolomide (TMZ) and cisplatin

which has been used in patients following primary tumour resection with relapse-free survival and overall survival rates better with this regimen compared to interferon therapy alone (52). Interferon-α2b can also be used as an adjuvant therapy for patients following resection of primary oral mucosal melanoma who have had a poor response to chemotherapy, with a longer relapse-free survival rate compared to a control group (53).

Conclusion

Although HNMM is an aggressive disease, primary tumour resection is the best treatment that also provides additional prognostic indicators. Elective neck dissection is indicated for patients with lymph node metastases, especially in oral mucosal melanomas where there is an increased frequency, but its role in the cN0 neck is controversial. Adjuvant external beam radiotherapy is generally advocated with chemotherapy and targeted therapy being used for distant metastatic or unresectable disease.

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