Review Article

Epidemiology, staging and management of mucosal melanoma of the head and neck: a narrative review

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Background and Objective: Mucosal melanoma of the head and neck (MMHN) are rare, aggressive neoplasms of melanocyte origin that remain incompletely understood and have a poor prognosis, with high rates of locoregional recurrence and distant metastasis. Several recent studies having expanded understanding of MMHN, we undertook a review of the latest evidence pertaining to its epidemiology, staging, and management.

Methods: A literature search was conducted for peer-reviewed articles reporting and discussing the epidemiology, staging, and management of MMHN. PubMed, Medline, Embase and the Cochrane Library were searched to identify relevant publications.

Key Content and Findings: MMHN remains an uncommon disease. The current TNM staging system for MMHN provides inadequate risk stratification, and consideration of an alternative staging model such as one based on a nomogram may be justifiable. Tumour resection with clear histological margins remains the cornerstone of optimal treatment. Adjuvant radiotherapy may improve locoregional control but does not appear to affect survival. Immune checkpoint inhibitors and c-KIT inhibitors demonstrate promising efficacy in patients with advanced or unresectable mucosal melanomas, and warrant further research exploring the utility of combination therapies. Their roles as adjuvant therapies have not been determined. The efficacy of neoadjuvant systemic therapy is also not yet clear, although early results suggest that it may improve outcomes.

Conclusions: New insights into the epidemiology, staging and management of MMHN have transformed the standard of care for this rare malignancy. Nonetheless, the results of ongoing clinical trials and future prospective studies are required to better understand this aggressive disease and optimise its management.

Keywords: Mucosal melanoma; head and neck; epidemiology; staging; management

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Introduction

Mucosal melanoma of the head and neck (MMHN) is a rare, aggressive neoplasm arising from melanocytes. In approximately 70% of patients MMHN originates in the sinonasal tract, in 20% in the oral cavity, and infrequently in other primary locations such as the pharynx and larynx (1-3). Reported 5-year overall survival (OS) rates for patients with MMHN range from 20–40%, with a median recurrence free survival (RFS) of only 24 months (4-9). This grave prognosis arises from a combination of factors, including aggressive biological behaviour, frequently late clinical presentation and challenges in resection due to the tumour's proximity to critical structures (10).

Due mainly to the relative rarity of the disease, mucosal melanoma is poorly understood and data on MMHN remain particularly difficult to interpret. This is because studies investigating MMHN often do not analyse them separately from mucosal melanomas arising at other anatomical sites (including gynaecological, urological, and gastrointestinal tract) or even from cutaneous melanomas, impeding the extraction of data specific to MMHN. Furthermore, mucosal melanomas arising in different subsites even within the head and neck region have been shown to differ from a pathogenetic point of view (11,12), complicating analyses of the aetiology and mechanisms underlying the natural history of this heterogeneous group of malignancies.

In light of the rapidly changing landscape of treatment for cutaneous melanomas following the recent introduction of effective systemic therapies, as well as a growing controversy surrounding the prognostic utility of the current TNM staging system for mucosal melanomas, a comprehensive overview of current knowledge of MMHN was considered both timely and relevant. We therefore undertook a literature review to assess all the available evidence pertaining to the epidemiology, staging, and management of MMHN, and to highlight the potential directions of future research. The article was written in accordance with the Narrative Review Reporting Checklist (https://cco.amegroups.com/article/view/10.21037/cco-23-16/rc).

Methods

PubMed, Medline, Embase and the Cochrane Library were searched on November 22, 2022 for literature reporting the epidemiology, staging and management of MMHN (*Table 1*). The time frame of the conducted search was from 01/01/2000 to 01/11/2022. All studies included were peer-reviewed and available in the English language. The databases were searched using combinations of MMHN, management, staging and epidemiology based on both text words and MeSH headings. MeSH headings included but were not limited to "head and neck neoplasms", "melanoma", "mucosal", "epidemiology", "neoplasm staging", "disease management", "immunotherapy", "radiotherapy", and "treatment outcome" in various combinations. Abstracts were screened for relevant articles, and references from the full-text articles were assessed to identify additional studies. All co-authors contributed to and assessed the literature selected for inclusion in this review.

Results

From the literature review, 444 unique titles were identified, of which 108 specific titles focused on MMHN epidemiology (n=14), staging (n=28), and treatment (n=66) were included. A brief summary of the included studies is provided in https://cdn.amegroups.cn/static/public/10.21037cco-23-16-1.pdf.

Epidemiology

Mucosal melanoma is a rare malignancy, representing only 1.3% of all melanomas and 0.03% of all new cancer diagnoses (1). Approximately 40–55% of all mucosal melanomas arise in head and neck sites, with the majority of MMHN originating in the sinonasal tract (70%) and oral cavity (20%). Their origin at other primary sites such as the larynx and pharynx has also been reported (1-3). MMHN most commonly develops between the fifth and eighth decades of life, with a median age at presentation of approximately 60 years. This is one to two decades later than cutaneous melanoma (1,13,14). While most series demonstrate a comparable distribution between sexes (15,16), both slight male and slight female preponderances have been reported for sinonasal and oral cavity melanomas (13,17,18). Whereas for cutaneous melanomas exposure to UV light is a well-established risk factor, aetiological factors for mucosal melanomas remain largely undefined. Although epidemiological studies currently suggest that smoking, ill-fitting dentures, and ingested/inhaled carcinogens including tobacco and formaldehyde are potential causative factors for MMHN, strong evidence for these correlations is lacking (15,19,20).

Several studies have observed a slight trend towards an increasing incidence of MMHN. For instance, Marcus *et*

Table 1 Search strategy summary for literature included in review

Items	Specification
Date of search	November 22, 2022
Databases and other sources searched	PubMed, Medline, Embase, Cochrane Library
Search terms used	Head and neck neoplasms, mucosal melanoma, radiotherapy, immunotherapy, staging, epidemiology, management
Timeframe	January 1st, 2000 to November 1st, 2022
Inclusion and exclusion criteria	All studies included were peer-reviewed and available in the English language
Selection process	All authors contributed and reviewed the selected literature

al. utilised the Surveillance, Epidemiology, and End Results (SEER) database to demonstrate an increase in the reported incidence of MMHN in the USA from 1987 to 2009 [annual percentage change (APC) 2.4%; P<0.01], primarily driven by nasal cavity lesions (APC 2.7%; P<0.01) while that of non-nasal cavity lesions remained stable (21). Causative factors underlying this trend remain unclear (17,18,21); possibilities that have been suggested include cigarette smoking and infection with the human papilloma virus (HPV). Importantly, the rise in incidence of MMHN has been much less dramatic than that of cutaneous melanoma, and the incidence of mucosal melanomas across all anatomical sites has remained relatively stable overall (1,15).

As a group, mucosal melanomas tend to constitute a greater proportion of all melanomas in non-white ethnicities. In a study by Altieri *et al.* of the population-based California Cancer Registry from 1988 to 2013 (n=1,919), although only 1% of melanomas occurring in non-Hispanic whites were mucosal, mucosal melanomas accounted for 15% of all melanomas in Asian/Pacific Islanders, 9% of non-Hispanic blacks, and 4% of Hispanics (22). In China, mucosal melanomas were reported to account for 22.6% of all melanomas (n=522) in a prospective study (23), while in Japan oral melanomas alone comprised 7.5% of all melanomas in a nationwide survey (n=295) (24). Combined with increasing reports of more advanced mucosal melanomas at presentation in Asian/Pacific Islander patients (22,25), these findings underscore the heterogeneity of MMHN, and highlight the need for further elucidation of the genetic and environmental factors associated with this aggressive malignancy.

Staging

There is a need for adequate risk-based stratification of MMHN to indicate and communicate prognosis, guide appropriate treatment, and facilitate the exchange of information between physicians. Yet staging of MMHN remains challenging. The first dedicated staging system for MMHN was established in 1970 by Ballantyne *et al.*, who categorised the malignancy into 3 stages (I–III): localised, regionally disseminated (with cervical lymph node metastasis), and with distant metastasis (26). While widely adopted due to its simplicity, the clinical prognostic value of Ballantyne's model was limited by (I) its inability to account for the depth of tumour invasion; (II) its emphasis on regional lymph node metastasis, which is uncommon in MMHN; (III) its limited prognostic value for most patients, as the majority of initial presentations of MMHN are with localised (Stage I) disease (27,28). Thus, Prasad *et al.* proposed a microstaging system in 2004, which further classified localised MMHN based on the histological extent of tissue invasion (29). This modified Ballantyne/Prasad model, however, requires histological assessment that can only be performed following surgical resection of the tumour.

In 2009, the American Joint Committee against Cancer established its first prognostic staging system for MMHN in its 7th edition staging manual (AJCC7; *Tables 2,3*) (30). Prognostic stage groupings were defined by the extent of the primary tumour (T), regional lymph node involvement (N), and distant metastasis (M). Of note, this is the only TNM staging system in AJCC7 not to define T1 and T2 categories, which were omitted to reflect the overall poor prognosis of MMHN even for small superficial lesions (30). Although several studies have advocated for its prognostic utility, an emerging body of evidence now indicates that AJCC7 staging fails to provide sufficient risk stratification in the evaluation of MMHN (6,31-39). For instance, both Michel *et al.* and Houette *et al.* concluded that AJCC7

Table 2 AJCC 7th edition staging criteria for MMHN

TNM stage	Description
Primary tumour (T)	
T3	Tumours limited to the mucosa and immediately underlying soft tissue, regardless of thickness or greatest dimension; for example, polypoid nasal disease, pigmented or nonpigmented lesions of the oral cavity, pharynx, or larynx
T4a	Moderately advanced disease Tumour involving deep soft tissue, cartilage, bone, or overlying skin
T4b	Very advanced disease
	Tumour involving brain, dura, skull base, lower cranial nerves (IX, X, XI, XII), masticator space, carotid artery, prevertebral space, or mediastinal structures
Regional lymph node(s) (N)	
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis present

AJCC, American Joint Committee on Cancer; MMHN, mucosal melanoma of the head and neck; T, tumor; N, node; M, metastasis.

Table 3 AJCC 7th edition prognostic stage groupings for MMHN

Prognostic stage	T	N	M
III	T3	N0	M0
IVA	T4a	N0	M0
	T3-T4a	N1	M0
IVB	T4b	Any N	M0
IVC	Any T	Any N	M1

AJCC, American Joint Committee on Cancer; MMHN, mucosal melanoma of the head and neck; T, tumor; N, node; M, metastasis.

provides less reliable prediction of RFS and OS for sinonasal melanomas compared to the non-specific AJCC staging system for cancers of the nasal cavity and paranasal sinuses (36,38), while Prinzen *et al.* and Flukes *et al.* observed no statistically-significant association between the AJCC7 prognostic stages and disease-specific survival (DSS) or OS (33,37).

As a consequence of this contention in the literature, the latest edition of the AJCC Staging Manual (8th ed., published in 2017) omits the AJCC7 prognostic stage groupings as part of its formal definition, despite using the same TNM model as in its previous iteration (30,40). However, several authors have suggested that there are also intrinsic faults with the AJCC's current definition of T stage for MMHN, proposing that the classification with only three T stages is too limited to be predictive (6,32,41). For instance, Schmidt *et al.* reported no difference in the OS rates of patients with T3 and T4a MMHN, while Torabi *et al.* found no significant difference in OS for those with T3 and T4a mucosal melanomas occurring outside the sinonasal cavity (6,42).

To address this staging limitation, Lechner *et al.* suggested that the AJCC8 staging should be expanded to further stratify the T3 stage for sinonasal melanomas based on whether the tumour is localised to the nasal cavity or has extended into the paranasal sinuses (41). The notion of incorporating tumour site into prognostic staging for sinonasal melanomas is reinforced by current literature, as previous reports consistently demonstrate worse survival outcomes associated with paranasal sinus melanomas over nasal cavity melanomas (6,38,43-45). Importantly, however, given that the AJCC8 staging system applies to all MMHN, it remains unclear how T3 and T4a staging can be improved for mucosal melanomas in other head and neck subsites. This is particularly relevant for pharyngeal and laryngeal melanomas, the staging of which which remain largely unexplored in the literature due to their rarity (16).

In addition, further studies are required to explore whether other histopathological features [e.g., primary tumour volume (33)] may provide superior delineation of T stage over tumour subsite in determining the prognosis of patients with MMHN.

On the other hand, the authors of some contemporary studies have proposed entirely new systems for TNM staging of MMHN. For instance, Cui *et al.* recently proposed a novel unified TNM staging system inclusive of all mucosal melanomas beyond the head and neck (2). Whilst this proposal theoretically has the advantage of improving the ease of staging and standardisation of reporting for mucosal melanomas, it has several limitations that cannot be overlooked. First, the histological description provided for the proposed T stage is not appropriate for sinonasal tumours, as no muscularis propria or adventitia separate the nasal or paranasal mucosa from cartilage and bone. This renders the proposed T2 and T3 categories redundant. Second, no stage is offered for T1–4N0M1 disease, which incorrectly suggests that all patients with distant metastasis will also have regional node metastasis. Third, the proposal by Cui *et al.* does not account for the potential confounding effect of varying treatment modalities in their cohort, which is particularly pertinent given the recent introduction of immune checkpoint inhibitors (ICIs) to the paradigm of melanoma treatment (41,46,47). Finally, only OS is explored as an endpoint for survival. As Cui *et al.*'s multivariable analysis suggested that Eastern Cooperative Oncology Group (ECOG) performance status was an independent prognostic factor (P<0.001) in the patient cohort with distant metastasis, additional evaluation of melanoma specific survival (MSS) or RFS may be required to provide a more refined staging system.

Lastly, it is also important to consider the broader question of whether the TNM model remains the most reliable method of determining prognosis for patients with cancer. While AJCC staging has become widely adopted in clinical practice worldwide due to its user-friendly design and consistent performance, it has also been increasingly criticised due to its inability to reflect genetic and molecular features of carcinogenesis, host-tumour interactions, and additional tumour factors that exist beyond the TNM categories (48). Indeed, in several types of cancers, more nuanced prognostic models such as nomograms have garnered attention for their ability to generate more precise prediction when compared with the traditional TNM staging system (48-52). In the context of MMHN, Lu *et al.* recently utilised five independent risk predictors (age, location, T stage, N stage, and surgery) to establish the first nomogram for MMHN, demonstrating superior prediction of 1-year and 3-year MSS and OS with the nomogram over the AJCC TNM staging system in both internal and external validation cohorts (52). While this nomogram is limited by its lack of inclusion of immunotherapy, evaluation of additional histopathological parameters such as perineural invasion, and external validation beyond the SEER database to determine its generalisability, it highlights the question of whether it may be time to think beyond the TNM staging system for cancer staging.

Management

Surgical resection

Owing to the rarity of MMHN, treatment guidelines are often based not on extensive evidence but rather on small retrospective case series with considerable potential for bias. Nonetheless, complete tumour resection remains the cornerstone of treatment for patients with resectable MMHN, with guidelines in the USA [National Comprehensive Cancer Network (NCCN)] and Australia (Cancer Council Australia) currently recommending upfront surgery for resectable AJCC stage T3 and T4a MMHN (53). Surgery for MMHN can be performed using either an open or an endoscopic approach, with neither option demonstrating a superior effect on OS in most series of MMHN (54-56). Interestingly, however, endoscopic resection appears to result in a shorter length of stay but a higher rate of unplanned hospital readmission in sinonasal melanomas (54,57,58). As with all malignancies, it is imperative that the therapeutic strategy for MMHN is tailored to the individual, taking into account the tumour stage, site and previous management, as well as the patient's comorbidities and preferences.

The importance of clear margins in the surgical management of MMHN is well established. Penel *et al.* reported a 21-fold increased risk of death associated with positive margins, while Lee *et al.* demonstrated a significantly increased rate of distant metastasis (14–71%) and decreased OS associated with failure to achieve local control (59,60). Despite substantial and ongoing research seeking to establish the optimal width of excision margins for cutaneous melanomas (61), there remains a dearth of studies which report surgical margins beyond clear or positive margin status for of MMHN (59). As for most head and neck cancers, the NCCN currently

recommends a 1.5–2.0 cm surgical margin for MMHN (62). However, obtaining complete pathological clearance presents a particular challenge in MMHN, due to its frequent anatomical proximity to vital structures and its characteristically lentiginous, sometimes multifocal pattern of growth (63). In addition, even with clear resection margins and satisfactory local control, more than 50% of patients ultimately develop distant metastasis (64). In the context of local failure, Manolidis *et al.* used pooled data (n=484) to demonstrate that re-excision can salvage approximately 25% of cases of local failure; however, this carries the risk of considerable morbidity and reduced quality of life (64). Thus, although clear margins do offer the best chance of achieving local control, this philosophy must be tempered by knowledge of the aggressive nature of MMHN and their frequent location in anatomically challenging sites.

While a therapeutic neck dissection is performed routinely in MMHN patients with clinical evidence of lymph node metastases, the treatment of a node-negative neck in patients with MMHN remains controversial. In the context of sinonasal melanomas, there is a relatively low incidence of regional dissemination; this finding, together with increasing evidence that lymph node status is not a significant predictor of survival in patients with sinonasal melanoma, has led most authors to endorse a conservative approach regarding elective neck dissection (END) (5,65,66). On the other hand, NCCN guidelines currently recommend END for oral mucosal melanomas, based on the greater incidence of lymph node metastasis and regional recurrence observed in this cohort (28,31). Yet contemporary studies demonstrate mixed survival benefits for END in patients with oral melanomas: Torabi *et al.* and Moya-Plana *et al.* did not report any significant improvement in OS associated with END, while Wu *et al.* showed increased OS following END for nodular but not macular oral melanomas (27,42,67). Recent data also suggest that sentinel lymph node biopsies may be useful in the identification of MMHN patients who could benefit from END; however, this remains an area of ongoing research (37,68,69).

Radiation therapy

Although melanoma has historically been considered a relatively radioresistant tumour, radiotherapy now represents an integral part of local treatment for MMHN (70). In the context of its use as a definitive treatment, a recent systematic review and meta-analysis of 22 studies (n=2,489) established that there was an inferior 5-year OS [relative risk (RR) 1.2, P=0.0006] when primary radiotherapy was used with curative intent when compared to surgery alone in the treatment of MMHN (71). However, with the advent of new techniques such as carbon-ion radiation therapy (CIRT), neutrons, and proton therapy, several series have reported a lower rate of radiation-induced toxicity and increased therapeutic efficacy (71-75). For instance, in a large, multicentre retrospective study reported by Koto *et al.* (n=260), CIRT achieved superior local control and OS over historical data in which photon radiation therapy was used, and demonstrated comparable survival with previously reported data following surgery (2-year OS, 69.4%; 2-year local control rate, 83.9%) (72,76). No fatal complications were noted in that study (72). Meanwhile, a phase II study of proton therapy for MMHN (n=32) by Zenda *et al.* reported promising 1-year local control rates and 3-year OS of 75.8% and 46.1%, respectively; this finding was similar to that of Fuji *et al.*, who reported comparable outcomes with proton therapy as compared to primary surgery (5-year OS, 51%; 5-year DFS, 38%) (74,75). Thus these findings confirm the utility of definitive radiotherapy in patients with non-operable MMHN, and highlight the potential of next-generation radiotherapy techniques in the treatment of this aggressive malignancy.

In most series, adjuvant post-operative radiotherapy is utilised in patients with advanced or recurrent MMHN following surgical resection with close or involved margins, or in patients with resected high-risk nodal disease. The NCCN currently defines high-risk nodal disease as mucosal melanoma involving (I) two or more lymph nodes with adverse features; (II) any lymph nodes ≥3 cm in size; (III) extranodal soft tissue extension; or (IV) recurrence in a nodal basin after previous surgery (62). Importantly, however, current data suggest that radiotherapy after primary resection significantly improves the rate of local disease control but does not confer any significant improvement in OS (9,28,34,77-80). This finding was recently confirmed ina meta-analysis by Li *et al.* of 12 retrospective studies (n=1,593), in which no significant reduction in risk of death was found for MMHN patients treated with postoperative radiotherapy [hazard ratio (HR), 1.07; 95% CI: 0.8–1.36; P=0.903] (81). Such lack of a survival benefit has largely been attributed to the high risk of systemic relapse observed in patients with MMHN (39,71); therefore, since increasing the intensity of local treatment does not improve OS, clinical studies should instead focus on exploring systemic therapies to reduce the

risk of distant recurrence.

To date, no consensus has been reached with respect to the optimal radiotherapy fractionation schedule for MMHN. The theoretical rationale for using hypofractionation is based on radiobiologic studies which suggest that melanoma cells have a high capacity to repair sublethal damage (82). In a multi-institutional retrospective study in Japan, Wada *et al.* reported that high dose per fraction regimens (≥3 Gy) were associated with better outcomes in terms of both local control and survival; however, this result was only significant in univariable analysis (83). Krengli *et al.* and Samstein *et al.*, meanwhile, found no significant association between dose per fraction and OS (28,43). In addition, hypofractionation in the setting of MMHN is limited by its proximity to the eyes and the central nervous system, which are highly sensitive to high fraction doses and may therefore be more readily damaged by hypofractionation (84). Thus, future studies are warranted to optimise radiotherapy regimens in the setting of MMHN.

Systemic therapy

Given that treatment failure in MMHN is usually attributable to distant metastasis, there is a need to determine effective systemic therapy for patients both as an adjuvant and as a primary modality in patients with unresectable tumours (39). Historically, the standard-of-care for metastatic melanoma was dacarbazine chemotherapy, despite its poor objective response rate (ORR) of approximately 20% and lack of proven survival benefit in randomised controlled studies (85-87). In 2011, a landmark phase III study of 502 patients with previously untreated metastatic cutaneous melanoma established the efficacy of ipilimumab (an anti-CTLA-4 ICI) when given in combination with dacarbazine compared to dacarbazine alone (median OS, 11.2 *vs.* 9.1 months; HR for death, 0.72, P<0.001) (85). This served as the foundation for the introduction of immunotherapy into the field of melanoma treatment, which has subsequently revolutionised the therapeutic approach for advanced or unresectable cutaneous melanoma.

While large-scale phase III clinical trials investigating the activity of systemic drug treatments for mucosal melanoma have been hindered by the rarity of the disease, data regarding the safety and efficacy of ICIs is rapidly accumulating. Currently, three ICIs are approved for use in the USA and Australia for the treatment of unresectable or metastatic mucosal melanoma: ipilimumab (an anti-CTLA-4 inhibitor), nivolumab, and pembrolizumab (both anti-PD-1 inhibitors). In a recent pooled analysis of five clinical trials [CA209-003 (88); CA209-038 (89); CheckMate066 (90); CheckMate037 (91); CheckMate067 (92)], combined nivolumab and ipilimumab therapy in the treatment of advanced mucosal melanoma demonstrated a superior ORR (37.1%; 95% CI: 21.5–55.1%) over nivolumab alone (23.3%; 95% CI: 14.8–33.6%) or ipilimumab alone (8.3%; 95% CI: 1.8–22.5%) (47). Additionally, combined ICI therapy conferred greater median progression-free survival (PFS) (5.9 months; 95% CI: 2.2 to not reached) than nivolumab alone (3.0 months; 95% CI: 2.2–5.4) or ipilimumab alone (2.7 months; 95% CI: 2.6–2.8), demonstrating durable clinical responses of mucosal melanoma to immunotherapy (47). The superior efficacy of combined ICI therapy for mucosal melanoma has been confirmed in subsequent clinical trials and in a recent systematic review (n=1,262) (93-95).

Importantly, however, several factors complicate the routine use of combined ICI therapy in clinical practice. First, nivolumab with ipilimumab confers a substantially higher incidence of grade 3 or 4 treatment-related adverse events and adverse event-related discontinuation (40.0% and 17.1%, respectively) as compared to nivolumab monotherapy (8.1% and 2.3%, respectively) in patients with mucosal melanomas (47). In addition, combined ipilimumab and nivolumab appears to demonstrate only modest efficacy in mucosal melanoma as compared to its cutaneous counterpart, with ORR and PFS of 60.4% and 11.7 months respectively reported in patients with cutaneous melanomas (47). Furthermore, a recent multicentre study of mucosal melanoma in Japanese patients (n=329) demonstrated no significant differences between nivolumab monotherapy and combination therapy with ipilimumab in regard to ORR, PFS, or OS (96). Similarly, Dimitriou *et al.* did not find a significant improvement in ORR or survival outcomes except in the case of naso-oral melanomas (46). Therefore, in aggregate, future studies are urgently required to establish the clinical efficacy and tolerability of ICIs when used to treat mucosal melanomas.

The utility of targeted therapies has also been investigated in patients with mucosal melanoma. However, mucosal melanoma tends to harbour fewer *BRAF* mutations than its cutaneous counterpart, rendering BRAF inhibitors alone or in combination with *MEK* inhibitors largely ineffective (97,98). Instead, mutations in the receptor tyrosine kinase *KIT* have been found in approximately 40%

of mucosal melanomas, providing a rationale for the use of c-KIT inhibitors such as imatinib, nilotinib, dasatinib, or sunitinib (99). In a recent meta-analysis of 19 studies (n=601) investigating the utility of these four c-KIT inhibitors in patients with advanced mucosal, acral, or chronically sun-damaged melanoma, Steeb *et al.* reported that the pooled ORR was 14% (95% CI: 6–24%) for mucosal melanoma, with OS and PFS of 5.2–6.9 months and 2.5–2.9 months, respectively (100). At least one severe adverse event was reported in 45% of the cohort (95% CI: 34–57%) (100). Thus, given the relatively low response rates and high toxicity observed in these recent studies, the utility of c-KIT inhibitors may lie in their use as combined therapy with other treatment agents in patients with mucosal melanoma.

It is also relevant to discuss the utility of systemic therapy in the adjuvant setting for patients at high risk of recurrence or death from mucosal melanoma. To date, large randomised controlled trials of ipilimumab, nivolumab, pembrolizumab, and combination dabrafenib-trametinib (for patients with *BRAF* V600 E/K mutations) consistently demonstrate improved RFS when used in the adjuvant setting for cutaneous melanoma as compared to placebo alone, with ipilimumab further showing improved OS in the EORTC-1071 trial (101-104). However, there is currently insufficent evidence to suggest that adjuvant systemic therapy provides any survival benefit for mucosal melanoma (105). While Lian *et al.* demonstrated a trend towards improved OS and RFS with temozolomide-cisplatin over high-dose IFN-α2b and observation alone after resection of mucosal melanoma (n=189), this 2013 study remains the only published randomised evidence in support of systemic therapy for mucosal melanoma in the adjuvant setting (106). Furthermore, the chemotherapy regime of temozolomide-cisplatin has no reported survival benefit in metastatic mucosal melanoma and predates the introduction of immunotherapy and targeted therapy, which renders extrapolation difficult in the current clinical environment (105,106). Although the currently ongoing CheckMate238 trial evaluating adjuvant nivolumab versus ipilimumab includes a cohort of patients with mucosal melanoma (n=29/906, 3.2%), such small numbers of patients have precluded any meaningful subgroup analyses to date (107). The role of adjuvant systemic therapy for mucosal melanoma therefore remains to be elucidated, and further preclinical and clinical trials of their efficacy and tolerability are required before their adoption in clinical practice.

Neoadjuvant systemic therapy for patients with advanced melanomas has recently become of significant interest. Theoretically, upfront neoadjuvant immunotherapy is posited to stimulate stronger anti-tumour immune responses as compared to its use in the adjuvant setting, and it may facilitate surgical resection by downstaging the tumour (108,109). The use of ICIs in the neoadjuvant setting has produced promising response rates for advanced resectable melanoma of cutaneous origin, with Amaria *et al.* reporting an ORR of 73% and a pathologic complete response rate of 45% with combined ipilimumab and nivolumab therapy (109-111). While evidence specific for mucosal melanoma is currently limited, some preliminary data for mucosal melanoma have been published, reporting responses and tolerability. In a recent phase II study of patients with resectable mucosal melanomas, treatment with neoadjuvant toripalimab with axitinib was associated with a pathological response rate (PRR) of 28.6% but with an incidence of grade 3 or 4 treatment-related adverse events of 23.8% (112). These findings were similar to those of Ho *et al.*, who evaluated the utility of neoadjuvant anti-PD1 ± anti-CTLA4 in resectable mucosal melanoma and demonstrated an ORR of 47%, a PRR of 35%, and a 3-year OS of 55% (113). These studies support further evaluation of neoadjuvant ICI therapies for mucosal melanoma, and emphasise the importance of ongoing clinical trials (NCT03698019, NCT04180995, NCT05545969, NCT03313206, NCT04622566, NCT02519322) to investigate the utility of ICIs in the management of patients with mucosal melanoma.

Finally, the utility of novel combinations of therapeutic agents currently represents a rapidly expanding area of research in the field of mucosal melanoma. For instance, several studies have reported a meaningful synergistic effect of combining radiotherapy with ICIs in the treatment of mucosal melanoma, with Kim *et al.* suggesting that ICIs may confer a potentially radiosensitising effect and increase local control without causing severe toxicity (114). To date, three single-centre, retrospective studies have corroborated an ORR >50% with the use of radiotherapy combined with anti-PD-1 antibody, which was higher than achieved with either treatment as a single modality (93,114-116). Furthermore, no grade 3, 4, or 5 adverse events occurred in patients receiving multimodal therapy (114-116). Synergy may also exist between ICIs and targeted therapy agents: Sheng *et al.* recently investigated the efficacy of axitinib [a vascular endothelial growth factor (VEGF) receptor inhibitor] and toripalimab (an anti-PD-1 ICI) in patients with metastatic mucosal melanoma, and demonstrated

promising antitumour activity with an ORR of 48.3% (95% CI: 29.4–67.5%) and median PFS of 7.5 months (117). A number of phase I and II clinical trials investigating novel combinations of other therapeutic modalities are currently underway (93,100,118), and represent an exciting avenue of further exploration in the management of patients with mucosal melanoma.

Conclusions

MMHN is a rare tumour type and its treatment remains challenging. The prognostic performance of the current TNM staging system for mucosal melanomas is widely recognised as being unsatisfactory, warranting efforts to (I) refine the current definition of the T stage; or (II) investigate entirely novel staging systems such as nomograms. For resectable MMHN, surgical excision with negative margins remains the standard of care. Adjuvant radiotherapy does not improve survival outcomes but is useful in achieving better locoregional control. While immunotherapy confers only modest efficacy in mucosal as compared to cutaneous melanomas, ICIs and c-KIT inhibitors demonstrate promising response rates in ongoing clinical trials and further investigation of their long-term utility is required. In addition, the role of END, optimal radiation therapy strategies, and the efficacy and timing of systemic therapies and their use in combination with radiation therapy are yet to be clearly defined. These represent promising and exciting avenues for future research in the field of mucosal melanoma.

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