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Risk-based stratification in head and neck mucosal melanoma

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ABSTRACT

Background: Head and neck mucosal melanoma (HNMM) is a rare and aggressive disease with a high metastatic potential. Two staging systems are currently available: one specific to HNMM (mmTNM) and one specific to primary tumour sites (sccTNM). Our main objective was to assess the prognostic value of both of these classifications in order to allow accurate risk-based classification.

Methods: We performed a retrospective cohort study of patients with HNMM treated consecutively between 2000 and 2017. All of the patients were restaged using the mmTNM and the sccTNM. A prognostic analysis was carried out according to both staging systems.

Results: There were 96 patients with an HNMM in our cohort, of whom 80 underwent surgical treatment followed by radiotherapy. The median overall survival (OS) and progression-free survival (PFS) for the operated patients were 39 months (95% CI, 21.6–56.4 months) and 18 months (95% CI, 6.5–29.5 months), respectively. A paranasal sinus localization was associated with lower survival compared to a nasal cavity primary localization ($p < 10^{-4}$). Both of the classifications correlated with OS, PFS, and distant metastasis-free survival. High-risk HNMM were characterized as T4/stage IV by the mmTNM and T3-4/stage III-IV by the sccTNM. Given the primary tumour location, both TNM classifications were suitable for risk-stratification of sinonasal mucosal melanomas. However, combining both TNM, we defined new stages mmT3A and mmT3B according to sccTNM with a more accurate risk stratification ($p < 10^{-4}$).

Conclusions: Both of the classifications should be combined, in order to improve the risk-stratification of patients with HNMM.

Introduction

Head and neck mucosal melanoma (HNMM) is a rare neoplasm, accounting for 1–4% of all melanomas [1,2], 55% of all mucosal melanomas, and only 4% of all sinonasal malignancies [3]. Its incidence has increased over the past half-century, although no causal risk factors have been identified to date [4,5]. The pathological diagnosis is complex given its scarcity, the numerous differential diagnoses (metastasis of cutaneous melanoma, neuroendocrine carcinoma, etc.), and the possibility of amelanotic and/or ulcerated subtypes [6]. Thus, expert pathologists are required for diagnostic confirmation. In the head and neck area, approximately 70% of HNMM originate in the sinonasal tract (SNMM) and 20% in the oral cavity (OCMM) [1,7]. For SNMMs, the anterior portion of the nasal septum, the head of the inferior turbinate, and the medial wall of the maxillary sinus are the most frequent primary tumour sites. In the oral cavity, the hard palate and the maxillary gingiva are usually involved. Other primary localizations, such as pharyngeal and laryngeal cases, have rarely been reported [1,7].

HNMM is very aggressive, with a high metastatic potential and a poor prognosis. Indeed, 5-year overall survival rates range from 20% to 40%, with a median PFS of approximately 24 months [8–14]. A combination of surgery with postoperative radiotherapy (PORT) appears to be the standard of care in resectable HNMM, although no consensual therapeutic guidelines have been established to date. Indeed, some

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authors have reported a benefit of postoperative radiotherapy in patients with mucosal melanoma, albeit mostly in local control [9,13]. Short-term metastatic progression appears to be the main issue in HNMM.

Recently, immune checkpoint inhibitors have yielded promising results in metastatic mucosal melanoma, with objective response rates of approximately 30% and durable clinical responses [15–18]. Therapeutic intensification should, therefore, be evaluated in high-risk HNMM, combining surgery with PORT and/or immunotherapy. Such therapeutic algorithms have been performed in high-risk cutaneous melanoma, resulting in a significant survival benefit [19,20].

Thus, a risk-based stratification is required to adequately select patients for intensification clinical trials in HNMM. Two classifications are currently available: the TNM stage specific to HNMM (mmTNM) and the TNM stage specific to primary tumour site for carcinoma (sccTNM). However, both of these staging systems have pros and cons and they may be complementary.

We analysed patients with an HNMM treated at our comprehensive cancer centre to compare the prognostic value of the AJCC/UICC TNM staging systems for HNSCC and for HNMM, with the aim of improving risk-based stratification of HNMM patients.

Material and methods

This study was performed once approval was received from the local Research Ethics Committee, in accordance with the World Medical Association – Declaration of Helsinki – ethical principles for medical research. This was a monocentric study of prospectively collected cases in the Head and Neck Cancer Committee Database of our institution. We reviewed patients treated at our cancer centre between 2000 and 2017 for HNMM. Given the rarity of this tumour, every histological sample was reviewed by expert pathologists in order to confirm this difficult diagnosis. The TNM stage was initially assessed both clinically and radiologically (CT scan, MRI ± PET scan). All of the patients were restaged retrospectively according to the American Joint Committee on Cancer (AJCC) 7th edition staging system for HNMM (mmTNM) and the AJCC 7th edition staging system for nasal cavity, paranasal sinuses, and oral cavity malignancies (sccTNM) [21]. According to REFCOR guidelines (French Rare Head and Neck Cancer Expert Network), the treatment procedure for every patient with a M0 resectable HNMM was a surgical resection of the primary tumor followed by adjuvant radiotherapy. No postoperative radiotherapy (PORT) was performed in case of poor general condition or refusal of treatment. We analysed the following potential prognostic factors: epidemiological criteria (age > 65 years, age > 70 years, and gender), the primary tumour site, mmTNM stage, sccTNM stage, lymph node management, surgical procedure performed with curative intent, and PORT.

The descriptive analysis characterized the studied population in terms of frequencies, percentages, medians, and ranges; and the data were compared using Chi-squared tests or Fisher's exact tests. The Kaplan-Meier method was used to analyse overall survival (OS) and progression-free survival (PFS). OS and PFS were defined as the time from the diagnosis to the occurrence of an event or to the last follow-up. Events for OS were death from any cause, and events for PFS were disease recurrence or progression and death from any cause. Survival curves were compared using the log-rank test for the univariate analysis (UVA). The statistical analyses were performed using IBM SPSS Statistics for Windows software, version 23 (IBM Corp., Armonk, N.Y., USA). The reported p-values were two-sided when available, and p-values below 0.05 were considered significant.

Results

We analysed 96 patients (51 M/45F) with an HNMM treated consecutively at our centre (Table 1). The median age was 63 years (range, 22–92 years) with 35 patients (36.5%) > 65 years and 24 (25%) > 70 years. The most frequent primary site was the nasal cavity (n = 48), as expected, followed by the oral cavity (n = 20), the paranasal sinuses (n = 20), and the pharynx (n = 8). The median follow-up was 19.5 months (range, 1–176 months). Twelve patients (12.5%) had distant metastasis at the time of diagnosis, of whom three were treated aggressively with curative intent along with surgery of the primary. Seven patients (7.3%) presented with a non-resectable primary tumour, of whom four received local radiotherapy and three received only systemic treatments and/or supportive care. The disease TNM according to the mmTNM and sccTNM staging systems are reported in Table 2.

Table 1
Characteristics of patients with a head and neck mucosal melanoma treated between 2000 and 2017 at our centre.

Characteristics		Overall cohort No. of patients
Total		96
Primary site	Paranasal sinus	46
	Nasal cavity	22
	Oral cavity	20
	Pharynx	8
AJCC stage for head and neck mucosal melanoma	Stage III	47
	Stage IVA	33
	Stage IVB	4
	Stage IVC	12
Treatment	Surgery with curative intent	80
	Postoperative radiotherapy	69

In the whole cohort, the median OS was 27 months (95% CI, 13.3–40.7) with 2-year and 5-year OS rates of 52.4% and 38.2%, respectively. However, the 5-year OS rate according to the primary location was 55.6% for the nasal cavity, 37.5% for the pharynx, 35.5% for the oral cavity, and 5.8% for the paranasal sinuses. Among the patients with SNMM, mmTNM stage IV was more frequent for the paranasal sinuses (16/20) than for the nasal cavity (15/48). A paranasal sinus localization was associated with lower survival compared to a nasal cavity primary localization ($p < 10^{-4}$), with a median OS of 8 months (95% CI, 3.9–12.1) and 83 months (95% CI, 31.3–134.7), respectively. This difference remained significant after adjustment for the TNM stage. In the overall cohort, OS stratification according to either the mmTNM or the sccTNM staging system was similar (Fig. 1) and distinguished two main groups of patients. According to the mmTNM, patients with stage III disease (n = 47) had a better OS than patients with stage IV disease ($p < 10^{-4}$). In the sccTNM, patients with stage I-II disease (n = 51) had a better OS than patients with stage III-IV disease ($p < 10^{-4}$). In UVA, gender and age (> 65 or > 70 years old)

Table 2
Association between the AJCC stage for head and neck mucosal melanoma and for head and neck carcinoma in 96 patients with a head and neck mucosal melanoma treated at our centre between 2000 and 2017.

		AJCC stage for head and neck mucosal melanoma				
		III	IVA	IVB	IVC	Total
AJCC stage for head and neck carcinoma	I	32	2	0	0	34
	II	13	4	0	0	17
	III	2	7	2	0	11
	IVA	0	17	0	0	17
	IVB	0	3	2	0	5
	IVC	0	0	0	12	12
	Total	47	33	4	12	96

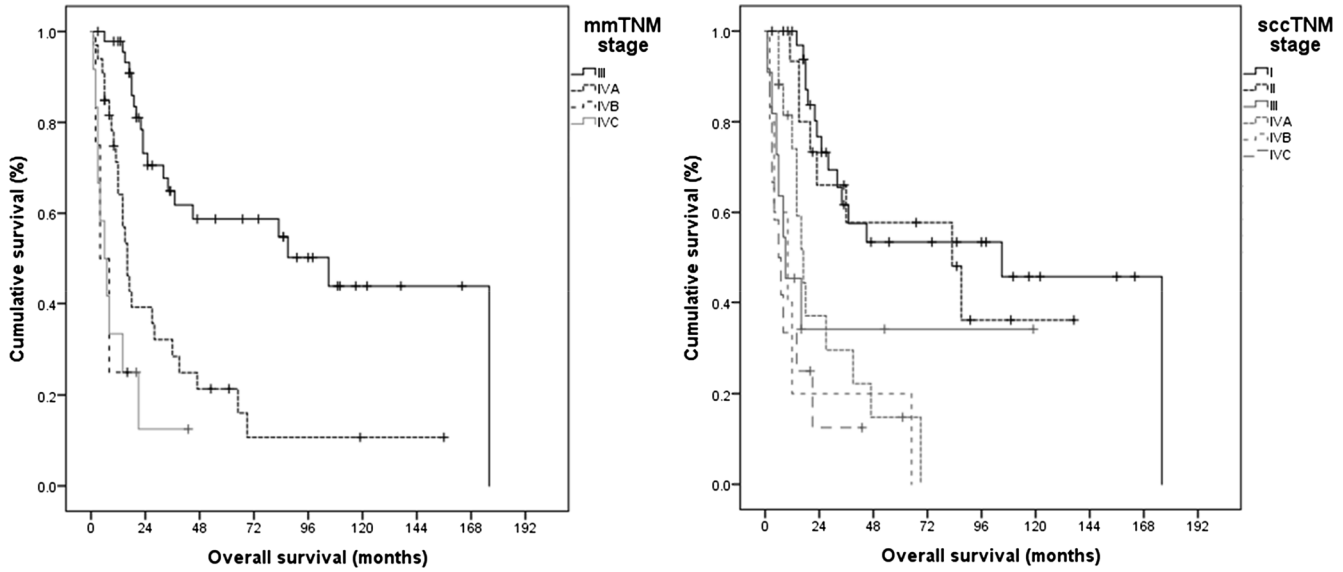

Fig. 1. Survival stratification in 96 patients treated for a head and neck mucosal melanoma between 2000 and 2017 at our centre, according to the AJCC TNM staging system either for head and neck mucosal melanoma (mmTNM) or for head and neck carcinoma (sccTNM).

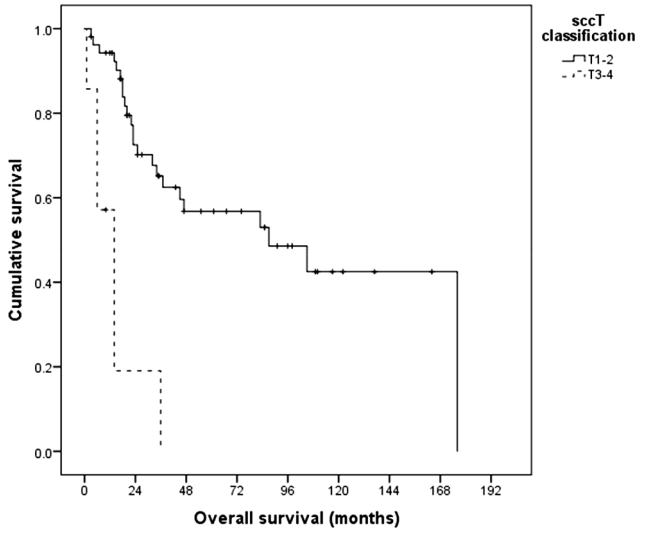

Fig. 2. Survival stratification in 60 patients with a mmT3 head and neck mucosal melanoma, according to T-classification of the AJCC TNM staging system for head and neck carcinoma (sccTNM).

were not associated with OS (p = .380, p = .963, and p = .807, respectively). However, the absence of distant metastasis at diagnosis and surgical resection of the primary were associated with higher OS ($p < 10^{-4}$ for both). The absence of clinical nodal involvement was associated with higher OS (p = .011) in the overall cohort but not in the patients who underwent surgery of the primary (p = .129), since clinical nodal involvement at diagnosis was associated with the presence of distant metastasis (p = .0088). Therefore, the T classification was further analysed in patients operated as a surrogate of the prognostic TNM stage for stratification. We, then, combined sccT- and mmT-classifications, to stratify further high-risk patients. Overall survival was dramatically lower in patients with a mmT3/sccT3-4 tumor than in patients with a mmT3/sccT1-2 ($p < 10^{-4}$), with a 5-year OS of 0% versus 56.8% respectively (Fig. 2). Notably, in mmT4a or T4b patients, there was no significant difference in survival between patients with a sccT1-2 tumor and patients with a sccT3-4 tumor (p = .091 and p = .182, respectively).

Eighty patients (38 M/42F) underwent oncological surgery of the primary tumour with curative intent. The primary sites were sinonasal, the oral cavity, and the pharynx, in 59, 17, and 4 patients, respectively. The median age was 62.5 years (range, 28–92 years). A neck dissection (ND) was performed in 25 patients (31.2%) and was associated with an oral or a pharyngeal tumour rather than a sinonasal tumour ($p < 10^{-4}$) (85.7% ND for oral or pharyngeal sites versus 11.9% ND for sinonasal sites) and with mmTNM stage IV disease rather than stage III (p = .0073), mainly because of the N classification (a ND was performed in 90% of the cN+ patients and in 22.9% of the cN0 patients). Sixty-nine patients (86.2%) received a PORT.

Seventeen patients (21.2%) had a local recurrence at the first event. The median delay from surgery to local recurrence was 32 months (range, 3–106 months). The 2-year and 5-year rates of local control were 89.6% and 72.2%, respectively. The margin status was available for 74 patients (92.5%). Clear margins were achieved in 64.9% of cases (48/74). Interestingly, in our series, the margin status was not correlated with OS, PFS or local control. The only factor associated with better local control was a pharyngeal localization (p = .013). PORT failed to result in a significant improvement in local control in UVA (p = .072), even with adjustment for the T classifications or TNM disease stages, probably because of the limited number of events. Forty-four patients (55%) had a distant metastasis recurrence as the first event, of whom 31 (38.7%) had a distant recurrence only. The median delay from surgery to distant metastasis was nine months (range, 2–108 months). The 2-year and 5-year rates of distant metastasis-free survival were 46.7% and 33.2%, respectively. Factors associated with shorter distant metastasis-free survival (DMFS) were a mmT3 versus a mmT4 (p = .007), a sccT1-2 versus a sccT3-4 ($p < 10^{-4}$), a stage III versus a stage IV mmTNM classification (p = .001), a stage I-II versus a stage III-IV sccTNM classification ($p < 10^{-4}$), but not the tumour site (p = .742) or clinical nodal involvement (p = .278).

The median OS and PFS in operated patients were 39 months (95% CI, 21.6–56.4 months) and 18 months (95% CI, 6.5–29.5 months), respectively. The 2-year and 5-year OS rates were 61.4% and 44.7%, respectively, with 2-year and 5-year PFS rates of 44.7% and 28.2%, respectively. There was no difference in OS or PFS (p = .635 and p = .730, respectively) between the localizations. However, the 5-year OS rate according to the primary site was 58.1% for the nasal cavity, 50% for the pharynx, 39% for the oral cavity, and 9.5% for the paranasal sinuses, while the 5-year PFS rate was 40.2% for the nasal cavity, 0% for the pharynx, 16.3% for the oral cavity, and 7.1% for the paranasal sinuses. A paranasal sinus primary site was associated with lower

OS and PFS compared to a nasal cavity primary site ($p < 10^{-4}$ for both). Both OS and PFS stratification according to either the mmTNM or the sccTNM were similar and distinguished two main groups of patients. With the mmTNM, patients with stage III disease had a better OS and PFS than patients with stage IV disease ($p < 10^{-4}$ for both), while according to the sccTNM, patients with stage I-II disease had a better OS and PFS than patients with stage III-IV disease ($p < 10^{-4}$ for both). Patients with a mmT3 primary tumour had a better OS and PFS than patients with a mmT4 primary tumour ($p < 10^{-4}$ for both) while patients with a sccT1-2 tumour had a better OS and PFS than patients with a sccT3-4 tumour ($p < 10^{-4}$ for both). Once more, when combined sccT- and mmT-classifications, OS was lower in patients with a mmT3/sccT3-4 tumor than in patients with a mmT3/sccT1-2 ($p = .003$), with a 5-year survival of 0% versus 57.6% respectively. In mmT4a operated patients, there was no significant difference in survival between patients with a sccT1-2 tumor and patients with a sccT3-4 tumor ($p = .238$, with a 5-year OS of 33.3% and 22.2%, respectively).

We then separately analysed the patients operated with curative intent for a given primary tumour location. In patients with an SNMM ($n = 59$), once more, both OS and PFS stratification according to either the mmTNM or sccTNM were similar and distinguished two main groups of patients. Using the mmTNM, patients with stage III SNMM had a better OS and PFS than patients with stage IV SNMM ($p < 10^{-4}$ for both) while with the sccTNM classification, patients with a stage I-II SNMM had a better OS and PFS than patients with a stage III-IV SNMM ($p < 10^{-4}$ for both). Once again, the T classification was a surrogate of the TNM stage for both OS and PFS stratification in patients with an SNMM. Patients with a mmT3 SNMM had a better OS and PFS than patients with a mmT4 SNMM ($p < 10^{-4}$ for both), whereas patients with a sccT1-2 SNMM had a better OS and PFS than patients with a sccT3-4 SNMM ($p < 10^{-4}$ for both). However, when considering the patients with an OCMM ($n = 17$), no OS or PFS stratification was feasible according to either the mmTNM or the sccTNM. With the mmTNM, no difference was observed for OS and PFS between patients with stage III and stage IV OCMM ($p = .141$ and $p = .203$, respectively). According to the sccTNM, the OS and PFS of patients with stage I-II OCMM did not differ from patients with stage III-IV OCMM ($p = .489$ and $p = .418$, respectively). Thus, the T classification, like the TNM stage, was not associated with either OS or PFS in patients with an OCMM. Patients with a mmT3 primary tumour did not have a better OS and PFS than patients with a mmT4 primary tumour ($p = .432$ and $p = .476$, respectively), while patients with a sccT1-2 OCMM did not have a better OS and PFS than patients with a sccT3-4 OCMM ($p = 0.091$ and $p = 0.175$, respectively). Due to the very small number of patients with a pharyngeal mucosal melanoma operated with curative intent ($n = 4$), no statistics were performed.

Finally, we combined T-classifications of mmTNM and sccTNM into a new T-classification. The mmT3/sccT1-2 tumors were considered as combined-T3A, mmT3/sccT3-4 as combined-T3B, and mmT4A-4B were considered as combined-T4 (Fig. 3). We therefore identified high-risk patients as patients with a T3B-T4 tumor, as compared to patients with a T3A tumor ($p < 10^{-4}$).

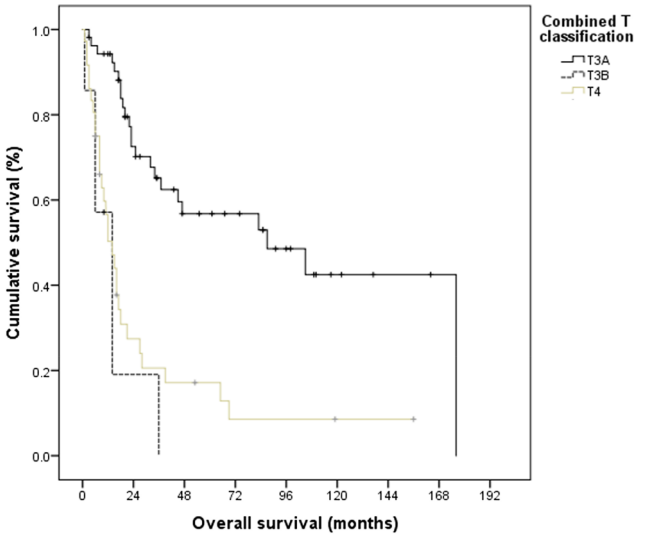

Fig. 3. Survival stratification in 96 patients treated for a HNMM between 2000 and 2017 at our centre, according to the combined T-classification between AJCC TNM staging system for HNMM and for head and neck carcinoma. T3A lesions are mmT3/sccT1-2 tumors, T3B lesions are mmT3/sccT3-4 tumors, T4 lesions are mmT4A-4B tumors.

Discussion

To the best of our knowledge, the current study is one of the largest reported series of patients with HNMM treated at a single institution. The monocentric design of this study and the prospective data collection of these rare cases in our Head and Neck Cancer Committee database allowed us to assume homogeneity in the therapeutic algorithm. Indeed, at our cancer centre, all patients with an HNMM are evaluated by a multidisciplinary board including dedicated head and neck and skull base surgeons, radiation oncologists, and onco-dermatologists.

Our cohort confirmed the aggressiveness and poor prognosis of HNMM, with its high metastatic potential being responsible for a high recurrence rate. Indeed, even for patients who receive a combination of surgical resection followed by adjuvant radiotherapy, the oncological outcomes are poor, with a median OS and PFS of 39 months and 18 months, respectively, with distant metastases being the main oncological issue. The clinical characteristics of our cohort and the oncological outcomes are consistent with the literature [8–14]. As reported previously, we showed that the TNM stage, the possibility to perform a surgical resection, and the primary tumour site were major prognostic factors [8–13]. However, unlike some previous studies, several prognostic factors such as age (over 65 or 70 years of age) and PORT were not significant in our cohort [22].

Given the poor oncological outcomes in HNMM, even after surgery followed by PORT, intensification of the therapeutic algorithm needs to be discussed. Thus, high-risk HNMMs should be accurately identified. Risk stratifications for HNMM have been established several times with different classifications [3,23]. In 1970, Ballantyne established the first staging system, but its application was difficult because only three stages were defined with a dedicated stage (stage II) for nodal involvement, which is rare in HNMM, and one stage for distant metastasis (stage III), which is infrequent at diagnosis. The Ballantyne/Prasad classification was then described in 2004, adding the depth of invasion evaluation. However, this staging system required that surgical resection of the tumour had been performed. Thus, a specific TNM staging system, dedicated to HNMM, was established by the American Joint Committee on Cancer (AJCC) in 2009, defining only 3 T-stages as T3, T4a, and T4b, with no consideration of the primary tumour site. The main issue with this specific mmTNM classification is that the majority of patients are T3N0M0 at diagnosis. However, this T3N0 group is heterogeneous; a better distinction between low and high risk T3 HNMM could hence be of value.

We compared the mmTNM and the sccTNM in our cohort, and we found that both were suitable for prognostic evaluation of patients with SNMM. Indeed, high-risk SNMM in the mmTNM were T4 and stage IV, while in the sccTNM they were T3-T4 and stages III-IV. However, for mucosal melanoma arising from the nasal fossa (the most frequent subtype of HNMM), bone invasion corresponds with an mmT4a (high-risk) or to a sccT2-T3-T4a (low- to high-risk) depending on the exact localization. The same problem can occur for an mmT3 arising from the nasal fossa. Indeed, the tumour may be a small lesion of the inferior turbinate (a sccT1) or a locally advanced “superficial” lesion extending from the inferior turbinate into the maxillary sinus (a sccT3). Thus, the

mmTNM and the sccTNM should be combined to provide a more accurate risk stratification of SNMM. According to these results we defined, in a combined-TNM, the T3A (mmT3 with sccT1-T2) and T3B (mmT3 with sccT3-4) stages allowing us to identify in the mmT3 SNMM two sub-groups of different prognosis, as shown in Fig. 2. Only one previous study in the literature, on a smaller cohort, has reported the potential application of the sccTNM for SNMM, although it failed to demonstrate the prognostic value of the mmTNM [23]. In our study population, the main oncological event appeared to be the occurrence of distant metastasis. In the surgical group, the primary tumour site and the N status were not prognostic factors of DMFS, while both T classifications (mm and scc) and the TNM stages were predictive. This emphasizes the primary importance of such classifications.

Our study population included a significant cohort of patients with OCMM, although this primary site is infrequent with no consensual therapeutic guidelines. Nodal metastases appear to be more frequent at diagnosis, probably due to the major lymphatic network in the oral cavity. However, the prognostic value of nodal involvement is not clear for HNMM considering the correlation, in our cohort, between nodal involvement and distant metastases, while Amit et al. recently reported that it was not a significant predictor of outcome in SNMM [24]. Interestingly, in our study, both the mmTNM and sccTNM stages were not significant prognostic factors of outcomes for OCMM. We are inclined to hypothesize that, in this small subgroup of patients, the behaviour of OCMM differed, thus requiring a specific classification. Further studies with larger cohorts are hence clearly required.

In terms of the primary tumour location, HNMM arising from the paranasal sinuses should be considered as high risk irrespective of the TNM stage. Indeed, as previously reported [8–13], we observed that SNMM arising from paranasal sinuses were the subtype of HNMM with the poorest prognosis. This can be explained by the complexity of achieving oncological resection with clear margins at these particular locations due to the proximity to key anatomical structures, such as the orbit, skull base, and internal carotid artery [25]. Moreover, there was a trend, although non-significant, of a higher incidence of distant metastasis in this subgroup of SNMM. Analysis of larger cohorts could prove to be useful to confirm these data.

Risk stratification appears mandatory in HNMM management, not only for prognostic analysis but also to consider therapeutic intensification. Indeed, given its poor prognosis despite primary tumour resection with clear margins followed by PORT, a change in the therapeutic algorithm should be considered.

Thus, considering the high metastatic risk in HNMM despite local control with a combination of surgery with radiotherapy, the role of neoadjuvant and/or adjuvant systemic therapies should be evaluated. Immune checkpoint inhibitors have yielded promising results for metastatic mucosal melanoma, with an ORR of approximately 25 to 35% and durable clinical responses with anti-PD1 antibodies [16,26]. Better ORRs have been reported with a combination of anti-PD1 and anti-CTLA4 immunotherapies [17]. Moreover, adjuvant immunotherapy has allowed for a substantial decrease in the occurrence of distant metastases in high-risk cutaneous melanoma as well as a significant survival benefit [19]. Recently, neoadjuvant immunotherapy has been used with promising results in resectable lung tumours and high-risk cutaneous melanomas. Indeed, high pathological complete response rates have been reported along with significantly improved oncologic outcomes [20,27,28]. We are currently evaluating this neoadjuvant approach in patients with resectable HNMM in a multicentric prospective clinical trial (NCT03313206).

Conclusion

In our experience, both of the AJCC staging systems for HNMM and for HNSCC are equally efficient for risk-stratification of HNMM according to survival. T classification of the primary tumour is an excellent surrogate of the TNM disease stage in patients who undergo oncological surgery of the primary tumour with curative intent. High-risk patients had a T4 primary tumour or stage IV disease according to the HNMM staging system, or a T3-4 primary tumour or stage III-IV disease according to the HNSCC staging system. Both of these classifications should be combined, in order to achieve more accurate risk assessment. Thus, such high-risk patients should be selected for future treatment-intensification clinical trials.

Declaration of Competing Interest

None declared.

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