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Original Research

Oncologic outcomes, prognostic factor analysis and therapeutic algorithm evaluation of head and neck mucosal melanomas in France

A. Moya-Plana [a,*], A. Aupérin [b], R. Obongo [a], A. Baglin [c], F.R. Ferrand [a,d], B. Baujat [e], N. Saroul [f], O. Casiraghi [g], S. Vergez [h], P. Herman [i], F. Janot [a], J. Thariat [j], B. Vérillaud [i], L. de Gabory [k], REFCOR members[l]

[a] *Head and Neck Oncology Department, Gustave Roussy Cancer Campus, Villejuif, France*
[b] *Biostatistics Department, Gustave Roussy Cancer Campus, Villejuif, France*
[c] *Department of Pathology, Lariboisière Hospital, Paris, France*
[d] *Medical Oncology Department, HIA Begin, Saint Mandé, France*
[e] *Head and Neck Surgery Department, Tenon Hospital, Paris, France*
[f] *Head and Neck Surgery Department, Clermont-Ferrand University Hospital, Clermont-Ferrand, France*
[g] *Department of Pathology, Gustave Roussy Cancer Campus, Villejuif, France*
[h] *Head and Neck Surgery Department, Toulouse University Hospital Center, Toulouse, France*
[i] *Head and Neck Surgery Department, Lariboisière Hospital, Paris, France*
[j] *Radiation Oncology Department, Baclesse Cancer Center, Caen, France*
[k] *Head and Neck Surgery Department, Pellegrin Hospital, Centre Michelet, Bordeaux, France*

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* *Corresponding author*. Gustave Roussy Cancer Campus, 114 rue Edouard Vaillant, 94805, Villejuif.
E-mail address: antoine.moya-plana@gustaveroussy.fr (A. Moya-Plana).

[l] Réseau d'Expertise Français des Cancers ORL Rares (French Rare Head and Neck Cancer Expert Network): S. Albert, G. Andry, E. Babin, C. Bach, J.-M. Badet, C. Badoual, A.C. Baglin, A. Banal, B. Barry, E. Baudin, B. Baujat, R.J. Bensadoun, C. Bertolus, J.-P. Bessède, D. Blanchard, C. Borel, A. Bozorg-Grayeli, R. Breheret, P. Breton, L. Brugel, G. Calais, O. Casiraghi, E. Cassagnau, L. Castillo, P. Ceruse, F. Chabolle, D. Chevalier, J.C. Chobaut, O. Choussy, A. Cosmidis, A. Coste, V. Costes, L. Crampette, V. Darrouzet, P. Demez, P. Dessi, B. Devauchelle, L. Digue, G. Dolivet, F. Dubrulle, S. Duflo, X. Dufour, C. Even, S. Faivre, N. Fakhry, C. Ferron, F. Floret, L. de Gabory, R. Garrel, L. Geoffrois, L. Gilain, A. Giovanni, A. Girod, B. Guerrier, S. Hans, P. Herman, P. Hofman, M. Housset, R. Jankowski, F. Jegoux, M. Juliéron, M.-C. Kaminsky, F. Kolb, J. Lacau St Guily, L. Laccoureye, B. Lallemant, P. Lang, E. Lartigau, J.-P. Lavieille, M. Lefevre, X. Leroy, O. Malard, F. Massip, O. Mauvais, J.-C. Merol, J. Michel, T. Mom, S. Morinière, E. de Monès, G. Moulin, A. Moya-Plana, G. Noel, G. Poissonnet, J.-M. Prades, D. de Raucourt, E. Reyt, C. Righini, Y. Marie Robin, F. Rolland, B. Ruhin, N. Sarroul, P. Schultz, E. Serrano, O. Sterkers, V. Strunski, A. Sudaka, M. Tassart, S. Testelin, J. Thariat, A. Timochenko, B. Toussaint, E. Uro Coste, G. Valette, T. Van den Abbeele, A. Varoquaux, F. Veillon, S. Vergez, B. Vérillaud, M. Wassef.

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KEYWORDS
Mucosal melanoma;
Sinonasal;
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Prognosis;
Oral cavity

Abstract ***Background:*** Head and neck mucosal melanoma (HNMM) is aggressive and rare, with a poor prognosis because of its high metastatic potential. The two main subtypes are sinonasal (sinonasal mucosal melanoma [SNMM]) and oral cavity (oral cavity mucosal melanoma [OCMM]). Consensual therapeutic guidelines considering the primary tumour site and tumour-node-metastasis (TNM) stage are not well established.
Material & methods: Patients with HNMM from the prospective national French Rare Head and Neck Cancer Expert Network database between 2000 and 2017 were included. Clinical characteristics, treatment modalities, outcomes and prognostic factors were analysed.
Results: In total, 314 patients were included. The 5-year overall survival (OS) and progression-free survival (PFS) rates were 49.4% and 24.7%, respectively, in the surgery group; no long-term survivors were observed when surgery was not feasible. Moreover, even after surgery, a high recurrence rate was reported with a median PFS of 22 months. In multivariate analysis, Union for International Cancer Control (UICC) stage and tumour site correlated with PFS and OS. Postoperative radiotherapy (PORT) improved the PFS but not OS in patients with small (T3) SNMM and OCMM tumours. Nodal involvement was more frequent in patients with OCMM ($p < 10^{-4}$), although, as in SNMM, it was not a significant prognostic predictor.
Conclusion: Even early HNMM was associated with poor oncologic outcomes due to distant metastases despite surgical resection with clear margins. Lymph node metastases had no impact on the prognosis, suggesting treatment de-escalation in cervical node management. PORT might be useful for local control.

1. Introduction

Head and neck mucosal melanoma (HNMM) is a rare neoplasm, accounting for 1–4% of all melanomas [1,2], 50–60% of all mucosal melanomas and only 4% of sinonasal malignancies [3]. As with cutaneous melanomas, the incidence of HNMM has increased over the last half century, although no causal risk factors have been identified [4]. Whole-genome sequencing analyses have demonstrated a radically unique genetic profile without any 'exposure to UV radiation' signature [5–7].

Two main subtypes are described in the head and neck; 70% originate in the sinonasal tract (sinonasal mucosal melanoma [SNMM]) and 20% in the oral cavity (oral cavity mucosal melanoma [OCMM]) [1,8]. SNMMs are usually localised in the anterior portion of the nasal septum, the head of the inferior turbinate and the medial wall of the maxillary sinus, whereas OCMMs mostly arise from the hard palate and the maxillary gingiva. Primary pharyngeal and laryngeal cases are rarely observed.

The pathologic diagnosis is complex, considering that numerous differential diagnoses (sinonasal undifferentiated carcinoma, neuroendocrine carcinoma and sarcomas) are possible, particularly for amelanotic and ulcerated subtypes [9]. Thus, it seems of primary importance to have expert pathologists and a well-organised national network.

Mucosal melanoma (MM) is an aggressive disease with high metastatic potential. Its prognosis is poor, with 5-year OS rates ranging from 20 to 40% [10–15]. The use of radiotherapy and its combination with surgery is controversial in melanoma. Indeed, these tumours are known to have poor radiosensitivity (e.g. no indications for radiotherapy in cutaneous melanoma), whereas some studies have observed a benefit in patients with MM [11,14]. Given its rarity, multicentric cohort studies are necessary to obtain a better understanding of this tumour to improve its management. Indeed, few published data are available with no established therapeutic guidelines.

The French Rare Head and Neck Cancer Expert Network (REFCOR) is a multidisciplinary group founded in 2008 by the French National Institute of Cancer. It comprises ENT surgeons, oncologists, radiotherapists, radiologists and pathologists drawn from 36 tertiary French referral centres. The REFCOR maintains a national database of prospectively collected rare cancer cases.

The primary objective of our study was to describe the oncologic outcomes of patients with HNMM in our multicentric REFCOR cohort. The secondary objectives were the identification of specific prognostic factors, the evaluation of our therapeutic algorithms and the impact of postoperative radiotherapy (PORT) on specific subgroups of patients with HNMM.

2. Material and methods

2.1. Data collection

This was a national, prospective and multicentric study of patients with HNMM included in the REFCOR database between 2000 and 2017. Patients were

informed and signed a consent form, in accordance with the French law. Considering the rarity of this tumour, every histologic sample was reviewed by expert pathologists to confirm this difficult diagnosis. The tumour-node-metastasis (TNM) stage was initially assessed both clinically and radiologically. The N1 status was then confirmed by the pathologist when a neck dissection was performed. All the patients were retrospectively restaged in accordance with the American Joint Committee on Cancer 7th edition staging system for HNMM [16].

Epidemiological, clinical, histological and therapeutic data were collected prospectively in the national database. We analysed the following as potential prognostic factors: epidemiological criteria (age > 65 years, gender and tobacco consumption), primary tumour site, TNM stage, multifocal presentation, type of surgery, lymphatic node management, surgical excision margins and the use of radiotherapy.

2.2. Statistical analysis

We defined progression-free survival (PFS) as the time from diagnosis to the first recurrence at any location (local, regional or distant). Patients who did not experience disease recurrence were censored at the date of the last follow-up for living patients or at the date of death for patients who died from other causes. Overall survival (OS) was defined as the time from diagnosis to death from any cause or to the last follow-up for living patients.

Prognostic analyses of OS and PFS were performed using the log-rank test for univariate analyses (UVAs) and the Cox model for multivariate analyses (MVAs) among the patients M0 initially and treated with surgery. We analysed gender, age (≤65 years versus > 65 years), TNM stage and tumour location. Among patients with T3 tumours, we studied the impact of adjuvant radiotherapy (RT) on OS and PFS. The prognostic analysis was also performed in the SNMM and OCMM subgroups of patients.

All tests were two-sided. A P-value < 0.05 was considered significant. All analyses were performed using SAS, version 9.4.

Table 1
Patient and tumour characteristics.

Characteristics	All patients	SNMM subgroup	OCMM subgroup
	314 patients	226 patients	45 patients
Gender			
Male	153 (48.7%)	101 (44.7%)	31 (68.9%)
Female	161 (51.4%)	125 (55.3%)	14 (31.1%)
Mean age [range], y	66.6 [22, 96]	67.2 [28, 96]	64.0 [22, 92]
Primary tumour site			
Nasal fossa	181 (58.2%)	181 (80.1%)	
Sinus	45 (14.5%)	45 (19.9%)	
Oral cavity	45 (14.5%)		45 (100%)
Other	43 (13.7%)		
T stage at diagnosis			
T3	174 (69.3%)	121 (67.2%)	25 (64.1%)
T4	77 (30.7%)	59 (32.8%)	14 (35.9%)
With T4a	58 (23.1%)	44 (24.4%)	12 (30.8%)
N stage at diagnosis			
N0	216 (83.4%)	170 (90.9%)	26 (65.0%)
N1	43 (16.6%)	17 (9.1%)	14 (35.0%)
Metastasis at diagnosis	33 (12.6%)	18 (9.5%)	8 (19.5%)
Stage at diagnosis			
III	139 (54.7%)	107 (58.5%)	17 (42.5%)
IVA	61 (23.8%)	45 (24.6%)	9 (22.5%)
IVB	22 (8.6%)	13 (7.1%)	6 (15.0%)
IVC	33 (12.9%)	18 (9.8%)	8 (20.0%)
Therapeutic strategy			
Surgery alone	85 (27.3%)	59 (26.2%)	13 (29.6%)
Surgery + RT	155 (49.8%)	121 (53.8%)	18 (40.9%)
RT alone	27 (8.7%)	14 (6.2%)	9 (20.5%)
Other treatment	44 (14.2%)	31 (13.8%)	4 (9.1%)
Therapeutic strategy according to M stage			
M0, surgery	227 (73.0%)	172 (76.4%)	29 (65.9%)
M0, no surgery	33 (10.6%)	22 (9.8%)	5 (11.4%)
M1	33 (10.6%)	18 (8.0%)	8 (18.2%)
Margins in M0/surgery			
R0	105 (68.6%)	78 (70.3%)	14 (60.9%)
R1	48 (31.4%)	33 (29.7%)	9 (39.1%)

OCMM, oral cavity mucosal melanoma; RT, radiotherapy; SNMM, sinonasal mucosal melanoma.

3. Results

3.1. Patient and tumour characteristics

In total, 314 patients (from 36 centres) were included in this study. The patient and tumour characteristics are shown in Table 1.

The mean age was 66.6 years (range, 22–-96 years) with a male:female ratio of approximately 1:1. The primary tumour site was mainly the nasal fossa (58.2%), sinuses (14.5%) and oral cavity (14.3%).

At diagnosis, the majority were T3 (69.3%) and N0 (83.4%), whereas distant metastases were observed in 12.6%. In this cohort, no sentinel node biopsy was performed. Considering the primary tumour site, compared with SNMM, patients with OCMM had more nodal and distant metastases (9.1% versus 35% [p < 0.0001] and 9.5% versus 19.5% [p = 0.098], respectively). Interestingly, no correlation was observed between the nodal involvement and the T stage (p = .35

in the whole cohort and p = .83 in the Surgery/M0 subgroup).

3.2. Oncologic outcomes in patients with head and neck mucosal melanoma

The median follow-up was 45.5 months. To evaluate the impact of surgery in our therapeutic armamentarium, we divided the patients into three subgroups as follows: surgery/M0 (with or without adjuvant RT), no surgery/M0 (with or without adjuvant RT) and M+. The 'surgery/M0' group was mostly composed of T3 (74%) and T4a (22.5%) HNMM; Union for International Cancer Control (UICC) stages were generally III (61.7%) and IVA (26.3%) (Table 2). The 'no surgery/M0' group was composed of patients with T4b HNMM and/or patients who were not eligible for surgery because of their poor general condition and comorbidities.

The oncologic outcomes are shown in Table 3. As expected, the 'surgery/M0' group had a better prognosis ($p < 10^{-4}$), with a median OS and median PFS of 49 months and 22 months, respectively. Moreover, the two other subgroups, in whom surgery was not feasible, had similarly poor prognoses.

However, even in the 'surgery/M0' group, the median PFS was low because of the high rate of distant metastases (Fig. 1). The local, regional and distant recurrence rates were 16.9%, 12.6% and 57.7%, respectively.

Table 2
'Surgery/M0' group characteristics.

Characteristics	All patients	SNMM subgroup	OCMM subgroup
Gender			
Male	101 (50.8%)	73 (49.0%)	18 (64.3%)
Female	98 (49.2%)	76 (51.0%)	10 (35.7%)
Mean age [range], y	65.1 [25, 96]	65.6 [28, 96]	63.2 [25, 92]
Primary tumour site			
Nasal fossa	128 (65.3%)	128 (85.9%)	
Sinus	21 (10.7%)	21 (14.1%)	
Oral cavity	28 (14.3%)		28 (100%)
Other	22 (11.1%)		
T stage at diagnosis			
T3	124 (73.4%)	93 (72.7%)	16 (64.0%)
T4	45 (26.6%)	35 (27.3%)	9 (36.0%)
T4a	30	21	3
N stage at diagnosis			
N0	155 (89.6%)	124 (93.9%)	19 (76.0%)
N1	18 (10.4%)	5 (6.1%)	6 (24.0%)
Stage at diagnosis			
III	112 (66.3%)	86 (67.2%)	14 (56.0%)
IVA	48 (28.4%)	36 (28.1%)	8 (32.0%)
IVB	9 (5.3%)	6 (4.7%)	3 (12.0%)
Therapeutic strategy			
Surgery alone	64 (32.2%)	43 (28.9%)	13 (46.4%)
Surgery + RT	135 (67.8%)	106 (71.1%)	15 (53.6%)
Surgical margins			
R0	97 (68.3%)	73 (70.2%)	13 (59.1%)
R1	45 (31.7%)	31 (29.8%)	9 (40.9%)

OCMM, oral cavity mucosal melanoma; RT, radiotherapy; SNMM, sinonasal mucosal melanoma.

Table 3
Oncologic outcomes according to initial M stage and operability.

Oncologic outcomes	Surgery/M0 (n = 199)	No surgery/M0 (n = 24)	M+ (n = 27)	Log-rank p-value
Overall survival				<0.0001
Median	49.0 months	16.7 months	8.3 months	
3-year rate	60.2%	36.8%	25.6%	
5-year rate	49.4%	0%	0%	
PFS				<0.0001
Median	22.0 months	9.0 months	5.0 months	
3-year rate	33.1%	8.5%	8.6%	
5-year rate	24.7%	0%	0%	

PFS, progression-free survival.

3.3. Prognostic analysis

The prognostic analysis was performed initially in the 'surgery/M0' group and was based on 199 patients (more than 227 patients) who were followed up (Fig. 2).

With regards to OS, no association was found with age, gender, multifocal presentation, resection margin status or N stage. Primary tumour site ($p < 10^{-4}$), T stage (p = .0145) and UICC stage (p = .005) were the prognostic factors in UVA, whereas only tumour site (p = .005) and UICC stage (p = .0047) were linked to OS in MVA. Considering the primary tumour site, tumours in the nasal fossa had a better prognosis than those arising from the sinuses. Patients with OCMM, however, appeared to have the same oncologic outcomes as patients with nasal fossa melanoma.

With regards to PFS, no association was observed with age, gender, multifocal presentation, resection margin status or N stage. As in the OS analysis, primary tumour site (p = .0011), T stage (p = .0095) and UICC stage (p = .0053) were prognostic factors in UVA, whereas only tumour location (p = .0093) and UICC stage (p = .00126) were linked to PFS in MVA.

In the T3 subgroup of patients (n = 123), no benefit of PORT in OS (p = .59) and PFS (p = .0649) was observed.

In the SNMM subgroup, primary tumour site (sinus versus nasal fossa, p = .0004) and UICC stage (p = .0411) remained key prognostic factors for OS in MVA. Only tumour location had a prognostic value for PFS in MVA (p = .0002). Interestingly, in the subgroup of patients with T3 SNMM (n = 93), PORT was associated with a significantly improved PFS both in UVA (p = .0261) and MVA (p = .0097) with an hazard ratio (HR) of 0.47 (Fig. 3). The role of PORT was not investigated in T4a-T4b stages because of the small number of patients and the clear tendency to post-operatively irradiate locally advanced tumours (Table 4).

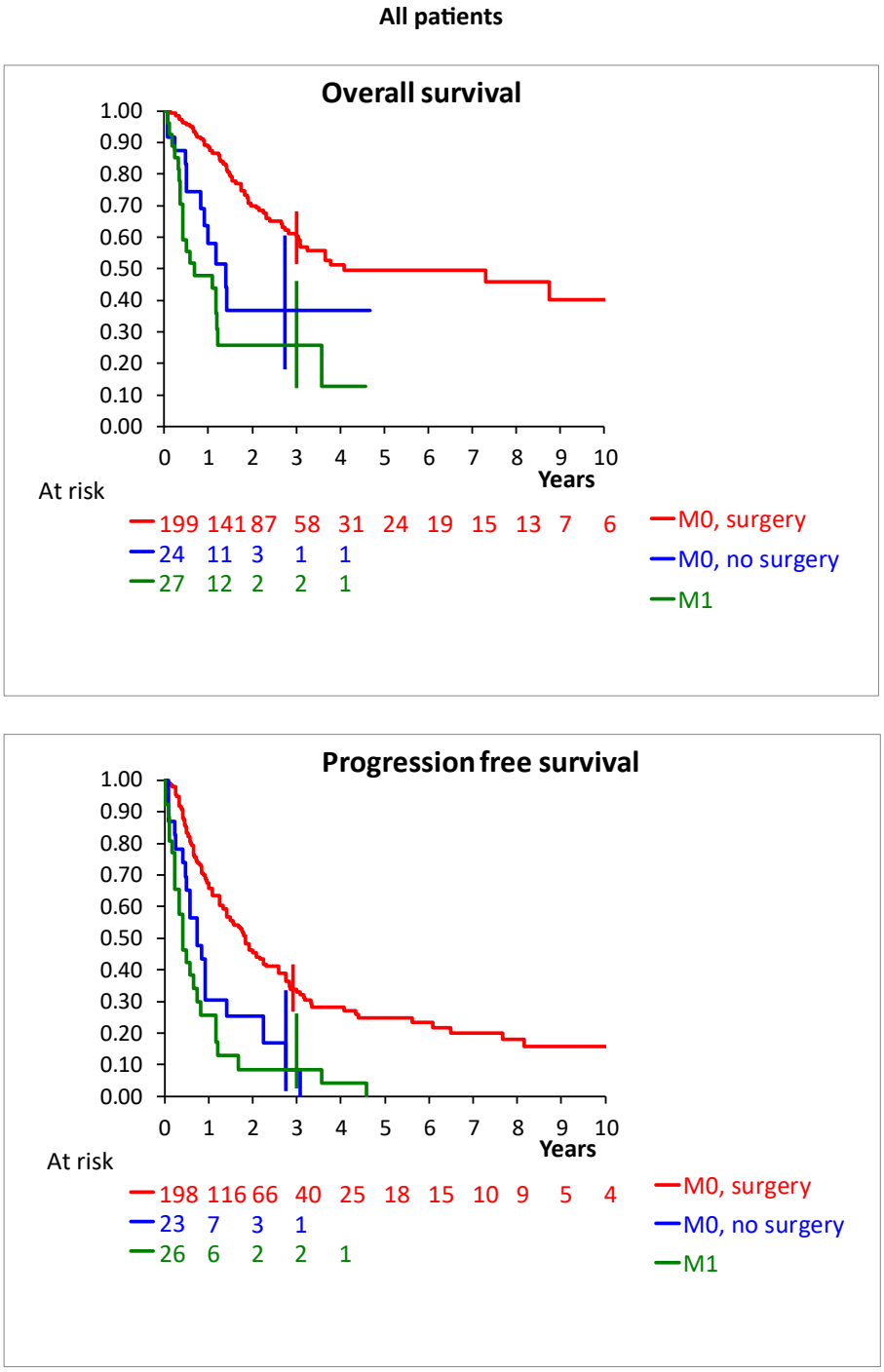

Fig. 1. Overall survival and progression-free survival in the whole HNMM cohort according to M stage and operability. HNMM, head and neck mucosal melanoma.

Considering the small cohort size of patients with OCMM, it was not possible to perform an accurate statistical prognostic analysis. However, the observed trends were similar to those seen in patients with SNMM. Indeed, among patients with T3M0 OCMM, PORT seemed to improve local control, with a better PFS (but no beneficial effect on OS), whereas N stage was not linked to OS or PFS.

4. Discussion

This cohort was collected by a French national network, the REFCOR, which has facilitated this prospective multicentric collaborative study on HNMMs. Given the rarity of HNMMs, multicentric national networks are necessary for the collection of cases, organisation of national tumour boards and development of therapeutic

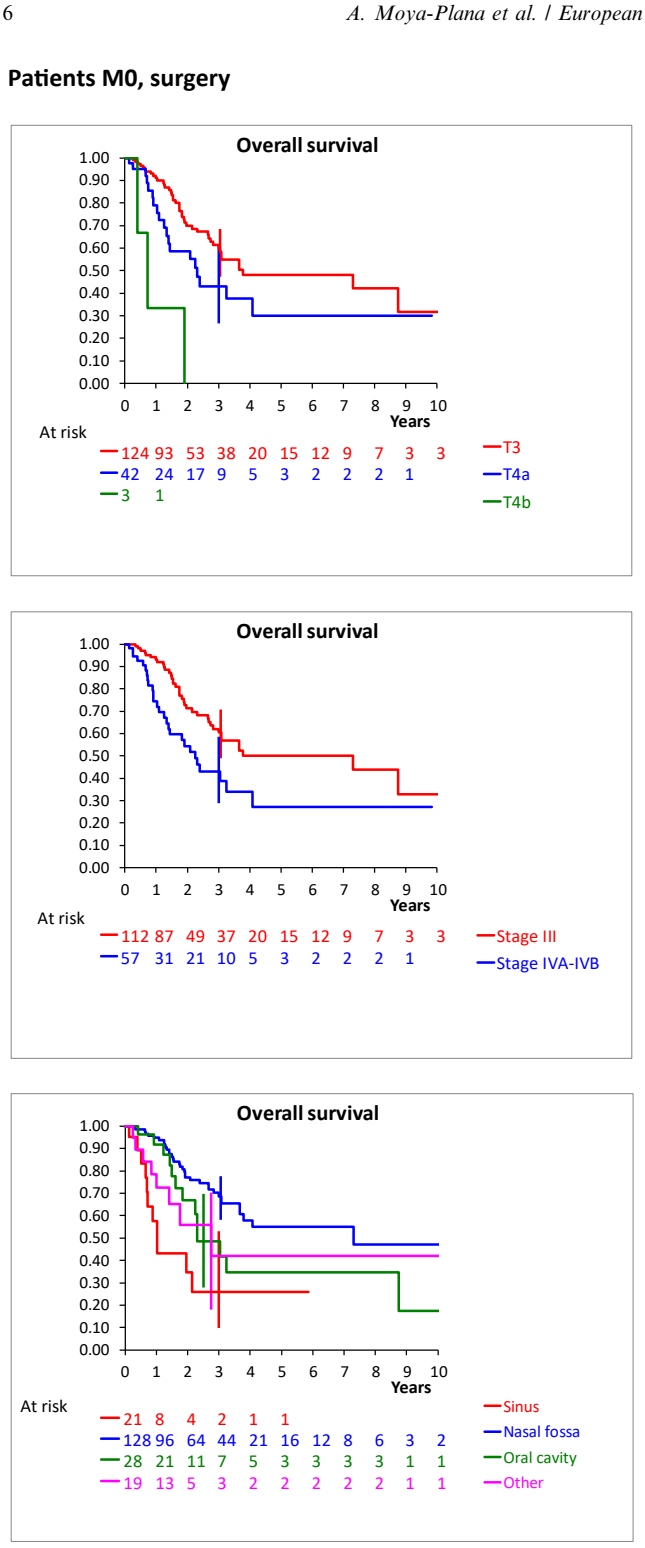

Fig. 2. Overall survival (A) and progression-free survival (B) in the 'surgery/M0' subgroup according to primary tumour location, T stage and Union for International Cancer Control (UICC) stage.

guidelines. Moreover, it allows us to gather cohorts with a significant number of patients in a relatively short period of time, unlike in monocentric studies, usually conducted over decades. We can, then, hypothesise that our study population is more homogeneous and comparable with regard to the types of treatments received (pathological diagnosis, surgical techniques and radiotherapy). Thus, we analysed more than 300 patients with HNMM, which is one of the largest cohorts in the literature. The follow-up is substantial, approximately four years. Indeed, given the aggressiveness and poor prognosis of HNMM, most oncologic events occur early in the course of the disease [10–14].

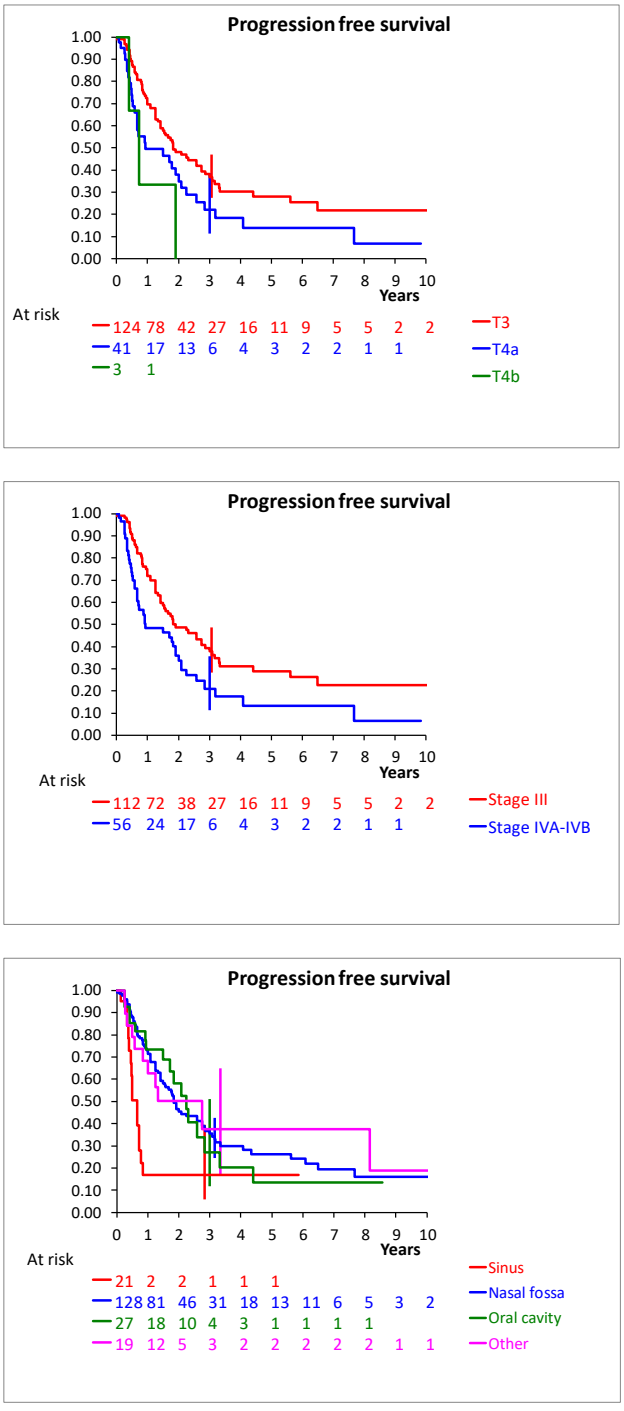

Fig. 2. (*continued*).

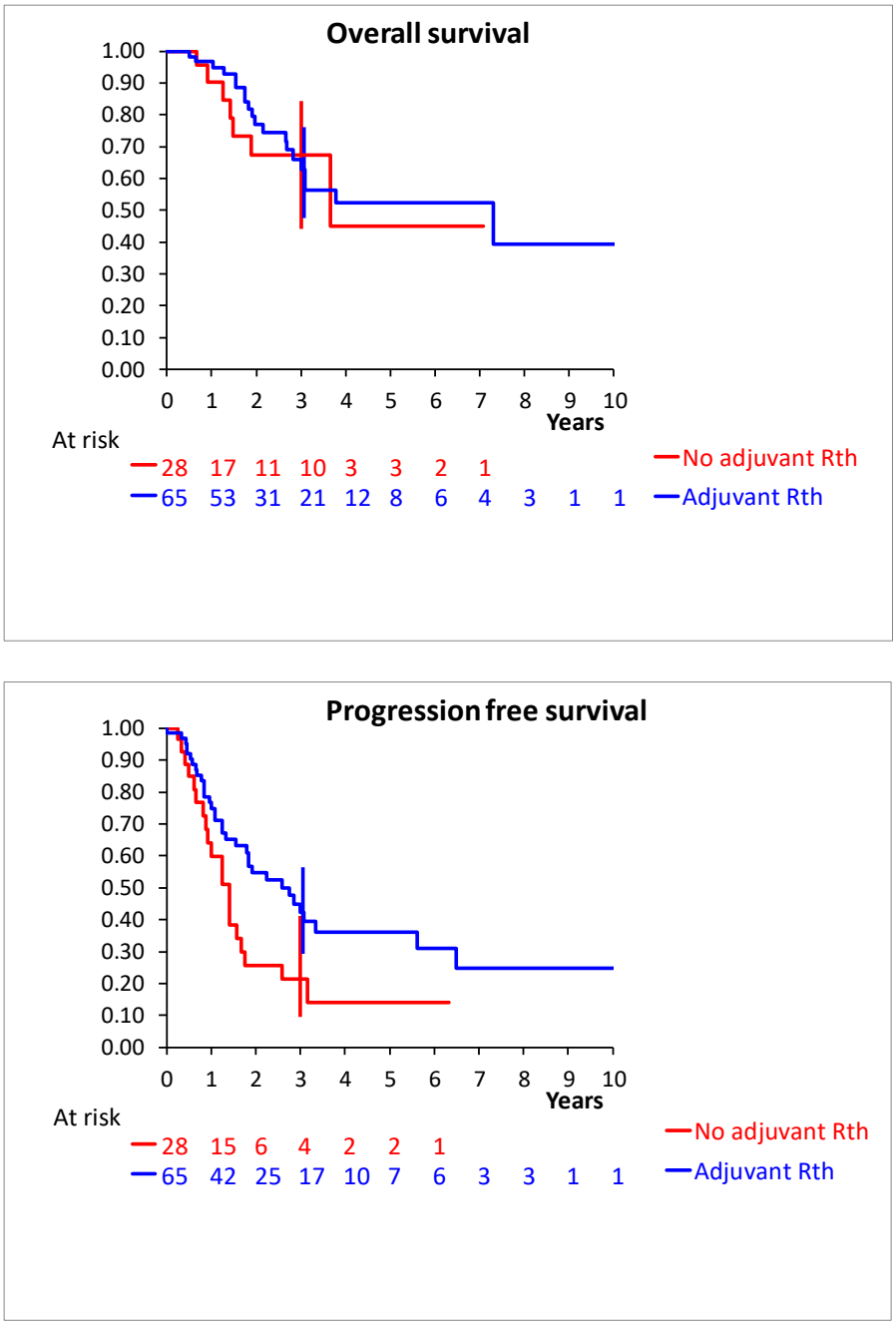

Fig. 3. Benefit of adjuvant radiotherapy in the T3 SNMM subgroup. SNMM, sinonasal mucosal melanoma.

The epidemiological and clinical characteristics are consistent with the literature [1,2]. Our study confirmed the high metastatic rate and poor oncologic outcomes of HNMM. Indeed, even in the 'surgical/M0' subgroup, the median OS and PFS were 49 months and 22 months, respectively, whereas more than half of the patients developed distant metastases during the follow-up period. These data are comparable with those previously reported [10–14].

In the whole population of patients with HNMM, the main prognostic factors were T stage, primary tumour location and UICC stage, whereas other reported factors such as age, gender, tobacco consumption, multifocal presentation, resection margin status, N stage and PORT had no prognostic value. Multifocal disease, a frequent clinical presentation, is known to be linked to local failure [17]. However, our analyses did not find such a correlation. This could be explained by the

Table 4
Adjuvant radiotherapy in patients with non-metastatic SNMM treated with surgery, according to T stage.

T stage	No adjuvant RT	Adjuvant RT	Total
T3	28 (29.7%)	65 (70.3%)	93
T4a	4 (12.5%)	28 (87.5%)	32
T4b	1 (33.3%)	2 (66.7%)	3
Total	33	95	128

RT, radiotherapy; SNMM, sinonasal mucosal melanoma.

extended use of transnasal endoscopic surgery, which probably allows better visualisation of the surgical field than transfacial approaches [18]. In sinonasal tumour surgery, resection margin status is always difficult to assess because of the complex anatomy and frequently piecemeal resection (regardless of the approach) [19,20]. This could explain, in our cohort, the lack of prognostic value of these data. Moreover, unlike in head and neck squamous cell carcinoma, prognosis in patients with HNMM is more strongly correlated with distant metastases than local failure.

In the surgical/M0 subgroup, which represents the large majority of patients at the time of diagnosis, MVA identified only UICC stage and primary tumour location as prognostic factors. Indeed, the T stage in HNMM, with only T3/T4a-b, seems to be too limited to be predictive. Interestingly, N status was not linked to oncologic outcomes in SNMM, as was recently described by Amit *et al.* [21]. Although nodal involvement is rare in patients with SNMM, it should not be considered as a strong prognostic factor. These data have to be confirmed in larger cohorts, given the scarcity of nodal metastases in patients with HNMM at diagnoses.

With regard to the primary tumour location, patients with HNMM from the nasal fossa had a significantly better prognosis than those with HNMM from the paranasal sinus ($p < 10^{-4}$), as previously reported [11,14]. Interestingly, the outcomes of OCMM are not significantly different from those of nasal fossa melanoma. This finding could be linked to the possibility of achieving oncologic resection in these particular locations. Indeed, the surgical resection of paranasal sinus malignancies is a highly complex procedure because of the proximity to key anatomical structures, such as the orbit, skull base and internal carotid artery [20].

Thus, at diagnosis, oncologic outcomes in patients with HNMM seem to be driven only by the presence of distant metastases and the feasibility of performing a surgical resection. Surgery remains the cornerstone of the therapeutic strategy, especially given the very poor prognosis of non-resectable tumours and the very low rate of mutations that are eligible for targeted therapies in HNMM [6,7].

The benefit of PORT in HNMM has been discussed in several studies [12,14,22]. PORT seems to improve local control but has no effect on OS. This observation emphasises the correlation between distant metastases and OS in patients with this particular sinonasal tumour in which local recurrence is not the main cause of oncologic events and mortality, unlike in patients with sinonasal squamous cell carcinoma or intestinal-type adenocarcinoma [20]. In our cohort, we studied the potential benefit of PORT with regard to the localisation and T stage. We found no benefit for OS or PFS in either the whole 'surgery/M0' group or the T3 subgroup. However, a clear impact on PFS was observed in patients with T3 SNMM. This result is of primary importance because T3 SNMM is the most common clinical presentation of HNMM. The indication for PORT in such small tumours, for which surgery is usually feasible with clear margins, is usually debated by multidisciplinary tumour boards. Moreover, given the very low rate of nodal involvement, our guidelines for PORT recommend sparing the cervical lymph nodes in N0 SNMM, inducing a significantly lower morbidity. Finally, optimising local control in patients with HNMM seems important in terms of quality of life, given the high morbidity of uncontrolled local recurrence in patients with sinonasal tumours. However, in our study, there may be a treatment selection bias. To limit it, we selected only T3 patients in our prognostic analysis of the impact of PORT. We excluded T4 HNMM from this analysis, a subgroup where PORT was almost systematically realised. Thus, PORT was performed for T3 patients according to therapeutic algorithm of each centre, limiting the patients' selection bias.

OCMM remains rare, and consensual therapeutic guidelines are difficult to establish. Our study population included a significant cohort of patients with OCMM. This subgroup analysis showed a higher rate of nodal metastases ($p < 10^{-4}$) at diagnosis. An anatomical explanation could be based on the presence of a more important lymphatic network in the oral cavity (particularly the tongue) than in the nasal fossa. However, we found that, despite a higher lymphophily, cervical lymph node invasion seems to have no prognostic significance in the OCMM surgical group. Moreover, as in SNMM, PORT seems only to provide a benefit in terms of local control in patients with T3 OCMM. Thus, a change could be discussed in our treatment algorithm, with a potential therapeutic de-escalation with regard to cervical node management, avoiding the potential morbidity of elective neck dissection and PORT in patients with N0 HNMM.

Recently, some studies reported encouraging results of immune checkpoint inhibitors for unresectable and/or metastatic MM with, for anti–PD-1 antibodies, an objective response rate (ORR) of approximately 25–35% and durable clinical responses [23–26]. Combination of nivolumab with ipilimumab seems to be another promising option with a better efficacy and a similar safety profile compared with nivolumab alone [25]. Considering the high metastatic rate in HNMM

despite the relatively good local control, the combination of surgery with adjuvant immunotherapy should be evaluated, as is used in high-risk cutaneous melanoma with a significant survival benefit [27]. Neoadjuvant therapy is the next step in the management of this aggressive malignancy [28]. Indeed, the postoperative period after tumour resection may be associated with a 'surgery-induced immunosuppression' leading to potential tumour dissemination [29]. Using neoadjuvant anti–PD-1 antibodies, tumour-specific T cells are supposed to expand in the primary tumour and/or lymph node metastases so as to spread and destroy the potential micrometastases [30]. In resectable lung tumours, neoadjuvant nivolumab induced a major pathologic response in 45% of cases with no need to postpone the surgery because of potential side-effects [30]. In cutaneous melanoma, Amaria et al. [31] recently showed that treatment with neoadjuvant and adjuvant targeted therapy was associated with high pathologic complete response (pCR) rates and improved outcomes compared with primary surgery. Recently, in high-risk resectable melanoma, a study compared neoadjuvant nivolumab alone or combined with ipilimumab followed by surgical resection and adjuvant nivolumab. The combination induced higher response rates (until 45% of pCR) and also a significant toxicity with 73% of grade III adverse events [32]. We are, also, evaluating this therapeutic approach for patients with resectable HNMM in a multicentric prospective clinical trial (NCT03313206).

5. Conclusion

This prospective multicentre cohort study confirmed the poor prognosis of patients with HNMM because of its high metastatic potential, even in the surgical subgroup when clear margins were achieved. The primary tumour site is an important parameter, considering the rate of nodal involvement, distant metastasis and oncologic outcomes. Interestingly, N status seems to have no prognostic significance (for SNMM and OCMM), suggesting a therapeutic de-escalation in N0 HNMM. Surgical resection remains, however, the cornerstone of the therapeutic armamentarium. Adjuvant RT did not seem to significantly impact OS or PFS in the entire cohort. However, in patients with small tumours such as T3 SNMM, PORT has a benefit for local control. Thus, the addition of systemic therapies such as immune checkpoint inhibitors must be considered, given the poor prognosis, the high metastatic risk and unusual molecular profile.

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Conflict of interest statement

None declared.

Appendix A. Supplementary data

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