Eur J Dermatol 2018; 28(5): 654-60

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Prognostic factors and incidence of primary mucosal melanoma: a population-based study in France

Background: Few population-based studies on the incidence and prognosis of primary mucosal melanoma (PMM) are available. *Objectives:* The first objective was to evaluate disease-specific survival of PMM, overall and according to specific locations, and to identify prognostic factors. The second objective was to assess the global incidence of PMM compared to cutaneous melanoma and to specify the relative frequency of each affected location. *Materials & Methods:* A retrospective population-based study of incident PMM diagnosed between 2004 and 2014 was conducted, relying on the regional melanoma registry of the French Champagne-Ardenne region (1.34 million inhabitants). *Results:* Thirty-nine cases were identified, including 17 head and neck (13 sinonasal and four oral), 12 vulvovaginal, six conjunctival, and four anorectal PMMs. Some 76.9% of cases were revealed by late symptoms. The median disease-specific survival time was 23.9 months and the five-year disease-specific survival rate was 31.8%. Univariate and multivariate analyses led to identification of primary tumour size and the presence of nodal or visceral macrometastases at diagnosis as adverse prognostic factors, while Breslow thickness and ulceration were unreported in 41% of cases and failed to display any prognostic value. Compared to other locations, conjunctival PMMs had a smaller tumour size and better prognosis. The annual incidence rate was 0.18/100,000 and the incidence ratio between PMM and cutaneous melanoma was 1/50. *Conclusion:* This population-based study confirms the rarity, delayed diagnosis, and severity of PMM, suggesting that improving prognosis will require specific, targeted therapies.

Article accepted on 08/02/2018

Key words: primary mucosal melanoma, prognosis, incidence

Primary mucosal melanoma (PMM) is a heterogeneous subtype of melanoma, which is rare compared to cutaneous melanoma [1]. It includes head and neck (HNM), vulvovaginal (VVM), conjunctival (CM), and anorectal (ARM) melanomas. Compared to cutaneous melanoma, the prognosis of PMM is very poor, with an overall five-year disease-specific survival rate evaluated at around 25% [1]. Little is known about incidence, distribution according to different mucous locations, and prognostic factors. Previous prognostic studies have led to heterogeneous results. Variable adverse prognostic factors depending on anatomical site have been identified, including tumour thickness, maximum tumour diameter, absence of complete surgical resection with sufficient margins, and presence of distant metastases [1-6]. On the other hand, better survival rates were observed in patients with VVM and CM compared to other locations [7-9].
Most of these studies were hospital-based, leading to possible recruitment biases, and to our knowledge, only one population-based study including PMM of any location has been conducted [10].
The first objective of this population-based French study was to evaluate disease-specific survival of PMM overall and according to specific locations, and to identify prognostic factors. The second objective was to assess the global incidence of PMM compared to cutaneous melanoma and to specify the relative frequency of each affected location.

Material and methods

Population and inclusion criteria

The study was based on the population of Champagne-Ardenne, a north-eastern region of France, with 1.34 million inhabitants [11]. All incident cases of PMM diagnosed between January 2004 and December 2014, of residents of Champagne-Ardenne, were eligible for the

doi:10.1684/ejd.2018.3398

To cite this article: Beaudoux O, Riffaud L, Barbe C, Grange F. Prognostic factors and incidence of primary mucosal melanoma: a population-based study in France. *Eur J Dermatol* 2018; 28(5): 654-60 doi:10.1684/ejd.2018.3398

study. The regional melanoma registry (OMECHA) was used to identify cases. This registry relies on the systematic transmission of pathology reports by all private and hospital pathology laboratories in the region, as well as those in neighbouring parts of the surrounding regions that are liable to diagnose melanomas in residents of Champagne-Ardenne, as previously reported [12-14]. To identify mucosal locations of melanoma, pathologists were asked to select and transmit reports based on codes of the French national nomenclature for anatomical sites: sinonasal (AF and AS), oral cavity (BX and BV), vulvovaginal (GV), ocular (OE), and anorectal (DQ and DR).

Data collection

The French data-protection authority (Commission nationale de l'informatique et des libertés) authorized the study (No. 91 6350). Data were collected based on a review of all pathological reports, which included medical records for patients followed at the regional university hospital or at the main private medical centres. For patients followed in smaller institutions or by private physicians, questionnaires were sent to referent general practitioners, dermatologists, and/or surgeons. Clinical and histological data at diagnosis included: age; sex; melanoma location and sublocation; circumstances of diagnosis, either following clinical symptoms or a systematic medical examination; date of first symptoms; date of histological diagnosis; time between first symptoms and diagnosis; tumour size, defined as the maximum tumour diameter; Breslow thickness; ulceration; whether the tumour was pigmented, achromatic or mixed; clinical stage at diagnosis; and whether or not a complete surgical excision could be performed.
Anatomical locations and sublocations were classified as follows: HNM (subclassified as cases which developed in the oral cavity, nasal cavity, nasal sinus, or both nasal cavity and nasal sinus); VVM (subclassified as vulvar or vaginal melanomas); CM; and ARM (subclassified as anal, anorectal, or rectal melanomas).
For tumour staging at diagnosis, cases were classified irrespective of the anatomical location, as follows: local stage (L : primary tumour of any size without nodal or visceral dissemination); regional microscopic stage (Rmicro : any case with microscopic involvement identified by sentinel lymph node biopsy); regional macroscopic stage (Rmacro : any case with macroscopic nodal metastasis diagnosed clinically or by medical imaging); and disseminated stage (M : any case with distant metastasis).
Outcome data were recorded from medical records until 30 September 2015 and included any local or regional recurrences, any distant metastases, date of last follow-up visit, status at last follow-up visit, and date and cause of death.

Statistical analysis

Data are described using mean and standard deviation for quantitative variables and number and percentages for qualitative variables.
Comparisons between subgroups of patients were performed using the Chi^2 test, Fisher's exact test, Student's *t*-test, or Wilcoxon test, as appropriate.
The survival curves of PMM overall and according to different locations and characteristics were established using the Kaplan-Meier method. Prognostic factors were identified based on univariate analysis using the log rank test and multivariate analysis using the Cox proportional hazard model. Factors significant at the 0.10 level based on univariate analysis were included in a stepwise regression multivariate analysis with entry and removal limits set at 0.10. A p-value < 0.05 was considered significant. Statistical analysis was performed using SAS statistical software (SAS Inc., Cary, NC).

Results

Identification and incidence of mucosal melanoma

Pathology reports for 57 cases were first identified as possible PMM by the regional registry. Six cases were excluded after review of medical records because their clinical history was suggestive of mucous metastases from a primary cutaneous melanoma. Twelve patients had an uveal melanoma and were therefore not included. The final study group comprised 39 cases, including 17 HNM, 12 VVM, six CM, and four ARM.
The annual incidence rate of PMM in the Champagne-Ardenne region was evaluated at 0.18/100,000. During the same period, 1,583 cases of primary cutaneous melanoma were diagnosed in residents of the Champagne-Ardenne region, corresponding to an annual incidence rate of 8.92/100,000. The incidence ratio between mucosal and cutaneous melanoma was 0.02 (*i.e.* 1/50).

Anatomical locations and sublocations of mucosal melanomas

These 39 PMM were distributed as follows: 17 HNM, including four cases of the oral cavity and 13 sinonasal melanomas (eight cases of the nasal cavity, three cases of the nasal sinus, and two cases involving both the nasal cavity and nasal sinus); 12 VVM, including four vaginal melanomas and eight vulvar melanomas; four ARM, including two anorectal, one rectal and one anal melanoma; and six CM.

Clinical and pathological characteristics of PMM at diagnosis

The clinical and pathological characteristics of the entire series are shown in *table 1*.
The mean age was 70.7 ± 13.3 years, without significant difference according to location. A female predominance was observed in the entire study group, only related to the inclusion of VVM, whereas no genital melanoma was diagnosed in males during the study period. Some 85% of HNM, VVM, and ARM were diagnosed following symptoms, whereas at least three of six CM were asymptomatic and diagnosed during a systematic medical examination. The median time between first symptoms (when present) and diagnosis was three months (range: 1-36). Median tumour size for HNM, VVM, and ARM was 30 mm (range: 0.7-60), with no difference between groups, and was only 3 mm (range: 2-11) for CM. Breslow thickness was only

Table 1. Clinical and histological features of all cases of PMM ($n = 39$) according to anatomical location.

	All PMM ($n = 39^*$)	HNM ($n = 17^*$)	VVM ($n = 12^*$)	CM ($n = 6^*$)	ARM ($n = 4^*$)	*p*-value
Age (years): mean ± SD	70.7 ± 13.3	66.8 ± 4.4	70 ± 12.6	75.9 ± 16.4	70 ± 9.6	0.54
Sex						
Male	12 (30.8)	8 (47)	0 (0)	2 (33.3)	2 (50)	0.02
Female	27 (69.2)	9 (53)	12 (100)	4 (66.7)	2 (50)	
Circumstances of diagnosis						
Symptoms	30 (76.9)	15 (88.4)	9 (75)	2 (33.3)	4 (100)	0.004
Systematic medical examination	6 (15.4)	1 (5.8)	2 (16.7)	3 (50)	0 (0)	
Time between 1st symptoms and diagnosis (months)[a]: median (range)	3 (1-36)	3 (1-36)	2 (1-28)	1 (1-7)	5 (1-6)	0.9
Tumour size (mm): median (range)	23 (0.7-60)	30 (0.7-60)	20 (15-60)	3 (2-11)	30 (15-37)	0.02
Breslow thickness[b]						
In situ	3 (13)	1 (14.2)	1 (10)	1 (50)	0 (0)	0.36
0.1-4 mm	4 (17.4)	1 (14.2)	2 (20)	1 (50)	0 (0)	
4.01-8 mm	5 (21.7)	3 (42.8)	2 (20)	0 (0)	0 (0)	
> 8 mm	11 (47.9)	2 (29)	5 (50)	0 (0)	4 (100)	
Median: range (mm)	8 (1.78-22)	8 (4-12)	9 (1.78-22)	2	10 (8-15)	
Ulceration[c]						
Present	18 (78.3)	8[a] (100)	7 (70)	1[d] (33.3)	2 (100)	0.1
Absent	5 (21.7)	0 (0)	3 (30)	2 (66.7)	0 (0)	
Pigmentation[d]						
Pigmented	26[c] (66.7)	14[c] (82.3)	7 (58.3)	2 (33.3)	3 (75)	0.1
Achromatic	9 (23.1)	2 (11.7)	4 (33.3)	2 (33.3)	1 (25)	
Mixed	3 (7.7)	0 (0)	1 (8.4)	2 (33.3)	0 (0)	
Staging at diagnosis						
L	27 (69.2)	13 (76.5)	6 (50)	6 (100)	2 (50)	0.35
Rmicro	2 (5.1)	0 (0)	2 (16.7)	0 (0)	0 (0)	
Rmacro	7 (17.9)	3 (17.6)	3 (25)	0 (0)	1 (25)	
M	3 (7.8)	1 (5.9)	1 (8.3)	0 (0)	1 (25)	

L: primary tumour of any size without nodal or visceral dissemination; Rmicro: any case with microscopic involvement identified by sentinel lymph node biopsy; Rmacro: any case with macroscopic nodal metastasis diagnosed clinically or by medical imaging; M: any case with distant metastasis.

[*] *Data are expressed as n (%) unless otherwise indicated.*

[a] *18 with missing data.*

[b] *29 with missing data.*

[c] *32 with missing data.*

[d] *Two with missing data.*

documented in 59% of cases. Unknown Breslow thickness was much more frequent for HNM (58.9%) and CM (66.7%) than for VVM (16.7%) and ARM (0%). The presence or absence of ulceration was only documented in 59% of cases. In most of these cases (78.3%), ulceration was present, more often in HNM, VVM and ARM (85%) than in CM (33.3%). Ten of 33 cases (30.3%) of HNM, VVM and ARM exhibited macroscopic nodal or distant metastases at diagnosis, whereas no CM exhibited extramucosal dissemination at diagnosis. No difference in location was observed according to age, time between first symptoms and diagnosis, Breslow thickness, and pigmentation.

Follow-up data and prognostic factors

The follow-up data are shown in *table 2*. In the entire study group, 23 of 39 cases (59%) achieved complete resection following surgery. Among them, 12 cases (52.2%) had a local recurrence diagnosed after a median time of 11.6 months (range: 6.7-41.1). At diagnosis or during the course of the disease, 19 of 39 patients (48.7%) had macroscopic nodal metastases and 21 of 39 (53.8%) had distant metastases. Twenty-five of 39 patients (64.1%) died from melanoma, including seven patients who died without distant metastases; five patients died following bulky locoregional extension of HNM, one patient died of HNM nine days after the first surgery, and one patient died from uncontrolled bleeding two months after diagnosis of a locally advanced vaginal tumour. Conversely, three patients with distant metastases were still alive at the end of the study.

The median disease-specific survival time was 23.9 months (range: 0.3-169.9). The five-year disease-specific survival rate was 31.8%. The disease-specific survival curves for the entire study group and according to location are presented in *figures 1A, B*. Patients with CM had a significantly better survival rate than those with other mucosal locations ($p = 0.03$; *figure 1C*). Among sinonasal melanomas, those restricted to the nasal cavity had a better prognosis than those involving the sinus with or without nasal cavity

Table 2. Follow-up data of 39 patients with PMM.

	All PMM ($n = 39$)	HNM ($n = 17$)	VVM ($n = 12$)	CM ($n = 6$)	ARM ($n = 4$)
Complete resection status after surgery[a]	23 (59%)	8 (47%)	9 (75%)	3 (50%)	3 (75%)
Local disease recurrence[a]	12 (52.2%)	6 (75%)	5 (55.5%)	0	1 (25%)
Median time between surgery and local recurrence: months[a] *(range)*	11.6 (6.7-41.1)	12.5 (6.7-41.1)	10 (7-27.2)	-	21.3b
Status at last follow-up visit[c]					
Melanoma-related death	25	14	7	1	3
With metastases	18	8	6	1	3
Without metastases	7	6	1	0	0
Other cause of death	5	1	1	3	0
Alive in remission	5	1	2	2	0
Alive with disease	3	1	2	0	0
Median disease-specific survival: months (range)	23.9 (0.3-169.9)	15 (0.3-169.9)	24 (0.3-103)	48[b]	6 (3-52)

[a] *Two with missing data*
[b] *Only one with known value.*
[c] *One with missing data.*

involvement ($p = 0.01$; *figure 1D*). We were unable to show any prognostic difference according to sublocations within the other major locations.

Based on univariate survival analysis of the entire series, tumour size ($p = 0.003$) and macroscopic metastases (Rmacro or M stage) at diagnosis ($p < 0.0001$) were significantly associated with melanoma-related death, whereas Breslow thickness (when available), ulceration (when available), age, and sex had no prognostic value.

Based on multivariate analysis, tumour size (HR = 1.07; 95% CI: 1.027-1.12; $p = 0.002$) and macroscopic metastases at diagnosis (HR = 25; 95% CI: 5-111; $p < 0.0001$) remained adverse significant prognostic factors. Disease-specific survival curves according to stage are shown in *figures 2A, B*.

Discussion

In the present study, we included all cases of PMM diagnosed during an 11-year period in a French region with 1.34 million inhabitants. To our knowledge, only one previous population-based study of PMM of any location has been conducted, relying on the Surveillance Epidemiology and End Results (SEER) database in the USA [10]. In this French study, we evaluated the incidence rate of PMM at 0.18/100,000 and the incidence ratio between mucosal and cutaneous melanoma at 1/50, which is comparable to the ratio of 1/100 observed in the American study [10].

Our study also confirms the relative frequency of the different mucosal sites, with HNM and VVM being the most frequent locations, as observed previously [10, 15].

We observed that PMM have distinctive major clinical characteristics, as compared to cutaneous melanomas, with important consequences for classification and prognostic factors. Notably, information regarding Breslow thickness and ulceration was missing in nearly half of our cases, which was comparable to earlier data [9], making the staging system used for cutaneous melanomas, mainly based on Breslow thickness and histological ulceration, irrelevant for PMM. To date, there has been no reproducible consensus classification system for mucosal melanoma [1, 16, 17]. Various systems have been used depending on location, including the Ballantyne system for ARM and VVM [1, 18, 19], the American Joint Committee on Cancer (AJCC) staging for HNM [20], and the AJCC TNM classification for sinonasal tract carcinomas for sinonasal melanoma [21]. In the present study, the classification according to tumour extent at diagnosis (L, Rmicro, Rmacro or M), which is close to the Ballantyne system, was therefore found to be relevant.

Our results confirm the very poor prognosis of PMM overall, with a median specific survival rate of 23.9 months, and a five-year disease-specific survival rate of 31.8%, which is comparable to the relative survival rate of 34% observed in the American population-based study [10]. By contrast, the five-year survival rate of patients with cutaneous melanoma at any stage at diagnosis has been recently evaluated at 83% in Europe [22].

The prognosis of PMM, however, was not homogeneous. Notably, a significant difference in survival was observed between CM and other anatomical sites (*figure 1A*), in accordance with other studies [7, 9, 23]. The better prognosis for the conjunctival location could be mainly explained by the frequent earlier diagnosis of CM, compared to internal and less visible sites. Indeed, 50% of CM were diagnosed based on simple visual examination in patients without symptoms, and the median tumour size was much lower for CM (3 mm) compared to other sites (23 mm).

Based on multivariate analysis, only tumour size and stage at diagnosis (M or Rmacro *versus* Rmicro or L) significantly impacted disease-specific survival. Breslow thickness could not be validated as a significant prognostic factor. In contrast to primary cutaneous melanoma, the value of Breslow thickness as a useful prognostic parameter has not been consistently attested in PMM [3, 6, 15, 24]. In the population-based study by Bishop *et al*., PMM cases were classified according to disease extent, but Breslow thickness was not recorded [10]. In a large German study of 444 patients with PMM, Breslow thickness was unknown in 54% of cases [15]. In our population-based study, Breslow thickness was not specified in 41% of pathological reports, particularly for HNM (58.9%), possibly because of

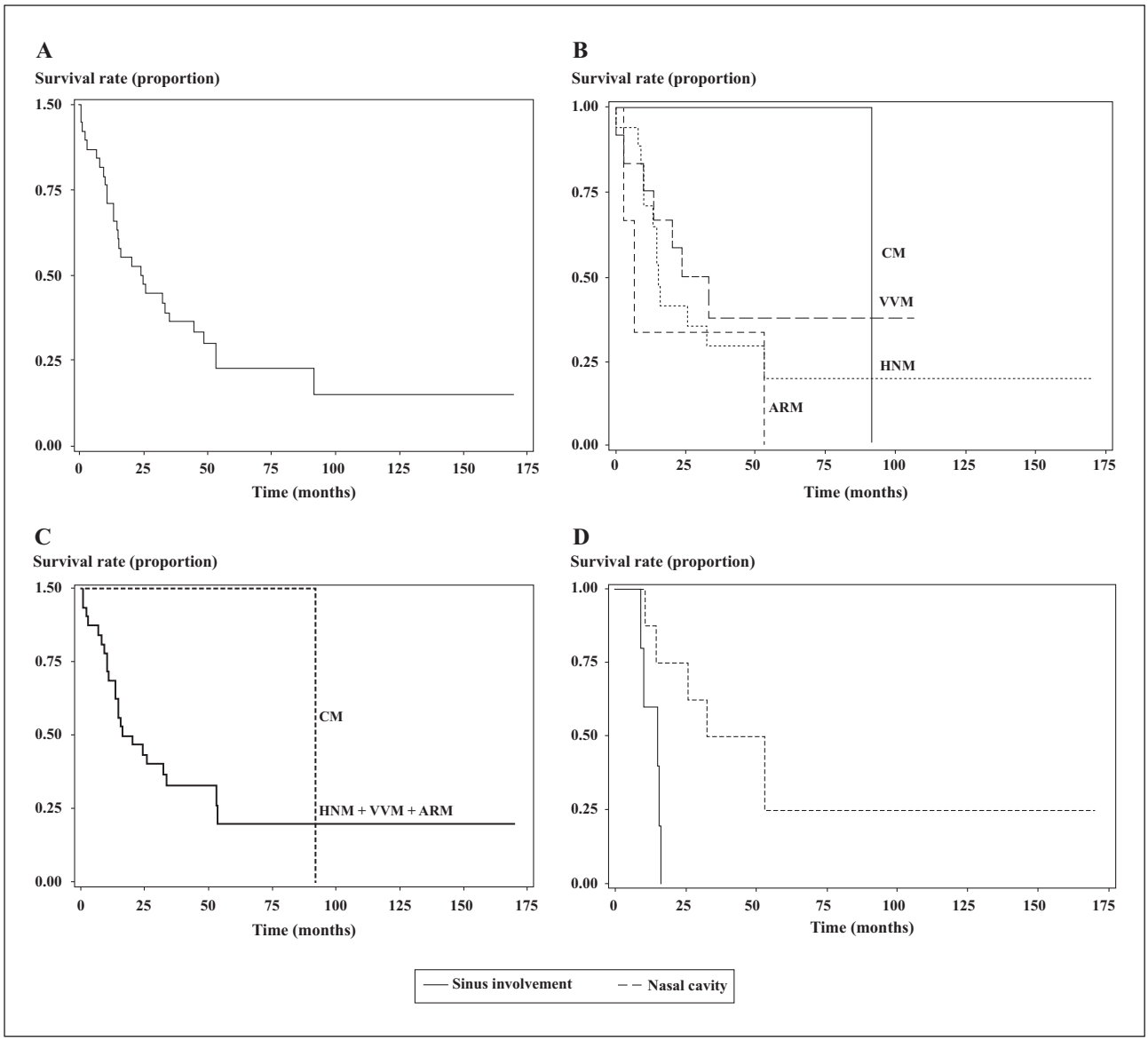

Figure 1. Melanoma-specific survival: **A)** of all cases of PMM; **B)** according to primary anatomical location (HNM, VVM, CM, and ARM; $p = 0.08$); **C)** according to location: conjunctiva compared to other anatomical sites (HNM, VVM and ARM; $p = 0.03$); and **D)** in patients with sinonasal melanomas according to sublocation: nasal cavity only *versus* sinus involvement ($p = 0.01$). PMM: primary mucosal melanoma; HNM: head and neck melanoma; VVM: vulvovaginal melanoma; CM: conjunctival melanoma; ARM: anorectal melanoma.

large tumour size and incomplete surgical resection (53%). In addition, some 70% of tumours with a known Breslow thickness were thicker than 4 mm, 47.9% were thicker than 8 mm, and very few were *in situ* tumours or tumours in radial growth phase, as described by Saida *et al*. [25]. Furthermore, 25.7% of patients had macroscopic nodal or visceral metastases at diagnosis. This predominance of very thick, large and/or metastatic tumours may explain why tumour size in the present study and disease extent both in the present study and previous studies [6, 15, 26] may supplant Breslow thickness as major prognostic indicators for PMM. Apart from its retrospective design, the main limitation of this study is the small sample size, due to the rarity of PMM. This prevented us from performing relevant prognostic analyses for some subgroups of PMM according to location. Previous studies found poorer outcomes in female patients with vaginal melanoma, compared to those with vulvar melanoma [10, 27, 28], while no difference in survival was consistently reported between anal and rectal melanoma [29], and oral *versus* sinosasal melanoma [26, 30], respectively. Our study was underpowered regarding investigation of possible differences according to these subgroups. Among sinonasal melanomas, however, we found a significantly better survival rate in patients with exclusive nasal involvement, compared to those with sinus involvement (*figure 1D*). Indeed, all five patients with tumours involving the sinus, including two cases with nasal involvement and three cases without, died within seven to 15 months of diagnosis. These data are concordant with other recent studies [31, 32].

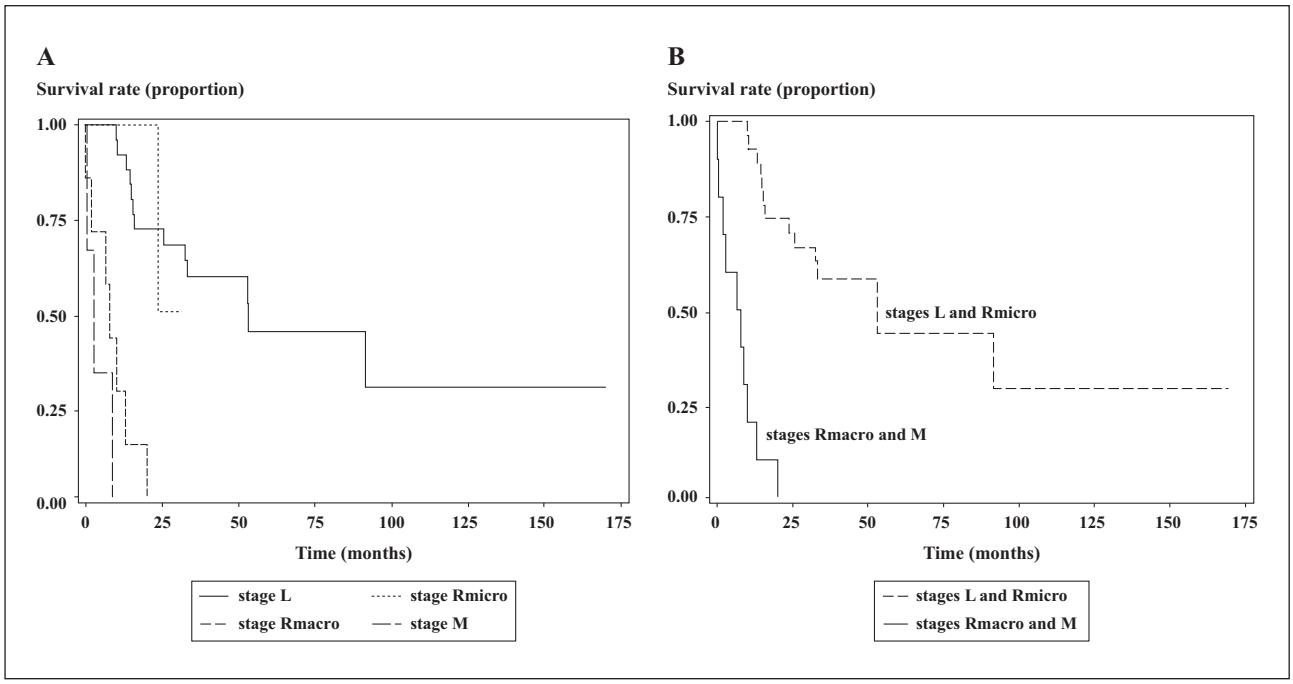

Figure 2. Melanoma-specific survival of all cases of primary mucosal melanoma: **A)** classified as L, Rmicro, Rmacro or M ($p < 0.0001$); **B)** classified as Stage L and Rmicro ($n = 29$) *versus* Stage Rmacro and M ($n = 10$) ($p < 0.0001$). L: local stage (*i.e.* primary tumour of any size without nodal or visceral dissemination); Rmicro: regional microscopic stage (*i.e.* any case with microscopic involvement identified by sentinel lymph node biopsy); Rmacro: regional macroscopic stage (*i.e.* any case with macroscopic nodal metastasis diagnosed clinically or by medical imaging); M: disseminated stage (*i.e.* any case with distant metastasis).

Considering the surgical management of ARM and VVM, many studies have suggested that radical surgery provides no survival benefit for patients, compared to conservative local excision, given that both methods lead to poor outcomes [33-36]. Surgical risks associated with radical excisions in these locations are high. It is noteworthy that seven patients in our study died without having developed distant metastases following major surgery or unresectable bulky disease.

Another limitation of the present study is the absence of genetic analyses of tumour samples. Previous studies, including whole-genome sequencing, reported that mucosal melanomas are characterized by a relatively low mutational burden [37, 38]. *BRAF* and *NRAS* mutations are much less frequent in PMM than in cutaneous melanomas, while *KIT* mutations are more frequent. The rate of *BRAF*, *NRAS* and *KIT* mutations in large cohorts of PMM have been recently evaluated at 6.4-13%, 8-13.6%, and 7-11.6%, respectively [6, 15, 39]. Recently, *TERT* promoter mutations were described in 8% of sinonasal melanomas [40, 41], and *GNAQ* or *GNA11* mutations were found to occur in 9.5% of PMM at various sites [42]. Other somatic mutations occasionally identified in PMM include PI3K-AKT signalling pathway mutations and *TP53* mutation [43, 44]. In view of the genetic evidence for the existence of distinct molecular pathways, subsets of PMM could be further defined based on their molecular genetic profiles.

This study confirms the rarity and very poor prognosis of PMM and identifies tumour size and nodal or visceral macrometastases at diagnosis as major adverse prognostic factors. Considering that most PMM are asymptomatic until a late stage and that these rare tumours are not amenable to early diagnosis, improving prognosis will require better genetic characterization, which will lead to specific targeted therapies. ■

Disclosure. *Funding: Robert Debré University Hospital, Reims, France. Conflicts of interest: none.*

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