

ORIGINAL RESEARCH

Acral lentiginous melanoma histotype predicts outcome in clinical stage I-II melanoma patients: an International multicenter study

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Background: In the American Joint Committee on Cancer (AJCC) classification, acral lentiginous melanoma (ALM) histotype ALM is not included as an independent prognostic factor; in small series its negative prognostic impact on disease-free survival (DFS) and overall survival (OS) has been linked to the greater Breslow thickness (BT).

Patients and methods: The study was carried out at four referral melanoma centers (three Italian and one Polish). Clinical consecutive patients with stage I-II melanoma, who were diagnosed, treated, and followed up between January 1998 and March 2018 in annotated specific databases were included.

Results: Overall, 6734 were evaluable, 4349 with superficial spreading melanoma (SSM), 2132 with nodular melanoma (NM), and 253 with ALM. At univariable analysis, a statistically significant worse DFS [hazard ratio (HR) 2.72, 95% confidence interval (CI) 2.24-3.30; $P < 0.001$] and OS (HR 2.67, 95% CI 2.15-3.32; $P < 0.001$) were found in patients with ALM compared with SSM. Similarly, the NM histotype was associated with a worse prognosis compared with the SSM histotype (DFS: HR 2.29, 95% CI 2.08-2.52; $P < 0.001$ and OS: HR 2.21, 95% CI 1.99-2.46; $P < 0.001$). At multivariable analysis, after adjusting for age, sex, BT, ulceration, and the sentinel lymph node status, a statistically significant worse DFS [adjusted HR (aHR); ALM versus SSM) 1.25, 95% CI 1.02-1.52; $P = 0.028$] was confirmed for patients with ALM. For patients with NM, instead, no impact of histology was found in terms of DFS [aHR (NM versus SSM) 1.04, 95% CI 0.93-1.15; $P = 0.513$] and OS [aHR (NM versus SSM) 0.96, 95% CI 0.86-1.08; $P = 0.548$].

Conclusions: ALM is associated with a worse long-term DFS. Our results could have important clinical implications for patients' stratification in future clinical trials and the incorporation of ALM histotype in the new AJCC classification as an independent prognostic factor.

Key words: melanoma, acral, disease-free survival, overall survival

INTRODUCTION

Cutaneous melanoma is a neoplasm derived from the melanocytes of the skin. It accounts for 1%-3% of all malignancies and all cancer deaths worldwide.¹ Unlike most solid tumors for which incidence has either decreased or stabilized, the worldwide incidence rate for cutaneous

melanoma is increasing much more rapidly than for any other malignancies.¹

The four major clinicopathological melanoma subtypes are superficial spreading melanoma (SSM), lentigo maligna melanoma (LMM), nodular melanoma (NM), and acral lentiginous melanoma (ALM). According to the most recent World Health Organization (WHO) classification, melanomas are divided into those etiologically related to sun exposure and those that are not, as determined by their mutational signatures, anatomic site, and epidemiology.^{2,3} Melanomas arising on the sun-exposed skin are further classified on the basis of the degree of dermal solar elastosis into low versus high cumulative sun damage melanomas.^{2,3}

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The prognostic impact of histopathology is unclear.^{4,5} Some studies have shown no significant role⁵ while in others, its impact was confined to thin melanomas.⁶ Finally, even in large cohorts in which the prognostic impact of melanoma histotype was assessed, some important prognostic factors, including the sentinel lymph node (SLN) status, were missing. Furthermore the follow-up was relatively short to draw firm conclusions.^{6,7}

Unlike SMM and NM, ALM (now defined acral melanoma according to WHO classification) accounts for ~2%-3% of all melanomas. The term ALM, introduced by Reed,^{8,9} refers to a clinical and histopathological entity of a melanoma subtype occurring in the glabrous acral skin, such as on the palms, soles, and nail apparatus. Several small case series of ALM have been reported; however, because this subtype of melanoma is rare, these studies have been limited by sample size.

Hence, a large study is needed to overcome the small sample size of previous studies and draw conclusions on prognostic value of ALM.

In this study, by interrogating independent prospectively collected databases, we provide robust data investigating the long-term independent impact of ALM histotype on disease-free survival (DFS) and overall survival (OS) of patients affected by early-stage melanoma.

PATIENTS AND METHODS

Eligible cases included patients with a diagnosis of SSM, NM, ALM, or LMM, without evidence of distant metastases, diagnosed, treated, and followed up prospectively in three Italian Melanoma Intergroup (IMI) Centers between 1998 and 2018 (Istituto Nazionale Tumori of Milan, Papa Giovanni XXIII Cancer Center Bergamo, Dermatologic Clinic of the University of Florence, Italy) and at the Maria Skłodowska-Curie National Research Institute of Oncology (MSCNRI), Warsaw, Poland, between 1998 and 2013. *In situ* melanomas were excluded.

By definition, ALM was diagnosed when the following features occurred in an acral primary cutaneous melanoma (PCM): the lentiginous pattern of proliferation of atypical melanocytes at the border of the tumor, with the possible upward migration of large nests to the stratum corneum, marked acanthosis, a broadened horny layer, and elongation of rete ridges. NM melanomas were defined as polypoid/exophytic or nonpolypoid tumors composed of a predominantly tumorigenic proliferation of atypical pigmented and/or amelanotic melanocytes. By convention, in NM the intraepidermal component at the lateral shoulder extended for less than three rete ridges beyond the dermal component.^{2,3} Randomly selected cases of NM and ALM were reviewed independently by two expert dermatopathologists (DM and AS-C) aimed at evaluating their interobserver concordance on hematoxylin–eosin-stained representative glass slides.

The clinical and pathological parameters extracted from the database included sex (female/male), age (continuous variable in years), date of diagnosis of the primary tumor,

ulceration (absent/present), Breslow thickness (BT; continuous variable in millimeter), histotype (SSM/NM/ALM), SLN status (negative/positive), and follow-up.

Approval to conduct the study was obtained from the local Ethical Committees of the participating centers.

Statistical methods

The aim of this analysis was to evaluate the prognostic value of the ALM histotype in patients diagnosed with PCM on DFS and OS.

DFS was defined as the time between diagnosis and disease relapse or death from any cause. OS was defined as the time interval between diagnosis and death from any cause. Patients who had not relapsed/died or died were censored at the date of the last follow-up visit or at 10 years from diagnosis, whichever comes first. Continuous variables were described using mean and standard deviation, the median with the first and third quartiles, and range, whereas categorical variables were described using frequencies and percentages. A chi-square test was carried out to compare the distributions of categorical variables. Then, *t*-test, analysis of variance, or Kruskal–Wallis test, as appropriate, were carried out to compare the distributions of continuous variables.

The effect of the histology on DFS and OS was evaluated using the univariable and multivariable Cox proportional hazard models stratified by center. All the multivariable models included demographical (age and sex) and clinical (BT, ulceration, and SLN status) prognostic characteristics. Results of the analysis were expressed as hazard ratios (HRs) and 95% confidence intervals (95% CIs). The proportionality of hazards for the histology was assessed by means of the Kolmogorov-type supremum test and evaluating the statistical significance of the interaction of covariates with time. In case of evidence of no proportionality of hazards, the Cox model including also the interaction with time was developed and HRs at 3 and 5 years were provided. The survival curves were estimated with the Kaplan–Meier (KM) method and compared using the log-rank test.

Given the length of follow-up, a non-negligible proportion of deaths could be not related to melanoma. Therefore a sensitivity analysis on OS was performed considering as event only deaths following the disease recurrence.

Statistical significance was set at $P < 0.05$ for a bilateral test. The analysis was carried out using SAS (Statistical Analysis System, SAS Institute, Version 9.4).

RESULTS

Between January 1998 and March 2018, 11317 consecutive patients were diagnosed with PCM in three IMI centers and one Polish center (Supplementary Figure S1, available at <https://doi.org/10.1016/j.esmooop.2022.100469>). Overall, 1576 patients were excluded because the histology was not SSM, NM, ALM, or LMM or was unknown and 26 patients due to the presence of metastasis at diagnosis. For 2424 patients the SLN status was unknown and for 81 patients with a positive SLN the lymphadenectomy was not

performed or was performed after the relapse. Therefore, these patients were excluded from the analysis to avoid potential bias. Moreover, among patients with LMM only 54 relapses and 55 deaths were observed; therefore we decided to focus the analysis on patients with SSM, ALM, or NM histology. Finally, 10 patients were excluded due to unavailability of information about relapse and death and 259 because one or more prognostic factors (age, sex, BT, ulceration) were missing. Therefore the total number of patients analyzed were 6734 (4349 with SSM, 2132 with NM, and 253 with ALM).

Demographic and clinical characteristics at diagnosis, according to country and melanoma histotype, are reported in [Supplementary Table S1](#), available at <https://doi.org/10.1016/j.esmooop.2022.100469> and [Table 1](#), respectively.

At a median follow-up of 109.3 months (interquartile range 64.2-120.0), relapse was reported for 650 patients (14.9%) with SSM, 729 patients (34.2%) with NM, and 92 patients (36.4%) with ALM. Moreover, 736 patients (16.9%) with SSM, 758 patients (35.6%) with NM, and 93 patients (36.8%) with ALM died. Relapse or death occurred in 932 patients (21.4%) with SSM, 934 patients (43.8%) with NM, and 116 patients (45.8%) with ALM.

[Figure 1A](#) shows the KM curves of DFS according to melanoma histotypes. [Table 2](#) reports the univariable and multivariable analyses of DFS.

At univariable analysis, a statistically significant worse DFS (HR 2.72, 95% CI 2.24-3.30; $P < 0.001$) was found in patients with ALMs compared with SSMs. Similarly, the

NM histotype was associated with a worse DFS compared with the SSM histotype (HR 2.29, 95% CI 2.08-2.52; $P < 0.001$).

At multivariable analysis, only for patients with ALMs a statistically significant worse DFS was confirmed [adjusted HR (aHR; ALM versus SSM) 1.25, 95% CI 1.02-1.52; $P = 0.028$]. No statistically significant interaction was found between the SLN status and the histotype.

Because evidence of nonproportional hazard was detected for the NM histology in the DFS analysis, aHRs of these variables at 3 and 5 years were calculated. The HR for NMs compared with SMMs was 1.02 (95% CI 0.91-1.14) and 0.90 (95% CI 0.77-1.04) at 3 and 5 years, respectively.

[Figure 1B](#) shows the KM curves of OS according to melanoma histotypes. [Table 3](#) reports the univariable and multivariable analyses of OS.

At univariable analysis, a statistically significant worse OS compared with SSMs was found both in patients with ALMs (HR 2.67, 95% CI 2.15-3.32; $P < 0.001$) and in patients with NM histotype (HR 2.21, 95% CI 1.99-2.46; $P < 0.001$). At multivariable analysis, no impact of histology was detected in terms of OS.

Considering only deaths occurring after relapse, at univariable and multivariable analyses a statistically significant worse survival was found for patients with ALM (aHR 1.38, 95% CI 1.06-1.80; $P = 0.016$) but not for and patients with NM (aHR 1.01, 95% CI 0.88-1.17; $P = 0.857$), compared with SSM. Details are reported in [Table 4](#). [Figure 1C](#) shows the KM curves of OS according to melanoma histotypes.

Table 1. Demographics and clinical characteristics				
Characteristics	Superficial spreading melanoma (N = 4349)	Nodular melanoma (N = 2132)	Acral lentiginous melanoma (N = 253)	Overall P value
Center				—
Milan, Italy	3339 (76.8)	1245 (58.4)	187 (73.9)	
Warsaw, Poland	593 (13.6)	803 (37.7)	51 (20.2)	
Bergamo, Italy	349 (8.0)	59 (2.8)	12 (4.7)	
Florence, Italy	68 (1.6)	25 (1.2)	3 (1.2)	
Age at surgery		<0.001 ^a	<0.001 ^a	<0.001
Mean (SD)	52.7 (15.2)	55.9 (15.3)	62.7 (13.8)	
Median (Q1-Q3)	52.3 (41.3-64.7)	56.6 (45.1-68.0)	64.0 (53.0-74.1)	
Range	16.0-93.3	13.3-92.8	19.1-93.0	
Sex		0.077 ^a	0.024 ^a	0.009
Male	2191 (50.4)	1124 (52.7)	109 (43.1)	
Female	2158 (49.6)	1008 (47.3)	144 (56.9)	
Breslow thickness		<0.001 ^a	<0.001 ^a	<0.001
Mean (SD)	1.9 (1.9)	4.3 (5.5)	4.3 (6.3)	
Median (Q1-Q3)	1.3 (1.0-2.2)	3.0 (2.0-5.0)	2.8 (1.5-5.0)	
Range	0.1-30.0	0.2-156.0	0.1-75.0	
Breslow thickness		<0.001 ^a	<0.001 ^a	<0.001
Up to 1 mm	1352 (31.1)	86 (4.0)	35 (13.8)	
1.01-2.00 mm	1807 (41.5)	481 (22.6)	60 (23.7)	
2.01-4.00 mm	871 (20.0)	844 (39.6)	77 (30.4)	
>4.00 mm	319 (7.3)	721 (33.8)	81 (32.0)	
Ulceration		<0.001 ^a	<0.001 ^a	<0.001
Absent	3250 (74.7)	982 (46.1)	119 (47.0)	
Present	1099 (25.3)	1150 (53.9)	134 (53.0)	
Sentinel lymph node status		<0.001 ^a	<0.001 ^a	<0.001
Negative	3493 (80.3)	1455 (68.2)	171 (67.6)	
Positive	856 (19.7)	677 (31.8)	82 (32.4)	

Q1-Q3, first-third quartile; SD, standard deviation.

^aIn case of an overall significant P value, the comparisons between each histology with the superficial spreading histology were performed.

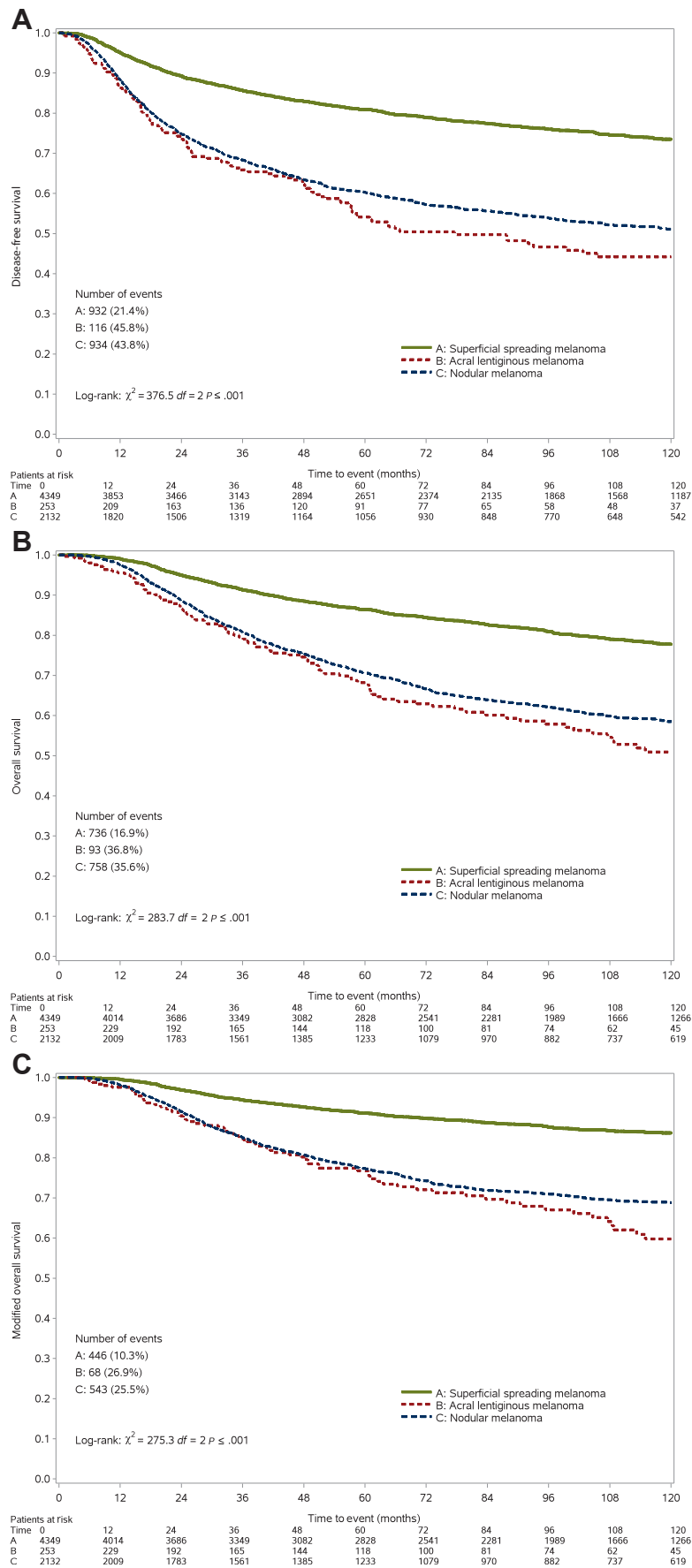


Figure 1. Kaplan–Meier curves, according to histology, of (A) disease-free survival, (B) overall survival, and (C) overall survival considering death after relapse only (sensitivity analysis).

	Univariable models		Multivariable model	
	HR (95% CI)	P value	HR (95% CI)	P value
Histology (reference: superficial spreading melanoma)				
Acral lentiginous melanoma	2.72 (2.24-3.30)	<0.001	1.25 (1.02-1.52)	0.028
Nodular melanoma	2.29 (2.08-2.52)	<0.001	1.04 (0.93-1.15)	0.513
Breslow thickness (reference: up to 1 mm)		<0.001		
1.01-2.00 mm	2.45 (1.99-3.00)	<0.001	1.99 (1.61-2.44)	<0.001
2.01-4.00 mm	6.63 (5.45-8.07)	<0.001	3.71 (3.01-4.57)	<0.001
>4.00 mm	11.78 (9.65-14.37)	<0.001	5.51 (4.42-6.86)	<0.001
Age at surgery (1-year increase)	1.03 (1.03-1.04)	<0.001	1.02 (1.02-1.03)	<0.001
Female sex	0.66 (0.60-0.72)	<0.001	0.77 (0.71-0.85)	<0.001
Ulceration	3.30 (3.02-3.61)	<0.001	1.67 (1.52-1.85)	<0.001
Positive sentinel lymph node (reference: negative)	2.82 (2.58-3.09)	<0.001	1.89 (1.72-2.08)	<0.001

95% CI, 95% confidence interval; HR, hazard ratio.

Supplementary Figure S2, available at <https://doi.org/10.1016/j.esmoop.2022.100469>, reports the results of the subgroup analyses on DFS according to BT and ulceration. A statistically significant shorter DFS, compared with patients with SSMs, was detected for patients with NMs with a BT up to 1 mm (aHR 2.67, 95% CI 1.59-4.51; $P < 0.001$) or ranging between 1.01 and 2.00 mm (aHR 1.31, 95% CI 1.06-1.63; $P = 0.014$). Supplementary Figure S3, available at <https://doi.org/10.1016/j.esmoop.2022.100469> reports the results of the subgroup analyses on OS according to BT and ulceration. A statistically significant shorter OS, compared with patients with SSMs, was detected for patients with NMs with a BT up to 1 mm (aHR 2.44, 95% CI 1.34-4.44; $P = 0.004$), whereas a longer OS was detected in patients with NMs with a BT ranging between 2.01 and 4.00 mm (aHR 0.81, 95% CI 0.68-0.97; $P = 0.019$).

DISCUSSION

In this study, we have shown that in early-stage PCMs, the ALM histotype is associated with a worse long-term DFS compared with the SSM histotype, independently from the SLN status and the other well-known prognostic factors. To our knowledge, this is one of the largest studies evaluating the prognostic role of ALM histotype with long-term follow-up. All patients were diagnosed, treated in referral centers,

with strict adherence to the guidelines applicable at the time of melanoma treatment.

According to the WHO and American Joint Committee on Cancer (AJCC) classification, melanoma histotype has limited independent prognostic significance. However, the pathological subtype of melanoma may be included in the synoptic pathological report of PCM.^{2,7} The histologic subtype is recommended as a noncore (optional) element in the pathology report by International Collaboration on Cancer Reporting guidelines,¹⁰ while the desmoplastic subtype is considered as a core element.¹⁰ Indeed, there is some evidence to support that PCMs with desmoplastic histologic subtype have a lower risk of nodal and distant metastases and increased response to immunotherapy.¹¹

Our results build on the important clinical and translational background.

It is well known that histopathologic subtypes are also associated with different profiles of driver mutations and different patterns of local growth and metastatization.¹²⁻¹⁴ Furthermore, there is some preliminary evidence that melanoma histotype may respond differently to systemic target and immunotherapies. In a recent study, NM remained an independent risk factor for death upon treatment with BRAF inhibitors.¹³ Interestingly, in the Check-Mate 238 trial, there was no statistical, clinical benefit of using nivolumab over ipilimumab for patients with ALM in comparison with other histotypes.¹⁵ Taken together, this

	Univariable models		Multivariable model	
	HR (95% CI)	P value	HR (95% CI)	P value
Histology (reference: superficial spreading melanoma)				
Acral lentiginous melanoma	2.67 (2.15-3.32)	<0.001	1.15 (0.92-1.44)	0.206
Nodular melanoma	2.21 (1.99-2.46)	<0.001	0.96 (0.86-1.08)	0.548
Breslow thickness (reference: up to 1 mm)		<0.001		
1.01-2.00 mm	2.34 (1.85-2.95)	<0.001	1.83 (1.45-2.31)	<0.001
2.01-4.00 mm	6.29 (5.04-7.86)	<0.001	3.28 (2.59-4.15)	<0.001
>4.00 mm	11.24 (8.98-14.06)	<0.001	4.83 (3.77-6.18)	<0.001
Age at surgery (1-year increase)	1.04 (1.03-1.04)	<0.001	1.03 (1.03-1.03)	<0.001
Female sex	0.58 (0.53-0.65)	<0.001	0.68 (0.61-0.75)	<0.001
Ulceration	3.57 (3.22-3.95)	<0.001	1.88 (1.68-2.10)	<0.001
Positive sentinel lymph node (reference: negative)	2.89 (2.61-3.19)	<0.001	1.96 (1.77-2.18)	<0.001

95% CI, 95% confidence interval; HR, hazard ratio.

Table 4. Effect of histology on modified overall survival (sensitivity analysis). Univariable and multivariable Cox proportional hazards models stratified by center

	Univariable models		Multivariable model	
	HR (95% CI)	P value	HR (95% CI)	P value
Histology (reference: superficial spreading melanoma)				
Acral lentiginous melanoma	3.18 (2.46-4.10)	<0.001	1.38 (1.06-1.80)	0.0160
Nodular melanoma	2.48 (2.17-2.83)	<0.001	1.01 (0.88-1.17)	0.857
Breslow thickness (reference: up to 1 mm)				
1.01-2.00 mm	3.50 (2.44-5.02)	<0.001	2.82 (1.96-4.05)	<0.001
2.01-4.00 mm	10.97 (7.77-15.49)	<0.001	6.10 (4.26-8.73)	<0.001
>4.00 mm	20.06 (14.18-28.36)	<0.001	9.29 (6.43-13.44)	<0.001
Age at surgery (1-year increase)	1.03 (1.02-1.03)	<0.001	1.02 (1.01-1.02)	<0.001
Female sex	0.66 (0.58-0.75)	<0.001	0.77 (0.68-0.87)	<0.001
Ulceration	3.71 (3.27-4.21)	<0.001	1.79 (1.56-2.06)	<0.001
Positive sentinel lymph node (reference: negative)	3.25 (2.87-3.67)	<0.001	2.04 (1.79-2.13)	<0.001

Modified overall survival was defined as overall survival considering as event deaths following the disease recurrence only.
95% CI, 95% confidence interval; HR, hazard ratio.

accumulated evidence suggests that histotypes may harbor diverse clinical behavior upon systemic treatment.

ALMs are characterized by peculiar immune features in the tumor microenvironment. ALMs show increased numbers of M2 macrophages in both peritumoral and intratumoral compartment compared with SSM and this is significantly associated with poor prognostic features.¹⁶ Furthermore ALMs have been associated with lower levels of tumor-infiltrating lymphocytes (TILs) compared with other melanoma histotypes.¹⁷ Interestingly, an association between lower levels of the tumor-suppressor proteins and lower density of CD3+ and CD8+ TILs have been reported, suggesting a probable relationship between the tumor behavior and TIL immune response in ALMs.¹⁷ Taken together, these observations suggest that ALMs show an immune-suppressive microenvironment that in turn correlates with poor prognostic features. Our study extends these translational results by providing robust clinical evidence that ALM is an independent prognostic feature. The ALM subtype was also suggested to have independent negative prognostic value in some studies, mainly from the Asian population, but limited data are available on the Western population.¹⁸⁻²¹ Our study is in agreement and extends the results of a recent small study evaluating the impact of ALM histotype in patients with T1 stage.²²

Our results showing lack of prognostic impact of NM are in agreement with some recent studies⁵; and are in disagreement with other recent studies that suggested NM histotype to be associated with higher mortality in the Surveillance, Epidemiology, and End Results (SEER) Registry study of stage I-III melanomas,¹³ and in the Australian population-based registry.^{23,24}

Recently, Dessinioti et al.⁶ evaluated in a multicenter study the impact of NM compared with SSM subtypes in thin melanomas, concluding that NM was associated with aggressive pathological characteristics and a higher risk of melanoma-specific death. In this study, NM had a higher rate of ulceration and regression. However, in multivariate analysis, authors adjusted for sex, age, BT, and ulceration, but did not include SLN status (as these data were not available), making these results difficult to interpret in

terms of current staging requirements.⁶ Moreover, the authors did not perform any pathological review that might potentially lead to misclassification bias, and the median survival follow-up time was limited.

There are several strengths of our study, including (i) a very large cohort of patients to address the prognostic impact of melanoma histotype; (ii) data collected into specific databases with information regarding demographics, diagnosis, surgical procedures, histopathological characteristics; (iii) the availability of long-term follow-up, which allowed to investigate mature data on DFS and OS. Moreover, the study was run by IMI and Polish centers with the expertise and homogeneous melanoma management; and (iv) randomly selected cases of NM and ALM were reviewed independently by two expert dermatopathologists and concordance was 100%.

We are also aware of some limitations, including our analysis's retrospective nature, which cannot definitively exclude patient selection bias. In addition, although inter-observer reproducibility on NM was assessed in randomly selected cases, the histopathological review was not centralized, even though the cases were from major referral melanoma centers using agreed definitions of melanoma histotypes. Factors that could affect outcomes, such as molecular characteristics and additional treatments, were not studied. Furthermore, melanoma-specific survival could not be evaluated because we could not exclude other causes of death considering the median length of follow-up close to 10 years. Finally, because TILs were not reported in all centers, our analysis was not adjusted for this covariate.

In conclusion, our results may have important clinical implications for the stratification of patients in future clinical trials and for the incorporation ALM histotype in the new AJCC classification as an independent prognostic factor. We suggest that this melanoma histotype should be included as a core element in the pathology report.

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DISCLOSURE

The authors have no conflicts of interest to declare.

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