The prognostic value of tumor mitotic rate in children and adolescents with cutaneous melanoma: a retrospective cohort study

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The prognostic value of tumor mitotic rate in children and adolescents with cutaneous melanoma: A retrospective cohort study

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Background: Mitotic rate is a strong predictor of outcome in adult patients with primary cutaneous melanoma, but for children and adolescent patients this is unknown.

Objective: We sought to assess the prognostic value of primary tumor mitotic rate in children and adolescents with primary melanoma.

Methods: This was a cohort study of 156 patients who were <20 years of age and who had clinically localized cutaneous melanoma. Patients <12 years of age were classified as children and those 12 to 19 years of age as adolescents. Clinicopathologic and outcome data were collected. Recurrence-free and melanoma-specific survival were calculated. Univariable and multivariable analyses were performed using Cox proportional hazard models.

Results: Thirteen of 156 patients (8%) were children. The mitotic rate was ≥1/mm^2 in 104 patients (67%) and correlated with increasing Breslow thickness. A positive sentinel node was found in 23 of 61 patients (38%) in whom a sentinel lymph node biopsy specimen was obtained. The median follow-up was 61 months. Five-year melanoma-specific and recurrence-free survival rates were 91% and 84%, respectively. Mitotic rate was a stronger predictor of outcome than tumor thickness and was the only factor independently associated with recurrence-free survival.

Limitations: This research was conducted at a single institution and the sample size was small.

Conclusion: Mitotic rate is an independent predictor of recurrence-free survival in children and adolescents with clinically localized melanoma. (J Am Acad Dermatol 2020;82:910-9.)

Key words: adolescent; children; dermatopathology; melanoma; mitosis; mitotic rate; oncology; pathology; pediatric; prognosis; recurrence.

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This study was approved by the Melanoma Institute Australia Research Committee and the Sydney Local Health District Ethics Review Committee (Protocol No. X15-0454 and HREC/11/RPAH/444).

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Melanoma is the most common skin cancer in children and adolescents.[1] Still, <1% of all melanomas occur in patients <20 years of age.[2] Because of its rarity, the published literature on melanoma in children and adolescents is sparse and treatment is primarily based on adult guidelines.

Tumor mitotic rate is one of the strongest predictors of survival in adults with clinically localized primary cutaneous melanoma.[3-7] Evidence suggests that the mitotic rate is lower in melanomas occurring in children and adolescents than in other age groups.[8] Few studies have assessed the prognostic value of mitotic rate in childhood and adolescent melanoma.[8-12] Most reports including >100 children and adolescents with melanoma did not evaluate the effect of mitotic rate on prognosis or had many missing values.[2,13-20]

CAPSULE SUMMARY

- Tumor mitotic rate is one of the strongest independent predictors of outcome in adult patients with melanoma.
- In children and adolescents with melanoma, mitotic rate is also an important predictor of survival.
- Tumor mitotic rate should be assessed and reported in all childhood and adolescent cases of melanoma to aid prognostic stratification and treatment planning.

The purpose of this study was to assess the prognostic significance of mitotic rate in clinically localized primary cutaneous melanoma in children and adolescents. Secondary aims were to report the clinicopathologic features in a large cohort of melanoma patients <20 years of age, to compare children with adolescent patients, and to assess the relationship between mitotic rate and tumor thickness in this age group.

METHODS

Patients

The prospectively collected database of Melanoma Institute Australia (MIA) was queried for this retrospective cohort study. Between 1993 and 2013, 259 melanoma patients <20 years of age were managed at MIA. To be included in the current study, a diagnosis of primary cutaneous melanoma had to have been confirmed by ≥1 MIA-affiliated pathologists. Borderline lesions, such as atypical Spitz nevi/tumors, melanocytomas, or atypical melanocytic proliferations, were excluded after pathology review (n = 27). Patients were also excluded if they had melanoma in situ (n = 34), a metastasis from an unknown primary melanoma (n = 5), multiple primary melanomas (n = 5), mucosal melanoma (n = 1), macrometastasis at diagnosis (n = 4), or if an MIA-affiliated pathologist could not review the pathology slides (n = 27). One hundred fifty-six patients fulfilled the inclusion criteria. Institutional review board approval was obtained (Sydney South West Area Health Service institutional ethics review committee protocol no. X15-0454).

Data collection

Patients who present to MIA for management of their melanoma after a diagnosis has been established have their pathology slides reviewed by ≥1 MIA-affiliated pathologists at the Royal Prince Alfred Hospital in Sydney, Australia. The primary tumor pathologic characteristics are assessed and recorded in a second pathology report (the "MIA pathology report") and the histopathology slides are returned to the source pathology laboratory. The data used in this study were extracted from MIA pathology reports. In cases with missing data and when the histopathology slides were still available, the cases were rereviewed any missing data were recorded.

Data on demographics, primary tumor characteristics, sentinel node (SN) status, recurrence, treatment, and follow-up were obtained. Patients were stratified by age into 2 groups: <12 years of age (children) and 12 to 19 years of age (adolescents). Twelve years of age was selected to represent the onset of puberty.[21]

Mitotic rate

Tumor mitotic rate was measured according to the recommendations of the 1982 International Pathology Workshop.[22] Mitoses were recognized by the presence of extensions of chromatin extending from a condensed chromatin mass. The number of mitoses was counted in a 1-mm^2 area (approximately 5 high power fields). The count started in the dermal area of the tumor with the greatest density of mitoses (the "hot spot") and continued in immediately adjacent, nonoverlapping fields.[22,23]

Statistical analysis

Baseline characteristics were summarized using median (interquartile range) for continuous variables and proportions for categorical variables. Characteristics of childhood and adolescent patients were compared using the Pearson χ^2 or Fisher exact test for categorical features and the Mann–Whitney U test for continuous variables. Melanoma-specific

Abbreviations used:

CI: confidence interval
HR: hazard ratio
MIA: Melanoma Institute Australia
MSS: melanoma-specific survival
RFS: recurrence-free survival
SN: sentinel node
SNB: sentinel node biopsy

survival (MSS) was calculated as the time from initial diagnosis until melanoma-related death. Patients who died from nonmelanoma causes or those still alive at last follow-up were censored. Recurrence-free survival (RFS) was defined as the time from diagnosis until recurrence or death. Censoring occurred at the end of follow-up. Univariable and multivariable analyses using Cox proportional hazard models were used to assess the prognostic value of covariates for RFS and MSS. Mitotic rate was the variable of interest in this study. Other known prognostic factors in adult melanoma, such as gender, age, primary tumor site, Breslow thickness, ulceration, and SN status were investigated in a univariable analysis.[5,8,24,25] Given the number of patients who developed recurrence (n = 28), only the 2 covariates with $P < .20$ from the univariable analysis and with <10% missing values were included in the multivariable model. The proportional hazards assumption was checked for the included variables.

P values were 2-sided and $P < .05$ was considered statistically significant. Statistical analyses were performed with SPSS software (version 25; IBM SPSS, Chicago, IL).

RESULTS

Patient and tumor characteristics

Baseline characteristics of the 156 patients are shown in Table I. The median age was 17.5 years (range 1-19 years). Thirteen patients (8%) were children at the time of diagnosis, while 143 (92%) were adolescents. Melanomas were most often thin (median Breslow thickness 1.0 mm), nonulcerated (65%), and located on the trunk (34%). The mitotic rate was ≥1/mm^2 in 104 patients (67%) and correlated with increasing Breslow thickness (Fig 1).

Sentinel node biopsy (SNB) specimens were obtained in 61 patients, with 23 (38%) having a positive SN. Of the 77 patients with tumors >1 mm thick, 48 (62%) underwent SNB. Nineteen SN-positive patients (83%) underwent completion lymph node dissection. Additional nodal metastases were found in 4 of these patients (21%). None of the 4 SN-positive patients who did not have completion lymph node dissection developed a recurrence.

Childhood versus adolescent patients

Substantial differences in characteristics were observed between the childhood and adolescent patients (Table I). Childhood melanomas (n = 13) were thicker (median 2.7 mm vs 1.0 mm; $P = .002$) and were more often located in the head and neck region (n = 5; 38%); adolescent melanomas (n = 143) were most frequently located on the trunk (n = 51; 36%). Melanoma subtype was also different between the 2 groups, with Spitzoid melanoma (n = 8; 62%) being the most common subtype in children and superficial spreading melanoma (n = 59; 41%) the most common in adolescent patients ($P = .007$). Ulceration (n = 4 [31%] in children vs n = 22 [15%] in adolescents; $P = .12$) and mitotic rate ≥1 (n = 10 [77%] in children vs n = 94 [66%] in adolescents; $P = .15$) were not significantly different. There was no significant difference ($P = .26$) in the frequency with which SNB was performed between children (n = 7; 54%) and adolescent patients (n = 54; 38%). Prepubertal patients had more often a positive SN than adolescent patients but this difference was not statistically significant (n = 5 [71%] vs n = 18 [33%]; $P = .09$).

Recurrence and survival

The median follow-up time was 61 months (interquartile range 10-111 months). Melanoma recurrence occurred in 28 patients (18%), and 16 patients (10%) died. Regional lymph nodes were the most common site of first recurrence (19 patients), while 5 patients had their first recurrence at a distant site. All patients whose first recurrence was in a regional node had a negative SN. The time between diagnosis of the primary melanoma and first recurrence ranged from 3 months to 13 years. Five patients (31%) had a recurrence after >5 years. MSS at 5 years was 91% (95% confidence interval [CI] 86-96%) and 10-year MSS was 88% (95% CI 81-95%). Five-year RFS was 84% (95% CI 77-90%) and 10-year RFS was 77% (95% CI 67-86%). Table II shows the characteristics of the 16 patients who died. One patient was 10 years old when her melanoma was diagnosed, while the other patients were adolescents. MSS and RFS were not significantly different between the 2 age groups ($P = .83$ and $P = .54$, respectively). Mitoses were present in the primary melanomas of 14 patients (88%) and 2 patients (13%) had melanomas with a Breslow thickness <1 mm. Ten patients received chemotherapy, while 3 patients received targeted therapy or immunotherapy.

Table I. Clinicopathologic characteristics

Characteristic	All patients (n = 156)	Childhood patients (n = 13)	Adolescent patients (n = 143)	*P* value*
Gender, n (%)				
Male	82 (53)	4 (31)	78 (55)	.15
Female	74 (47)	9 (69)	65 (45)	
Primary tumor site, n (%)				
Head and neck	37 (24)	5 (38)	32 (22)	.30
Upper limb	35 (22)	4 (31)	31 (22)	
Lower limb	31 (20)	2 (15)	29 (20)	
Trunk	53 (34)	2 (15)	51 (36)	
Breslow thickness, n (%)				
0-1 mm	79 (51)	3 (23)	76 (53)	.003
1.01-2 mm	41 (26)	2 (15)	39 (27)	
2.01-4 mm	25 (16)	4 (31)	21 (15)	
>4 mm	11 (7)	4 (31)	7 (5)	
Median (interquartile range)	1.0 (1.3)	2.7 (3.8)	1.0 (1.1)	.002
Mitotic rate (per mm^2), n (%)				
<1	43 (28)	2 (15)	41 (29)	.51
≥1	104 (67)	10 (77)	94 (66)	
Missing	9 (6)	1 (8)	8 (6)	
Median (interquartile range)	2 (5)	3 (5)	2 (4)	.15
Ulceration, n (%)				
Absent	102 (65)	6 (46)	96 (67)	.12
Present	26 (17)	4 (31)	22 (15)	
Missing	28 (18)	3 (23)	25 (17)	
Tumor type, n (%)				
Superficial spreading melanoma	61 (39)	2 (15)	59 (41)	.007
Nodular melanoma	23 (15)	2 (15)	21 (15)	
Spitzoid melanoma	29 (19)	8 (62)	21 (15)	
Other	2 (1)	0 (0)	2 (1)	
Missing	41 (26)	1 (8)	40 (28)	
Clark level, n (%)				
II	41 (26)	3 (23)	38 (27)	.001
III	49 (31)	0 (0)	49 (34)	
IV	61 (39)	8 (62)	53 (37)	
V	3 (2)	2 (15)	1 (1)	
Missing	2 (1)	0 (0)	2 (1)	
Sentinel node biopsy, n (%)				
Performed	61 (39)	7 (54)	54 (38)	.26
Not performed	95 (61)	6 (46)	89 (62)	
Sentinel node status, n (%)				
Negative	38 (62)	2 (29)	36 (67)	.09
Positive	23 (38)	5 (71)	18 (33)	
Total no. of sentinel nodes, median (interquartile range)	3 (3)	1 (2)	3 (2)	.05
Recurrence, n (%)				
Yes	28 (18)	1 (8)	28 (20)	.46
No	128 (82)	12 (92)	115 (80)	
Site of first recurrence, n (%)				
Local	1 (4)	1 (100)	0	.04
In-transit	3 (11)	0 (0)	3 (11)	
Regional nodal	19 (68)	0 (0)	19 (70)	
Distant	5 (18)	0 (0)	5 (19)	
Last follow-up status, n (%)				
No evidence of disease	135 (87)	12 (92)	123 (86)	1.0
Alive with disease	2 (1)	0 (0)	2 (1)	
Died from disease	16 (10)	1 (8)	15 (10)	
Died from unknown cause	2 (1)	0 (0)	2 (1)	
Missing	1 (1)	0 (0)	1 (1)	

*Comparison of children and adolescent patients.

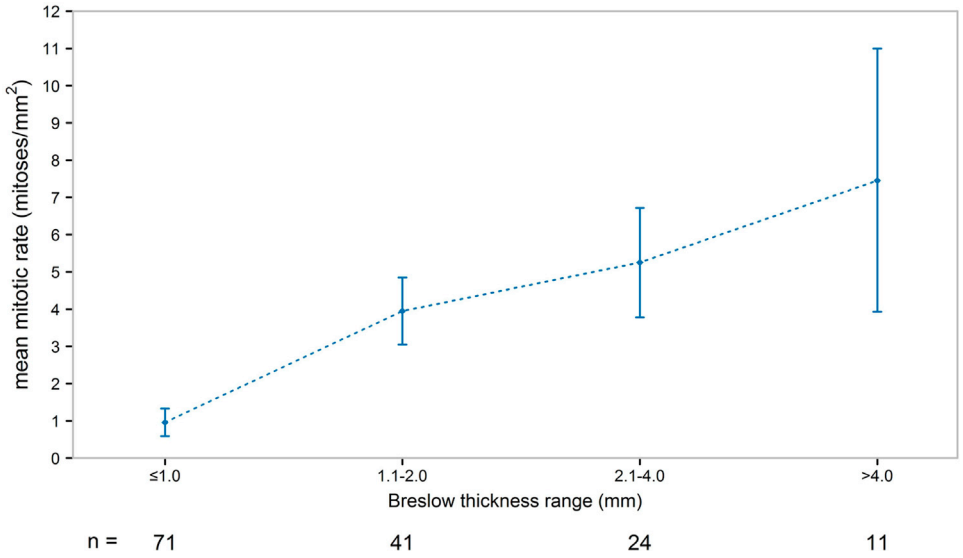

Fig 1. Mitotic rates versus Breslow thickness of primary melanomas.

Prognostic factors

On univariable analysis, Breslow thickness (P = .001), mitotic rate (P < .001), and melanoma subtype (P = .04) were found to be significantly associated with RFS. Gender, age, ulceration, primary tumor site, and SN status were not significantly associated with RFS. Figure 2 shows the RFS curves according to mitotic rate. On multivariable analysis including mitotic rate and Breslow thickness, mitotic rate correlated independently with RFS (hazard ratio = 1.2 [95% CI 1.1-1.3]), while Breslow thickness did not (HR = 1.1 [95% CI 0.9-1.2]). The univariable analysis indicated a significantly increased risk of melanoma-related death with increasing mitotic rate (P = .001). The other covariates were not significantly associated with MSS (Table III). Multivariable analysis could not be performed for MSS because of an insufficient number of events (16 melanoma-related deaths). Supplemental Table I (available online at DOI 10.17632/s7f9jsz9yj.1) shows the univariable and multivariable analysis of RFS and MSS of adolescents.

DISCUSSION

This single institution cohort study shows that tumor mitotic rate is the most important independent prognostic factor for RFS in children and adolescents with clinically localized melanoma, with a marginally stronger influence than tumor thickness. Having accurate information about the mitotic rate of the primary melanoma could improve prognostic stratification and treatment planning for individual patients in these age groups. It is important that this parameter is evaluated and recorded in all melanoma pathology reports.

In adults, the prognostic importance of mitotic rate has been demonstrated in numerous large, independent studies.[3-7] Although mitotic rate was an essential part of the 7th edition of the American Joint Committee on Cancer melanoma staging system, it has been scarcely studied in childhood and adolescent melanoma.[25] The rarity of melanoma in these patients, with an annual incidence rate of around 5 per million individuals, is probably one of the main reasons for the lack of studies.[26] Larger childhood and adolescent melanoma studies generally use data from the National Cancer Database or the Surveillance, Epidemiology, and End Results database.[2,13,15] Although valuable, these databases have several limitations. For instance, central pathology review is lacking, recurrence rates are not available, and details of key tumor characteristics such as Breslow thickness, ulceration and mitotic rate are frequently necessary.

Breslow thickness is the strongest prognostic feature in primary cutaneous melanoma in adult patients.[27] Interestingly, Breslow thickness was not a significant predictor for melanoma-specific survival in our study of childhood and adolescent patients. A similar finding was also reported in a study based on the National Cancer Database.[15] Another large multicenter study showed that primary tumor site and gender were independent prognostic factors for MSS, while mitotic rate and Breslow thickness were not.[8] However, 2 previous studies did show that Breslow thickness was an independent predictor of recurrence.[12,28]

Table II. Characteristics of patients who died of melanoma

Patient	Age, y	Gender	Site	Tumor type	Breslow thickness, mm	Mitotic rate, per mm^2	Ulceration	SNB	CLND	Site of first recurrence	Time until recurrence, months	Time between recurrence and death, months	Treatment after recurrence
1	17	M	Lower limb	NM	2.7	5	Absent	Positive	Negative	In transit	145	40	Isolated limb infusion, radiotherapy, local surgery, neurosurgery, and chemotherapy
2	18	M	Upper limb	SSM	1.6	14	Absent	Positive	Negative	Distant	17	4	Whole brain radiotherapy and chemotherapy
3	16	M	Trunk	NM	4.2	13	Present	Positive	Positive (1 node)	In transit	5	14	Local surgery, radiotherapy, and chemotherapy
4	19	M	Trunk	Unknown	1.5	4	Absent	Positive	Negative	Distant	102	16	Radiotherapy, targeted therapy (dabrafenib), and immunotherapy (ipilimumab)
5	19	F	Head and neck	SSM	1.0	1	Absent	Negative	NA	Regional node	8	4	Neck dissection, adjuvant radiotherapy, and chemotherapy
6	15	F	Lower limb	Spitzoid	1.0	Unknown	Unknown	Not performed	NA	Regional node	130	35	Inguinal lymph node dissection, radiotherapy, immunotherapy (ipilimumab), and targeted therapy (dabrafenib)
7	16	M	Trunk	NM	1.6	5	Present	Not performed	NA	Regional node	26	24	Axillary lymph node dissection and chemotherapy
8	18	F	Lower limb	NM	2.4	7	Absent	Not performed	NA	Regional node	17	20	Inguinal lymph node dissection, local surgery, chemotherapy, and targeted therapy
9	18	M	Upper limb	NM	3.3	13	Present	Not performed	NA	Regional node	8	13	Axillary lymph node dissection, local surgery, radiotherapy, and chemotherapy

Continued

Table II. Cont'd

Patient	Age, y	Gender	Site	Tumor type	Breslow thickness, mm	Mitotic rate, per mm^2	Ulceration	SNB	CLND	Site of first recurrence	Time until recurrence, months	Time between recurrence and death, months	Treatment after recurrence
10	19	M	Trunk	NM	4.0	10	Present	Not performed	NA	Regional node	5	31	Axillary lymph node dissection and adjuvant radiotherapy
11	19	M	Upper limb	SSM	1.1	1	Present	Not performed	NA	Regional node	107	14	Axillary lymph node dissection, adjuvant radiotherapy, and chemotherapy
12	19	F	Trunk	SSM	1.7	2	Absent	Not performed	NA	Regional node	3	31	Axillary lymph node dissection, further treatment is unknown
13	18	M	Trunk	Unknown	1.8	4	Unknown	Not performed	NA	Regional node	16	20	Axillary lymph node dissection, adjuvant radiotherapy, metastasectomy, no chemotherapy
14	10	F	Head and neck	NM	1.8	5	Unknown	Not performed	NA	Local	4	18	Neck dissection, adjuvant radiotherapy, and chemotherapy
15	18	M	Head and neck	SSM	0.4	0	Unknown	Not performed	NA	Distant	156	59	Metastasectomy, further treatment is unknown
16	18	F	Trunk	SSM	0.9	3	Absent	Not performed	NA	Distant	42	20	Metastasectomy, radiotherapy, and chemotherapy

CLND, Completion lymph node dissection; *F*, female; *M*, male; *NA*, not applicable; *NM*, nodular melanoma; *SNB*, sentinel node biopsy; *SSM*, superficial spreading melanoma.

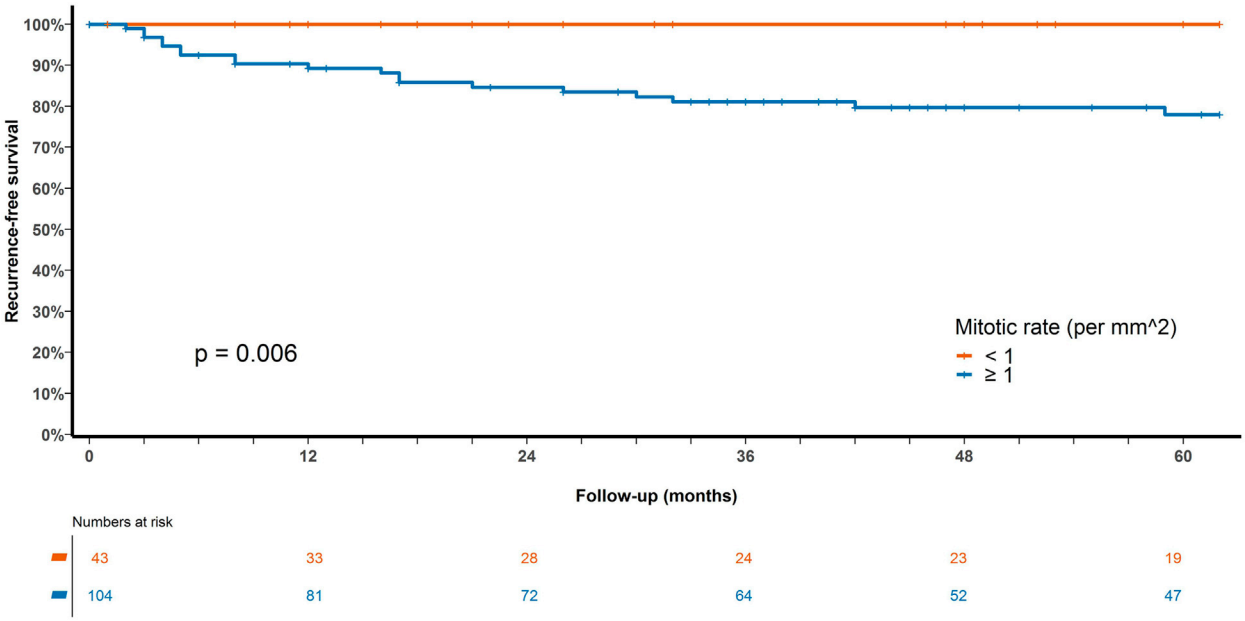

Fig 2. Recurrence-free survival of patients with melanoma according to mitotic rate.

Table III. Univariable and multivariable analysis of recurrence-free survival and melanoma-specific survival

		Recurrence-free survival				Melanoma-specific survival	
		Univariable		Multivariable		Univariable	
Variables	n	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Gender	156		.28				.31
Male		1.0 (reference)				1.0 (reference)	
Female		0.7 (0.3-1.4)				0.6 (0.2-1.6)	
Age (per 1-year increase)	156	1.1 (0.9-1.2)	.28			1.1 (0.9-1.3)	.46
Breslow thickness (per 1 mm increase)	156	1.2 (1.1-1.4)	.001	1.1 (0.9-1.2)	.48	1.1 (0.9-1.5)	.30
Mitotic rate (per mm^2)	147	1.2 (1.1-1.3)	<.001	1.2 (1.1-1.3)	.005	1.3 (1.1-1.5)	.001
Ulceration	132		.24				.16
Absent		1.0 (reference)				1.0 (reference)	
Present		1.7 (0.7-4.3)				2.3 (0.7-7.3)	
Primary tumor site	156		.35				.48
Lower limb		1.0 (reference)				1.0 (reference)	
Trunk		1.0 (0.4-2.9)				2.7 (0.6-11.1)	
Head and neck		1.7 (0.6-4.6)				1.4 (0.3-7.4)	
Upper limb		0.6 (0.2-2.0)				1.2 (0.2-6.1)	
Tumor type	115		.04				.20
Superficial spreading		1.0 (reference)				1.0 (reference)	
Nodular		2.9 (1.2-7.1)				2.3 (0.8-6.9)	
Spitzoid		0.6 (0.2-2.3)				0.3 (0-2.5)	
Other		—				—	
Sentinel node status	61		.24				.08
Negative		1.0 (reference)				1.0 (reference)	
Positive		2.8 (0.5-15.3)				7.1 (0.8-64.2)	

CI, Confidence interval; *HR*, hazard ratio.

On univariable analysis, MSS was significantly worse with increasing mitotic rate. Unfortunately, multivariable analysis could not be performed for MSS because of an insufficient number of events (16 melanoma-related deaths).[29] In line with our results, 3 previous melanoma studies in young patients showed that the presence of mitoses was associated with an increased risk of metastasis on univariable

analysis. However, when adjusted for other prognostic factors, this association was not seen, possibly because of the small sample sizes or the number of missing values in these studies.[10,12,28] No significant effect on overall survival has been found.[9,11]

In line with previous reports, childhood patients had thicker melanomas than adolescent patients in our study.[11-13,18] The primary tumor location was also different for the 2 groups, with head and neck sites being more common in children and the trunk being the most frequent location in adolescents.[13,15] Patients with melanoma who are in their late teens are sometimes inappropriately classified as children. Our results confirm that melanoma behaves differently in children and adolescents but MSS and RFS were similar. In contrast, a previous study reported better survival for children.[30] This may reflect the fact that cases reported as borderline tumors, such as atypical Spitz tumors, were specifically excluded in our study, whereas these may have been classified as melanoma in other studies.[31]

Metastatic disease was identified in 38% of the patients who underwent SNB in our study. Previous studies had reported SN positivity rates of between 18% and 50% in children and adolescents with melanoma.[11,12,20,28,32-34] Contrary to previous studies, RFS and MSS were not significantly different for SN-positive and SN-negative patients in our study.[14,18,20] Paradoxically, young patients have a higher incidence of SN metastasis but a more favorable survival than adults.[8,13,32] The reasons for this remain unclear but superior function of the immune system in younger patients has been proposed as a possible explanation.[33] In childhood and adolescence, melanomas frequently resemble benign lesions, which makes them hard to diagnose both clinically and pathologically.[34] Almost 50% of the melanomas in young adults do not fulfill the classic melanoma ABCD criteria.[35] Recent genomic analysis showed that melanomas in adolescents and young adults harbor mutation patterns that differ from those in older patients.[36]

Five-year MSS was 91% in our study and 5-year RFS was 84%. Several previous studies reported comparable survival rates with 5-year MSS ranging from 89% to 97% and 5-year RFS ranging from 68% to 90%.[9,11,18,37,38] Of the 15 patients who died of melanoma and in whom mitotic rate was assessed, 10 had a tumor mitotic rate of $<6/mm^2$. Five of 28 patients with recurrence (31%) experienced that recurrence after >5 years. As in adults, children and adolescents remain at risk of recurrence even after ≥10 years.[20,39] Childhood and adolescent patients are also twice as likely to develop a subsequent melanoma compared with adult patients.[40] This emphasizes the importance of continuing follow-up of patients who develop melanoma when they are young for longer than the usual 5-year period recommended in the melanoma management guidelines of some countries.[41]

The strengths of our study include the relatively large cohort of patients. In addition, pathology slides of all patients were reviewed by experienced pathologists, increasing the reliability of the diagnosis and of histologic and staging data. There are also several limitations affecting the study. Because of the moderate number of events, multivariable analysis could not be performed for MSS and only mitotic rate and Breslow thickness could be included in the multivariable analysis for RFS. Supplemental Table II (available online available at DOI 10.17632/s7f9jsz9yj.1) shows the unstable multivariable analysis of RFS and MSS including Breslow thickness, mitotic rate, and ulceration. Although all cases were reviewed by an MIA-affiliated pathologist, some histologic parameters were missing. The pathology slides of some patients were not available for reassessment. Other limitations are the retrospective design, the arbitrary age cutoff that was used to separate children and adolescents, referral bias, and the short follow-up of some patients.

In summary, our study indicates that mitotic rate is an important prognostic feature for RFS in children and adolescents who develop melanoma, and it is therefore essential that this parameter be assessed and reported in the primary tumors of all young melanoma patients. Although mitotic rate was the only independent predictor of RFS, a larger study is required to confirm these results. By extrapolating the number of recurrences in our study, approximately 500 children and adolescent patients would be needed to assess the prognostic value of the other prognostic factors that are common in adults. A collaborative study involving multiple melanoma centers would be needed.

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