# Prognostic factors in distinct melanoma types

Ipenburg, N.A.

# CHAPTER 4

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

Norbertus A. Ipenburg
Serigne N. Lo
Ricardo E. Vilain
Lodewijka H.J. Holtkamp
James S. Wilmott
Omgo E. Nieweg
John F. Thompson
Richard A. Scolyer

*Journal of the American Academy of Dermatology*. 2020 Apr;82(4):910-919

## ABSTRACT

**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. 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%) who underwent sentinel node biopsy. The median follow-up was 61 months. Five-year melanoma-specific and recurrence-free survival 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.

## INTRODUCTION

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]



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.

## PATIENTS AND 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, Sydney, Australia. The primary tumor pathological 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 and 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 12–19 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's $\chi^2$ or Fisher's exact test for categorical features and the Mann-Whitney *U* test for continuous variables. Melanoma-specific 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 two covariates with P-value <0.20 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 two-sided and P<0.05 was considered statistically significant. Statistical analyses were performed with SPSS 25.0 software for Mac (IBM SPSS, Chicago, IL).

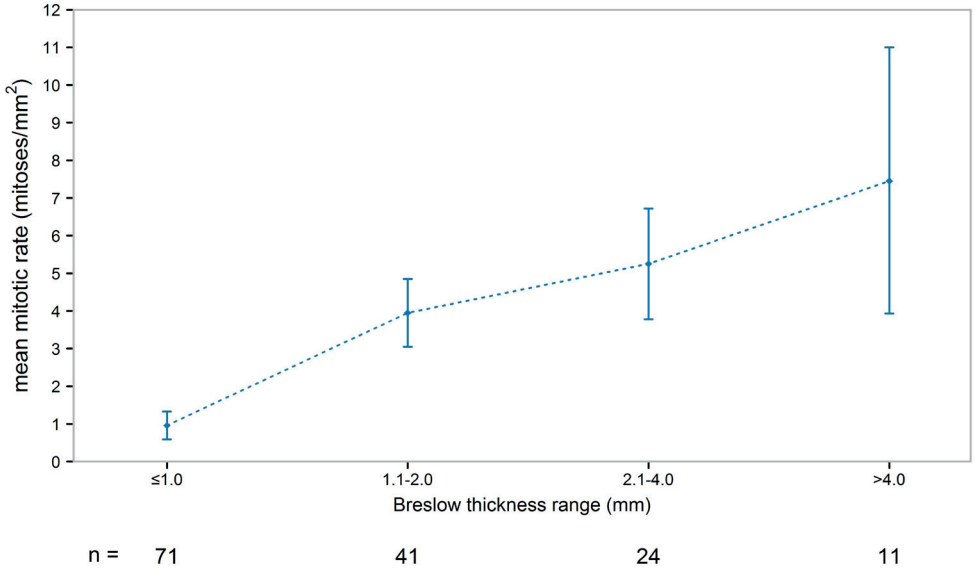
## RESULTS



### *Patient and tumor characteristics*

Baseline characteristics of the 156 patients are shown in Table 1. 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 (Figure 1).

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




Sentinel node biopsy (SNB) was performed 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 a completion lymph node dissection developed a recurrence.

### *Childhood versus adolescent patients*

Substantial differences in characteristics were observed between the childhood and adolescent patients (Table 1). Childhood melanomas (n=13) were thicker (median 2.7 mm vs. 1.0 mm; P=0.002) 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=0.007). Ulceration (n=4 (31%) in children vs. n=22 (15%) in adolescents; P=0.12) and mitotic rate ≥ 1 (n=10 (77%) in children vs. n=94 (66%) in adolescents; P=0.15) were not significantly different. There was no significant difference (P=0.26) 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=0.09).

Table 1. Clinicopathological characteristics.

| **Characteristic** | **All patients (*n* = 156)** | **Childhood patients (*n* = 13)** | **Adolescent patients (*n* = 143)** | **P-value*** |
|---|---|---|---|---|
| **Gender** | | | | |
| Male | 82 (53) | 4 (31) | 78 (55) | 0.15 |
| Female | 74 (47) | 9 (69) | 65 (45) | |
| **Primary tumor site** | | | | |
| Head and neck | 37 (24) | 5 (38) | 32 (22) | 0.30 |
| 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** | | | | |
| 0 – 1 mm | 79 (51) | 3 (23) | 76 (53) | 0.003 |
| 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) | 0.002 |
| **Mitotic rate** (per mm2) | | | | |
| <1 | 43 (28) | 2 (15) | 41 (29) | 0.51 |
| ≥1 | 104 (67) | 10 (77) | 94 (66) | |

| | | | | |
|---|---|---|---|---|
| Missing | 9 (6) | 1 (8) | 8 (6) | |
| Median (interquartile range) | 2 (5) | 3 (5) | 2 (4) | 0.15 |
| **Ulceration** | | | | |
| Absent | 102 (65) | 6 (46) | 96 (67) | 0.12 |
| Present | 26 (17) | 4 (31) | 22 (15) | |
| Missing | 28 (18) | 3 (23) | 25 (17) | |
| **Tumor type** | | | | |
| Superficial spreading melanoma | 61 (39) | 2 (15) | 59 (41) | 0.007 |
| 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** | | | | |
| II | 41 (26) | 3 (23) | 38 (27) | 0.001 |
| 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** | | | | |
| Performed | 61 (39) | 7 (54) | 54 (38) | 0.26 |
| Not performed | 95 (61) | 6 (46) | 89 (62) | |
| **Sentinel node status** | | | | |
| Negative | 38 (62) | 2 (29) | 36 (67) | 0.09 |
| Positive | 23 (38) | 5 (71) | 18 (33) | |
| **Total no. of sentinel nodes** - median (interquartile range) | 3 (3) | 1 (2) | 3 (2) | 0.05 |
| **Recurrence** | | | | |
| Yes | 28 (18) | 1 (8) | 28 (20) | 0.46 |
| No | 128 (82) | 12 (92) | 115 (80) | |
| **Site of first recurrence** | | | | |
| Local | 1 (4) | 1 (100) | 0 | 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** | | | | |
| 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) | |

Values in parentheses are percentages unless indicated otherwise; * comparison of children and adolescent patients.

*Recurrence and survival*

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%). Appendix 1 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 two age groups (P=0.83 and P=0.54). 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.

### *Prognostic factors*

On univariable analysis, Breslow thickness (P=0.001), mitotic rate (P<0.001), and melanoma subtype (P=0.04) 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 (HR)=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=0.001). The other covariates were not significantly associated with MSS (Table 2). Multivariable analysis could not be performed for MSS due to an insufficient number of events (16 melanoma-related deaths).



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

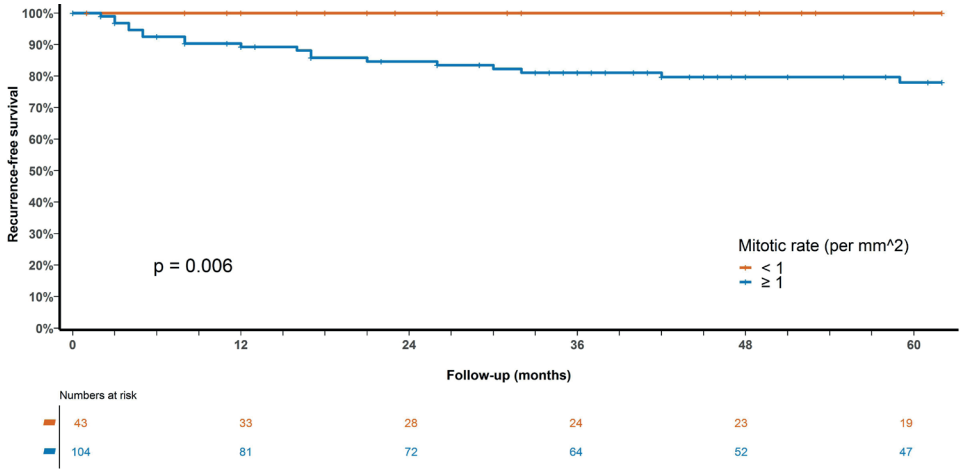


Table 2. Univariable and multivariable analysis of recurrence-free survival and melanoma-specific survival.

| | | 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 | | 0.28 | | | | 0.31 |
| Male | | (reference) | | | | (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) | 0.28 | | | 1.1 (0.9 – 1.3) | 0.46 |
| **Breslow thickness** (per 1 mm increase) | 156 | 1.2 (1.1 – 1.4) | 0.001 | 1.1 (0.9 – 1.2) | 0.48 | 1.1 (0.9 – 1.5) | 0.30 |
| **Mitotic rate** (per $mm^2$) | 147 | 1.2 (1.1 – 1.3) | <0.001 | 1.2 (1.1 – 1.3) | 0.005 | 1.3 (1.1 – 1.5) | 0.001 |
| **Ulceration** | 132 | | 0.24 | | | | 0.16 |
| Absent | | 1.0 (reference) | | | | 1.0 (reference) | |
| Present | | 1.7 (0.7 – 4.3) | | | | 2.3 (0.7 – 7.3) | |
| **Primary tumor site** | 156 | | 0.35 | | | | 0.48 |
| 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 | | 0.04 | | | | 0.20 |
| 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 | | 0.24 | | | | 0.08 |
| Negative | | (reference) | | | | (reference) | |
| Positive | | 2.8 (0.5 – 15.3) | | | | 7.1 (0.8 – 64.2) | |

HR: hazard ratio; CI: confidence interval

## DISCUSSION

This single institutional 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 (AJCC) 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, 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 (SEER) 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 missing.

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, two previous studies did show that Breslow thickness was an independent predictor of recurrence.[12,28]

On univariable analysis, MSS was significantly worse with increasing mitotic rate. Unfortunately, multivariable analysis could not be performed for MSS due to an insufficient number of events (16 melanoma-related deaths).[29] In line with our results, three 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 two groups, with head and neck sites being more 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 prior 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 developed melanoma when they are young for more 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. Supplementary Table 2 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 histological parameters were missing. The pathology slides of some patients were not available for reassessment. Other limitations are the retrospective design, the arbitrary age cut-off that was used to separate children and adolescents, referral bias, and the short follow-up of some patients.



## CONCLUSION

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 numbers 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.

## REFERENCES


1. de Vries E, Steliarova-Foucher E, Spatz A, Ardanaz E, Eggermont AMM, Coebergh JWW. Skin cancer incidence and survival in European children and adolescents (1978-1997). Report from the Automated Childhood Cancer Information System project. *Eur J Cancer*. 2006;42(13):2170-2182.
2. Strouse JJ, Fears TR, Tucker MA, Wayne AS. Pediatric melanoma: risk factor and survival analysis of the surveillance, epidemiology and end results database. *J Clin Oncol*. 2005;23(21):4735-4741.
3. Azzola MF, Shaw HM, Thompson JF, et al. Tumor mitotic rate is a more powerful prognostic indicator than ulceration in patients with primary cutaneous melanoma: An analysis of 3661 patients from a single center. *Cancer*. 2003;97(6):1488-1498.
4. Francken AB, Shaw HM, Thompson JF, et al. The prognostic importance of tumor mitotic rate confirmed in 1317 patients with primary cutaneous melanoma and long follow-up. *Ann Surg Oncol*. 2004;11(4):426-433.
5. Thompson JF, Soong S-J, Balch CM, et al. Prognostic significance of mitotic rate in localized primary cutaneous melanoma: an analysis of patients in the multi-institutional American Joint Committee on Cancer melanoma staging database. *J Clin Oncol*. 2011;29(16):2199-2205.
6. Wat H, Senthilselvan A, Salopek TG. A retrospective, multicenter analysis of the predictive value of mitotic rate for sentinel lymph node (SLN) positivity in thin melanomas. *J Am Acad Dermatol*. 2016;74(1):94-101.
7. Mandalà M, Galli F, Cattaneo L, et al. Mitotic rate correlates with sentinel lymph node status and outcome in cutaneous melanoma greater than 1 millimeter in thickness: A multi-institutional study of 1524 cases. *J Am Acad Dermatol*. 2017;76(2):264-273.e2.
8. Balch CM, Soong S, Gershenwald JE, et al. Age as a prognostic factor in patients with localized melanoma and regional metastases. *Ann Surg Oncol*. 2013;20(12):3961-3968.
9. Freemyer B, Hamilton E, Warneke CL, et al. Treatment outcomes in pediatric melanoma-Are there benefits to specialized care? *J Pediatr Surg*. 2016;51(12):2063-2067.
10. Paradela S, Fonseca E, Pita-Fernández S, Prieto VG. Spitzoid and non-spitzoid melanoma in children: a prognostic comparative study. *J Eur Acad Dermatol Venereol JEADV*. 2013;27(10):1214-1221.
11. Averbook BJ, Lee SJ, Delman KA, et al. Pediatric melanoma: Analysis of an international registry. *Cancer*. 2013;119(22):4012-4019.
12. Paradela S, Fonseca E, Pita-Fernández S, et al. Prognostic factors for melanoma in children and adolescents: a clinicopathologic, single-center study of 137 Patients. *Cancer*. 2010;116(18):4334-4344.
13. Lorimer PD, White RL, Walsh K, et al. Pediatric and Adolescent Melanoma: A National Cancer Data Base Update. *Ann Surg Oncol*. 2016;23(12):4058-4066.
14. Mu E, Lange JR, Strouse JJ. Comparison of the use and results of sentinel lymph node biopsy in children and young adults with melanoma. *Cancer*. 2012;118(10):2700-2707.
15. Lange JR, Palis BE, Chang DC, Soong S-J, Balch CM. Melanoma in children and teenagers: an analysis of patients from the National Cancer Data Base. *J Clin Oncol*. 2007;25(11):1363-1368.
16. Brecht IB, Garbe C, Gefeller O, et al. 443 paediatric cases of malignant melanoma registered with the German Central Malignant Melanoma Registry between 1983 and 2011. *Eur J Cancer*. 2015;51(7):861-868.
17. Brecht IB, De Paoli A, Bisogno G, et al. Pediatric patients with cutaneous melanoma: A European study. *Pediatr Blood Cancer*. 2018;65(6):e26974.

18. Moore-Olufemi S, Herzog C, Warneke C, et al. Outcomes in Pediatric Melanoma. *Ann Surg*. 2011;253(6):1211-1215.
19. Aldrink JH, Selim MA, Diesen DL, et al. Pediatric melanoma: a single-institution experience of 150 patients. *J Pediatr Surg*. 2009;44(8):1514-1521.
20. Han D, Zager JS, Han G, et al. The unique clinical characteristics of melanoma diagnosed in children. *Ann Surg Oncol*. 2012;19(12):3888-3895.
21. Euling SY, Herman-Giddens ME, Lee PA, et al. Examination of US puberty-timing data from 1940 to 1994 for secular trends: panel findings. *Pediatrics*. 2008;121 Suppl:S172-91.
22. McGovern VJ, Cochran AJ, Van der Esch EP, Little JH, MacLennan R. The classification of malignant melanoma, its histological reporting and registration: a revision of the 1972 Sydney classification. *Pathology*. 1986;18(1):12-21.
23. Scolyer RA, Shaw HM, Thompson JF, et al. Interobserver reproducibility of histopathologic prognostic variables in primary cutaneous melanomas. *Am J Surg Pathol*. 2003;27(12):1571-1576.
24. Joosse A, Collette S, Suciu S, et al. Superior outcome of women with stage I/II cutaneous melanoma: pooled analysis of four European Organisation for Research and Treatment of Cancer phase III trials. *J Clin Oncol*. 2012;30(18):2240-2247.
25. Balch CM, Gershenwald JE, Soong SJ, et al. Final version of 2009 AJCC melanoma staging and classification. *J Clin Oncol*. 2009;27(36):6199-6206.
26. Austin MT, Xing Y, Hayes-Jordan AA, Lally KP, Cormier JN. Melanoma incidence rises for children and adolescents: an epidemiologic review of pediatric melanoma in the United States. *J Pediatr Surg*. 2013;48(11):2207-2213.
27. Gershenwald JE, Scolyer RA, Hess KR, et al. Melanoma staging: Evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA Cancer J Clin*. 2017;67(6):472-492.
28. Cordoro KM, Gupta D, Frieden IJ, McCalmont T, Kashani-Sabet M. Pediatric melanoma: Results of a large cohort study and proposal for modified ABCD detection criteria for children. *J Am Acad Dermatol*. 2013;68(6):913-925.
29. Peduzzi P, Concato J, Feinstein AR, Holford TR. Importance of events per independent variable in proportional hazards regression analysis II. Accuracy and precision of regression estimates. *J Clin Epidemiol*. 1995;48(12):1503-1510.
30. Bartenstein DW, Kelleher CM, Friedmann AM, et al. Contrasting features of childhood and adolescent melanomas. *Pediatr Dermatol*. 2018;35(3):354-360.
31. Elder DE, Massi D, Scolyer RA, Willemze R. *WHO Classification of Skin Tumours*. 4th ed.; 2018.
32. Livestro DP, Kaine EM, Michaelson JS, et al. Melanoma in the young: Differences and similarities with adult melanoma: A case-matched controlled analysis. *Cancer*. 2007;110(3):614-624.
33. Howman-Giles R, Shaw HM, Scolyer R a, et al. Sentinel lymph node biopsy in pediatric and adolescent cutaneous melanoma patients. *Ann Surg Oncol*. 2010;17(1):138-143.
34. Mitkov M, Chrest M, Diehl NN, Heckman MG, Tollefson M, Jambusaria-Pahlajani A. Pediatric melanomas often mimic benign skin lesions: A retrospective study. *J Am Acad Dermatol*. 2016;75(4):706-711.e4.
35. Carrera C, Scope A, Dusza SW, et al. Clinical and dermoscopic characterization of pediatric and adolescent melanomas: Multicenter study of 52 cases. *J Am Acad Dermatol*. 2018;78(2):278-288.
36. Wilmott JS, Johansson PA, Newell F, et al. Whole genome sequencing of melanomas in adolescent and young adults reveals distinct mutation landscapes and the potential role of germline variants in disease susceptibility. *Int J Cancer*. 2019;144(5):1049-1060.

37. Le Q, Norris D, McClean CA, et al. Single institution experience of paediatric melanoma in Victoria, Australia. *Australas J Dermatol*. 2017;58(2):117-121.

38. Réguerre Y, Vittaz M, Orbach D, et al. Cutaneous malignant melanoma in children and adolescents treated in pediatric oncology units. *Pediatr Blood Cancer*. 2016;63(11):1922-1927.

39. Stanelle EJ, Busam KJ, Rich BS, et al. Early-stage non-Spitzoid cutaneous melanoma in patients younger than 22 years of age at diagnosis: Long-term follow-up and survival analysis. *J Pediatr Surg*. 2015;50(6):1019-1023.

40. Jung GW, Weinstock MA. Clinicopathological comparisons of index and second primary melanomas in paediatric and adult populations. *Br J Dermatol*. 2012;167(4):882-887.

41. Trotter SC, Sroa N, Winkelmann RR, Olencki T, Bechtel M. A global eeview of melanoma follow-up guidelines. *J Clin Aesthetic Dermatol*. 2013;6(9):18-26.

**Appendix 1.** Characteristics of patients who died of melanoma.

| **Patient** | **Age** | **Gender** | **Site** | **Tumor type** | **Breslow thickness** (mm) | **Mitotic rate** (/mm2) | **Ulceration** | **SNB** | **CLND** | **Site of first recurrence** | **Time until recurrence** (months) | **Time between recurrence and death** (months) | **Treatment after recurrence** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 17 | Male | Lower limb | NM | 2.7 | 5 | Absent | Positive | Negative | In transit | 145 | 40 | Isolated limb infusion |
| | | | | | | | | | | | | | Radiotherapy |
| | | | | | | | | | | | | | Local surgery |
| | | | | | | | | | | | | | Neurosurgery |
| | | | | | | | | | | | | | Chemotherapy |
| 2 | 18 | Male | Upper limb | SSM | 1.6 | 14 | Absent | Positive | Negative | Distant | 17 | 4 | Whole brain radiotherapy |
| | | | | | | | | | | | | | Chemotherapy |
| 3 | 16 | Male | Trunk | NM | 4.2 | 13 | Present | Positive | Positive (1 node) | In transit | 5 | 14 | Local surgery |
| | | | | | | | | | | | | | Radiotherapy |
| | | | | | | | | | | | | | Chemotherapy |
| 4 | 19 | Male | Trunk | Unknown | 1.5 | 4 | Absent | Positive | Negative | Distant | 102 | 16 | Radiotherapy |
| | | | | | | | | | | | | | Targeted therapy (dabrafenib) |
| | | | | | | | | | | | | | Immunotherapy (ipilimumab) |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 5 | 19 | Female | Head and neck | SSM | 1.0 | 1 | Absent | Negative | NA | Regional node | 8 | 4 | Neck dissection<br>Adjuvant radiotherapy<br>Chemotherapy |
| 6 | 15 | Female | Lower limb | Spitzoid | 1.0 | Unknown | Unknown | Not performed | NA | Regional node | 130 | 35 | Inguinal lymph node dissection<br>Radiotherapy<br>Immunotherapy (ipilimumab)<br>Targeted therapy (dabrafenib) |
| 7 | 16 | Male | Trunk | NM | 1.6 | 5 | Present | Not performed | NA | Regional node | 26 | 24 | Axillary lymph node dissection<br>Chemotherapy |
| 8 | 18 | Female | Lower limb | NM | 2.4 | 7 | Absent | Not performed | NA | Regional node | 17 | 20 | Inguinal lymph node dissection<br>Local surgery<br>Chemotherapy<br>Targeted therapy |
| 9 | 18 | Male | Upper limb | NM | 3.3 | 13 | Present | Not performed | NA | Regional node | 8 | 13 | Axillary lymph node dissection<br>Local surgery<br>Radiotherapy<br>Chemotherapy |
| 10 | 19 | Male | Trunk | NM | 4.0 | 10 | Present | Not performed | NA | Regional node | 5 | 31 | Axillary lymph node dissection<br>Adjuvant radiotherapy |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 11 | 19 | Male | Upper limb | SSM | 1.1 | 1 | Present | Not performed | NA | Regional node | 107 | 14 | Axillary lymph node dissection<br>Adjuvant radiotherapy<br>Chemotherapy |
| 12 | 19 | Female | Trunk | SSM | 1.7 | 2 | Absent | Not performed | NA | Regional node | 3 | 31 | Axillary lymph node dissection<br>Further treatment is unknown |
| 13 | 18 | Male | Trunk | Unknown | 1.8 | 4 | Unknown | Not performed | NA | Regional node | 16 | 20 | Axillary lymph node dissection<br>Adjuvant radiotherapy<br>Metastasectomy<br>No chemotherapy |
| 14 | 10 | Female | Head and neck | NM | 1.8 | 5 | Unknown | Not performed | NA | Local | 4 | 18 | Neck dissection<br>Adjuvant radiotherapy<br>Chemotherapy |
| 15 | 18 | Male | Head and neck | SSM | 0.4 | 0 | Unknown | Not performed | NA | Distant | 156 | 59 | Metastasectomy<br>Further treatment is unknown |
| 16 | 18 | Female | Trunk | SSM | 0.9 | 3 | Absent | Not performed | NA | Distant | 42 | 20 | Metastasectomy<br>Radiotherapy<br>Chemotherapy |

SNB: sentinel node biopsy; CLND: completion lymph node dissection; SSM: superficial spreading melanoma; NM: nodular melanoma; NA: not applicable