Melanomas in children and adolescents: Clinicopathologic features and survival outcomes

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Background: Melanomas in the first 2 decades of life are uncommon and poorly understood.

Objective: To assess clinicopathologic features and survival of children (≤11 years) and adolescents (12-19 years) diagnosed with melanoma.

Methods: A pooled cohort of 514 patients was analyzed (397 Dutch, 117 Australian; 62 children, 452 adolescents). Pathology reports were reevaluated to determine melanoma subtypes. Multivariable Cox models were generated for recurrence-free survival (RFS) and overall survival (OS).

Results: Melanoma subtypes were conventional melanoma (superficial spreading, nodular, desmoplastic, and acral lentiginous), spitzoid melanoma, and melanoma associated with a congenital nevus in 428, 78, and 8 patients, respectively. Ten-year RFS was 91.5% (95% confidence interval [CI], 82.4%-100%) in children and 86.4% (95% CI, 82.7%-90.3%) in adolescents (P = .32). Ten-year OS was 100% in children and 92.7% (95% CI, 89.8%-95.8%) in adolescents (P = .09). On multivariable analysis possible only for the adolescent cohort due to the small number of children, ulceration status, and anatomic site were associated with RFS and OS, whereas age, sex, mitotic index, sentinel node status and melanoma subtype were not. Breslow thickness >4 mm was associated with worse RFS.

Limitations: Retrospective study.

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Conclusions: Survival rates for children and adolescents with melanomas were high. Ulceration, head or neck location and Breslow thickness >4 mm predicted worse survival in adolescents. (J Am Acad Dermatol 2023;88:609-16.)

Key words: adolescence; age; children; melanoma; survival.

INTRODUCTION

Cutaneous melanomas are rare in children and much less common in adolescents than in later life.[1-7] Management of these young patients currently follows guidelines developed for adults. Better understanding of melanoma occurring in the first 2 decades of life is, therefore, warranted. The current study sought to evaluate melanoma patients <20 years of age by pooling 2 large independent datasets, one population-based (from the Netherlands) and other from the Melanoma Institute Australia (MIA), a large Australian melanoma treatment center. The primary aim was to document clinicopathologic variables, survival outcomes, and prognostic features of melanomas diagnosed in children (≤11 years of age) and adolescents (12-20 years of age).

CAPSULE SUMMARY

- Melanomas in children and adolescents are uncommon and poorly understood.
- In a study of 62 children and 452 adolescents with melanomas, primary tumor ulceration, head/neck location, and Breslow thickness >4 mm predicted worse survival. Melanomas in children may be biologically distinct and require management that differs from that in adults.

PATIENTS AND METHODS

Collection of data

The study included all patients aged <20 years diagnosed with invasive melanoma in the Netherlands between January 2000 and December 2014. Patient information was retrieved from PALGA (Pathologisch Anatomisch Landelijk Geautomatiseerd Archief), the Dutch Pathology Registry.[8] Follow-up data were obtained from the Netherlands Cancer Registry. Follow-up was calculated from date of diagnosis to date of death or recurrence, the date last known to be alive or January 1, 2018, whichever occurred earlier. Ethical approval granted by the board of PALGA.

A similar search of the prospectively-maintained MIA database was performed to identify melanoma patients treated at MIA over the same period. To eliminate potential referral bias, patients initially treated elsewhere but later referred to MIA for follow-up or further management were excluded. Prospective approval for use of the data was obtained from all patients and from the Ethics Committee of the Sydney Local Health District.

Study population

To achieve sufficient numbers of events for meaningful analysis, the Dutch and MIA cohorts were combined. Patients initially diagnosed with clinically-detected stage III disease or stage IV disease, were excluded. For each patient, demographic characteristics were collected, including date of diagnosis, age at diagnosis (categorized as children [≤11 years old] and adolescents [12-19 years old], sex, primary tumor anatomic site and date of recurrence, defined as either cutaneous recurrence [local or in transit], nodal recurrence, or distant metastasis), and death from any cause. Pathologic data collected included Breslow thickness, melanoma subtype, ulceration status, mitoses, and sentinel node (SN) status. The Netherlands Cancer Registry recorded only the presence or absence of mitoses in each primary melanoma whilst the MIA database included the number of mitoses per mm^2, in each case. Primary and secondary outcome measures were recurrence-free survival (RFS) and overall survival (OS). Pathology reports were reviewed to reassess melanoma subtype; this was categorized as (1) conventional melanoma (superficial spreading, nodular, desmoplastic, or acral lentiginous), (2) spitzoid melanoma, and (3) melanoma associated with a congenital nevus (CN). Patients whose diagnosis was Spitz/spitzoid melanocytoma/atypical Spitz/spitzoid tumor (n = 47) or pigmented epithelioid melanocytoma (n = 1) were excluded from the study. Each case was classified following a careful examination of the histopathology report by a histopathologist with specialized expertise in the diagnosis of melanocytic tumors.

Statistical analysis

Kaplan-Meier curves were generated for RFS and OS, and log-rank tests were used to assess survival differences between children and adolescents. Multivariable Cox proportional hazard models were used to identify factors associated with survival

Abbreviations used:

HR: hazard ratio
IQR: interquartile range
OS: overall survival
RFS: recurrence-free survival
SN: sentinel node

in the adolescent cohort. Additional methods are detailed in Supplementary Materials. Statistical analyses were performed using R version 3.6.1.[9] A two-sided P value of $< .05$ was considered significant.

The study adhered to the STROBE guidelines for reporting observational studies (Supplementary Table I, available via Mendeley at https://doi.org/10.17632/92y5khgv55.1).[10]

RESULTS

Clinicopathologic differences between melanomas in children and adolescents

Fig 1 shows the distribution of age at diagnosis in the combined cohorts. Table I shows the clinicopathologic features of the 62 children and 452 adolescents.

Females predominated in both the adolescents (61.7%) and the children (54.8%). The median Breslow thickness was 2.7 mm (interquartile range [IQR], 1.0-4.1) in children and 1.0 mm (IQR, 0.6-1.8) in adolescents. Conventional melanoma was the most common form of melanoma in both age groups (58.1% in children and 86.7% in adolescents). Superficial spreading melanoma (SSM) was the most common subtype of conventional melanoma in both children (66.7%) and adolescents (83.4%), followed by nodular melanoma (children 30.6%, adolescents 15.8%). Spitzoid melanomas comprised 35.5% of melanomas in children and 12.4% in adolescents. In patients who had a SN biopsy performed, it was positive in 7 children (36.8%) and 40 adolescents (31.5%). Supplementary Table II, available via Mendeley at https://doi.org/10.17632/92y5khgv55.1 shows clinicopathologic characteristics of the children and adolescents, stratified for the Dutch and Australian cohorts.

Clinicopathologic differences between melanoma subtypes

In total, 78 patients were diagnosed with a spitzoid melanomas (22 children and 56 adolescents) (Table I). Eight patients (4 children, 4 adolescents) were diagnosed with melanomas associated with a CN. Clinicopathologic differences between patients with spitzoid melanomas, conventional melanomas, and patients with melanomas associated with a CN are shown in Supplementary Table IV, available via Mendeley at https://doi.org/10.17632/92y5khgv55.1.

Recurrence and death

Follow-up data were available for 475 patients (92.4%). In total, 3 children and 43 adolescents developed a recurrence. All 3 children had ulcerated primary melanomas located on the head or neck (see Supplementary Table III, available via Mendeley at https://doi.org/10.17632/92y5khgv55.1); 2 were ≤2 years old and one was 10 years old at the time of diagnosis. Two tumors were diagnosed as spitzoid melanomas and one as SSM. Ten-year RFS was 91.5% in children and 86.4% in adolescents ($P = .32$) (Fig 2) after a median follow-up of 8.8 years (IQR, 4.0-11.4) in children and 7.8 years (IQR, 3.8-11.7) in adolescents. No children and 24 adolescents died. Ten-year OS was 100% in children and 92.7% in adolescents ($P = .09$) (Fig 3).

Supplementary Table I and II, available via Mendeley at https://doi.org/10.17632/92y5khgv55.1 depict the Kaplan-Meier survival curves stratified for melanoma subtype. There was no significant difference between melanoma subtypes; adolescent patients with spitzoid melanomas, SSMs, and nodular melanomas had 10-year RFS rates of 94.8%, 85.5%, and 85.7%, respectively ($P = .49$). Ten-year OS rates were 94.4% (95% confidence interval [CI], 87.0%-100%), 92.8% (95% CI, 89.2%-96.5%), and 90.9% (95% CI, 83.6%-98.8%), respectively, ($P = .69$).

Of the 8 patients with melanomas associated with a CN, only one (an adolescent) developed recurrence, 3.8 years after the initial melanoma diagnosis. Recurrence did not occur in the remaining patients after a median follow-up of 7.6 years (IQR, 3.2-10.2). None of the 8 patients died (median follow-up, 7.4 years; IQR, 4.3-9.8).

In multivariable Cox analyses for RFS and OS in adolescents (Table II) melanoma subtype, SN status, and age were not significantly associated with survival. Patients with melanomas located on the lower limb had higher RFS and OS rates than those with head or neck melanomas (hazard ratios [HRs] 0.13 [95% CI, 0.03-0.49] and 0.09 [95% CI, 0.02-0.48], respectively). Similarly, patients with melanoma located on the upper limb had higher RFS rates (HR, 0.26 [95% CI, 0.07-0.94]). Ulceration was associated with worse RFS and OS (HRs 2.88 [95% CI, 1.29-6.45] and 3.58 [95% CI, 1.18-10.80], respectively). Only patients whose melanomas were >4.0 mm in Breslow thickness had higher RFS rates than those diagnosed with melanomas ≤1.0 mm (HR, 7.61 [95% CI, 2.16-26.75]).

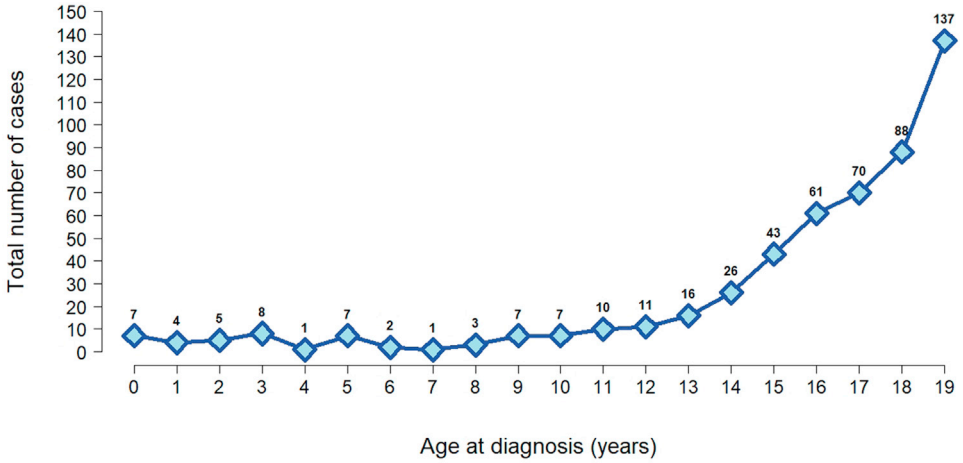

Fig 1. Distribution of melanoma cases by age at diagnosis. The median age at diagnosis was 5 years (interquartile range [IQR], 2-10) in children and 17 years (IQR, 16-19) in adolescents.

DISCUSSION

In this study the clinicopathologic features and survival outcomes of patients diagnosed with melanomas in the first and second decades of life were documented and analyzed. Melanomas in children were much less common and all survived, while survival of adolescents with melanomas was high but some died of melanoma. Breslow thickness >4 mm, the presence of ulceration and localization on the head or neck was associated with worse survival in adolescents.

De Lange et al[11] analyzed information derived from the U.S. National Cancer Database for 3158 melanoma patients ≤19 years old (median follow-up 4.9 years). They reported a male predominance (56.7%) in the 164 patients under the age of 10, whereas in the current study a female predominance (54.8%) was found in children aged ≤11 years. This female predominance was observed in both the Dutch and the MIA children (54.5% and 57.1%, respectively). A female predominance was also found in Australian nation-wide data reported by Friedman et al[12], with 41 (60.3%) of the 68 children aged ≤ 11 years of age being female. In patients aged 10 to 19 years, de Lange et al[11] reported a female predominance (n = 1564 (56.9%)), concordant with our findings in the Dutch cohort. In their recent comprehensive review of sex incidence differences in melanoma worldwide, which assessed data from 30 countries, a key finding by Olsen et al was that in all countries, females had higher rates of melanoma than males in early life.[13] In later life the incidence in males began to exceed the incidence in females, with the balance switching from female predominance to male predominance at different ages in different countries. The switch was earliest in Australia, so that overall, there was a male-to-female incidence ratio of 1.47, whereas at the other end of the range the switch was much later in Denmark, where the overall male-to-female ratio was 0.67. The differences in male-to-female incidence patterns appeared to be due to sex-specific differences in melanoma incidence at different anatomic sites, with higher rates of lower limb melanoma in early life in females and higher rates of head or neck melanoma in later life in males.

In the current study, only 3 children developed recurrences (all in regional lymph nodes). These findings support the hypothesis that melanoma in childhood might be a distinct biological entity of low-grade malignancy.[14,15] Another explanation could be related to inherent differences between the immune system of children compared to adults,[16] In other disease states, such as SARS-CoV-2 infection, the better outcomes and lower mortality in children have been partly attributed to immune-related differences, such as the more robust innate immune response,[17] and the comparatively 'naïve' antibody response in children.[18] Such differences in immune responses may similarly lead to more effective antitumor immune responses in children with melanomas; however, this is speculative and further research in this area is needed.[19] It is also possible that some of the tumors with morphological characteristics of melanomas may not in fact have been biologically malignant.

It has been suggested that there are 3 distinct types of melanomas in children as follows: (1) conventional adult-type melanomas; these include SSMs (which are often BRAF [v-raf murine sarcoma viral oncogene homolog B1]-mutant), nodular, and, less commonly, desmoplastic and acral melanomas; (2) melanomas arising in a CN (which are often NRAS

Table I. Clinicopathologic features of children and adolescents diagnosed with melanoma

Characteristic	Children (≤11 y old, *n* = 62)	Adolescents (12-19 y old, *n* = 452)
Sex (*n*)		
Female	34 (54.8%)	279 (61.7%)
Male	28 (45.1%)	173 (38.3%)
Primary site (*n*)		
Head or neck	17 (27.4%)	69 (18.3%)
Trunk	10 (16.1%)	169 (44.8%)
Upper limb	10 (16.1%)	52 (13.8%)
Lower limb	23 (37.1%)	87 (23.1%)
Not known	2	75
Breslow thickness in mm (*n*)		
<0.8	13 (21.0%)	160 (35.4%)
≤0.8-1.0	6 (9.7%)	82 (18.1%)
1.1-2.0	9 (14.5%)	116 (25.7%)
2.1-4.0	18 (29.0%)	64 (14.2%)
>4.0	16 (25.8%)	30 (6.6%)
Subtype (*n*)		
Spitzoid melanoma	22 (35.5%)	56 (12.4%)
Conventional melanoma	36 (58.1%)	392 (86.7%)
Superficial spreading	24	327
Nodular	11	62
Desmoplastic	0	2
Acral lentiginous	1	1
Associated with congenital nevus	4 (6.5%)	4 (0.9%)
Ulceration (*n*)		
No	35 (72.9%)	284 (83.0%)
Yes	13 (27.1%)	58 (17.0%)
Not known	14	110
Mitoses (*n*)		
No	3 (15.0%)	71 (33.3%)
Yes	17 (85.0%)	142 (67.7%)
Not known	42	239
SN status (*n*)		
Negative	12 (63.2%)	87 (68.5%)
Positive	7 (36.8%)	40 (31.5%)
Not performed	43	325

SN, Sentinel node.

[neuroblastoma ras viral oncogene homolog]-mutant); and (3) Spitz melanomas (malignant Spitz tumors), which are characteristically associated with the presence of kinase gene fusions resulting in constitutive activation of the kinase, the most common involving ALK (anaplastic lymphoma kinase) and ROS1 (c-ros oncogene 1).[20-22] The presence of one of these kinase fusions defines the Spitz pathway of neoplasia; that is benign, intermediate, and malignant tumors can all occur with one of these fusions. Benign tumors (Spitz nevi) and intermediate tumors (Spitz melanocytomas which were previously frequently designated as atypical Spitz tumors) are much more common than Spitz melanomas (termed "malignant Spitz tumors" in the WHO [World Health Organization] classification of skin tumors),[23,24] and each entity can also harbor these defining kinase fusions. Distinction between Spitz nevi, Spitz melanocytomas, and Spitz melanomas is principally based on morphological assessment, sometimes supplemented by immunohistochemical studies and/or molecular analysis such as fluorescence in-situ hybridization or comparative genomic hybridization.[25] Some authors regard Spitz melanomas as a subtype of spitzoid melanomas.

Conventional, adult-type melanomas occurring in children and adolescents have similar morphological and molecular features. Melanomas rarely arise in small congenital nevi but occur in 3% to 10% of patients with giant congenital nevi.

Most melanomas in adolescents harbor a high mutation burden, which is associated with UV radiation exposure, as in their adult counterparts, representing a conventional or "adult-type" melanoma.[20,22] However, the rate of BRAF mutations is significantly higher in adolescents than in adult melanoma patients, which is consistent with the higher rate of SSM in these patients. It is generally considered that children aged <10 years develop melanomas in a CN or they are diagnosed with Spitz (kinase fusion-associated) melanomas.[20] However, in our study conventional-type melanomas were the most common subtype in the latter population. Bartenstein et al described the outcomes of spitzoid proliferations in 622 children and adolescents <20 years old, and reported no deaths; however, only 3 cases of melanoma were included in the study.[26] We report a similar finding in children but found 3 cases of spitzoid melanoma in adolescents who died of their disease. Therefore, while the biology of adolescent melanomas appears generally similar at the molecular level to that of adult-type melanomas, melanomas in children often arise via different molecular mechanisms.

Strengths of this study include the large sample size and use of nationwide data as well as data from a well-maintained institutional database. This enabled analysis of data for as many eligible patients as possible, and increased the generalizability of the results. Nevertheless, the total number of those ≤11 years of age was still only 62, since melanoma in this age group is rare. Another limitation concerning patients with a melanoma associated with a CN is that the Dutch database contains only pathology-based information, so we were, therefore, not able to retrieve clinical information, such as the size of the

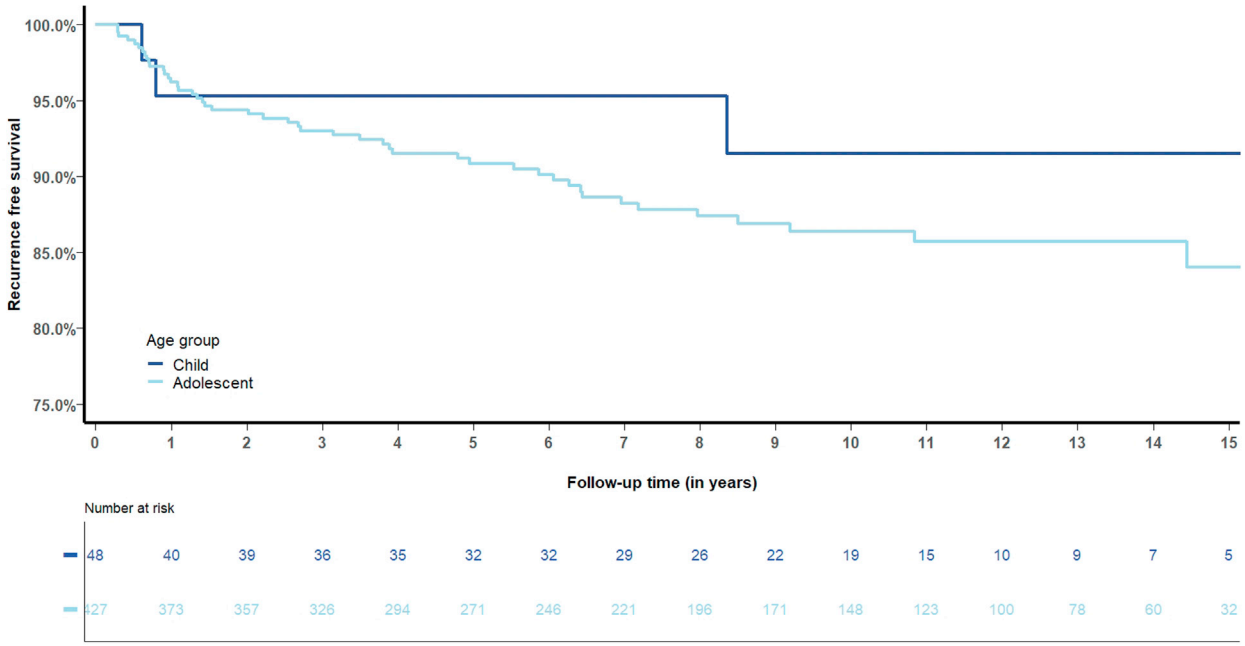

Fig 2. Recurrence-free survival of children and adolescents (Kaplan-Meier curves).

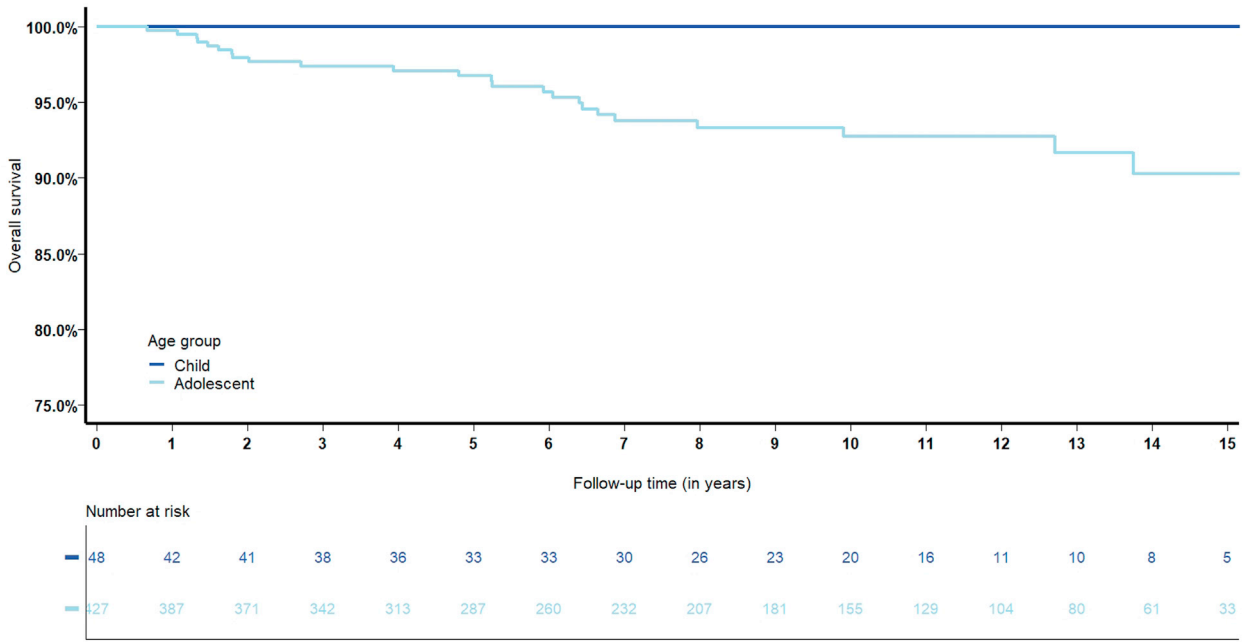

Fig 3. Overall survival of children and adolescents (Kaplan-Meier curves).

CN and whether the CN had satellites or not. A final limitation of the study is that due to its retrospective nature we were not able to review all histopathology slides to confirm the diagnosis of melanoma. This would have been especially interesting in these patients, as the histopathologic diagnosis of melanoma in children can be challenging. The ratio of melanoma diagnosis in children compared to adolescents in the Dutch cohort was higher than in the MIA cohort, which suggests that the Dutch pathologists may have had a lower threshold for diagnosing melanoma in children than MIA pathologists, who have considerable expertise and experience in melanoma diagnosis. Histopathologic criteria utilized by pathologists for diagnosing melanoma in children and adolescents, and the threshold for providing this diagnosis in young patients are issues that may require refinement, and warrant

Table II. Overall survival and recurrence-free survival (multivariable Cox analyses) for adolescent patients with spitzoid melanomas, superficial spreading melanomas and nodular melanomas (n = 445)

		OS (24 events)		RFS (47 events)	
Variable	**Class**	**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**
Subtype	Spitzoid melanoma	1		1	
	SSM	1.11 (0.26-4.76)	0.89	2.97 (0.79-11.24)	.11
	NM	1.16 (0.25-5.50)	0.85	1.42 (0.36-5.55)	.62
Age	Per 5 y	0.87 (0.25-3.05)	0.83	0.82 (0.33-2.07)	.68
Sex	Male	1		1	
	Female	2.01 (0.79-5.09)	0.14	0.919 (0.48-1.72)	.76
Breslow	≤1.0 mm	1		1	
	1.1-2.0 mm	0.94 (0.29-3.06)	0.91	1.70 (0.76-3.82)	.19
	2.1-4.0 mm	0.83 (0.18-3.79)	0.81	1.65 (0.56-4.85)	.36
	>4.0 mm	4.49 (0.82-24.52)	0.08	7.61 (2.16-26.75)	.002*
Site	H&N	1		1	
	Trunk	0.46 (0.17-1.26)	0.13	0.52 (0.24-1.11)	.09
	Upper limb	0.33 (0.08-1.41)	0.13	0.26 (0.07-0.94)	.04*
	Lower limb	0.09 (0.02-0.48)	0.005*	0.13 (0.03-0.49)	.0002*
	Not known	NA	NA	0.41 (0.13-1.23)	.11
Ulceration	No	1		1	
	Yes	3.58 (1.18-10.80)	0.02*	2.88 (1.29-6.45)	.01*
	Not known	1.46 (0.47-4.56)	0.51	1.09 (0.46-2.60)	.85
Mitoses	No	1		1	
	Yes	3.02 (0.30-30.91)	0.35	3.91 (0.72-12.20)	.11
	Not known	3.62 (0.40-32.74)	0.25	4.41 (0.89-21.84)	.06
SN status	Negative	1		1	
	Positive	3.99 (0.98-16.22)	0.06	2.16 (0.82-5.72)	.12
	Not performed	2.59 (0.68-9.91)	0.17	1.51 (0.61-3.70)	.37

Patients with melanomas associated with a congenital nevus (n = 8), desmoplastic melanomas (n = 2) and acral lentiginous melanomas (n = 2) were excluded because of insufficient numbers for multivariable analysis.
CI, Confidence interval; *H&N*, head and neck; *HR*, hazard ratio; *NA*, not applicable; *OS*, overall survival; *RFS*, recurrence-free survival; *SN*, sentinel node.
*Denotes statistical significance.

consideration in future studies. For example, the presence of more than occasional dermal mitoses in a melanocytic tumor occurring in an adult patient would usually signify a diagnosis of melanoma[27] but the presence of even a few dermal mitoses within a melanocytic tumor occurring in a child would not be inconsistent with a diagnosis of Spitz nevus or CN.[28] Ultimately, integration of morphologic features with molecular profiling may be required to further refine the accuracy of diagnosis of melanoma and borderline tumors in children and adolescents.[29]

CONCLUSIONS

Melanomas occurring in the first and second decades of life have clinicopathologic features that are distinct from those of conventional adult melanomas. All children in this study survived, and the survival rate of adolescents with melanomas was high. The clinicopathologic variables associated with worse survival in adolescents diagnosed with melanomas were Breslow thickness >4 mm, the presence of ulceration, and head or neck location. Recent molecular analyses of melanomas occurring in children and adolescents have provided important new insights into their pathogenesis and classification. Our data suggest that adolescent melanomas are often similar to adult-type melanomas, whilst those which occur in young children frequently occur via different molecular mechanisms. In the future it is likely that further understanding of these molecular mechanisms and ability to classify melanomas based on their molecular characteristics will assist in further refining prognostic estimates and possible guiding treatment for young patients with melanoma.

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Conflicts of interest

RAS has received fees for professional services from F. Hoffmann-La Roche Ltd, Evaxion, Provectus Biopharmaceuticals Australia, Qbiotics, Merck Sharp & Dohme, GlaxoSmithKline, Bristol-Myers Squibb, Dermpedia, Novartis, Myriad, NeraCare and Amgen. JFT has received honoraria for advisory board participation from GSK, Merck Sharpe & Dohme Australia, Provectus Inc and Bristol Myers Squibb Australia, and travel and conference expenses from GSK, Provectus Inc and Novartis. The other authors have no conflicts to disclose.

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