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Early-Stage Non-Spitzoid Cutaneous Melanoma in Patients Younger Than 22 Years of Age at Diagnosis: Long-Term Follow-Up and Survival Analysis

Eric J. Stanelle, MD¹, Klaus J. Busam, MD², Barrie S. Rich, MD¹, Emily R. Christison-Lagay¹, Ira Dunkel, MD³, Ashfaq A. Marghoob, MD⁴, Allan Halpern, MD⁴, Daniel G. Coit, MD⁵, and Michael P. La Quaglia, MD^{1,*}

¹Pediatric Surgical Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY

²Dermatopathology Service, Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY

³Department of Pediatrics, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY

⁴Department of Dermatology, Memorial Sloan Kettering Cancer Center, New York, NY

⁵Gastric and Mixed Tumor Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY

Abstract

Purpose—We evaluated prognostic factors among young patients with early stage melanoma, with particular attention to survival, recurrence, and development of a second primary melanoma.

Methods—We retrospectively reviewed patients (age <22 years) with pathologically confirmed in-situ and stage 1 non-Spitzoid melanoma treated at our institution from 1980–2010, assessing demographics, clinical presentation, treatment, disease-specific survival, recurrence-free survival, and probability of developing a second primary melanoma.

Results—One hundred patients with in-situ melanoma (n=16) or stage 1A (n=48) or 1B (n=36) melanoma were identified. Median age was 19.4 years (range, 11.2–21.9), and median followup was 7.6 years (range, 0.1–31.7). Median tumor thickness was 0.76 mm (range, 0.23–2.0). No lesions were ulcerated. All patients underwent wide local excision with negative margins, and 21 had a concomitant negative sentinel lymph node biopsy (SLNB). Sixteen patients developed recurrences, and 8 subsequently died of progressive melanoma. There were 2 non-melanoma-related deaths. Endpoints were 20-year overall survival (77.4%), melanoma-specific mortality (20.1%), recurrence rate (34.0%), and probability of developing a second primary melanoma

*Corresponding Author: Michael P. La Quaglia, MD, Pediatric Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, Telephone: 212-639-7002, Fax: 212-717-3373, laquaglm@mskcc.org.

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(24.7%). Greater tumor depth and Clark level were associated with worse prognosis, but age, sex, and tumor mitotic rate were not correlated with recurrence or survival.

Conclusion—Among younger early-stage melanoma patients, greater lesion depth conferred higher recurrence risk and mortality. Our data did not define the role of sentinel lymph node biopsy in this group.

Keywords

Melanoma; adolescent; prognosis; recurrence

BACKGROUND

Melanoma in children and young adults is rare, accounting for 1% to 4% of all melanoma diagnoses and 1% to 3% of all pediatric malignancies [1]. However, the incidence in the pediatric/adolescent population appears to be rapidly increasing. An analysis of the National Cancer Institute (NCI) Surveillance, Epidemiology and End Results (SEER) database demonstrated that pediatric melanoma increased by 46% per year of age and by 2.9% per year overall from 1973–2001 [2]. Survival outcomes for pediatric and adolescent patients are similar to those in adults [3–5]. Because the majority of analyses to date have patients with all stages of melanoma, there is a paucity of data specifically evaluating in situ and early-stage melanomas in the pediatric and adolescent population.

Establishing a reliable pathological diagnosis in patients with early-stage melanoma can be challenging. Santillan and colleagues recently found that when thin melanomas (< 1 mm in thickness) and melanoma in-situ (MIS) are reviewed by a senior dermatopathologist, there are frequent and often clinically meaningful alterations of the original diagnosis that subsequently affect management and overall prognosis [6]. Part of the difficulty in accurately identifying early-stage melanomas arises from the histologic similarity to spitzoid lesions (benign spitz nevi, atypical spitz tumors, and spitzoid melanoma) [7–12]. Because atypical spitzoid and/or spitzoid melanomas have a better prognosis than malignant melanomas [12–15], any analysis of melanoma outcomes that does not exclude spitzoid lesions may overestimate the survival rates among patients with conventional melanomas. In addition to the diagnostic challenge presented by early-stage melanomas, there is also considerable variability in the clinical management of these patients [16]. Current management algorithms for early-stage melanoma in the pediatric/adolescent population are extrapolated from the adult literature, as there are few reports that specifically address this age group.

The aim of this study was to correlate clinical parameters with overall survival, disease-specific survival, recurrence-free survival, and development of a second primary melanoma in pediatric and adolescent patients with pathologically confirmed early-stage, non-Spitzoid melanomas.

METHODS

After approval by the MSKCC institutional review board (IRB waiver #WA0417-04[9]), records were retrospectively reviewed for the period May 1, 1980 to May 30, 2010 to

identify all patients 22 years of age and younger with the diagnosis of melanoma in situ (MIS) or stage 1A/1B melanoma as defined by the American Joint Committee on Cancer (AJCC) classification system [17]. The pathology of each primary lesion and additional primaries were individually reviewed by a single dermatopathologist (KJB) with expertise in both thin melanomas and spitzoid-type lesions. Spitzoid lesions were excluded from the study. Sentinel lymph node biopsies (SLNB) and/or regional lymph node dissections (LND) were also independently reviewed by the same senior dermatopathologist. The endpoints of analysis included disease-specific survival, recurrence, and development of a second primary melanoma. Variables correlated with these endpoints included: depth, Clark level, primary site (upper and lower extremity, head and neck, and trunk/back), mitotic rate 1 mm^2 , age, and sex. No lesion was ulcerated, precluding analysis of this variable.

Overall survival was calculated from time of diagnosis to death from any cause. Two patients in this analysis died, but it was not clear whether the deaths were due to melanoma or were treatment-related. They are included as deaths in the overall survival curve and as a competing risk in Gray's analysis. Disease-specific survival (DSS) was calculated from the time of diagnosis to the time of death from disease or last recorded follow-up. Recurrence-free survival (RFS) was defined as the time from first definitive surgical resection to the date of documented recurrence. Second primary melanoma-free survival was calculated from the time of first diagnosis until development of the second primary. DSS, RFS and second primary-free survival were analyzed using Gray's test for the discrete covariates and the Wald test from a competing risks regression model for age and tumor depth (analyzed as continuous variables). The Wilcoxon signed-rank test was used to compare tumor depth distributions. Statistical calculations were performed R statistical software, using the "survival" and "cmprsk" packages (the R Project/R Foundation for Statistical Computing, Vienna, Austria, <http://www.r-project.org>). Significance was defined as a *P* value of <0.05 and reported confidence intervals at the 95% level.

RESULTS

Demographics and Lesion Characteristics

One hundred patients were identified with a median age of 19.4 years (range, 11.2–21.9 y; interquartile range [IQR], 17.5–21.0 y) at diagnosis. All patients were white, and 71% were female. The most common primary site was the back and/or trunk (47%), followed by the lower extremity (22%), upper extremity (18%), and head/neck region (13%). Thirty-two patients presented with an increase in the size of a known lesion, while 25 presented after noticing an entirely new lesion. Seventeen patients presented after noticing a color change within a lesion and 16 patients were diagnosed after a routine surveillance biopsy. Presenting signs/symptoms were unknown for 2 patients.

Based on AJCC staging criteria, 16 patients had melanoma in-situ (Stage 0), 48 had stage 1A melanoma, and 36 had stage 1B disease. Of the patients with stage 1B, 13 had lesions $<1 \text{ mm}$ thick but with mitoses $1/\text{mm}^2$ (range, $1\text{--}7/\text{mm}^2$). Median lesion thickness was 0.76 mm for non in-situ lesions (range, 0.23–2.0 mm), and none of the lesions were ulcerated. Clark levels were known for 94 of 100 patients, as follows: level 1 in 15 (16%) patients, level 2 in 31 (33%) patients, level 3 in 29 (31%) patients, and level 4 in 19 (20%) patients.

Mitosis counts were available for 44 (52%) of the 84 patients with stage 1 disease, and 21 of those 44 had mitoses ≥ 1 per mm².

Treatment

All patients underwent wide local excision of the primary lesion and all resection margins were microscopically clear. Sentinel lymph node biopsy (SLNB) was performed in 21 patients (21%) at the time of primary lesion excision; none had regional nodal metastasis. Analysis of the sentinel node frozen section for one patient revealed melanocytes; a subsequent formal regional LND was performed, but only benign melanocytes were found on permanent pathology. Two additional patients had lower-extremity lesions and underwent formal regional LND at the time of the wide excision, but nodal disease was not found. No patient received adjuvant therapy unless disease recurred. Of 32 patients with a lesion thickness between 0.51–1.00 mm, 10 had ≥ 1 mitotic figures per mm². Of these 10 patients, three underwent SLNB; all were negative for nodal metastasis and none developed recurrent disease. The remaining seven patients who did not undergo SLNB, and three developed recurrences: one at the primary site, one in regional nodes, and one both in the nodes and as distant metastases. Only 10 of 23 patients with lesions >1 mm underwent SLNB at the time of excision of the primary lesion. None initially had nodal disease; however, one patient did develop regional nodal metastasis approximately 4 months later, at which point a formal LND revealed three positive nodes. This patient subsequently received interferon and local radiotherapy and is currently alive with no evidence of disease at 5.5 years of follow-up. Disease recurred in 4 of 13 patients with lesions >1 mm who did not undergo SLN evaluation. Three developed nodal metastasis at 0.85, 3.5, and 7.9 years, and the remaining patient developed distant disease in the brain and liver at 11.1 years. Three of these four patients have died as a result of disease progression (Table 1).

Disease Recurrence and Mortality

The median overall follow-up was 7.6 years (range, 0.1–31.7 y) and the median time to recurrence was 3.5 years (range, 0.3–14.0 y). Sixteen (16%) patients developed recurrent disease and eight subsequently died. For patients who ultimately died of melanoma progression, the median tumor depth was 1.3 mm (interquartile range [IQR], 1.0–1.6 mm) compared with 0.5 mm (IQR, 0.3–0.9 mm) in survivors ($P<0.001$). There were no deaths below a Breslow level of 0.75. Local recurrences arose in the regional lymph nodes ($n=9$) and at the primary site ($n=2$), and systemic recurrences were in the liver ($n=3$), brain ($n=1$), and lung ($n=1$). Disease stages at recurrence were stage 1B ($n=10$), stage 1A ($n=5$), and MIS ($n=1$). All patients with recurrent disease at the primary site underwent wide re-excision. All nine patients with recurrent nodal disease underwent regional LND, which revealed 1 to 14 positive nodes per patient. Local and systemic recurrences were present in one patient, who underwent bilateral pulmonary metastasectomies in addition to receiving systemic therapies. Adjuvant therapies were administered to 13 of 16 patients with recurrence and included radiotherapy, interleukin-2, interferon, chemotherapy, and vaccine treatments (Table 1). The patient with local recurrence at the primary site received wide re-excision only, while the patient with regional nodal disease underwent regional LND. These two patients are alive with no evidence of disease at 25.4 and 7.3 years of follow-up, respectively. The third patient with both regional and systemic disease is alive at 10.7 years of follow-up. He has

completed wide re-excision and regional LND for his recurrent regional disease and is now receiving interferon for the recurrent systemic disease.

The 10- and 20-year overall survivals were 90.3% (95% CI: 82.2–99.1%), and 77.4% (95% CI: 82.2–91.1%) (Figure 1A). The probability of melanoma-related death was 7.0% (95% CI: 6.8–7.2 %) at 10 years, and 20.1% (95% CI: 19.3–20.9%) at 20 years from diagnosis (Figure 1B). The probability of first melanoma recurrence was 20.4% (95% CI: 19.8–26.4%) at 10 years and 34.0% (95% CI: 32.7–35.3%) at 20 years from initial surgery (Figure 1C). The probability of development of a second primary melanoma was 17.4% (95% CI: 16.9–17.9%) at 10 years from initial diagnosis and 24.7% (95% CI: 24.2–25.2%) at 20 years. Greater tumor depth and Clark level correlated with higher rates of both disease-specific death and recurrence (Table 2; Figure 2), while a family history of melanoma was associated with an increased rate of second primary melanomas ($P<.008$; Table 2). The complete results of our univariate analysis for all three endpoints are presented in Table 2.

Second Primary Lesions

Fourteen (14%) patients developed a first additional primary melanoma after their initial diagnosis. All new lesions were widely excised. Eight of the second primaries were melanoma in-situ, while 5 were stage 1A disease with a median thickness of 0.77 mm (range, 0.44–0.85 mm). The remaining patient had a stage 2A lesion that was 1.5 mm thick with 3 mitosis/mm² and ulceration. This patient underwent a SLNB with his wide excision that was negative for nodal metastasis. The median time from the initial diagnosis until the identification of an additional primary melanoma was 4 years (range, 1 mo –16.5 y). A family history of melanoma was associated with an increased risk of development of a second primary melanoma (probability of 52% at 10 years vs 11% among those without family history).

DISCUSSION

The incidence of melanoma in young patients is increasing, and identification of factors that affect survival, recurrence rate, and development of second primary melanomas is essential for adequate therapy and development of follow-up protocols. Many series do not distinguish between melanoma and Spitzoid lesions, including Spitzoid melanoma, that have a higher rate of regional nodal involvement at diagnosis but a better prognosis and generally occur in younger age groups. Currently, there is a notable lack of such data on early-stage, non-Spitzoid melanoma in pediatric and adolescent patients and this is one of the first studies to address prognostic factors in this age group with a very long follow-up time. The first observation to make is that recurrence and late mortality are not negligible in this cohort despite the fact that these are lower-stage melanomas. As can be seen in Figure 1, we identified late recurrences and deaths, as reported in the literature for older populations. Recurrences were observed up to 14 years after initial surgery, and late disease-specific mortality up to 11 years after diagnosis. This is in concordance with previously published adult data demonstrating that thin melanomas have the capacity to recur both locally and systemically many years after the first definitive treatment [18]. Since late recurrence is possible, certain patients might benefit from more prolonged and intense follow-up and/or

treatment intensification. Apropos of this, we identified Breslow thickness and Clark level as correlates of recurrence and disease-specific mortality. They are highly correlated and the small number of events for each endpoint precluded multivariate analysis. However, it is reasonable to conclude, based on a number of recent studies, that tumor depth is the primary predictive factor. In the present analysis there were no deaths observed in patients with in-situ lesions, or with tumors <0.75 mm. This would constitute a low-risk group. The question remains as to whether treatment intensification in patients with thicker lesions is justified.

Since only 21 (21%) of our patients underwent sentinel lymph node biopsy, it is tempting to speculate that increased use of this procedure might influence outcome. Current recommendations regarding SLNB in patients with low-stage melanoma are debatable but there is some consensus that patients with lesions >1 mm should undergo sentinel lymph node evaluation. Further, according to recent recommendations, patients with lesion thickness between 0.51 mm and 1.0 mm and mitosis $\geq 1/\text{mm}^2$ should also undergo SLNB [17]. AJCC staging for melanoma recognizes the mitotic index of a tumor as a negative prognostic indicator (although not an independent one) and uses mitosis as a modifier to reclassify from stage 1A to 1B those tumors that are ≥ 1 mm thick. It is important to realize that in 5 of the 8 disease-specific deaths, distant parenchymal metastases rather than regional lymph nodes were the first site of recurrence. Further, two of these patients had undergone negative sentinel lymph node biopsies; one recurred in lung while the other developed liver metastases. There is an association between increased mitotic index and the development of distant metastases with consequent negative impact on disease-specific survival. This has been validated by other investigators [18–20]. Mitotic index, by itself, did not correlate with outcome in this series but this retrospective analysis is hampered by the relatively low number of patients in which this was determined. Other authors have also noted that mitotic index is not an independent prognostic factor but is most useful when combined with tumor depth. Importantly, regional node dissection precipitated by finding positive sentinel lymph nodes does not affect melanoma mortality. Thus, it seems reasonable to conclude that sentinel lymph node biopsy in this group of patients will not lead to meaningful therapeutic interventions and is best avoided in this group of patients. It may be more productive to examine the newer molecular markers that are emerging (e.g., BRAF mutations) in the primary tumor to guide management and prognosis [21].

Ulceration of the primary melanoma has also been identified in some large series as an important prognostic determinant [22, 23] but none of our patients presented with ulceration so we could not analyze this factor. Likewise, because of a low number of prepubertal patients in our cohort, we could not analyze features specific to this population. In the literature, prepubertal age has been associated with an increased incidence of nodal involvement but this has not translated into an increased mortality [24, 25]. Importantly, most series do not discriminate Spitzoid melanoma/tumors from other forms. We found no effect of age on either recurrence or melanoma-specific survival and this has also been noted in one large analysis of SEER data [2]. Finally, although male patients are reportedly at greater risk than females, we did not observe this in our cohort [2, 26, 27]. Data that identifies male sex as a negative prognostic indicator usually correlates maleness with an increased frequency of regional nodal involvement or other known negative factors.

Finally, 14 second primary melanomas were noted in our patients; one of these occurred 6.5 years after the first melanoma. The only factor associated with this was a family history as has been reported by others as well[28]. In particular, these families often demonstrate a fair-skinned phenotype with inability to tan. Male gender, increased age (>80 years), and Breslow thickness of 2 mm have also been correlated with second melanomas. It is interesting to note that second cancers of all kinds have developed in association with cutaneous melanoma[29, 30].

In summary, we have presented a large series of adolescent patients with low-stage, non-Spitzoid cutaneous melanoma with a relatively long median follow-up. These data indicate a significant recurrence, and melanoma-specific mortality with tumor depth as the predominant prognostic factor. These data do not support a role for sentinel lymph node biopsy based on pattern of recurrence. Expanded molecular analysis of the primary tumor offers the greatest hope for a deeper understanding of tumor biology and more rational interventions.

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Fig. 1. Kaplan-Meier analyses of overall survival (A), disease-specific death (B), and recurrence (C) in our patient cohort.

Fig. 2. Kaplan-Meier curves demonstrating the higher probability of disease specific death among patients with greater tumor depth (A) and higher Clark level (B).

Tumor Characteristics and Treatment for Patients with Recurrent Disease (n=16)

Table 1

I D	Location	Thick ness (mm)	Sta ge	Clas sification	Initial Surgical Management	PFS (years)	Recurrent Disease Location	Additional Surgical Management *	Salvage Treatments	Status
1	Back/trunk	0	In-Situ	2	WLE	3.8	Local LN	LND (1/16)	Vaccine	NED
2	Head/neck	1.0	1A	3	WLE	10.5	Liver/brain	None	CT+IF+IL-2	DOD
3	Upper extremity	1.0	1B	4	WLE	6.8	Primary site	Re-WLE	None	NED
4	Back/trunk	0.9	1A	3	WLE	5.0	Brain/lung	None	XRT	DOD
5	Upper extremity	0.8	1B	4	WLE	8.5	Local LN/diffuse	LND (1/13)	XRT, IF	AWD
6	Back/trunk	0.75	1A	4	WLE	5.3	Local LN	LND (2/35)	None	DOD
7	Back/trunk	0.69	1A	3	WLE	3.4	Local LN	LND (14/23)	Vaccine GM2	NED
8	Lower extremity	0.67	1B	3	WLE	14.0	Local LN	LND (1/25)	Vaccine HSP	NED
9	Back/trunk	0.3	1A	3	WLE	1.3	Local LN	LND (3/NA)	None	NED
10	Head/neck	2.0	1B	4	WLE+SLNB	0.31	Local LN	LND (3/84)	XRT, IF	NED
11	Head/neck	1.9	1B	3	WLE	0.85	Primary site, brain	Re-WLE, LND (5/24)	XRT, IF	DOD
12	Upper extremity	1.7	1B	4	WLE+LND	10.7	Lung/liver/brain	None	IL-2	DOD
13	Back/trunk	1.5	1B	3	WLE	3.5	Local LN	LND (1/15)	Vaccine GD3	DUK
14	Back/trunk	1.4	1B	4	WLE	11.1	Liver/brain	None	XRT	DOD
15	Back/trunk	1.4	1B	NA	WLE+SLNB	7.0	Liver/brain/bone	None	IL-2, CT, XRT	DOD
16	Head/neck	1.2	1B	4	WLE	7.9	Local LN, liver	LND (4/40), B-pulmonary metastasectomies	IL-2, Vaccine	DOD

PFS: Progression free survival, WLE: Wide local excision, SLNB: Sentinel lymph node biopsy, LND: Lymph node dissection, LN: Lymph node, CT: Chemotherapy, IF: Interferon, XRT: Radiotherapy, NED: No evidence of disease, DOD: Dead from disease, AWD: Alive with disease, DUK: Death of unknown cause, NA: Not available.

* Number after LND implies positive nodes/total nodes removed.

Table 2

Prognostic significance of patient and disease parameters

Patient or Disease Parameter	Disease Specific Death (<i>P</i> value)	Recurrence (<i>P</i> value)	Development of 2 nd Primary (<i>P</i> value)
Tumor depth (continuous)	0.002	0.013	0.20
Clark level	0.004	0.02	0.25
Primary site location	0.25	0.33	0.42
Mitoses (/mm ²)	0.12	0.14	0.99
Age (continuous)	0.30	0.30	0.86
Sex	0.56	0.65	0.82
Family history	0.99	0.77	0.008

Note: *P* values in bold are statistically significant.