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Sentinel lymph node biopsy is a prognostic measure in pediatric melanoma[☆]

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Abstract

Background/Purpose—Sentinel lymph node biopsy (SLNB)-based management has been shown to improve disease-free survival in adult melanoma, but there is scant evidence regarding the utility of SLNB in pediatric melanoma.

Methods—The 2004–2011 Surveillance, Epidemiology, and End Results database was queried for patients with primary cutaneous melanoma of Breslow depth > 0.75 mm and clinically negative nodes. Pediatric patients, defined as less than 20 years of age, were grouped by whether they underwent SLNB or not. Kaplan–Meier analysis was performed to compare melanoma-specific survival (MSS) in propensity-matched groups.

Results—310 pediatric patients met study criteria: 261 (84%) underwent SLNB, while 49 (16%) did not. There was no difference in MSS between matched children who received SLNB and those who did not ($p = 0.36$). Among children who received SLNB, a positive SLNB was associated with worse MSS compared to a negative SLNB (89% vs. 100% at 84 months, $p = 0.04$). However, children with a positive SLNB had more favorable survival compared to patients > 20 years of age (88% vs. 66% at 84 months, $p = 0.02$).

Conclusions—SLNB does not confer a survival benefit to children with melanoma, but it provides valuable prognostic information regarding MSS.

Keywords

Malignant melanoma; Sentinel lymph node biopsy; Children

Although melanoma accounts for only 2% of all skin cancer diagnoses in the United States, its incidence has risen markedly over the past three decades in both the adult and pediatric populations [1–4]. Melanoma is the most common skin cancer in children, with 300–500 new pediatric cases diagnosed each year [3,5]. Currently, treatment of pediatric melanoma is adapted from studies of adult melanoma, despite differences in the pathophysiology, clinical presentation, and survival of children with melanoma compared to adults.

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In younger children, up to 40% of melanomas originate from large congenital nevi [6–8], and more than half of malignant melanoma arising from large congenital nevi occurs in the first decade of life [9]. At time of presentation, children are more likely to have thicker lesions, distant metastases, and positive lymph node status [10–12]. These findings may be because of delayed presentation, the tendency for benign lesions such as atypical Spitz tumors (AST) to mimic melanoma in children, or age-related differences in tumor biology. Some studies suggest that children with melanoma may present with more advanced disease but experience better or similar survival compared to adults [13–15]; however, this finding is controversial [16,17].

Despite these differences between children and adults with melanoma, current treatment guidelines for pediatric melanoma have been adapted from studies of adult melanoma. In adults, lymphatic mapping and sentinel lymph node biopsy (SLNB) have been studied in a randomized, prospective trial and are recommended to identify patients who would benefit from further treatment of regional disease [18–20]. For children with clinically localized stage I–II melanoma, SLNB also may provide a means to identify those at risk of worse survival, but evidence is limited. Studies that examine use of SLNB in children are derived from single-center experiences, in which small cohort sizes preclude multivariable adjustment and generalizability of the data [11,21,22]. Hence, we used the Surveillance, Epidemiology and End Results (SEER) Program, a large national cancer registry, to assess the clinical impact of SLNB in pediatric melanoma on a population level.

1. Materials and methods

1.1. Data source

The SEER Program of the National Cancer Institute is a population-based cancer registry that collects cancer outcomes for 30% of the U.S. population. The population included in SEER is representative of the U.S. in regard to socioeconomic status and education although sampled areas tend to have more foreign-born inhabitants. The release used in this study includes data for cases diagnosed between 1973 and 2011, and it is based on the November 2013 data submission from 17 SEER registries [23].

1.2. Study design

This study was considered exempt from review by the Duke University Institutional Review Board. Using the International Classification of Diseases for Oncology histology codes 8720–8790, all patients with melanoma of Breslow depth > 0.75 mm diagnosed between 2004 and 2011 were identified. Any patients with missing lymph node harvest data, nonmalignant pathology, history of any other malignancy, or those with clinically apparent metastatic disease (distant or within regional lymph nodes) were excluded. We selected the depth criterion based on the 2015 National Comprehensive Cancer Network (NCCN) melanoma guidelines that suggest consideration of sentinel lymph biopsy for melanoma with Breslow depth > 0.75 mm [24]. The study period was determined based on availability of data regarding lymph node status and treatment. Owing to the longevity observed in pediatric melanoma patients, our primary endpoint was melanoma-specific survival (MSS).

1.3. Statistical analysis

Pediatric patients (defined as less than 20 years of age) were identified within the initial cohort and stratified by whether they underwent nodal observation or SLNB-based management of the regional nodal basin. The latter was considered the “SLNB group” throughout the analysis. Baseline characteristics were compared using the Kruskal–Wallis test for continuous variables and χ^2 test for categorical variables. Multivariable logistic regression modeling was used to assess patient demographic and clinical characteristics that were predictive of utilizing SLNB.

In order to mitigate the effects of selection bias in the decision to perform SLNB, we developed propensity scores, defined as the conditional probability of undergoing SLNB. Groups were then matched using a 1:1 nearest neighbor algorithm on the following patient and tumor characteristics: age at diagnosis, sex, race, Breslow depth, presence of ulceration, and tumor location. Mitotic index could not be included in our match because of significant missing data. MSS was compared between propensity-matched groups using the Kaplan–Meier method. Using the same approach, a subset analysis was performed among patients who underwent SLNB to compare MSS between those with positive vs. negative SLNB status. Finally, in order to assess differences between children and adults, outcomes were compared between matched patients <20 years vs. ≥20 years of age who had a positive SLNB. A p value of less than 0.05 was considered statistically significant. Statistical analysis was performed using R version 3.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

2. Results

Among 30,527 patients with melanoma of Breslow depth > 0.75 mm, 310 (1%) were less than 20 years of age: 261 (84%) underwent SLNB while 49 (16%) did not. Baseline patient demographics and clinical characteristics of the pediatric cohort, stratified by use of SLNB or not, are shown in Table 1. Breslow depth (OR 1.21, $p = 0.10$) and ulceration (OR 3.33, $p = 0.11$) were not independent predictors of utilizing SLNB (Fig. 1). After propensity matching for patient age, sex, race, Breslow depth, ulceration and tumor location, SLNB did not improve MSS (96% vs. 100% at 84 months, $p = 0.36$, Fig. 2a).

In the subanalysis of pediatric melanoma patients who underwent SLNB, patients with positive SLNB status had greater Breslow depth (median 2.5 vs. 1.4 mm, $p < 0.001$) and a higher rate of ulceration (30% vs. 9%, $p < 0.001$) (Table 2). After matching, melanoma patients with a positive SLNB experienced worse MSS than those with a negative SLNB (89% vs. 100% at 84 months, $p = 0.04$, Fig. 2b).

Finally, we compared MSS between matched pediatric and adult patients with melanoma > 0.75 mm thick and positive SLNB status. Despite presence of microscopic nodal disease in both groups, children had significantly better survival than adults (88% vs. 66% at 84 months, $p = 0.02$, Fig. 2c).

3. Discussion

In this population level study of pediatric melanoma, we found that SLNB – with or without subsequent completion lymph node dissection (CLND) – was not associated with improved MSS, but positive SLNB did identify children with worse MSS. This finding is concordant with previous studies of both adult and pediatric melanoma, which have found positive regional lymph nodes to be associated with worse survival [3,14,20,25]. Since children with clinically localized melanoma are a heterogeneous group that includes those with true localized disease as well as those with subclinical regional disease or distant spread, our finding supports the use of SLNB in children with melanoma > 0.75 mm thick to identify those who may benefit from closer surveillance or adjuvant therapy.

In adults, the utility of SLNB has been established in both prospective and retrospective studies. The prospective Multicenter Selective Lymphadenectomy Trial (MSLT-1) was launched in 1994 and randomized patients in a 60:40 fashion to either SLNB or nodal observation in order to determine if SLNB and immediate CLND provided a survival benefit. Among patients with intermediate thickness melanoma (defined as 1.2–3.5 mm in thickness) who underwent SLNB, Morton et al. found that biopsy-based management did not improve MSS, but a positive SLNB was associated with significantly worse 10-year MSS, compared to a negative SLNB (62% vs. 85%, hazard ratio [HR] 3.09, $p < 0.001$) [20]. Subsequently, a retrospective population-based study echoed the results of MSLT-1: a positive sentinel lymph node was associated with significantly worse 5-year MSS in adults (65% vs. 89%, $p < 0.0001$) [25].

Although children with positive SLNB status experienced worse MSS, our study also showed that their survival was better than adults with similar extent of disease. Previous studies have reported comparable findings. In an institutional study of 20 children who underwent SLNB for melanoma, Roaten et al. observed a higher incidence of lymph node metastases but less disease recurrence, compared to adults [11]. In a case-matched analysis, Livestro et al. found a trend toward better MSS in children than adults, but the number of patients may have been too low to gain statistical significance [14]. Given the mounting evidence that pediatric patients with melanoma have better outcomes than adults, the appropriateness of basing pediatric care on adult studies is called into question. In addition to SLNB, other elements of adult melanoma care should be studied individually to determine their effectiveness in pediatric melanoma.

For example, a known positive sentinel lymph node leads to consideration of adjuvant therapies, which have been explored in adults without parallel studies in children. The NCCN guidelines recommend baseline imaging for staging, CLND as primary treatment, and consideration of interferon- α (IFN- α) as adjuvant therapy for node-positive melanoma. IFN- α has been studied through multiple randomized controlled trials in adults with melanoma, but results are conflicting [26–28]. Currently, the NCCN considers IFN- α a category 2b recommendation for stage IIb/IIc and III melanoma because of the low benefit-to-risk ratio and encourages clinicians to make decision about adjuvant IFN- α on an individual patient basis [24]. However, again, these guidelines have been generated specifically for adults without dedicated, similar studies in children.

Continued research to understand outcomes in pediatric melanoma will help define age-specific treatment algorithms and improve adherence to guidelines. In our study, we noted a lack of consensus in the decision to perform SLNB: clinical factors such as Breslow depth or presence of ulceration did not guide use of SLNB although these characteristics can portend higher risk of positive regional nodes. This variation in care may be related to the lack of evidence and of age-specific guidelines for pediatric melanoma, which can be addressed through further research on the disease.

We acknowledge that our study has several limitations that are inherent to any study that employs national databases, such as the lack of granularity of data and the potential for coding errors. Additionally, our study was retrospective and thus subject to selection bias, which we attempt to address through our statistical methodology using propensity matching. Finally, we could not account for the existence of variant lesions such as AST and melanocytic tumors of uncertain malignant potential, which are thought to behave differently from true melanoma [29,30].

Despite these limitations, this study provides valuable information about the role of SLNB in pediatric melanoma by using a large national study cohort and adjusting for disease severity. Given the relative infrequency of pediatric melanoma, a randomized study such as MSLT-1 that can accumulate sufficient power to show a difference may not be feasible. Hence, national databases provide a unique opportunity to study patterns of care and outcomes in pediatric melanoma with more patients than any single institutional study. We show that SLNB status is an important tool for risk stratification in children with clinically localized melanoma and support its continued clinical use. In the future, management of pediatric melanoma should be defined by studies focused on children, as their clinical outcomes differ from adults.

4. Conclusion

In this population-based study of 310 children with melanoma, we have demonstrated that positive sentinel lymph node status is associated with worse melanoma-specific survival. Our findings support the practice of performing a sentinel lymph node biopsy in children with clinically localized melanoma greater than 0.75 mm in thickness to provide prognostic information and guide clinical decision making.

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Fig. 1. Predictors of utilizing sentinel lymph node biopsy (SLNB) among pediatric patients with melanoma. Footnote: Black circles represent odds ratios for the independent association of each factor with use of SLNB; 95% confidence interval bounds are represented by the corresponding horizontal lines. Factors on the right of the dashed vertical line at 1.0 are independently associated with using SLNB.

Fig. 2.

(a) Melanoma-specific survival (MSS) of matched pediatric melanoma patients who underwent sentinel lymph node biopsy (SLNB) vs. observation only. (b) MSS of matched pediatric melanoma patients who underwent SLNB, stratified by pathologic sentinel lymph node status. (c) MSS of matched adult and pediatric patients with melanoma and positive sentinel lymph node status.

Table 1

Baseline characteristics of patients <20 years of age with melanoma of Breslow depth greater than 0.75 mm and clinically negative nodes, stratified by use of sentinel lymph node biopsy (SLNB) or not.

	No SLNB (N = 49)	SLNB (N = 261)	p Value
Age at Diagnosis	15 (9, 18)	16 (13, 18)	0.15
Sex			0.10
Male	53% (26)	40% (105)	
Female	47% (23)	60% (156)	
Race			0.02
White	84% (41)	94% (246)	
Black	2% (1)	2% (4)	
Other	14% (7)	4% (11)	
Primary Site			0.77
Face, Head and Neck	14% (7)	13% (35)	
Extremities	39% (19)	46% (121)	
Trunk	35% (17)	28% (74)	
Others	12% (6)	12% (31)	
Breslow Depth (mm)	1.5 (0.9, 2.6)	1.6 (1.1, 3.2)	0.16
Ulceration			0.06
Absent	95% (41)	85% (213)	
Present	5% (2)	15% (39)	
Mitotic Index			0.95
Nonmitotic	12% (1)	12% (4)	
Mitotic Rate 1/mm ²	88% (7)	88% (30)	
Positive Pathologic LN			
No	N/A	72% (188)	
Yes	N/A	28% (73)	
Mortality during Study Period	0% (0)	2% (5)	0.33

Footnote: Categorical variables are represented as percent (number) and continuous variables are represented as median (interquartile range). LN: lymph node.

Table 2

Baseline characteristics of patients <20 years of age with melanoma of Breslow depth greater than 0.75 mm who underwent sentinel lymph node biopsy (SLNB), stratified by pathologic SLNB status.

	SLNB Negative (N = 188)	SLNB Positive (N = 73)	p Value
Age	16 (13, 18)	15 (12, 18)	0.22
Sex			0.21
Male	38% (71)	47% (34)	
Female	62% (117)	53% (39)	
Race			0.11
White	95% (178)	93% (68)	
Black	1% (1)	4% (3)	
Other	5% (9)	3% (2)	
Primary Site			0.55
Face, Head and Neck	14% (26)	12% (9)	
Extremities	45% (85)	49% (36)	
Trunk	30% (57)	23% (17)	
Others	11% (20)	15% (11)	
Breslow Depth (mm)	1.4 (1.1, 2.6)	2.5 (1.5, 4.4)	<0.001
Ulceration			<0.001
Absent	91% (162)	70% (51)	
Present	9% (17)	30% (22)	
Mitotic Index			0.55
Nonmitotic	16% (4)	0% (0)	
Mitotic Rate 1/mm ²	84% (21)	100% (9)	
Mortality during Study Period	0% (0)	7% (5)	0.002

Footnote: Categorical variables are represented as percent (number) and continuous variables are represented as median (interquartile range).