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REVIEW

Pediatric melanoma: incidence, treatment, and prognosis

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Abstract: The purpose of this review is to outline recent advancements in diagnosis, treatment, and prevention of pediatric melanoma. Despite the recent decline in incidence, it continues to be the deadliest form of skin cancer in children and adolescents. Pediatric melanoma presents differently from adult melanoma; thus, the traditional asymmetry, border irregularity, color variegation, diameter >6 mm, and evolution (ABCDE) criteria have been modified to include features unique to pediatric melanoma (amelanotic, bleeding/bump, color uniformity, de novo/any diameter, evolution of mole). Surgical and medical management of pediatric melanoma continues to derive guidelines from adult melanoma treatment. However, more drug trials are being conducted to determine the specific impact of drug combinations on pediatric patients. Alongside medical and surgical treatment, prevention is a central component of battling the incidence, as ultraviolet (UV)-related mutations play a central role in the vast majority of pediatric melanoma cases. Aggressive prevention measures targeting sun safety and tanning bed usage have shown positive sun-safety behavior trends, as well as the potential to decrease melanomas that manifest later in life. As research into the field of pediatric melanoma continues to expand, a prevention paradigm needs to continue on a community-wide level.

Keywords: melanoma, pediatric, adolescent, childhood

Epidemiology

Melanoma is the deadliest form of skin cancer and is the second leading cause of cancer in adolescents and young adults aged 15–29 years.[1] The incidence of melanoma sharply increases with age from 1.1 per million in 1- to 4-year-olds to 10.4 per million in 15- to 19-year-olds.[2] Since the 1970s, the incidence of pediatric melanoma has increased with an average annual percent change of 2–2.9%.[3–5] However, updated analyses of the Surveillance, Epidemiology, and End Results (SEER) database show decreasing overall trends from 2000 to 2010.[6,7] Campbell et al[7] found an 11.6% decrease in pediatric melanoma per year for children <20 years of age from 2004 to 2010. Within this demographic, higher rates of melanoma exist for children of older ages.[8,9] There are also gender-based differences. Although females show a slightly higher incidence, both males and females show decreasing trends in melanoma incidence.[7] Females older than 4 years have a higher incidence of lower body melanoma, and males older than 10 years have a higher incidence of head and neck melanoma.[4] Furthermore, the majority of pediatric melanoma patients are non-Hispanic white. An analysis of SEER showed that 85% of melanoma cases in

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patients <18 years old were in non-Hispanic white patients, followed by Hispanic patients (5%) and Asian/Pacific Islander patients (2%).[3]

Risk factors

The majority of pediatric melanoma cases are sporadic and related to ultraviolet (UV) DNA damage.[9,10] UV light is associated with an increased risk of melanoma and changes in pigmentation.[5,11,12] This may have a more pronounced effect in older children and adults due to a cumulative UV exposure effect. Risk factors such as genetics, nevi, and family history can interact with UV exposure to cause melanoma in younger patients.[9]

Only 22% of pediatric melanoma patients have non-modifiable risk factors, including fair skin, xeroderma pigmentosum (XP), genetic susceptibility, pigmentation, age, nevi pattern, and family history.[12] XP is an autosomal recessive disorder associated with a defect in DNA excisional repair mechanisms, resulting in a 1000-fold increased risk of skin cancer. Associated skin malignancies include squamous cell carcinoma, basal cell carcinoma, and melanoma. Approximately 5% of individuals with XP develop melanoma by a median age of 19 years.[9] Familial melanoma accounts for ~1% of cases of melanoma.[13,14] Mutations in *CDKN2A* are associated with ~20–40% of families with three or more individuals with melanoma, while *CDK4* mutations have only been found in 17 families. Mutations in *CDKN2A* and *CDK4* are associated with atypical nevi, early-onset melanoma, and multiple primaries.[13,14] Other genes associated with an increased susceptibility to melanoma among families and the general population include mutations in *MITF*, which confer a population-wide increased odds of melanoma of 1.7–4.8.[15,16]

The presence of congenital nevi (CNM) is significantly correlated with melanoma. In a study of adolescents aged 15–19 years, the risk of melanoma was found to be 34 times higher in children with 100+ nevi and 15 times higher in children with 10+ large nevi >5 mm in diameter.[9,17] A similar study conducted in Australia examined children younger than 15 years. In that study, Whiteman et al[18] found multiple nevi and sun-sensitive characteristics, such as facial freckling and less tanning ability, to be indicative of a higher incidence of melanoma. Similarly, both inherited immunodeficiency and acquired immunosuppression, such as organ transplantation, are correlated with increased nevus density and higher rates of melanoma.[9] Immunosuppressed patients with concerning nevi should be monitored and evaluated extensively, as these patients have an increased risk of melanoma.

Pathology

Pediatric melanoma can be subclassified into the following three main categories: conventional melanoma (CM), melanoma arising in CNM, and spitzoid melanoma.[19] Differentiating between these subtypes is important because each type has different treatment options, risk factors, and histological findings. CMs show a high rate of single nucleotide variations (SNVs) that are characteristic of UV damage.[20] This includes *TERT*-p mutations that result in a C→T coding change. As a result of this SNV, CM tumor cells have increased oncogene activity.[20] CM also shows genetic similarity to adult melanoma, suggesting the potential for further research on treatments based on adult melanoma protocols.[19] CMs and CNMs may be differentiated by *BRAF* and *NRAS* mutations, respectively. *BRAF* mutations in CMs only affect the mitogen-activated protein kinase pathway, thus requiring a supplementary *PTEN* mutation to result in melanoma. Since *NRAS* functions in both the mitogen-activated protein kinase and the phosphatidylinositol 3 kinase/AKT pathway, an *NRAS* mutation in a CNM can lead to malignancy without a *PTEN* mutation.[20] This is supported by evidence that melanoma arising in CNMs shows a lower frequency of UV-related mutations, possibly due to a higher baseline risk.[19]

There is a broad spectrum of atypical melanocytic neoplasms, and the distinction between Spitz nevus, atypical Spitz tumor, spitzoid melanoma, and melanocytic tumors of uncertain malignant potential is controversial with little diagnostic agreement among dermatopathologists.[21–23] Many of these melanocytic lesions are misdiagnosed as benign and only recognized later to be malignant after they have recurred. In one study, 35% of the cases originally classified as spitzoid upon review were determined to be CMs with epithelioid or spindle cells.[22] Because of the difficulty in differentiating benign from malignant melanocytic lesions in pediatric patients, all histological slides should be reviewed by dermatopathologists highly experienced in the diagnosis of such lesions.

Comparative genomic hybridization (CGH), fluorescence in situ hybridization (FISH), and immunohistochemistry (IHC) have been used as ancillary diagnostic tools to differentiate between melanoma and benign nevi in adults.[24] Melanoma has a variety of patterns of chromosomal aberrations of multiple chromosomal gains and/or losses. Conversely, the majority of Spitz nevi patients have a normal karyotype.[25] Atypical Spitz tumors represent a heterogeneous group with distinct genetic subtypes, including *BRAF*V^{600E}/BAP1^{neg}, *HRAS* mutant with increased copies of 11p, and homozygous 9p21 deletion with negative p16 expression.[25–27] Additionally, kinase fusions of *ROS1*, *NTRK1*, *ALK*, *BRAF*, and *RET* are found in the entire spectrum of spitzoid neoplasms in a mutually exclusive pattern.[28] More recently, two 4-probe FISH assays targeting 6p25(*RREB1*), 11q13 (*CCND1*), 9p21 (*CDKN2A*), and 8q24(*C-MYC*) and 6p25 (*RREB1*), 6q23 (*MYB*), Cep6 (centromere 6), and 11q13 (*CCND1*) used to differentiate between melanoma and benign nevi have been applied to Spitz tumors.[22,29] However, caution must be exercised when evaluating an overall positive FISH assay as 20–23% of Spitz nevi are positive in at least one of the individual FISH probes.[22,29] In conjunction with FISH and histological features of atypical Spitz tumors, the application of IHC panels assessing the expression of proteins involved in cell cycle regulation (Ki67, p16) and melanocytic markers (HMB45) can also be helpful in classifying spitzoid lesions.[30,31]

The clinical progression of spitzoid lesions is different from melanoma. Up to 39% of patients with atypical Spitz tumors will have nodal metastases. However, unlike patients with melanoma, nodal disease does not confer the same high mortality risk and there is rarely further disease progression.[32–34] Several genetic markers have been identified as potential prognostic indicators. Among atypical Spitz tumors, gains in 6p25 (*RREB1*), 11q13 (*CCND1*), and homozygous deletions of 9p21 (*CDKN2A*) are associated with a higher risk of aggressive clinical behavior. *TERT*-p mutations, found in >90% of CM, may also be a marker of more aggressive behavior when present in spitzoid lesions.[20,35] Conversely, isolated 6q23 (*MYB*) loss and loss of 3p21 in *BAP1*-associated Spitz tumors are associated with a favorable clinical outcome.[27,29]

Presentation

It is important to understand the different manifestations of pediatric melanoma as it varies across age groups. Previously, it was believed that younger children present with later stage lesions that are more likely to appear on the head and neck.[3,36,37] Current research shows that melanoma location is relatively equally distributed across the body for children <10 years of age, although younger children of age 0–4 years have a slightly lower incidence of truncal melanoma. Older children and adolescents aged 10–19 years have a higher incidence of truncal melanoma.[7] Males also tend to present with lesions on the face and trunk, while females more often present with extremity tumors.[12,36,38]

Diagnosis

Early recognition is important to prevent progression of melanoma. Traditionally, the asymmetry, border irregularity, color variegation, diameter >6 mm, and evolution (ABCDE) criteria are used for clinical detection of melanoma. However, Cordoro et al[10] found that 60% of children aged <10 years and 40% of adolescents did not meet the traditional ABCDE criteria. As a result, up to 82% of diagnoses took >6 months after detection and 62% of diagnoses took >2 months.[10] Children presented with amelanosis, symmetry, regular borders, uniform color, and diameters of ≤6 mm. Cordoro et al[10] thus proposed the following criteria to encompass characteristics more specific to pediatric melanoma: A = amelanotic; B = bleeding, bump; C = color uniformity; D = de novo, any diameter; and E = evolution of mole.[10,37,39]

A high index of suspicion is necessary when evaluating children. Dermatoscopic examination is important to visualize the morphologic features of pigmented and nonpigmented lesions to differentiate melanoma from nevi.[34] Full-thickness biopsy is indicated for suspicious lesions. Excisional biopsies are recommended for concerning lesions. However, full-thickness punch biopsies are an acceptable alternative for specific locations (palms/soles, digits, face, or ears) or very large lesions. Shave biopsies can interfere with pathologic diagnosis and accurate measurements of Breslow thickness. Thus, shave biopsies should only be utilized for lesions with a very low index of suspicion.[40]

Management

The National Comprehensive Cancer Network (NCCN) outlined the surgical management of melanoma based on stages as follows:[40]

1. Stage 0 – melanoma in situ or stage IA or IB with thickness ≤0.75 mm, regardless of other features (ulceration or mitotic rate). Only a wide local excision (WLE) is warranted for these patients.
2. Stage IA – with a thickness 0.76–1.0 mm with no ulceration and a mitotic rate 0/mm^2. For patients without adverse features (such as lesions >0.75 mm, positive deep margins, lymphovascular invasions, and invasion into reticular dermis), only WLE is recommended. Both WLE and sentinel lymph node biopsy (SLNB) are recommended if adverse features are present.
3. Stage IB – with thickness 0.76–1.0 mm with ulceration or a mitotic rate ≥1/mm^2 or stage IB or II with thickness >1.0 mm, any feature (ulceration, any mitotic rate), and clinically negative nodes. Both WLE and SLNB are recommended for these patients.
4. Stage III – with clinically detected (palpable) positive nodes, microscopic satellites (from assessment of the primary lesion), and/or in-transit disease. For these patients, WLE and complete lymph node dissection (CLND) are warranted. CLND is recommended in cases with positive SLNB.

5. Stage IV – distant metastases. Resection of the tumor and metastases is possibly indicated depending on variable factors, including the location of primary tumor/ metastases and progression of disease.[41]

SLNB is a minimally invasive staging tool used to determine if CLND and adjuvant therapy are warranted due to regional lymph node metasatases.[42] In children, SLNB does not improve melanoma-specific survival, but it can be used as a prognostic indicator for poorer outcomes.[43] In a study of 310 children (<20 years old) with a melanoma of Breslow depth >0.75 mm, 261 underwent SLNB, with a melanoma-specific survival of 100% for the group with negative SLNB and 89% for the positive SLNB group.[42]

There are limited options for adjuvant therapy among pediatric patients with metastatic melanoma. Pediatric melanoma is a rare disease, and clinical trials for adults with metastatic melanoma have often excluded pediatric patients. Pegylated interferon alpha-2b (IFNα-2b) is an adjuvant that has positively influenced disease-free survival in adults after melanoma resection. IFNα-2b is also shown to be safe and feasible in children.[44] Ipilimumab is a novel treatment for metastatic melanoma in adults, which was fast tracked for US Food and Drug Administration (FDA) approval after demonstrating improved survival in a pivotal Phase III clinical trial.[45] Ipilimumab is a monoclonal antibody that binds to cytotoxic T-lymphocyte-associated antigen 4, blocking the downregulation of T-cell pathways that prevent autoimmunity. However, there are limited data on its efficacy in pediatric patients. While Phase I clinical trial among pediatric patients demonstrated safe toxicity levels, a Phase II clinical trial (NCT01696045) evaluating overall survival among pediatric patients with previously treated or untreated metastatic melanoma was terminated due to slow enrollment.[46,47] An ongoing Phase II clinical trial (NCT02304458) is evaluating the efficacy of ipilimumab in combination with another monoclonal antibody, nivolumab.[47] Vemurafenib is another promising agent for the treatment of melanoma with BRAF mutations. However, similar to ipilimumab, a Phase II clinical trial (NCT01519323) evaluating vemurafenib in pediatric patients with metastatic melanoma was terminated due to low enrollment.

Other ongoing trials include a vaccine study using the patient's own tumor cells to create a vaccine that was genetically modified to secrete GM-CSF to delay or stop the growth of the patient's tumor (NCT00258687), a Phase I/II study of pembrolizumab, and a Phase II study (NCT00539591) evaluating the combination of temozolomide with pegylated IFNα-2b.[48–50] Further research is necessary to be able to determine effective combinations and protocols for these medications among pediatric patients with metastatic or recurrent melanoma.

Outcomes

Survival for pediatric melanoma has improved over the past 30 years, possibly due to improved staging.[5] Five-year overall survival for all stages is 87–95%.[4,5,38,43] Similar to adults, the main predictor of outcomes in melanoma is the stage at the time of diagnosis.[4,5,38,43] Among patients with stage IV metastatic melanoma, the median survival time is <1 year and 5-year overall survival is <12%.[4] Children <10 years old are more likely to present with a higher stage disease, which may in part be due to delayed diagnosis of children with melanoma.[4,10,43]

Data are conflicting regarding the prognostic role of age, gender, tumor thickness, ulceration, and sentinel lymph node status. In some studies, younger children <10 years old have significantly poorer survival as compared to adolescents, while in other studies, adolescents have decreased survival compared to younger children.[4,9,43,51,52] The data are mixed regarding the contribution of patient gender to overall survival and the interaction with patient's age and overall survival.[4,5,38,43,53] Younger children often present with thicker tumors than adults.[4,7,36] However, the association between tumor thickness and survival may be different between adults and children.[4,53] Conversely, other studies have demonstrated that increasing tumor thickness is associated with poorer survival among pediatric melanoma patients.[5,38,43] Tumor ulceration is also more common among young children <10 years and is associated with worse outcomes.[7,38,43] In addition, tumor thickness and ulceration are strong predictors of sentinel lymph node metastases among children.[54] Similar to adults, a positive sentinel lymph node is associated with poorer prognosis.[54,55] The prognostic implications of other traditional risk factors among adults with melanoma, including vertical growth phase, vascular invasion, and high mitotic activity, do not appear to be correlated with an increased risk of mortality.[33,43,53]

Prevention

UV light causes direct DNA mutations that are correlated with CM.[5,12,56] The World Health Organization (WHO) has classified UV exposure as a class I carcinogen that is associated with a higher incidence of melanoma, especially in children with a higher exposure to sunlight and/or tanning beds.[11,12,57] UV exposure is a highly preventable cause of melanoma if sun-safety protocols are followed. The Surgeon General issued a notice about melanoma prevention and sun safety in 2014. This "Call to Action" is centered around five goals: increasing sun-safety behaviors, informing the public about risks and options, pushing policies for safe

Table 1 Strategies to reduce UV exposure in children

Intervention	Example
Tanning bed restrictions	a) State-level legislation limiting and banning tanning bed use among minors
Multilevel sun-safety counseling	a) In a cohort of 300 parents, 147 were given sun-safety counseling and 153 were provided a book, a swim shirt, and weekly text reminders about wearing sun screen
Community-wide sun-safety training	a) SunWise program was implemented in elementary schools in Arizona to teach children about sun-safety behaviors.
	b) SunSmart City program in New Jersey focused on working with parks, political advocacy, and small businesses to encourage sun-safety behaviors and education in the community

Abbreviation: UV, ultraviolet.

habits, reducing the harms of indoor tanning, and increasing monitoring and surveillance of outcomes.[58] Several strategies adopted to reduce UV exposure in children are listed in Table 1.

Indoor tanning confers a sixfold increased risk of developing melanoma among women younger than 30 years, and the first exposure typically starts in adolescents.[59–61] Tanning bed-related lesions may manifest in late adolescence, but they continue to have a harmful impact throughout a patient's lifetime as UV exposure continues to accumulate.[59,60,62] Public health efforts, including a black-box warning issued by the FDA and state-level legislation restricting their use by minors, have significantly decreased the use of indoor tanning among adolescents.[63–65]

Disseminating information of proper sun-protective behaviors (using sunscreen, staying in the shade, wearing wide brim hats, and wearing protective clothing) is important to prevent early acquisition of sunburn and UV-related DNA damage. Multicomponent interventions incorporating printed materials, interactive multimedia, and distribution of sun-protective products and community-wide and school-based prevention programs have been shown to increase adherence to clothing and sunscreen recommendations.[66–68] For example, the SunWise Program developed by the Environmental Protection Agency to educate elementary and middle school-aged children about sun-safety habits is estimated to have prevented >11,000 cases of skin cancer and 50 premature deaths by 2015.[69]

Future directions

Melanoma-specific survival for pediatric melanoma is increasing by 4% per year.[5] Furthermore, recent studies have demonstrated that the rate of pediatric melanoma is decreasing. The overall prevalence and incidence are both relatively low and will continue to decrease if effective public health campaigns continue to be implemented.[7] Future analyses of prevention techniques should begin to take into account cultural and sociological factors that affect adherence to sun-safety recommendations to ensure that preventions are not targeted solely at the fair-skinned individuals. For the Latino populations in the US, acculturation to US culture actually decreased sun-safety behaviors, partly related to a lack of perceived risk in darker-skinned populations.[70] This underscores the importance of diverse interventions that target all demographics impacted by pediatric melanoma.

Conclusion

Pediatric melanoma has a growing body of knowledge, but more work is needed in implementing effective prevention and treatment. Pediatric melanoma is still poorly studied and underrepresented in clinical trials.[71] Parallel studies between children and adult cohorts for surgical management and novel treatment options will allow standardized guidelines to be implemented.[42] Simultaneously, more sun-safety protocols and recommendations can be created based on existing interventions that continue to show great potential in decreasing rates of melanoma.

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