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What's new in pediatric melanoma: An update from the APSA cancer committee

Jennifer H. Aldrink [a,1], Stephanie Polites [b,1], Timothy B Lautz [c], Marcus M Malek [d], Daniel Rhee [e], Jennifer Bruny [f], Emily R Christison-Lagay [g], Elisabeth T Tracy [h], Shahab Abdessalam [i], Peter F. Ehrlich [j], Roshni Dasgupta [k], Mary T. Austin [l,*]

[a] Division of Pediatric Surgery, The Ohio State University College of Medicine, Nationwide Children's Hospital, Columbus, OH
[b] Division of Pediatric Surgery, Oregon Health and Science University, Portland, OR
[c] Division of Pediatric Surgery, Ann & Robert H Lurie Children's Hospital of Chicago, Northwestern University, Chicago, IL
[d] Division of Pediatric General and Thoracic Surgery, Department of Surgery, University of Pittsburgh School of Medicine, Pittsburgh, PA
[e] Division of Pediatric Surgery, Johns Hopkins School of Medicine, Baltimore, MD
[f] Division of Pediatric Surgery, University of Colorado, Children's Hospital Colorado, Aurora, CO
[g] Division of Pediatric Surgery, Yale University School of Medicine, New Haven, CT
[h] Division of Pediatric Surgery, Duke University Medical Center, Durham, NC
[i] Department of Pediatric Surgery, Boys Town National Research Hospital, Omaha, NE
[j] Department of Surgery, University of Michigan, Ann Arbor, MI
[k] Division of Pediatric General and Thoracic Surgery, Cincinnati Childrens Hospital Medical Center, University of Cincinnati, Cincinnati, OH
[l] Department of Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

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ABSTRACT

Background/Purpose: Melanoma is the most common skin cancer in children and often presents in an atypical fashion when compared to adults. The purpose of this review is to present an update on the epidemiology, surgical and medical management and prevention strategies in pediatric melanoma.
Methods: A comprehensive review of the current literature on the epidemiology, surgical and medical management and prevention of adult and pediatric melanoma was performed by the authors and the results of this review are summarized in the manuscript.
Results: Most recently, the incidence of melanoma in children has been declining, possibly owing to increased awareness and sun exposure prevention. The mainstay of therapy is surgical resection, often with sentinel lymph node biopsy. A positive sentinel node has prognostic value; however, completion node dissection is no longer recommended in the absence of clinically or radiographically positive nodes. Those with advanced disease also receive adjuvant systemic therapy using increasingly targeted immunologic therapies.
Conclusions: Sentinel lymph node positive patients no longer require completion lymph node dissection and instead may be followed by ultrasound. However, it is important to note that children have been excluded from most melanoma clinical trials to date, and therefore, recommendations for management are based on existing pediatric retrospective data and extrapolation from adult studies.
Level of evidence: IV.

Contents

* Corresponding author at: The University of Texas MD Anderson Cancer Center, 1400 Pressler, Unit 1484, Houston, TX 77030.
E-mail address: maustin@mdanderson.org (M.T. Austin).
[1] Equal contribution first authors.

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In 2018, there were 91,270 new cases of melanoma and 9320 deaths owing to melanoma in the United States [1]. Although only 0.4% of melanoma cases and 0.1% of melanoma deaths occur in patients less than 20 years old, there are approximately 500 new diagnoses of melanoma in children and adolescents in the United States each year [1]. The incidence varies by race and ethnicity with the highest incidence in Caucasians at 6.68 per million in persons less than 19 years old [2]. The incidence increases with age and is exceedingly rare in children less than 5 years old (0.87 per million children) [3]. Although reports prior to 2008 suggested that the incidence of melanoma in children was increasing [4], more recent studies show a declining incidence in both children and young adults [2–3,5]. This decline may be owing in part to the increased use of sun protective clothing and sunscreen as well as the adoption of more strict indoor tanning regulations [6].

The majority of childhood and adolescent melanoma occurs sporadically with most attributed to ultraviolet pathophysiology from risk factor (UV) exposure, especially in adolescents. Familial cases account for only 1% of melanoma in children [7–8], but nearly 25% of pediatric patients have a preexisting condition known to be associated with melanoma [9]. These conditions include dysplastic nevus syndrome, congenital melanocytic nevi, xeroderma pigmentosa, immunodeficiency, and prior malignancy and/or radiation therapy (Table 1). While rare, xeroderma pigmentosa confers a 2000-fold increased risk of developing melanoma. However, the strongest preexisting risk factor for developing melanoma in adolescence is the presence of more than 100 nevi with a diameter > 2mm [10].

In children and adolescents, the diagnosis of melanoma is often not considered owing to its rarity and atypical presentation. Concerning features in a skin lesion include rapid growth, bleeding or itching [11]. It has been shown that up to 60% of diagnoses in children less than 10 years and 40% of diagnoses in children ages 11–19 years do not meet traditional ABCDE criteria (**A**symmetry, **B**order irregularity, **C**olor variegation, **D**iameter > 6mm and **E**volution) [12]. Thus modified ABCDE criteria have been proposed to be used in addition to the traditional criteria to help identify suspicious skin lesions in children and adolescents [12]. These criteria include **A**melanotic, **B**leeding or **B**ump, **C**olor uniformity, **D**e novo and any **D**iameter, and **E**volution [12]. It is quite common for pediatric melanoma to be amelanotic, and amelanotic lesions are more often misdiagnosed as warts, pyogenic granulomas, or other benign skin lesions (Fig. 1). In addition, common features of pediatric melanoma include bleeding and uniform color distribution as opposed to color variegation more commonly seen in adult melanoma. They often arise de novo without a preexisting skin lesion and they may be any diameter. A recent study from the University of Michigan found nearly 80% of melanoma in prepubertal and 25% in adolescents are amelanotic and that the lack of pigmentation was associated with a median delay in diagnosis of 9 months [11]. Approximately 80% of patients present with localized disease with less than 5% presenting with distant metastases [1]. Furthermore, Hispanic patients are 3.5 times more likely to present with more advanced stage disease than non-Hispanic whites, likely owing to low suspicion of disease in patients with darker skin types [13].

There are three main categories of pediatric melanoma: conventional melanoma, melanoma arising in a congenital nevus, and spitzoid melanoma. Conventional melanoma is genetically similar to adult melanoma [14] and demonstrates a high rate of single nucleotide variations (SNVs) characteristic of UV damage [15]. Melanoma arising in congenital nevi demonstrates a lower frequency of UV-related mutations [14]. There remains some debate among dermatopathologists regarding the distinction between atypical spitz nevus, melanocytic tumors of uncertain malignant potential, and spitzoid melanoma [16–18]. In one study, 35% of spitzoid tumors were initially misdiagnosed as spitz nevus and upon later review were determined to be melanoma with epithelioid or spindle cells [17]. There is no single method to differentiate an atypical spitz nevus from a spitzoid melanoma; however, comparative genomic hybridization (CGH) is often helpful in that melanoma often has a variety of chromosomal aberrations compared to most spitz nevi which demonstrate a normal karyotype [19]. For this reason, it is essential that lesions concerning for melanoma be reviewed by a dermatopathologist with experience in diagnosing

Table 1
Pre-existing conditions associated with melanoma.

Congenital melanocytic nevus
Transplacental transmission
Xeroderma pigmentosa and other genetic disorders that affect tumor suppressor genes
Dysplastic nevi and dysplastic nevus syndrome
Immunosuppression
Sun-sensitive phenotype (facial freckling, inability to tan)
Family history of melanoma

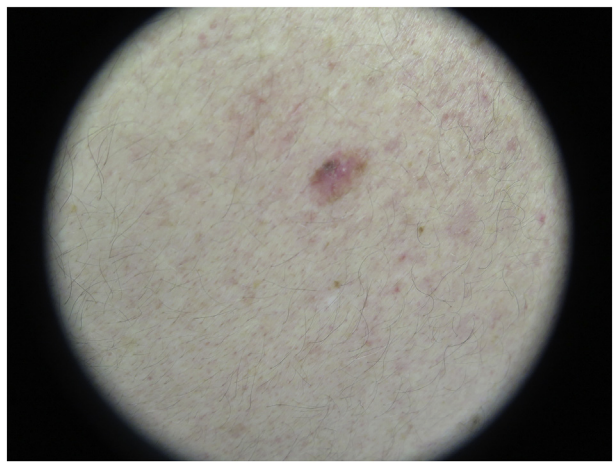

Fig. 1. Dermatoscopy of an amelanotic melanoma (photo courtesy of Dr. Kelly Nelson, The University of Texas MD Anderson Cancer Center, Houston, TX).

pediatric melanoma. If a lesion is determined to be a benign spitz nevus or atypical spitz nevus, excision with negative margins is indicated; however, spitzoid melanoma should be managed as melanoma per National Comprehensive Cancer Network (NCCN) guidelines [20].

1. Surgical management

Surgical excision of primary cutaneous melanoma is the keystone of curative therapy. In general, wide local excision with margins based on melanoma depth, with or without sentinel lymph node biopsy (SLNB) is performed. To this end, full thickness biopsy of suspicious lesions should be performed with a punch biopsy or a surgical excisional or incisional biopsy. Excisional surgical biopsies should include minimal margins (<3 mm) to avoid disrupting lymphatics which are crucial to potential SLNB mapping if pathologic evaluation determines the lesion to be melanoma. Small excisional biopsy margins also minimize the eventual size of wide local excision. While there are no recommended size criteria to proceed with excisional vs incisional biopsy, incisional biopsies should be reserved for larger lesions or those in cosmetically sensitive areas where excision may result in cosmetic or functional defects. Recent studies comparing adult melanoma outcomes by biopsy modality found no difference in disease free or overall survival.

1.1. Wide local excision

Despite differences in the epidemiology and pathology of melanoma in the pediatric population, recommendations for surgical management are based on those established for adults [21]. After confirmation of the diagnosis by an experienced dermatopathologist, wide local excision of the lesion or biopsy site should be performed. Wide local excision should extend to muscular fascia; deeper resections involving fascial or muscle resection are not beneficial [22]. When primary closure is not feasible or the excision is performed in a cosmetically or functionally-sensitive region such as the face, joints, hands, or feet, advanced tissue coverage options including grafts, flaps, or tension-releasing plasties may be performed. There is extensive literature on optimal margins for wide local excision of primary cutaneous melanoma based on lesion depth as defined by Breslow thickness which forms the basis of National Comprehensive Cancer Network (NCCN) guidelines for surgical management of melanoma [23].

The recommended surgical margins are shown in Table 2. Lesions ≤1.0 mm in depth require 1.0 cm margin while a 2.0 cm margin is indicated for lesions >2.0 mm in depth. Intermediate thickness lesions (1.0–2.0 mm) are recommended to have a 1.0–2.0 cm margin based on location and expected cosmetic and functional outcomes. The World Health Organization Melanoma Program performed a prospective randomized controlled trial of 612 adult patients with results published in 1988 demonstrating similar disease-free survival (DFS) and overall survival (OS) in patients with melanoma ≤2.0 mm treated with 1 vs 3 cm margins [24]. No patients with primary lesions ≤1.0 mm in depth experienced local recurrence, establishing the safety of narrow margins in this group. For patients with ≥2.0 mm depth melanoma, wide margins > 2 cm were not associated with improved recurrence free survival (RFS) or OS in several adult multicenter prospective randomized controlled trials [23]. However, the UK Melanoma Study Group found greater locoregional recurrence and decreased RFS in those with ≥2.0 mm depth lesions excised with 1 cm margins compared to 3 cm margins [25]. Long term follow-up of this study confirmed poorer melanoma-specific survival (MSS) in the 1 cm margin group [26].

Table 2
Recommended surgical margins for wide local excision of melanoma based on Breslow thickness.

Melanoma thickness	Wide local excision margin
Melanoma in situ	0.5–1.0 cm
≤1.0 mm	1.0 cm
>1.0 mm–2.0 mm	1.0–2.0 cm
>2 mm	2.0 cm
>4 mm	2.0 cm

The aforementioned clinical trials which form the basis of NCCN wide local excision margin recommendations excluded pediatric patients. There are retrospective data suggesting that children have decreased risk of local recurrence when compared to depth-matched adults and a trend toward decreased recurrence among younger children compared to adolescents [27–28]. This, coupled with the concern that children face worse cosmetic and functional outcomes than their adult counterparts to achieve the same margins, has led to some flexibility in tailoring margins to individual pediatric patient. Clinical trials evaluating optimal margins in pediatric patients with melanoma would be helpful however may not be feasible given relative rarity of this disease in children.

1.2. Sentinel lymph node biopsy

Melanoma may spread through lymphatics to regional lymph nodes as the first site of metastases. Regional node status is important for staging and prognosis and is often determined by SLNB, as up to 20% of clinically negative nodes will harbor melanoma and imaging is inadequate to identify microscopic lymph node metastases [29]. After injection of the technetium sulfur colloid radiotracer (Tc-99m) for SLNB, all possible nodal basins and intervening areas should be imaged in planar and/or cross-sectional views, as sentinel nodes in multiple nodal basins may occur. SLNB is typically performed at the same time as wide local excision of the primary lesion, and the operation should occur within 24 h of radiotracer injection, ideally under the same anesthetic for younger children who require sedation for radiotracer injection. Intradermal injection of blue dye around the primary lesion in the operating room may also be used to aid in sentinel node identification in conjunction with radiotracer, though recent studies suggest blue dye is not associated with increased SLNB accuracy. Methylene blue and isosulfan blue are the most frequently used blue dyes, with methylene blue being less expensive and associated with improved visualization compared to isosulfan blue.

Similar to wide local excision margins, the indications for SLNB are based on adult guidelines. For low risk melanoma with primary lesion depth <0.8 mm and no other concerning features such as ulceration, SLNB may be avoided. There is consensus that pediatric melanoma lesions with thickness ≥1.0 mm should undergo SLNB, as more than one third of pediatric patients will have pathologically positive sentinel nodes [30]. For lesions between 0.8 and 1.0 mm and those <0.8 mm with ulceration, SLNB should be offered with a discussion of risks and benefits with the patient and family [31]. SLNB has low procedural morbidity with a complication rate <5% (most commonly seroma). For patients with local recurrence after primary wide local excision alone, consideration should be given to SLNB, as it has prognostic value and is feasible based on data from patients who underwent successful lymphatic mapping following wide local excision [32–33]. Data specifically on accuracy of SLNB for local recurrence in the setting of prior WLE and SLNB, however, are lacking.

The value of SLNB in providing prognostic information for adult melanoma patients has been validated in the Multicenter Selective Lymphadenectomy Trial-1 (MSLT-I), a large prospective trial, which showed improved MSS at 10 years in adult patients with negative SLNB compared to those with melanoma positive sentinel nodes [34]. Surveillance, Epidemiology, and End Results (SEER) data of 261 patients less than age 20 who underwent SLNB found that MSS at 7 years was 100% in those with negative SLNB compared to 88% in those with positive SLNB [35]. National Cancer Database (NCDB) data demonstrated no difference in OS based on sentinel lymph node status in children less

than 11 years of age while older children 11–20 years of age had worse OS associated with a positive SLNB [36]. Similarly, in a single institution study of 109 pediatric melanoma patients, the odds of a positive SLNB increased with each year of age despite a lack of association between age and DFS or OS [37]. These findings highlight the need for further prospective studies in the pediatric population to determine the optimal role and implications of SLNB.

SLNB has been utilized previously as a method to assess malignant potential or behavior in pathologically equivocal lesions including atypical spitz lesions. However, the prognostic value in nonmelanoma lesions is uncertain, and concern exists for potential overtreatment with a procedure and its associated risks. Therefore, SLNB for such lesions is not recommended [30].

1.3. Completion lymph node dissection

For patients with clinically-evident regional lymph node metastases, completion lymph node dissection (CLND) is indicated. There has been a paradigm shift, however, in management of regional nodes following positive SLNB in the absence of clinically or radiologically-evident nodal metastases. Consistent with recommendations at that time, patients in the MSLT-I study underwent immediate CLND if the sentinel node demonstrated melanoma [34]. Two subsequent prospective randomized controlled trials, which included only adult patients, MSLT-II and DeCOG-SLT, found no difference in MSS or OS in patients with positive SLNB who underwent immediate CLND vs observation with ultrasound surveillance of the involved lymphatic basin [38–39]. Regional lymph node recurrence was greater in the observation group (23% vs 8%); however, complications including lymphedema were greater in the immediate CLND patients. Of note, no patients had clinically positive nodes at the time of SLNB and most metastases in the sentinel nodes were <1 mm. Those in the observation arm were followed closely with routine clinical exams and ultrasounds performed every four months for the first two years, every 6 months for years 3–5, and once yearly after 5 years.

The American Society of Clinical Oncology and the Society of Surgical Oncology now recommend either observation or CLND for adult patients with positive SLNB and the absence of high-risk features including extracapsular extension, primary tumor microsatellitosis, >3 involved sentinel nodes, >2 involved nodal basins, and patient immunosuppression [40]. These factors were exclusion criteria for the clinical trials, and the decision to proceed with either CLND or close observation should be undertaken after a thorough discussion of the risks and benefits of each approach. The NCCN recommends utilizing the follow-up exam and ultrasound scheduled utilized in MSLT-II for patients treated with observation. There are no pediatric-specific guidelines and children who undergo observation following a positive SLNB should follow the adult surveillance schedule. Given the frequency of this follow-up, especially in the first two years, special consideration should be given for CLND in those patients without access to follow-up at a high volume center capable of detecting nodal metastases on ultrasound. The advances in care resulting from adult melanoma clinical trials such as MSLT-I and MSLT-II highlight the importance of performing studies that include children in the future to optimize care in the pediatric population.

CLND has a significant risk of complications, with one in four patients developing lymphedema in adult reports [38]. In a retrospective study of 125 pediatric melanoma patients, nearly 40% of patients who underwent WLE and CLND experienced complications, compared to 11% when WLE was performed with SLNB [41]. Inguinal nodal dissections are associated with greater morbidity than axillary dissections in both adult and pediatric literature [41–42].

2. Adjuvant therapy

Systemic therapy is indicated for patients with regionally advanced or distant metastatic disease. Adjuvant therapy has evolved from generic immunologic therapy toward a more precision medicine approach, incorporating many of the known genetic mutations associated with melanoma into targetable treatment strategies. However, pediatric patients with melanoma have been absent from most of the prospective trials, and current treatment strategies for younger patients again must extrapolate from adult data. A summary of the applicable systemic therapies for advanced melanoma is seen in Table 3.

2.1. Locoregional disease

Low or intermediate dose interferon alpha-2b (IFNa-2b) given as adjuvant therapy for melanoma had been previously used for high risk disease but failed to demonstrate any improvement in OS. In addition, while some trials showed a benefit in RFS, others showed no difference [43–45]; therefore, this therapy for high-risk melanoma is not currently recommended [46–48].

High-dose interferon, which includes one month of intravenous induction followed by 11 months of subcutaneous interferon maintenance therapy is the only IFN dosing approved by the federal Food and Drug Administration (FDA) for the treatment of high-risk melanoma. Three trials evaluating the use of IFNa-2b for the treatment of adult melanoma have established this as the current standard for high risk melanoma. The Eastern Cooperative Group (ECOG) E1684 trial compared high-dose IFNa-2b with observation for the treatment of node positive or deep primary melanoma (>4mm) and reported a significant improvement in both RFS and OS at a median follow up of 6.9 years. While the RFS advantage persisted at the 12-year follow-up, the OS advantage was not maintained over time [49–50]. Patients in this study were stratified by age older or younger than 50 years, so the applicability to pediatric and adolescent groups is challenging to interpret. The Intergroup E1690 trial compared observation, high-dose IFNa-2b, and low-dose IFNa-2b in a randomized fashion for patients with T4 or node positive disease. An improvement in RFS but not OS was noted in the high-dose arm. However, there was significant crossover (31%) from the observation arm to the treatment arm for patients on study who developed nodal relapse, thereby explaining the lower OS in this

Table 3
Systemic therapies available for advanced melanoma.

Drug Name	Mechanism of Action/Target	Application
Interferon alpha-2b	Multifunctional immunoregulatory cytokine, stimulates B cells, activates NK cells	Stage IIB and III melanoma
Melphalan	Alkylating agent inhibits DNA and RNA synthesis	Regionally advanced melanoma used in isolated limb perfusion/infusion
Dacarbazine	Methylation of guanine in DNA strands, preventing cell division	Metastatic melanoma
Ipilimumab	Monoclonal antibody against CTLA-4	Unresectable stage III or metastatic melanoma
Nivolumab	Monoclonal antibody against PD-1	Unresectable stage III or metastatic melanoma
Pembrolizumab	Monoclonal antibody against PD-1	Unresectable stage III or metastatic melanoma
Vemurafenib	BRAF inhibitor	BRAF V600E mutation positive unresectable stage III or metastatic melanoma
Dabrafenib	BRAF inhibitor	BRAF V600E mutation positive unresectable stage III or metastatic melanoma
Selumetinib	Selective MEK1 and MEK2 inhibitor (downstream of BRAF/MAPK/ERK pathway)	BRAF-activating mutation positive melanoma
Trametinib	Selective MEK1 and MEK2 inhibitor (downstream of BRAF/MAPK/ERK pathway)	V600E mutated metastatic melanoma
Imatinib	Targeted c-KIT inhibitor	C-kit mutated melanoma

study [47]. The third large trial undertaken to evaluate the utility of IFNa-2b for the management of high-risk melanoma was Intergroup E1694. This study compared the use of high-dose IFNa-2b to GM2-KLH21 (GMK) vaccine, revealing significantly improved RFS and OS with high-dose IFNa-2b compared to GMK, and closed early in light of the convincing results [51]. In sum, the results of these three large cooperative adult studies, and a number of subsequent meta-analyses have clearly concluded the RFS is improved with the addition of high-dose IFNa-2b as adjuvant therapy for the treatment of high-risk melanoma, but the effect on OS is not conclusive [52–55]. Despite this lack of consensus, high-dose IFNa-2b is currently recommended as an option for adjuvant therapy for stage IIB and III melanoma outside the participation of a clinical trial.

The use of adjuvant IFNa-2b in children has been shown to be safe and is better tolerated than in adult patients [56–59]. A phase II study investigating the efficacy of IFNa-2b is in process, the results of which have not yet been reported (NCT005539591).

2.2. In-transit disease

For in transit metastases not amenable to surgical resection, isolated limb perfusion and limb infusion are techniques that enable delivery of high concentrations of chemotherapy to the affected extremity, thereby avoiding systemic exposure [60–63]. High doses of melphalan in combination with actinomycin-D or TNF-alpha are most commonly used for these limb perfusion or infusion techniques [64–65]. Complete response rates between 31% and 63% have been observed, with associated OS benefits [63–66].

2.3. Metastatic disease

2.3.1. Systemic chemotherapy (Table 2)

Prognosis for patients with stage 4 metastatic melanoma has historically been poor, with a median survival of less than one year and a 5-year survival of less than 10% [67–68]. While these statistics have improved with recent current combination therapy, 5-year overall survival for patients with metastatic disease are still reported at 23% [69]. The only two available agents approved for the treatment of metastatic melanoma until recently were dacarbazine (DTIC) and interleukin-2 (IL-2). DTIC has demonstrated some activity against melanoma with reported initial response rates as high as 20%–25%, however, durability was poor with a median response duration between 4 and 6 months, and a median survival time of 9 months with this single agent therapy [70]. IL-2 has been approved for the treatment of metastatic melanoma since 1998, after a report including 270 adult patients from 8 combined clinical trials showed an objective response rate of 16% and a complete response rate of 6% with a median durability of 8.9 months [52,71]. IL-2 is associated with significant systemic toxicity, and frequently requires intensive care monitoring and support. Other cytologic agents that have been utilized for metastatic melanoma include temozolomide, and paclitaxel with or without carboplatin, but response rates are poor, reaching 20% at best [72–73]. There are limited data describing the use of these agents in pediatric patients.

2.3.2. Anti-CTLA4

Recent developments of novel agents for the treatment of metastatic melanoma in adults have provided some reason for optimism. Ipilimumab is a monoclonal antibody directed against a T-cell receptor antigen (CTLA-4) and interferes with T-cell responses to antigen presenting cells. This agent was approved in 2011 by the FDA after the results of a phase III trial demonstrated that patients who received ipilimumab either alone or in combination with glycoprotein peptide (gp100) had a significantly improved OS compared to those who received gp100 alone (10.0 months vs 6.4 months; $p<0.001$) [74]. A second phase III study of patients with metastatic melanoma was performed comparing dacarbazine plus ipilimumab or dacarbazine plus placebo [75]. Patients receiving ipilimumab demonstrated a superior OS compared to the control group, with a median survival of 11.2 months vs 9.1 months, and a 3-year survival rate of 20.8% vs 12.2%, respectively ($p<0.001$) [75]. While these results show promise, immune-related side effects occurred in up to 60% of patients in these two trials [74–75]. Diarrhea and skin reactions were the most common events, but severe reactions required treatment with high-dose corticosteroids and were occasionally fatal. Prospective data in children and adolescents regarding CTLA-4 inhibitors are ongoing. A recent phase 1 study demonstrated ipilimumab to be safe in adolescents with unresectable melanoma, and a current phase II study is underway evaluating ipilimumab as single agent or in combination with nivolumab in pediatric patients with recurrent or refractory solid tumors including melanoma [76]. [NCT02304458].

2.3.3. BRAF inhibitors

Another pathway that is being targeted in the treatment of metastatic melanoma is the signaling kinase BRAF activating mutation, present in nearly half of patients [77]. Vemurafenib and dabrafenib are agents that specifically inhibit the intracellular signaling by a mutated BRAF [77]. In a phase III trial comparing vemurafenib to dacarbazine in patients with melanoma containing a V600 BRAF mutation, improved OS and progression-free survival (PFS) were seen with vemurafenib at 6 months [78]. Dose modifications were common owing to adverse reactions, occurring in 38%, with most of these reactions skin-related, including cutaneous squamous cell carcinoma followed by arthralgias. Vemurafenib is currently approved by the FDA for the treatment of metastatic or unresectable melanoma with the BRAF mutation. A phase I clinical trial in children demonstrated this drug to be safe, and early phase studies are ongoing to determine the tolerability and efficacy in this age group [79].

2.3.4. MEK inhibitors

MEK1 and MEK2 are other targets within the MAP kinase signal transduction pathway that are being targeted for therapy in patients with BRAF-mutated melanoma. Selumetinib was the first selective MEK inhibitor to be evaluated in a clinical trial for patients with metastatic melanoma and produced an objective response rate in patients harboring BRAF mutations, but not in wild-type tumors, highlighting the value of tumor-specific targeted agents for therapy [80]. Trametinib is an inhibitor of MEK1 and MEK2 that was recently shown to be superior to chemotherapy in adults in an open label phase III study with significantly improved PFS (4.8 months versus 1.5 months) and 6-month OS (81% versus 67%) [81]. This agent has been approved by the FDA for the treatment of adult patients with unresectable or metastatic melanoma with specific BRAF mutations but is not currently approved for use in children. Pediatric specific phase I testing is in progress.

2.3.5. PD-1 inhibitors

Programmed death (PD) and programmed death ligand (PDL) are proteins expressed on the surface of cells and as such are becoming attractive targets for the treatment of several malignancies including melanoma. PD and PDL inhibitors are a group of checkpoint inhibitors designed to prevent evasion of tumor cells from the body's immune system by blocking the interaction between T-cell PD-1 receptors and tumor PDL-1 ligand [82]. Pembrolizumab and nivolumab have been approved by the FDA for the treatment of adults with unresectable stage III and IV melanoma based upon the results of multiple clinical trials demonstrating their safety and efficacy [83–85]. As with other novel agents, early phase studies in children with advanced malignant melanoma are underway (NCT03407144) [86].

2.3.6. c-KIT inhibitor

KIT mutations occur with an incidence of <10% in adult melanoma most of which are acral or mucosal and are extremely rare in children [87]. The kinase inhibitor imatinib is a targeted c-KIT inhibitor and

achieves limited responses in 15%–50% patients with c-kit mutated melanoma [88–89]. Patient selection with specific molecular profiling is mandatory as imatinib is ineffective in patients with non-c-KIT mutated melanoma [90].

3. Outcomes

Historically, it was thought that survival for children with melanoma was similar to adults. While stage is the strongest predictor of survival for both children and adults, more recent literature suggests that survival of children with melanoma may be better than adults who present with a similar stage of disease [36,91]. Richards and colleagues found that pediatric patients with head and neck melanoma had improved survival for Stage 1, 2 and 3 disease but not Stage 4 disease when compared to adults [91]. Lorimer and colleagues utilized the National Cancer Database to compare OS between children ages 1–10 years, adolescents ages 11–20 years and adults > 20 years [36]. They found that OS was statistically better for children (HR 0.11; 95% CI 0.06–0.21) and adolescents (HR 0.22; 95% CI 0.19–0.26) when compared to adults (reference HR 1.0). They also noted that for children ages 1–10 years, nodal disease did not impact OS, and SLNB and CLND were not associated with improved OS. However, in adolescents, nodal disease was associated with a significant decrease in OS. A recent SEER study found disease-specific 5-, 15- and 30-year survival for children and adolescents with extremity melanoma is 96%, 94%, and 93%, respectively [92]. In this population-based study, 77% presented with localized disease, 15% with regional spread, and 1% with distant metastases. The 5-year OS in this study by extent of disease was 99% for localized, 87% for regional, and 50% for distant. The published 5-year OS for all stages and primary site locations is between 87% and 95% in children and adolescents with melanoma [93–96].

4. Prevention and advocacy

In 2009, the World Health Organization International Agency for Research on Cancer declared UV radiation-emitting tanning devices as a Class 1 carcinogen [97]. In 2014, the US Surgeon General issued a call to action to prevent skin cancer, noting that most cases of skin cancer are preventable and making skin cancer prevention a national priority [98]. Since then, there has been significant effort to improve awareness of sun exposure risk and to reduce the use of indoor tanning devices especially by adolescents. Ho and colleagues published the results of a randomized controlled trial that demonstrated improved sun protection behaviors for children of parents who received a multicomponent intervention that included a read-along book, a swim shirt, and weekly text message reminders to use sunscreen [99]. Recently, the Agency for Healthcare Research and Quality published a systematic review that identified 6 trials conducted among child or adolescent populations that evaluated the impact of primary-care behavioral interventions on sun burn and sun protection behaviors [100]. While there was no effect on parent-reported sunburn outcomes, behavioral interventions did positively impact sun protective behaviors including wearing sun protective clothing and sunscreen and seeking shade [99]. None of the studies reported on skin cancer outcomes.

Other reports have shown that legislation can be effective at reducing the use of indoor tanning devices. As of 2017, 17 states and the District of Columbia banned indoor tanning for minors less than 18 years old [101]. After Texas banned indoor tanning for minors in 2013, Tripp and colleagues reported 81% compliance with the ban as assessed by telephone interviews of indoor tanning facilities [102]. Furthermore, the results of the Youth Risk Behavior Survey demonstrated a significant decrease in the proportion of adolescents who reported the use of artificial sources of UV light for tanning from 15.6% in 2009 to 7.3% in 2015 [101]. In addition, several states have passed legislation similar to the SUNucate bill, a model legislation published by the American Society for Dermatologic Surgery Association that allows the use of sunscreen in schools, encourages the use of sun-protective clothing and calls for states to develop strategies to education children on the dangers of sun exposure. Despite these efforts and progress, approximately one-half of high school students and one-third of adults in the United States report at least one sunburn per year and 1 in 3 non-Hispanic white high school girls uses indoor tanning devices each year [103].

In 2018, the National Academy of Sciences convened a panel of 19 experts from multiple disciplines to explore perspectives on sun safety. They identified 5 themes upon which to build effective and sustainable approaches to changing sun safety behavior: 1) Expand the definition of risk to incorporate diverse populations; 2) Sun exposure behavior often occurs with other health-related behaviors some of which are positive; 3) Sun safety messages must be tailored to target population; 4) At risk persons for tanning disorders must be identified and treated and 5) Sun safety interventions must be scalable and utilize available technologies to do so [104]. As health care providers for a major at-risk population, it is important that pediatric surgeons are aware of effective melanoma prevention strategies and incorporate them into the care of their patients as much as possible.

According to ClinicalTrials.gov, there are more than 250 therapeutic trials actively recruiting patients with melanoma in the United States [105]. However, to date, there are no active melanoma-specific therapeutic trials in children and few are open that allow enrollment of adolescents. There are currently 5 therapeutic melanoma specific trials enrolling adolescent patients (1 study >= 16 years, 1 study >= 15 years and 4 studies >= 12 years). There are 5 studies enrolling patients that include children as young as 6 months for a variety of refractory solid tumor diagnoses including melanoma. There is one behavioral intervention study that evaluates the impact of an educational intervention administered in schools to children ages 9 to 15 years on the students' sun exposure behavior. Given the paucity of clinical trials for children and adolescents with melanoma, it is critical that pediatric surgeons advocate for our patients to be eligible for current clinical trials as well as continue to develop and study new therapeutic approaches for children and adolescents with melanoma.

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