13 Pediatric Melanoma and Atypical Melanocytic Neoplasms

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Introduction

Definition and Epidemiology

Pediatric melanoma is a malignant melanocytic lesion in a child from birth to the start of adulthood, variably defined as either age 18 or 21. Pediatric melanoma can be classified by the presence or absence of precursor lesions, age at presentation (see Fig. 13.1), histology, and staging criteria applied to adult melanoma. In children, it is often difficult to establish whether an abnormal melanocytic lesion is unequivocally cancer. Although this difficulty is sometimes due to reticence in diagnosing melanoma in young children, there are a significant number of abnormal melanocytic lesions that are difficult to characterize consistently. We term this broad class as atypical melanocytic neoplasms, and these can be classified based on pathology and metastatic potential [1, 2].

While it is the most common cutaneous malignancy in patients younger than 20 years of age, pediatric melanoma comprises only 0.3–2.0% of all melanomas and 1–3% of pediatric malignancies [3–5]. Melanoma is more prevalent in adolescents than in the younger pediatric population, and was expected to comprise 5% of all cancers diagnosed in this age group in 2017 [6]. Over the past 30 years, the incidence in prepubertal patients has remained stable, while it has been steadily rising in older children by 2.9% per year in the United States. This trend is also mirrored in other parts of the world [7, 8]. Caucasian children account for the majority of new diagnoses; however, the incidence continues to rise in the Hispanic and Native American populations [9]. The rise in melanoma is highest in female adolescents.

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A. I. Riker (ed.), *Melanoma*, https://doi.org/10.1007/978-3-319-78310-9_13

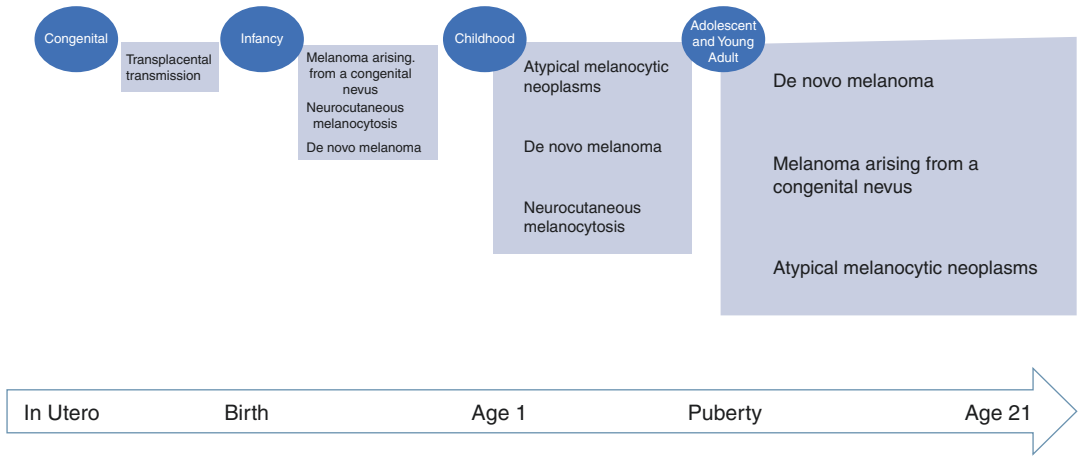

Fig. 13.1 Pediatric melanoma presentations according to age. The width of the textbox is roughly proportional to the incidence of melanoma (and/or atypical melanocytic neoplasms) occurring in each period (adapted from Sreeraman Kumar et al. [101])

Classification and Risk Factors

General Risk Factors

The risk factors for pediatric melanoma are somewhat age dependent. While genetic risk factors and benign precursor lesions are more common in prepubertal patients, the risk factors for adolescents are similar to those of adults: sun exposure, fair skin, and tanning bed use [8, 10].

Congenital/Neonatal Melanoma: In Utero to 1 Year

Congenital and neonatal melanoma is rare, and the incidence has remained steady over the past 30 years [4, 11].

Transplacental Transmission

Although it is extremely rare, melanoma can spread from mother to fetus via transplacental transmission. Available literature includes fewer than 30 cases and is mainly descriptive [12–16]. The factors that have been associated with this rare but devastating event are maternal diagnosis of node-positive disease >3 years prior to pregnancy, development of metastatic melanoma in the mother during the third trimester, primiparity, male fetal gender, birth at greater than 36 weeks gestation, and maternal age less than 30 [14, 17]. Clearly, some of these factors are associated with a patient's ability, desire, and/or willingness to become pregnant after a prior melanoma diagnosis. For example, younger women with no prior children and a long interval since their melanoma diagnosis may be more motivated to become pregnant and accept the risks associated with recurrence of their disease in the pre- or postpartum period.

For transplacental transmission to occur, metastatic melanoma must first lodge in and grow in the maternal side of the placenta, where it can be detected by histopathologic analysis conducted after delivery. In cases with placental metastases, two-thirds of infants were alive 1.5 years after birth, so the finding of melanoma in the placenta does not guarantee that transplacental transmission will occur [15, 17]. In the small number of cases where transmission to the fetus across the placenta has been reported, the diagnosis portends a poor prognosis, and the majority of these newborns ultimately die within the first year of life [15, 16, 18, 19]. Placental metastases have been reported even in mothers with early-stage melanoma, and thus we recommend thorough pathologic examination of the placenta after delivery in all women with a history of invasive melanoma. An evaluation showing no evidence of melanoma can provide the new mother with a strong sense of reassurance that transplacental transmission was unlikely to have occurred.

Proving that neonatal melanoma was transmitted transplacentally and not occurring de novo is possible. Karyotyping analysis or fluorescence in situ hybridization (FISH) can be used when transplacental melanoma transmission is suspected in males (as an XX chromosome in the tumor would confirm maternal origin). Efforts to quantify the copy number of sex chromosomes in genomic DNA purified from a fetal tumor biopsy specimen suspected to be of maternal origin have also been conducted [20].

Melanoma in a Giant Pigmented Nevus

Congenital melanocytic nevi (CMN) are present at, or very shortly after, birth. They are benign melanocytic proliferations and are classified by the size the lesions are projected to attain at adulthood, assuming growth congruent with the growth of the child, because the risk of malignant transformation rises with the size of the nevus. Small CMN are those projected to be less than 1.5 cm in diameter; medium CMN will be between 1.5 and 20 cm; and large CMN will be greater than 20 cm [21]. The definitions of what constitutes a giant (as opposed to a large) CMN vary. Some use body surface area measurements rather than projected adult size [22]. Giant CMN are either G1 (40–60 cm) or G2 (>60 cm), but other features besides nevus size, particularly satellite nevus counts and physical features such as color, surface change, and hypertrichosis, appear to also impact the risk of malignant transformation [23]. Location is also a factor: axial CMN are more likely to develop melanoma than CMN in extremities [24]. Giant CMN are most likely to give rise to pediatric melanoma, although the estimated risk varies. Small and medium CMN have a lifetime risk of 2–5%, but most of the melanomas within these nevi that do occur are diagnosed in adulthood, not in childhood. In contrast, patients with giant CMN are more likely to develop melanoma in adolescence or even early childhood.

A meta-analysis of 432 patients with CMN found that 0.7% developed melanoma, and a more recent, prospective, observational study of patients (median age of 6) noted two pediatric patients who developed melanoma [25, 26]. Although the median age of diagnosis for melanoma arising in CMN is 7 years, the median age of diagnosis for patients with fatal cases is 3 years [27]. The early onset of melanoma in CMN patients is the rationale for surgical removal of these lesions in early childhood. *NRAS* mutations have been seen in congenital nevi, and while the studies are conflicting *BRAF* V600E mutations may be seen in 12–30% of cases [28–30]. One-third of cases of fatal childhood melanoma arising in the setting of congenital nevi also had neurocutaneous melanocytosis [31].

Neurocutaneous Melanoma

Neurocutaneous melanoma is exceptionally rare. It originates in the background of neurocutaneous melanocytosis, which is also termed "congenital melanocytic nevus syndrome." This syndrome involves benign and malignant proliferation of melanocytes in the central nervous system, in conjunction with a giant CMN or with more than three small-to-medium CMN. As many as 4–11% of patients with giant CMN will develop symptomatic neurocutaneous melanocytosis [22, 26, 32]. Presenting symptoms include headache, vomiting, seizures, neuropsychiatric disturbance, or myelopathy, often the result of increasing intracranial pressure. Most patients develop symptoms by age 10 and have intractable seizures and neurocognitive delay [32]. Neurocutaneous melanocytosis is associated with the development of melanoma in 40–60% of cases. Patients may develop melanoma involving the skin, brain, or leptomeninges. Due to the difficulty of resection, risk of leptomeningeal infiltration, and lack of available targeted agents, the prognosis is poor [33, 34]. Genomic studies have indicated that *NRAS* mosaicism and post-zygotic mutations in codon 61 are associated with the onset of neurocutaneous melanocytosis [35]. Recent studies suggest the involvement of activated Wnt signaling as an additional factor leading to the varied natural histories of neurocutaneous melanocytosis. The mitogen-activated protein pathway (MAPK) may play a role, as its inhibition was noted to halt the development of neurocutaneous melanocytosis in animal studies [36]. One clinical case series investigating trametinib (a MEK

inhibitor) in patients with neurocutaneous melanoma demonstrated symptomatic improvement, though patients eventually succumbed to the disease [37].

De Novo/Sporadic Melanoma

There are only 14 cases of de novo melanoma in infancy reported to date [38, 39]. Of these, three have succumbed to the disease. There are no known risk factors, and diagnosis is challenging, given some histologic overlap with giant CMN. Comparative genomic hybridization may be helpful to establish the diagnosis [39].

Childhood Melanoma: 1 Year to Puberty

The most relevant biologic cutoff to divide childhood and adolescent melanoma seems to be puberty, when hormone-driven changes in melanocyte physiology occur. Although Tanner stage may be an accurate method of determining postpubertal adolescence, retrospectively ascertaining whether a child has undergone puberty is difficult. Thus, most studies use an arbitrary threshold of age 10 or 12 as a substitute to distinguish between prepubertal and postpubertal cases.

De Novo/Sporadic Melanoma

Most childhood melanomas are not associated with CMN or genetic syndromes. The risk factors for these sporadic cases have not been firmly established. However, such cases are primarily associated with UV radiation exposure, fair skin, and multiple nevi just as in adults [10]. Prepubertal patients, however, are more likely than adolescents to be non-Caucasian. Consequently, the role of UV exposure for these patients remains ambiguous [40].

Arising from Giant CMN and Dysplastic Nevi

Childhood melanomas, like neonatal melanomas, can develop from giant CMN. One-third of childhood melanomas originate from giant CMN or another precursor lesion, including common and dysplastic nevi [21, 22, 24, 33, 40–45].

CMN (Please See "Melanoma in a Giant Pigmented Nevus")

Spitz Nevi

Spitz nevi are benign melanocytic proliferations that present more commonly in the pediatric population. Like melanoma, they can be melanocytic or amelanotic, and can have irregular borders. However, most are less than 1 cm in diameter, and up to 80% spontaneously involute during childhood. Intermediate between benign Spitz nevi and melanoma are the atypical spitzoid tumors (AST). Some of these atypical, but not unequivocally malignant-appearing, lesions have the potential to metastasize (i.e., they are unrecognized melanomas). High-risk factors for recurrence and metastasis include ulceration, asymmetry, and large diameter. All patients with atypical Spitz tumors should be monitored carefully clinically, but particularly those with lesions with the aggressive features mentioned above. Immunohistochemistry (IHC) can be helpful in distinguishing AST from melanoma [46]. A new study revealed differences in miRNA expression levels between the two tumor types, particularly a decrease in the expression of miR-155-5p in spitzoid melanomas [47].

Genetic Syndromes

Germline mutations that result in alterations to cell cycle tumor suppressors and genes involved in DNA damage repair confer sensitivity to DNA damage. These are associated with an increased risk of melanoma in children, adolescents, and adults alike.

Xeroderma Pigmentosum

Xeroderma pigmentosum is an autosomal recessive genetic disorder of nucleotide excision repair. Affected individuals are sensitive to DNA damage by UV radiation. By age 8, they generally develop non-melanoma skin cancer; by age 21, 5–13% of xeroderma pigmentosum patients have been diagnosed with melanoma [45, 48].

Familial Melanoma Syndromes

Familial melanoma syndromes are not particularly well characterized in either the pediatric or the

adult populations. However, genomic studies are providing further insight into the mutations leading to multiple and recurrent melanomas. *CDKN2A* is the most common high-risk melanoma susceptibility locus. Mutations in this gene are associated with dysplastic (atypical) nevus syndrome, >100 nevi, nevi of buttocks/feet, multiple primary melanomas, and in some cases an increased risk for pancreatic cancer [49]. These germline mutations are present in <5% of prepubertal melanomas [50, 51]. Rarer familial melanoma syndromes include germline *BAP1*, *BRCA2*, and *MC1R* mutations. However, they are more closely associated with adult rather than pediatric melanoma.

Adolescent and Young Adult Melanoma

Adolescent and young adult melanoma comprises patients from puberty to age 21. The incidence in this cohort of pediatric melanoma continues to rise, largely due to the increasing rate in teenage girls [52]. The risk factors are thought to be similar to that for adults, which include ultraviolet radiation exposure, tanning bed use, fair skin, family history of melanoma, and presence of multiple and atypical nevi [40, 42, 43, 52–55]. Other risk factors include xeroderma pigmentosum and germline mutations involving cell cycle mediators, as for prepubertal melanoma.

Clinical Presentation

General

Pediatric melanoma presents with its own clinical signs and symptoms, which vary by age grouping, as do the epidemiologic factors enumerated above. In adult melanoma, the classic criteria are asymmetry, irregular borders, variation in color, diameter >6 mm, and evolution. However, 60% of prepubertal melanomas and 40% of adolescent melanomas do not exhibit these characteristics [43, 53, 56]. Cordoro et al. noted that 77% of patients younger than 10 years old presented with an amelanotic lesion, with Ferrari et al. noting that 88% of patients had well-circumscribed lesions [53, 57]. Accordingly, the traditional diagnostic criteria have been expanded to include the following new criteria for pediatric melanoma: amelanotic, bump/bleeding, uniform or no color, and de novo/any diameter (see Table 13.1) [3, 57]. While the criteria have not been validated in prospective studies, they nonetheless provide a framework for further evaluation.

Table 13.1 Characteristics of pediatric melanoma compared to the classic adult "ABCDE" criteria

	Classic adult melanoma	Pediatric melanoma
A	Asymmetry	Amelanotic
B	Border irregularity	Bump and bleeding
C	Color variation	Colorless or uniform color
D	Diameter	De novo development/any diameter
E	Evolution	Evolution

This table describes the classic features of adult melanoma and the additional features seen in pediatric melanoma (adapted from Cordoro et al. [57])

Congenital/Neonatal Melanoma

Congenital melanomas associated with maternofetal transmission develop in the background of maternal metastatic melanoma, and as such this potential risk can be of concern to pregnant women with a history of melanoma. Due to the risk of maternofetal melanoma transmission, we recommend the routine submission of the placenta at the time of delivery for pathologic analysis with IHC staining for melanocyte lineage antigens such as S-100 and/or Melan-A. The presence of melanoma cells on the fetal side of the placenta suggests potential maternal-fetal spread, and infants should be carefully monitored during the first year of life and beyond for signs and symptoms of metastatic melanoma. The majority of, if not all, neonatal melanoma cases arising from maternal-fetal transmission are diagnosed within the first year of birth [15, 18].

Infants with melanoma unrelated to transplacental transmission usually have melanoma from a CMN. Neonates have a distinct presentation from older patients in that they are less likely to arise from an atypical junctional proliferation or melanoma in situ. Patients tend to have pink or

dark papules within CMN or nodules in the dermal component of CMN. These are difficult to diagnose, given that features typically of concern, such as ulceration, can be found in benign proliferative nodules within CMN [27]. In cases of neurocutaneous melanocytosis, neonatal patients present with symptoms of increased intracranial pressure and other neurologic symptoms.

Childhood Melanoma: Age 1–Puberty

While there is no classic presentation of prepubertal melanoma, they tend to exhibit alternative diagnostic criteria, such as amelanosis, bleeding, nodularity with uniform color, and diameter <6 mm that persist after being monitored for an extended period of time. Prepubertal patients are more likely than adolescents to have extremity or head and neck presentation, nodular rather than superficial lesions, and multiple nevi [3, 4, 40].

Adolescent and Young Adult: Puberty–21

More than 75% of pediatric melanoma patients are diagnosed in adolescence or young adulthood. Similar to prepubertal patients, 40% will present with atypical presentations, such as amelanotic, symmetric papular, or a nodular appearance and "evolution." The most common pre-biopsy diagnosis in this age group is pyogenic granuloma [57]. In contrast to younger children, they are more likely to have superficial spreading, rather than nodular, melanomas and more likely to have a truncal primary site [4].

Initial Clinical and Pathologic Workup

The rarity of pediatric melanoma, along with the plethora of benign nevi in the pediatric population, makes the diagnosis of malignancy difficult. The potential for delay in diagnosis is quite high, with a recent study finding an initial clinical misdiagnosis in 25% of their cohort [58]. Among experienced pathologists, there was significant diagnostic disagreement, with a kappa coefficient of 0.3, indicating a low degree of inter-observer concordance [59].

Given the high rate of misdiagnosis and delay in diagnosis, suspicious melanocytic lesions should be biopsied and evaluated by an experienced dermatopathologist. Often, cutaneous lesions in children are initially diagnosed as warts, and subsequently treated with a variety of topical agents prior to biopsy. The clinical history, including the presence of a precursor lesion, CMN or nevus, demographics, color, size, extent of biopsy (excisional, partial excision/punch, shave), and photograph of the lesion, can all assist the dermatopathologist in the diagnostic process. The importance of collaboration between clinicians and pathologists by sharing clinical information that can assist in the diagnostic evaluation bears emphasis.

We recommend complete excisional biopsy with a narrow margin of normal skin, allowing for complete pathologic evaluation of both the lesion and its relationship to the surrounding epidermis and subcutis. Preserving the specimen with formalin fixation is adequate, even if specialized IHC and/or molecular testing are needed to evaluate the lesion, allowing for the routine handling of pediatric skin biopsies in the clinic [60, 61]. Fluorescence in situ hybridization (FISH), comparative genomic hybridization (CGH), and gene expression analyses are now increasingly being used as additional tests in the diagnostic process [27, 46, 47, 62, 63].

The initial histopathologic evaluation of the biopsy specimen includes commercially available IHC stains. Proliferation is assessed using mitotic count, augmented when necessary with phosphohistone H3 and/or the proliferation marker Ki-67 [64, 65]. The progressive loss of HMB-45 staining with increasing dermal depth demonstrates melanocytic maturation, characteristic of benign lesions, but is often lost in melanoma [66]. Melanoma, in comparison to benign lesions, is more likely to have increased mitotic activity, high-grade atypia, inflammation and mitotic figures deeper in the dermis, histologic asymmetry, and ulceration [27, 59]. However, there still

remains significant inter-observer variation in diagnosis with histological evaluation alone.

More recent studies have evaluated gene expression and CGH as methods of distinguishing malignant lesions from those without metastatic potential. Spitzoid lesions are the most common atypical lesions of uncertain potential. Atypical spitzoid tumors or melanoma may demonstrate a loss of p16 expression by homozygous deletion of *p16*/*CDKN2A*, but benign Spitz nevi rarely express p16 loss [67–69]. Loss of BAP1 expression has been shown in spitzoid-appearing benign and malignant melanocytic proliferations [70]. Recently, tyrosine kinase fusions involving ALK, ROS-1, NTRK-1, BRAF, or RET have been found in up to 40% of lesions with spitzoid histology. However, these have not yet been shown to be indicative of the metastatic potential of these lesions [62]. Isolated *HRAS* mutations and chromosome 11p gain have been identified in benign spitzoid lesions but not in melanoma (see Fig. 13.2a) [46, 71]. Increase in the copy number of *RREB1* (chromosome 6p25), *MYB* (6q23), and *CCND1* (11q13) is associated with lesions with metastatic potential, i.e., melanoma (see Fig. 13.2b) [46]. More recently, microRNA studies have shown potential to distinguish melanoma from benign lesions [72, 73]. A commercially available gene expression signature (myPath™, Myriad Diagnostics) has been shown to have good sensitivity and specificity on histologically unequivocal lesions, but its performance has only been evaluated in one study comparing results of FISH and myPath score in atypical lesions [74]. In this study, FISH was more frequently in agreement with the histologic diagnosis than myPath (70% vs. 64%).

Pathologic Classification

Spectrum of Melanocytic Neoplasia

The spectrum of melanocytic neoplasms in children ranges among congenital and acquired benign lesions, dysplastic nevi, blue nevi, Spitz nevi, pigmented epithelioid melanocytomas, and progress on to melanoma. There are many lesions along this spectrum that do not fit neatly into one diagnostic category, variably termed as borderline tumors, melanocytic tumors of uncertain malignant potential (MELTUMPS), spitzoid tumors of uncertain malignant potential (STUMP), and atypical Spitz tumors. Although observational, retrospective, and prospective studies have sought to evaluate the natural history of these atypical neoplasms [21, 24, 71, 75–81] considerable ambiguity persists and even among expert dermatopathologists diagnostic disagreement occurs [59]. We will refer to these lesions as "atypical melanocytic neoplasms" in this chapter.

Atypical spitzoid neoplasms are the most common atypical melanocytic neoplasms in the pediatric population, and distinguishing the benign ones from those with metastatic potential is challenging. "Spitzoid" refers to lesions with some, but not all, of the features of a typical (benign) Spitz nevus. Histologically, benign Spitz nevi tend to have uniform hyperplasia in the epidermis, maturation in the dermis, eosinophilic cytoplasm, low mitotic activity (less than 2 mm^2), and pale eosinophilic "Kamino bodies." Often, even benign lesions will have some variations. Thus, differentiating between atypical lesions with metastatic potential and those that are unequivocally benign is difficult.

Recent studies have used CGH, FISH, and more recently gene expression profiling to characterize the metastatic potential of atypical melanocytic neoplasms. These techniques are utilized when several (but not all) elements of either melanoma or a benign nevus are present in a case [82].

CGH evaluates gains and losses of segments of chromosomes across the 23 chromosome pairs (46 chromosomes). Melanomas are more likely than benign lesions to have multiple gains or losses in chromosomes. Karyotype alterations in chromosomes 1q, 6p, 6q, 7p, 8p, 8q, 9p, 10p, 11q, and 17q were found in melanoma and absent in Spitz nevi [46]. Bastian et al. reported that 96% of melanomas in their series had chromosomal gains or losses, while only 13% of atypical melanocytic neoplasms had abnormalities. In contrast to most benign nevi, which have normal karyotypes, and melanoma, which rarely exhibits an *HRAS* mutation, 15% of Spitz nevi and 70% of

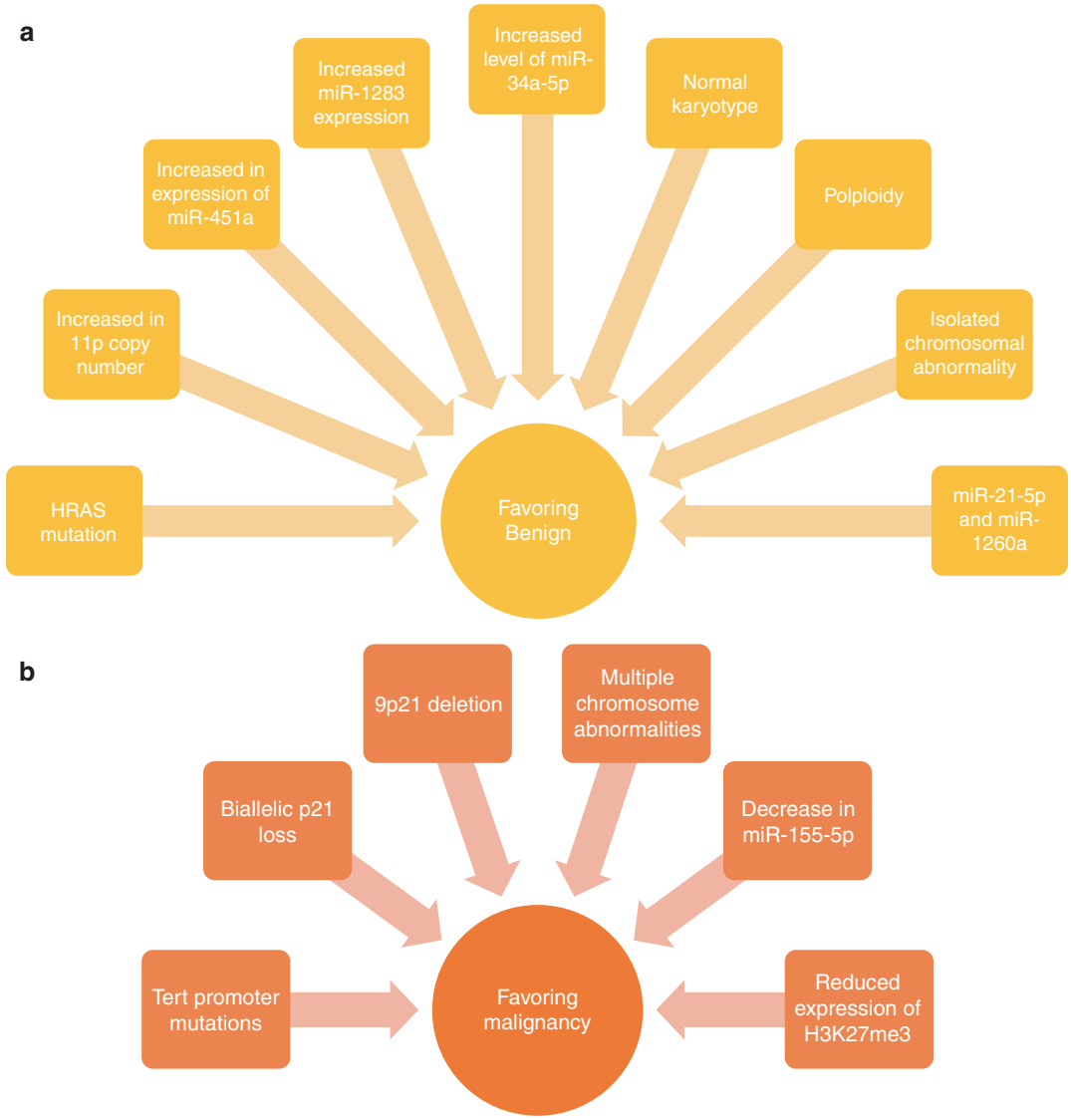

Fig. 13.2 (**a**) Common genetic and chromosomal abnormalities in benign (atypical) pediatric melanocytic neoplasms. (**b**) Common genetic and chromosomal abnormalities in pediatric melanoma

atypical Spitz neoplasms had an increase in the copy number of 11p at the *HRAS* locus [83]. Evaluation of a database of ambiguous melanocytic neoplasms revealed a chromosome 3p21 loss in 6.7% of cases, while loss of *BAP1* was associated with atypical spitzoid melanocytic tumors [84].

Multiple studies have now identified kinase fusions involving ALK, ROS-1, NTRK-1, BRAF, and RET in up to 51% of atypical spitzoid melanocytic tumors [62, 76, 85]. The identification of a fusion protein in a lesion may confer different metastatic potential and clinical evolution depending on the specific fusion. *ALK* mutations were more likely to be found in amelanotic lesions, with *NTRK-1* mutations associated with lesions found to have Kamino bodies and small, arranged nests. Mutations in the *BRAF* gene were more likely to be associated with high-grade atypia, sheets of dysplastic cells, copy number gains, and a predominance of epithelioid cells [86–88]. Lesions with *BRAF* mutations were

more likely to be diagnosed as, or develop into, a melanoma. However, the presence of a fusion protein has not yet been definitively shown to be associated with an adverse outcome or recurrence [89].

FISH utilizes nucleic acid probes that bind to portions of chromosomes to detect the presence or absence of known sequences. The first-generation FISH testing utilized probes targeting chromosomes 6p25 (the locus of gene *RREB1*), 6q23 (*MYB*), *Cep6* (the centromere of chromosome 6), and 11q13 (*CCND1*). The results were promising, with a sensitivity of 86.7%, and a specificity of 95.4% in the diagnosis of melanoma compared to benign nevi. The main concern raised was the identification of false-positive test results in tetraploid cases [90]. The next-generation FISH test targeted 6p25, 11q13, 9p21 (*CDKN2A*), and 8q24 (*cMYC*), and it reportedly has greater accuracy with histologically unequivocal melanocytic neoplasms. Nonetheless, in diagnostically challenging spitzoid melanocytic neoplasms, the sensitivity is less than 70%. However, it may be helpful as an adjunct study to assist in diagnosis. Gerami et al. reported that in their series of 64 patients with atypical Spitz tumors analyzed by FISH, 9 of the 11 patients who developed advanced disease or died had deletion of 9p21, which results in loss of *p16*/*CDKN2A* [77]. A later study of patients with fusion proteins revealed a recurrence in only those with 9p21 loss [89].

There are further studies investigating the role of epigenetics and hypermethylation as biomarkers of melanoma. In a study of patients with melanoma arising from CMN compared to proliferative nodules, there was reduced expression of H3K27me3 in melanomas but not in the (benign) proliferative nodules [91]. Increased telomerase activity, associated with mutations of the *TERT* promoter, was found in 12 of 15 melanomas and 2 of 26 atypical spitzoid tumors [92]. Another study of 54 patients with atypical spitzoid melanocytic neoplasms found *TERT* promoter mutations in the 4 patients who developed disseminated disease, but not in the 52 who remained free of disease [93]. Among adolescents and young adults, TERT promoter methylation with or without a TERT promoter mutation was associated with worse recurrence-free survival [94]. MicroRNA analysis of spitzoid lesions revealed a decrease in miR-155-5p in melanoma, with an increase in miR-451a, miR-1283, miR-34a-5p, miR-21-5p, and miR-1260a in benign lesions [47].

Taken together, each of these new tests could serve as additional diagnostic studies. Furthermore, there may be other clues in an atypical melanocytic lesion that may reveal its metastatic potential, in particular the involvement of regional draining lymph nodes. However, this, too, is contentious. A study of 541 patients with atypical spitzoid lesions noted 303 patients who underwent sentinel lymph node biopsy. Of these, 119 (39%) were found to have positive sentinel lymph nodes, with 97 subsequently undergoing a completion lymph node dissection. This study reported a median follow-up of 59 months, showing that 99% of patients with a positive sentinel lymph node were still alive. While this study suggests that atypical spitzoid lesions may have a higher rate of lymph node involvement than melanomas, the involvement of sentinel lymph nodes in atypical spitzoid neoplasms may not have the same negative prognosis as in patients with unequivocal melanoma [95].

Of unequivocal melanomas, the most common histologic subtype of melanoma in children is the superficial spreading subtype, which comprises from 9 to 62% of cases, depending on the study. Nodular melanomas are more commonly seen in prepubertal cases and comprise between 12 and 34% of cases. The incidence of spitzoid melanomas is thought to between 2 and 17% of pediatric melanomas (see Table 13.2), but this may be over- or underreported, as many studies did not report Spitz type as a distinct category.

Categorization of Pediatric Melanocytic Neoplasia

In addition to the diagnostic challenge of atypical melanocytic neoplasms, the lack of a standard terminology creates confusion between pathologists and clinicians regarding the exact nature of

Table 13.2 Histologic subtypes of pediatric melanoma based on single-institution series

	Superficial spreading (%)	Nodular (%)	Acral lentiginous	Spitzoid	Other/unclassified/ NOS (%)
Paradela et al. [44] (n = 128)	48	34	4%	Not reported separately	14
Livestro et al. [43] (n = 73)	62	12	1%	Not reported separately	25
Aldrink et al. [41] (n = 136)	49	21	4%	2%	24
Han et al. [56] (n = 62)	47	23	0%	4%	26
Cordoro et al. [57] (n = 60)	9	30	0%	13%	48
Brecht et al. [114] (n = 443)	51	15	2%	Not reported separately	32
Dean et al. [5] (n = 78)	38	12	Not reported separately	Not reported separately	50
Freemyer et al. [108] (n = 185)	35	29	2%	17%	17
Total (n = 1165)	46	21	2%	4%	28

a lesion. A recent study noted that the "Spitz" terminology was used by 90% of surveyed pathologists, but treatment recommendations varied widely [96, 97]. The lack of standardization makes it difficult for clinicians to adequately communicate the nature of the lesion, the risk for metastasis and death, as well as the treatment options to patients and their families. To create an objective scale, we adopted a system to classify melanocytic lesions from a spectrum of unequivocally benign to unequivocally malignant. This system is derived from the original 5-point "BiRAD" system for categorizing the results of mammography, and is similar to a proposal for categorizing dysplastic nevi [98, 99]. We have implemented this system in our practice and find it useful in our conversations between pathologist and clinician and the patient/family. It also allows us to better convey evolution of the diagnostic process to patients, wherein an initial uncertain diagnosis can be clarified as additional pathologic analyses are performed or new clinical features emerge [100, 101].

Category 1: Benign

The lesions in this category have histologic features characteristic of an unequivocally benign lesion, and include Spitz nevi, pigmented spindle cell nevi of Reed, blue nevi, deep-penetrating nevi, CMN, proliferative nodule in congenital nevi, benign melanocytic nevi, dysplastic melanocytic nevi, and speckled lentiginous nevi. No additional evaluation is necessary beyond complete excision, as appropriate [102].

Category 2: Atypical Melanocytic Neoplasm, Favor Benign

The atypical melanocytic neoplasms in this category have most, but not all, of the features of one of the unequivocally benign lesions noted above. There are a few nontypical features seen, such as focal areas of proliferation/mitoses, focal increases in cellularity, or focal cellular atypia. Alternatively, we use this category when an incomplete biopsy precludes full evaluation, and a benign diagnosis cannot be rendered with certainty. Thus, these lesions should all be completely excised to assess the areas of the lesion not sampled with the initial biopsy. After complete excision, no further evaluation or management is necessary for category 2 lesions.

Category 3: Atypical Melanocytic Neoplasm, Not Amenable to Further Classification

The lesions in this category have atypical features indicating possible metastatic potential, but no features allowing the pathologist to

definitively classify the lesion as likely malignant or likely benign. These have been given names like spitzoid tumors of uncertain malignant potential (STUMP), spitzoid atypical melanocytic proliferation of uncertain significance (SAMPUS), and melanocytic tumor of uncertain malignant potential (MELTUMP). This category also includes other melanocytic lesions for which the potential for recurrence or metastasis is unknown, such as the pigmented epithelioid melanocytoma, atypical cellular blue nevi, and BAP1-deleted melanocytic neoplasms.

CGH, FISH, and microRNA analysis can be helpful in further assessing the benign or malignant nature of these lesions. An atypical spitzoid lesion in category 3 by histopathologic criteria with a single chromosomal aberration in chromosome 11p might be appropriately recategorized as an atypical Spitz nevus, favor benign (category 2). An identical-appearing lesion with multiple FISH and chromosomal abnormalities in a high percentage of cells would be considered concerning for melanoma. This lesion would be more accurately reported as an atypical spitzoid lesion, favoring a spitzoid melanoma (category 4).

Category 3 lesions should always be completely excised. The re-excision specimen should be carefully examined for hints of any residual neoplasm that could allow for a more definitive diagnosis to be made. Furthermore, for patients with lesions in this category, sentinel node biopsy may be offered, with the understanding that the finding of lesional cells in the sentinel node may, or may not, allow for a reclassification as unequivocally malignant (see below).

Category 4: Atypical Melanocytic Neoplasm, Favor Malignant

The lesions in category 4 have a significant number of atypical features worrisome for malignancy, but they lack sufficient features to allow for the definite diagnosis of melanoma. These are lesions that have at least some potential to metastasize or recur, with numerous reports of category 4-type lesions leading to recurrence, metastatic disease, or death (and hence ultimate reclassification into category 5). While there are areas of overlap with this category and category 3, there are enough features to warrant more concern. Such features include Spitz-like neoplasms with high dermal cellularity, deep dermal or subcutaneous extension, high mitotic rate in the deep dermis, asymmetry and/or necrosis, or atypical cellular blue neoplasms that are large, with necrosis and/or increased mitoses >2/mm^2, with clinical features of ulceration and/or bleeding [58, 103, 104].

Category 4 lesions should always be excised to negative margins, and we generally recommend they be treated as an unequivocal melanoma of similar depth. At our institution, we would perform a sentinel lymph node biopsy for lesions 1 mm or thicker in Breslow's depth. CGH and FISH are often helpful and may provide sufficient evidence for the pathologist to render an outright malignant diagnosis (category 5). In contrast to category 3 lesions, lesional cells in the sentinel node, particularly in the parenchyma or growing in an expansile method, should be considered to represent evidence that the lesion is indeed malignant.

Category 5: Melanoma

Category 5 lesions express classic histopathologic features of an unequivocal melanoma. The number of melanomas in the pediatric population that exhibit spitzoid characteristics adds to the difficulty in rendering a diagnosis of unequivocal melanoma. However, when the classic features are present, a dermatopathologist should not hesitate to render this diagnosis simply because of the young age of the patient.

Further Evaluation and Reclassification of Atypical Melanocytic Neoplasms

Treatment decisions made on the initial biopsy specimen, particularly when based on a partial sampling of the lesion, are subject to change as subsequent information becomes available. Physicians, patients, and families must recognize the uncertainty involved with the diagnosis of pediatric melanocytic lesions. As additional studies are performed during the course of workup

and diagnosis, a lesion that initially could not be categorized unequivocally as either benign or malignant on initial biopsy may be reclassified into a different diagnostic category. All lesions in category 2, 3, or 4 should be completely excised to negative margins. The re-excision pathology should be evaluated by an experienced dermatopathologist. Further investigation with CGH, FISH, and expression profiling as well as sentinel node biopsy (for category 3 and 4 lesions) should be considered in diagnostically challenging cases; this may lead to a definitive diagnosis. Finally, long-term clinical follow-up can result in reclassification of a benign or an atypical lesion to malignant based on disease progression or metastasis.

Diagnostic and Treatment Paradigms for Pediatric Melanoma and Atypical Melanocytic Neoplasms

Preoperative Staging Workup

For patients diagnosed with unequivocal melanoma at initial biopsy, the next step in evaluation is a thorough physical examination. Of importance are determining the presence of any residual pigmented lesion at the primary site and examination of the regional lymph nodes. If the regional lymph nodes are enlarged or hard to examine, ultrasonography can be helpful. Often, an ultrasound-guided fine-needle aspiration can be performed in order to establish a diagnosis of stage III melanoma prior to resection.

Due to the risks of ionizing radiation in prepubertal children and adolescents [105, 106], CT and PET/CT scans should generally be used preoperatively only for the following indications: patients with clinically positive lymph nodes in whom a biopsy establishes stage III melanoma, and those with clinical signs and symptoms of metastasis. Newer protocols such as PET/MRI reduce exposure to ionizing radiation and may be preferable for evaluation, if available [107]. Patients with atypical lesions (categories 2, 3, or 4) should undergo a thorough evaluation of the regional lymph nodes, including ultrasonography, if necessary. Otherwise, preoperative radiologic imaging is not indicated for patients with these lesions. No routine laboratory tests are needed in pediatric patients with atypical or malignant lesions aside from those required for pre-surgical evaluation.

Given the rarity of pediatric melanoma and the multidisciplinary approach required for treatment, patients should routinely be referred to a specialized center. Freemeyer et al. compared patients treated at an NCI-designated comprehensive cancer center with patients treated at a non-designated center. There was a significant disease-free and overall survival benefit, particular for stage III and stage IV patients, when they underwent their initial surgical evaluation at an NCI-designated comprehensive cancer center [108].

Wide Excision

The primary treatment for localized cutaneous melanomas and for all atypical melanocytic lesions is surgical removal. A complete excision is recommended for all categories of atypical melanocytic neoplasms. For category 4 or 5 lesions (suspected or diagnosed melanoma), wide excision is indicated, even if the initial biopsy had negative margins. Due to the previous exclusion of children from randomized trials evaluating margin width, there is no standard margin of excision for pediatric melanoma. When compared to melanomas of the same thickness in adults, pediatric melanoma appears to have a lower risk of local recurrence [43, 109]. For children younger than 14, we use a 1 cm margin for melanomas regardless of thickness and in all primary sites. We have not seen any local recurrences with this protocol [56, 110]. For older children, we employ the standard adult guidelines for margins of excision: 1 cm for lesions $\leq$1 mm in thickness at all anatomical sites and for tumors 1–2 mm in thickness in locations where a wider margin would require a skin graft or result in severe deformity, and for tumors on the head and neck or distal extremities; we perform 2 cm margins for most thicker lesions. For category 2 and 3 lesions, we

utilize a maximum of a 1 cm margin, regardless of location. The goal of surgery is to achieve a final negative pathologic margin. In the rare cases where residual neoplasm is present at the excision margin, further re-excision is indicated. If re-excision of a category 2 or 3 lesion with less than a 1 cm margin uncovers a category 4 or 5 lesion, further excision is generally recommended.

Indications for Sentinel Lymph Node Biopsy

The role of sentinel lymph node biopsy in pediatric melanoma and atypical melanocytic neoplasms remains controversial. Sentinel lymph node biopsy is a well-tolerated procedure that enables accurate surgical staging, which can guide further treatment decisions. The majority of pediatric melanoma patients have node-negative disease and an excellent prognosis [11, 44, 54, 78, 111–114]. Such patients are at low risk for recurrence and can be followed with routine clinical and dermatologic surveillance. The significance of a negative sentinel node biopsy in reassuring to the patient and family should not be undervalued. In some cases, however, the sentinel lymph node or nodes contain cells identical to the primary tumor. In fact, the incidence of positive sentinel lymph nodes in atypical melanocytic neoplasms appears to be as great as, or greater than, that seen with pediatric melanoma [95]. For both atypical melanocytic neoplasms and pediatric melanoma, the incidence is higher than in adults with melanomas of similar thickness. However, the prognosis of sentinel node-positive pediatric patients is significantly better than for adults [43].

Indications for Sentinel Node Biopsy in Pediatric Melanoma

The argument for sentinel lymph node biopsy as a prognostic tool for pediatric melanoma is based on numerous studies that revealed that recurrence and death are more likely in patients with positive sentinel lymph nodes [1, 11, 114–116]. The risk of late side effects of removing one or two lymph nodes from a nodal basin is relatively low [117]. Over 20% of pediatric patients with clinically negative lymph nodes and a primary melanoma ≥1 mm in thickness are found to have positive sentinel lymph nodes. The indications for nodal evaluation in the pediatric population are similar to those for adults. In our practice, we utilize sentinel lymph node biopsies in pediatric patients with melanomas ≥1 mm in thickness in the absence of contraindications. We are selective for older children with lesions >0.75 mm in Breslow's thickness with ulceration and/or a mitotic rate ≥1/mm^2, as in adults [118]. Because very young children rarely present with melanomas less than 1 mm in depth, our knowledge of the value of a sentinel lymph node biopsy is limited in this population, but we would consider it on a case-by-case basis.

Indications for Sentinel Node Biopsy in Pediatric Atypical Melanocytic Neoplasms

Recent articles have argued for a limited role for sentinel lymph node biopsy in the absence of a definite diagnosis of melanoma, as the prognostic significance of a positive sentinel lymph node is unclear [65, 95, 119]. It is clear that lesional cells from benign nevi, like cellular blue nevi and Spitz nevi, can be found in regional lymph nodes, and therefore it is difficult to distinguish metastatic melanoma from benign nevus cells. Even patients with category 1 (unequivocally benign) nevi can have nodal nevi, collections of benign nodal melanocytes. The melanocytic deposits in benign Spitz nevi are similar in appearance to the primary lesion, most commonly subcapsular, and are small in size [120]. In contrast, the nodal melanocytes arising from category 4 atypical melanocytic neoplasms and melanoma are more likely to be present in the parenchyma of the lymph node. The presence of expansile tumor deposits, necrosis, nodal effacement, sheets of malignant cells rather than nest of melanocytes, and involvement of multiple lymph nodes would favor metastasis from a primary lesion that is melanoma. Many cases of atypical melanocytic neoplasms with nodal involvement have features that are between the characteristics of benign nodal melanocytes and unequivocal involvement

with melanoma. However, clinical studies have shown few, or even no, recurrences for atypical melanocytic neoplasms with positive sentinel nodes. There are a few small series of atypical melanocytic neoplasms managed with excision alone, showing no evidence of recurrent disease [1, 71, 75, 121]. A systemic review of 541 patients with atypical spitzoid lesions revealed that 39% of patients had nodal involvement, and at almost 5 years of follow-up 99% of patients with positive lymph nodes were alive without disease [95].

In contrast, we have seen multiple cases where patients initially diagnosed with pediatric atypical neoplasms developed recurrent melanoma and have even died, often many years after their initial diagnosis. Even in "unequivocal" pediatric melanoma, many of the recurrences and deaths from disease occur more than 5 years after initial diagnosis [56, 112, 118]. Thus, studies with short or incomplete follow-up must be carefully viewed with this in mind.

The most convincing case in favor of sentinel lymph node biopsy for pediatric atypical neoplasms is the uncertainty associated with the diagnosis. The variation in diagnoses, even among experienced dermatopathologists, is well noted. Cases of documented fatal outcomes were originally deemed as atypical or benign, when examined by experienced dermatopathologists in a blinded fashion [59, 122]. An atypical diagnosis from the initial biopsy may not accurately reflect the malignant nature of the lesion. Although the consequence of atypical cells in the sentinel node is not always clear, the presence of expansile nodules of tumor cells may expose a malignancy that otherwise would have been overlooked. The finding of negative sentinel nodes can reassure the patient and family that despite the uncertainty the patient has been treated appropriately if the diagnosis is indeed melanoma.

Surgical Management of the Sentinel Node-Positive Nodal Basin

The main aspects of managing of the pediatric melanoma patient with a positive sentinel lymph node are largely drawn from the adult literature. The standard of care is completion lymphadenectomy (radical lymph node dissection) after the diagnosis of a positive sentinel node biopsy [123]. In adults, involved non-sentinel nodes are found in only 15–20% of lymphadenectomy patients [124–126]. In the pediatric population, there is limited data on the rates of non-sentinel node involvement, with one study even suggesting that it may be lower than in adults, while another suggests that it is higher than in adults [111, 127].

The rates of lymphedema are lower for pediatric patients undergoing radical lymphadenectomy compared to adults. In our experience, the sensory neuropathy and numbness seen in the adult population after lymphadenectomy are rarely of lasting clinical significance in children. However, the infection risk of a radical lymph node dissection can be a problem, especially for younger patients who are more at risk for lifelong consequences. Conversely, teenagers and young adults may be noncompliant with the close follow-up recommended for node-positive patients not undergoing completion lymphadenectomy. Thus, we recommend a completion lymphadenectomy on a case-by-case basis. For each patient, we consider the extent of tumor involvement in the sentinel nodes, the number of sentinel nodes involved, the location of the positive sentinel node, the age of the child, the findings on the preoperative lymphoscintigraphy and the ability of the patient to be compliant with follow-up. For example, a young child may benefit greatly from even a few years of delay in performing a lymphadenectomy, which can decrease both the acute and late risks. Thus, in this case, we may defer a completion lymphadenectomy for a time in the future. Adolescents and older patients must be evaluated to ensure that they will be compliant with the follow-up schedule, which can last for years as they leave for college, employment, etc. Removing the regional nodes in a timely fashion (after a positive sentinel node biopsy) may be a preferred approach if long-term follow-up cannot be assured.

All patients with positive sentinel lymph nodes for whom completion lymph node dissection is deferred should undergo ultrasound surveillance of the involved nodal basin at least two

to three times per year. This should continue over a period of 3–5 years, followed by a decreased frequency of every 6–12 months. They are advised to return promptly to clinic if they develop any signs or symptoms of a recurrence.

Surgical Management of the Clinically Node-Positive Nodal Basin

Sentinel node biopsy can identify occult nodal metastasis and, in some cases, the management of patients with positive sentinel nodes can involve observation. However, the pediatric patient with clinically detected lymph node metastases should routinely undergo a radical lymphadenectomy of the involved nodal basin, unless there is evidence of distant metastatic disease. The same surgical principles used in adults to determine the extent of dissection are also utilized in children. As in adults, the role of pelvic ("deep") node dissection in patients with inguinal node-positive disease is inadequately defined. If the iliac or obturator nodes are deemed suspicious for metastatic disease by pre-surgical radiographic evaluation, the indication for lymphadenectomy is clear. However, deep lymphadenectomy should be considered for patients with numerous, large involved inguinal nodes, even in the absence of radiologic evidence of pelvic lymph node involvement. In adults, studies suggest that including the external iliac and obturator nodes with an inguinofemoral node dissection does not increase long-term morbidity [128, 129]. Our own experience in our practice in adults and children also supports this approach.

Adjuvant Systemic Therapy

Systemic adjuvant therapy is commonly used in the adult population with high-risk disease. Due to the exclusion of children from most previous melanoma trials, as well as the relative rarity of pediatric melanoma, there is limited information regarding adjuvant systemic treatment in the pediatric melanoma population.

Interferon α-2b

The best studied agent in pediatric melanoma is interferon α-2b, which is approved for use in the adjuvant treatment of adult node-positive melanoma [130]. Three single-institution studies have retrospectively evaluated the feasibility of using high-dose interferon α-2b in stage III resected pediatric melanoma [131–133]. Pediatric patients tolerated the treatment well and needed fewer dose adjustments than adult patients. In one study of five stage III patients, two patients required dose modification in the induction phase, while two patients required dose modification in the maintenance phase due to abnormal liver function tests [133]. A prospective study of 15 patients with sentinel node-positive melanoma underwent treatment with high-dose interferon, with 8 initially diagnosed with atypical melanocytic neoplasms and subsequently reclassified as melanoma. All patients enrolled in the study were able to complete the initial induction phase, and only one patient was unable to complete the maintenance phase due to toxicity. Two of 15 patients developed recurrent disease during treatment. One underwent complete resection and one died of metastatic melanoma. A third patient developed metastases after treatment and succumbed to disease [132].

Because subcutaneous injection of interferon α-2b three times a week is inconvenient, particularly in children, the pegylated interferon α-2b (peg-interferon) form may be a better option for children. It can be administered once a week [134–136] and has a more favorable pharmacokinetic profile that is suitable for maintenance therapy [137]. A recent study of a hybrid interferon and peg-interferon regimen in children and adolescents with resected high-risk melanoma confirmed that it was well tolerated. Of 23 patients on the trial, all patients completed induction therapy, 18 patients completed all prescribed therapy, and only 3 patients discontinued treatment due to toxicity. The quality-of-life scores showed an improvement after the intravenous component of the treatment (induction) was delivered [138]. Our preference in children with stage III melanoma, particularly before puberty, has been to utilize this hybrid approach with adjuvant interferon α-2b given IV for 1 month, followed by maintenance peg-inter-

feron weekly for 12 months. However, the development of newer adjuvant therapy regimens in adults has the potential to make all forms of interferon adjuvant therapy obsolete.

Alternative Adjuvant Regimen and Therapeutic Agents Under Evaluation

The side effects and duration of treatment for high-dose interferon have led to the investigation of alternate dosing regimens. SWOG S0008, an intergroup phase III randomized control trial, compared high-dose interferon for 1 year to biochemotherapy given for only 9 weeks (dacarbazine, cisplatin, vinblastine, interleukin-2, interferon, and granulocyte-stimulating factor given every 21 days for three cycles). While the study primarily included adult patients, children aged 10 and older were eligible for enrollment. For all patients enrolled, there was a statistically significant improvement in median recurrence-free survival (4 years for patients receiving biochemotherapy vs. 1.9 years for high-dose interferon) and 5-year recurrence-free survival (48% vs. 39%). Overall survival, however, was not different between the two study arms [139]. Age-specific results were not reported, but this study offers one alternative for postpubertal children unable to commit to a year of adjuvant therapy.

In recent years, there has been an explosion of new agents shown to improve survival in adults with metastatic melanoma, and older regimens like biochemotherapy and even interferon have almost entirely been abandoned. New options for treating unresectable metastatic melanoma may be beneficial in the adjuvant setting in children as they have proven to be in adults. Ipilimumab, a human monoclonal antibody to cytotoxic T-cell lymphocyte antigen 4, has been investigated in the adjuvant setting for stage III melanoma and found to have a significant 5-year recurrence-free survival benefit of 40.8 vs. 30.3% when compared to observation alone. There was an improvement in 5-year metastasis-free survival and overall survival, despite 53.3% of patients discontinuing treatment due to toxicity. However, there were a high number of grade 3 and 4 toxicities with ipilimumab, and 1.1% of patients in the ipilimumab arm died of immune-related adverse events [140]. The optimum dosing is currently being investigated. E1609 (NCT01274338) compares high-dose interferon to two doses of ipilimumab, the high-dose initial investigated in the adjuvant setting, and a lower dose consistent with that approved for use in metastatic disease, and includes children aged 15 and older. This will likely provide the first opportunity to evaluate these newer agents in the adjuvant therapy of melanoma in any portion of the pediatric population.

The use of anti-PD1 antibody therapy has particular promise in the adjuvant setting, given its lower toxicity and greater efficacy compared to ipilimumab [141]. Preliminary results of a randomized trial in adult patients with stage III melanoma show that the anti-PD1 antibody, nivolumab, is less toxic and improves relapse-free survival compared to high-dose ipilimumab [142]. There is no information yet available about the impact of anti-PD1 adjuvant therapy on overall survival, and no anti-PD1 agent has yet been directly compared to adjuvant interferon, although a clinical trial (S1404, NCT02506) has completed accrual. Most recently, randomized trials have shown the potential for targeted therapy with BRAF and MEK inhibitors (specifically dabrafenib and trametinib) as adjuvant [143] and neoadjuvant (preoperative) therapy [144] for adults with stage III melanoma harboring a BRAF V600 mutation. Pediatric oncologists are gaining experience with these drugs in a variety of childhood malignancies [145], and the field of adolescent and young adult oncology has created new collaborations between medical oncologists and pediatric oncologists. Hence it is likely that these promising findings will be applied to selected younger patients with stage III pediatric melanoma. While ideally clinical trials will be conducted in the pediatric population, the promising adult data makes it likely that reports will emerge with BRAF/MEK inhibitor cohorts being reported from larger volume centers.

Metastatic Disease

Systemic Therapy

Pediatric patients with metastatic melanoma should strongly consider enrollment in a clinical trial, as there is little knowledge about this

patient population in terms of efficacy and safety profile. Multiple trials in the adult stage IV melanoma population have shown an increase in survival with BRAF inhibitors (such as vemurafenib and dabrafenib), anti-PD1 antibodies (such as pembrolizumab and nivolumab), and the anti-CTLA antibody ipilimumab. Knowledge of the *BRAF* mutational status is an important component on making treatment decisions for stage IV melanoma. *BRAF* mutations are more common in adolescent and young adults with conventional melanoma than the prepubertal cohort and the older adult melanoma population [146]. There are multiple case reports of vemurafenib and other BRAF inhibitors being used in children for various malignancies (brain, thyroid, etc.) with known *BRAF* mutations with good response.

Melanomas in young children, especially those arising in congenital nevi, predominantly lack *BRAF* mutations, and hence cannot be treated with BRAF inhibitors [147]. A recent study evaluated the use of the MEK inhibitor trametinib for four pediatric patients with *NRAS* mutated melanoma of the central nervous system (congenital nevus syndrome/neurocutaneous melanocytosis). There was a transient improvement that lasted 1–9 months, but eventual progression and death in all these patients [37].

A Phase I trial of ipilimumab was conducted for pediatric patients with advanced solid tumors. Of 33 patients, 12 patients had melanoma. Dose-limiting toxicities were noted at 5 and 10 mg/kg. While there were no tumor responses observed, patients who developed immune-related toxicities after receiving ipilimumab had an improved duration in overall survival [148]. Ipilimumab is currently the only FDA-approved agent for treating pediatric melanoma [149].

Other commercially available agents include pembrolizumab, nivolumab, dabrafenib, and cobimetinib. There is little published data regarding the safety and efficacy of any of these agents in children under the age of 16. Recently, there was a case report involving a patient with congenital melanoma with widespread metastatic disease treated with nivolumab. The patient remains alive with stable disease after 1 year of therapy, which was well tolerated [150].

Palliative Radiation

In the pediatric melanoma population, radiation therapy is reserved for the treatment of unresectable disease or the palliation of metastatic disease, particularly brain lesions. Newer radiation techniques such as intensity-modulated radiation therapy (IMRT), proton beam radiation, image guidance, and stereotactic radiation have yielded more conformal treatments and increased sparing of normal tissue. Case reports and retrospective studies of stereotactic and fractionated radiation in the pediatric population suggest that modern techniques can be used safely in the pediatric population [151, 152]. We suggest that radiation be used selectively as an effective method of palliation.

Follow-Up

There are no specific follow-up recommendations available for pediatric melanoma patients. The National Comprehensive Cancer Center Guidelines for melanoma are typically followed. However, recurrences can occur more than 5 years after diagnosis due to the long natural history of pediatric melanoma [56]. Moreover, early detection of recurrence may allow for surgical intervention and/or a more favorable treatment outcome. These patients are also at risk of developing another (second primary) melanoma. Seventeen percent of pediatric melanoma patients in one series had another melanoma diagnosed within 10 years after initial diagnosis and 24% within 20 years after diagnosis [112]. Therefore, even beyond 5 years, these patients should continue to undergo annual examinations.

Prognosis of Pediatric Melanoma Based on Stage of Disease

Stage of disease is the major factor in determining the overall survival in pediatric melanoma, just as in adults, with localized disease having a more favorable prognosis. The prognosis is likely better for pediatric melanoma patients diagnosed prior to puberty versus in adolescence, and for both groups, better than adults of a similar stage [40, 53, 109]. However, age is not included in current staging systems.

Stages I–II: Localized Disease

Early-stage, localized pediatric melanoma portends an excellent prognosis, with multiple series reporting from 90 to 100% overall survival over 10 years for stage I disease, 79 to 100% for stage II disease with a disease-free survival of more than 70%, and 77.4% overall survival at 20 years [11, 40, 112]. Ulceration, increase in tumor thickness, and Clark level and nodular subtype are associated with a higher local recurrence and metastasis rate and a decreased overall survival, as in adult melanoma [114].

Stage III: Regional Metastatic Disease

Metastatic disease to regional lymph nodes is associated with decreased disease-free and overall survival in comparison to early-stage disease. A recent National Cancer Data Base analysis attempted to determine prognosis in prepubertal vs. postpubertal patients. In patients 10 years or younger, the prognosis was equivalent regardless of lymph node involvement, but a positive lymph node was a negative prognostic factor in adolescents. While the study is subject to retrospective bias and potential inclusion of atypical neoplasms, it is consistent with prior data suggesting that prepubertal patients have a more favorable prognosis than adolescents and both do better than adults with similar staged disease [109]. The overall survival for stage III patients at 10 years was 70–77% [11, 40, 153].

Stage IV: Distant Metastatic Disease

As in adults, distant metastasis in the pediatric population portends a poor prognosis, with 40% overall survival at 5 years and 0% at 10 years, as reported in a large registry series [11].

Prognosis of Atypical Melanocytic Neoplasms

Atypical melanocytic neoplasms are diverse in terms of histology, molecular makeup, and perhaps prognosis. The vast majority of patients with atypical melanocytic neoplasms have an excellent prognosis, yet deaths from melanoma have occurred in children whose initial lesion could not, even in retrospect, be definitely characterized as malignant. Recurrent or metastatic disease is more common in atypical melanocytic neoplasms with ulceration, diameter >1 cm, extension into the subcutaneous tissue, and higher numbers of mitoses. Atypical lesions in postpubertal children are associated with increased risk of metastasis compared to younger children, just as with unequivocal melanoma [80]. Recent studies suggest that lesions with 9p21 deletions and *TERT* promoter mutations have increased potential for recurrence and metastasis [77, 89, 92, 93]. The prognostic significance of sentinel lymph node biopsy is controversial (see Section "Indications for Sentinel Node Biopsy in Pediatric Atypical Melanocytic Neoplasms" above).

Future Directions and Challenges

Knowledge of pediatric melanoma, its natural history and epidemiology, is limited by the rarity of the disease, incomplete data about the cases that do occur, and variations in diagnosis and diagnostic terminology. Most studies are from single-institution series with comparatively small patient numbers, although there has been one large registry study published [11]. The plethora of malignant, atypical, and benign nevi continues to be challenging to distinguish, but recent studies further characterizing lesions with metastatic potential are encouraging. Discovering mutations in melanoma and having available agents to target these mutations provide children who otherwise would have had limited available treatments with potential options. However, for pediatric patients with unresectable or metastatic disease, access to clinical trials testing the latest therapeutic agents is limited. This limits our understanding of the safety profile of these medications as well as their efficacy in children. With greater national and international collaboration between institutions, prospective evaluation, clinical

trials, and discovery of tumor markers to assess metastatic potential as well as response to treatment, we will be able to further elucidate the appropriate management and to develop age-specific guidelines for pediatric melanoma.

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