Pediatric Melanoma and Atypical Melanocytic Neoplasms

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Abstract

Melanoma is uncommon in the pediatric age range, but is increasing in frequency and often presents with atypical features compared to the classic ABCDE criteria common to adult melanoma cases. Moreover, many melanocytic neoplasms in childhood pose diagnostic challenges to the pathologist, and sometimes cannot be unequivocally classified as benign nevi or melanoma. This chapter addresses the evaluation and management of pediatric patients with melanoma and atypical melanocytic neoplasms, including the roles of and unresolved questions surrounding sentinel lymph node biopsy, completion lymphadenectomy, adjuvant therapy, and treatment of advanced disease.

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1 Introduction

1.1 Definition

Pediatric melanoma is defined as a malignant melanocytic lesion in a child from birth to age of 18 or 21 years, depending on the cutoff employed for defining adulthood. In this chapter, unless otherwise specified when quoting studies using different age cutoffs, we consider pediatric cases to be under the age of 21 years. Pediatric melanoma can be further subclassified according to the specific age range at presentation (congenital, infantile, prepubertal childhood versus postpubertal adolescence; see Fig. 1), histologic subtype, presence or absence of precursor lesions, and by using the standard clinical and pathologic staging criteria applied to adult cases. A major issue in any discussion of pediatric melanoma is the difficulty frequently encountered in establishing whether or not a histologically abnormal melanocytic lesion is in fact unequivocally malignant. While some of the difficulty may stem from a relative hesitancy to diagnose melanoma in young children, there are clearly a number of abnormal melanocytic lesions that are difficult or impossible to reliably categorize as benign or malignant using currently available histopathologic criteria. The broad but concise term *atypical melanocytic neoplasm* is our

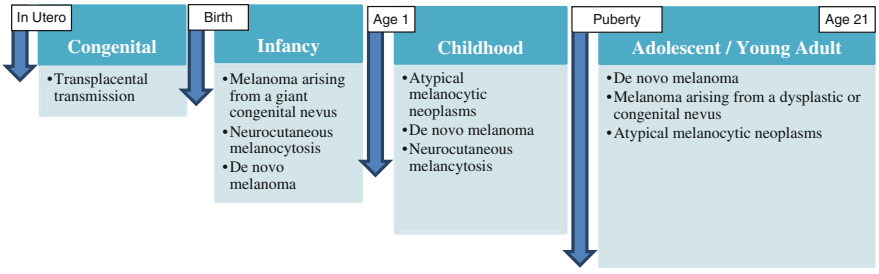

Fig. 1 Pediatric melanoma presentations in different age ranges. The length of the arrow is roughly proportional to the relative frequency of melanoma (and/or atypical melanocytic neoplasms) occurring in each interval, so melanoma occurring in utero due to transplacental transmission from the mother or presenting in the first year of life is least common, but pediatric melanoma becomes progressively more common in subsequent years, especially postpuberty

preferred name for this broad class of lesions, which like pediatric melanoma may be further subclassified based on histologic appearance and potential for recurrence and metastasis [71, 95].

1.2 Epidemiology

Pediatric melanoma accounts for 1–4 % of all cases of melanoma and 1–3 % of all pediatric malignancies [7]. It is the most common primary malignant tumor of the skin in patients younger than 20 years of age. Though the incidence of melanoma in children younger than 10 years has remained stable, the incidence of adolescent melanoma is increasing at a rate of 2.9 % per year in the USA over the past 3 decades [7, 101], with similar trends reflected throughout the world [1, 47].

There were estimated to be 450 new cases of melanoma diagnosed in children younger than 21 years in the USA in 2014 [105]. There is a slight female predominance, and the increase in incidence of melanoma is highest in female adolescents. While Caucasian children account for the majority of new diagnoses, the incidence continues to rise in the Hispanic and Native American populations [93].

1.3 Comparison with Adult Melanoma

Compared to adults, children present with thicker primary lesions and a higher incidence of sentinel lymph node metastases [44, 49, 61]. Melanoma in a child is more likely to arise from a precursor lesion such as a nevus and have an atypical clinical presentation that does not follow the typical ABCDEs of melanoma (Table 1), as well as to show unusual pathologic features [26, 35]. Specifically, lesions are more frequently non-pigmented and often have histologic features reminiscent of a Spitz nevus, so-called spitzoid features [86]. They are also more often of nodular histology. Non-whites, such as Hispanics and Asians, are overrepresented compared to adult melanoma [7]. Despite the later stage at presentation, pediatric melanoma appears to have a more favorable prognosis than adult melanoma of a similar stage [49, 61]. The overall survival in children with melanoma ranges from 70 to 80 % at 10 years [8].

Table 1 Comparison of "ABCDE" characteristics of adult and pediatric melanoma

	Hallmarks of adult melanoma	Alternative characteristics of pediatric melanoma
A	Asymmetry	Amelanotic
B	Border irregularity	Bump/bleeding
C	Color variation	Colorless/uniform color
D	Diameter	De novo/any diameter
E	Evolution	Evolution

Adapted from Cordoro et al. [26]

1.4 Classification and Risk Factors

1.4.1 General Risk Factors

The risk factors for pediatric melanoma differ slightly depending on age at presentation. Sun exposure, tanning bed use, and fair skin are more relevant risk factors in postpubertal patients, while prepubertal patients may be slightly more likely to have genetic risk factors [105, 111].

1.4.2 Congenital/Neonatal Melanoma: In Utero to 1 Year

Congenital and neonatal melanoma is very rare [112], and the available information is based on a small number of case reports. The incidence of congenital and neonatal melanoma has not increased appreciably over the past 30 years [7, 8].

Transplacental Transmission

Melanoma is one of the malignancies recognized to be able to spread from mother to fetus via transplacental transmission. Placental metastasis of melanoma is extremely rare, and fewer than 30 cases have been reported in the literature [3, 5, 90, 104]. The risk factors described to date include maternal diagnosis of node-positive disease greater than 3 years prior to pregnancy, metastatic melanoma manifesting in the mother during the third trimester, maternal age less than 30 years, primiparity, birth at greater than 36 weeks' gestation, and male fetal gender [5, 96]. Of the reported cases of placental metastatic melanoma, 60–67 % of infants were alive 18 months after birth [3, 96]. Fetal transmission across the placenta is even more rare, with eight cases reported to date [3, 117, 121]. Patients are often diagnosed at birth or within twelve months of birth. The prognosis is dismal, with six of the eight reported cases dying in the first year of life. There have been two reported cases of spontaneous regression [121]. Karyotyping has been performed on two cases of male fetal metastatic melanoma, showing an XX karyotype in both cases [117, 121]. If transplacental melanoma transmission is suspected, karyotyping analysis or fluorescence in situ hybridization (FISH) can be used in males for confirmation of the tumor's origin. New assays are available to quantify the copy number of sex chromosomes in genomic DNA purified from a fetal tumor biopsy specimen suspected to be of material origin [94]. Because the development of placental metastases has been noted in even early-stage melanoma patients, thorough sectioning and histologic examination of the placenta is advocated in all patients with a history of invasive melanoma.

Melanoma in a Giant Pigmented Nevus

Congenital melanocytic nevi (CMN) are melanocytic proliferations that present at or very shortly after birth. By definition, they are benign and are categorized by projected adult size: small (<1.5 cm in diameter), medium (1.5–20 cm), and large (>20 cm) [114]. The distinction between large and giant CMN has been inconsistent, with some defining giant CMN by various body surface area measurements instead of projected adult size [4]. A more recent classification system, which takes

into account nevus size as well as satellite nevus counts and physical features such as color, surface change, and hypertrichosis, classifies giant CMN as either 40–60 cm (G1) or >60 cm (G2) [92]. Giant CMN are more likely to give rise to pediatric melanoma, but estimates of risk vary markedly [130]. A 2006 meta-analysis of 6571 CMN patients found that 0.7 % developed melanoma at a mean age of 15.5 years [56]. The relatively early onset of melanoma in the setting of giant CMN is the basis for advocating surgical removal of these lesions early in life. Small and medium CMN have a reported lifetime risk of malignant transformation of 2–5 %, but most cases of melanoma arising in these lesions are diagnosed 6 in adulthood. CMN in axial locations are more likely to develop melanoma than CMN in the extremities [28].

Neurocutaneous Melanoma

Neurocutaneous melanoma is extremely rare. It arises in the setting of neurocutaneous melanocytosis, which can include both benign and malignant proliferations of melanocytes in the central nervous system associated with a giant CMN or with more than three small to medium CMN. 6–11 % of patients with giant CMN develop symptomatic neurocutaneous melanocytosis [4, 51]. Neurologic symptoms such as headache, vomiting, seizures, neuropsychiatric disturbance, or myelopathy typically present by age 10 and are associated with increased intracranial pressure and mass effect present on imaging [51]. 40–60 % of patients with neurocutaneous melanocytosis develop melanoma. These patients have a poor prognosis due to the difficulty of resection, limited treatment options, and risk of leptomeningeal infiltration [52, 99]. Genomic studies have suggested that NRAS mosaicism, in particular postzygotic mutations in codon 61, is associated with the onset of neurocutaneous melanocytosis [54].

De Novo/Sporadic Melanoma

De novo lesions are exceedingly rare among melanomas diagnosed within the first year of life, with fourteen cases reported to date [6, 112]. Of these, three children have succumbed to the disease. At present, there are no known risk factors. Diagnosis is challenging, because of some histologic overlap with giant CMN. Recently, comparative genomic hybridization (CGH) of two cases of de novo congenital melanoma was used to establish the diagnosis, revealing multiple chromosomal aberrations [112].

1.4.3 Childhood Melanoma: 1 Year to Puberty

While age cutoffs of 10–12 have been used in most studies to divide childhood from adolescent melanoma, it is likely that the most relevant biologic cutoff is to separate melanomas that arise before and after puberty. Tanner stage may be a more accurate method of distinguishing between childhood and postpubertal adolescence, when hormone-driven changes in melanocyte physiology likely occur. However, in retrospective reviews, determining whether a given child has or has not gone through puberty is quite difficult, hence the need to use clinical surrogates; a cutoff of either

10 or 12 remains appropriate for retrospective reviews or clinical trials that aim to separate childhood melanoma from adolescent cases.

De Novo/Sporadic Melanoma

The majority of childhood melanomas are sporadic and unassociated with congenital nevi or genetic syndromes. The risk factors in these cases have not been well established but likely include UV radiation exposure, fair skin, and multiple nevi [111]. However, compared to adolescent melanoma patients, prepubertal patients are more likely to be non-Caucasian and for this and other reasons, the specific role of UV exposure in this group remains quite unclear [57].

Arising from Giant CMN and Dysplastic Nevi

Similar to neonatal melanoma, childhood melanomas can also arise from giant CMN. One-third of childhood melanomas originate from giant CMN or another precursor lesion, including common and dysplastic nevi [2, 4, 28, 29, 57, 61, 85, 87, 99, 114].

Genetic Syndromes

Genetic mutations that confer sensitivity to DNA damage, alterations in cell cycle tumor suppressors such as p53, and mutations in other tumor suppressor genes are associated with a greater risk of melanoma in children, adolescents, and adults.

Xeroderma Pigmentosum

Xeroderma pigmentosum is an autosomal recessive genetic disorder of nucleotide excision repair, which makes affected individuals exquisitely sensitive to DNA damage by UV radiation. Affected patients will generally develop non-melanoma skin cancer at a median age of 8 years, while melanoma occurs in approximately 5–13 % of xeroderma pigmentosum patients by age 21 [17, 85].

Familial Melanoma Syndromes

Familial melanoma syndromes are not particularly well characterized in adults and even less so in children. Recent genomic studies identified mutations in *CDKN2A* or *CDK4* that can lead to multiple and recurrent melanomas. *CDKN2A* is the most common high-risk melanoma susceptibility locus; mutations in this gene are also associated with dysplastic (atypical) nevus syndrome, >100 nevi, nevi of buttocks/feet, multiple primary melanomas, and pancreatic cancer risk [15]. However, such germline mutations have been found to be present in less than 5 % of childhood melanomas [13, 79]. Other less common familial melanoma syndromes, such as those caused by germline *BAP-1*, *BRCA2*, and *MC1R* mutations, are generally associated with development of melanoma in adulthood rather than childhood.

1.4.4 Adolescent and Young Adult Melanoma

Adolescent and young adult melanoma encompasses patients from puberty to age 21. This is the segment of the pediatric population with the highest incidence of a diagnosis of melanoma. Moreover, it is the segment in which the incidence rate is rising most rapidly, particularly in teenage girls [125]. The risk factors are thought to be similar to those for adults: ultraviolet radiation exposure, tanning bed use, fair skin, family history of melanoma, and the presence of multiple and atypical nevi [29, 35, 57, 60, 61, 81, 125]. Other risk factors include xeroderma pigmentosum and germline mutations involving cell cycle mediators (see Sections "Xeroderma Pigmentosum" and "Familial Melanoma Syndromes" above).

2 Clinical Presentation

2.1 General

Pediatric melanoma presents with distinct clinical manifestations in comparison with adult melanoma [35, 44, 61]. In up to 60 % of childhood and 40 % of adolescent melanomas, the classical "ABCD" hallmarks of diagnosis in adults are not seen. In comparison with the traditional criteria of **a**symmetry, **b**order irregularity, **c**olor variation, **d**iameter ≥6 mm, pediatric patients were found to have more symmetric, raised, and amelanotic lesions with bleeding, uniform or no color, a diameter <6 mm, and de novo lesions. Therefore, a new set of criteria for diagnosis has been proposed for pediatric melanoma: amelanotic, bump/bleeding, uniform or no color, and de novo/any diameter (see Table 1) [26]. These new criteria, however, have neither been prospectively validated nor yet shown to decrease the ratio of normal to malignant lesions subjected to biopsy.

2.2 Congenital/Neonatal Melanoma

Since congenital melanomas arise in the setting of maternal metastatic melanoma, this potential risk is of great concern to pregnant patients with melanoma and their doctors. Congenital melanoma is often first recognized on the basis of a finding of gross or microscopic involvement of the placenta by metastatic melanoma. Thus, for pregnant women with a history of invasive melanoma, and especially for those with known stage III or IV melanoma, we advocate that the placenta should be submitted for gross and microscopic pathologic analysis, supplemented as necessary with immunohistochemical staining for melanocyte lineage antigens. The absence of placental involvement with melanoma is reassuring, while a finding of melanoma cells on the fetal side of the placenta is very concerning for potential maternal–fetal spread. Virtually all cases of neonatal melanoma arising from maternal transmission have manifested before 12 months of age [3, 117].

Neonates with melanoma that is not related to maternal–fetal transmission generally present with a history of a progressive nodule or nodules within a large congenital melanocytic lesion, or with neurologic symptoms or symptoms of increased intracranial pressure in the case of neurocutaneous melanocytosis.

2.3 Childhood Melanoma: Age 1–Puberty

Due to the rarity of melanoma in this age group, there are few series describing a typical clinical presentation. In addition to the lack of conventional ABCD criteria, affected patients are more likely to have darker skin phototypes (Fitzpatrick type III or IV), extremity location of primary, and a high overall number of nevi [26].

2.4 Adolescent and Young Adult Melanoma: Puberty–18

Over three-quarters of pediatric melanoma arise in this subgroup of patients. As with younger patients, atypical presentations such as lack of visible pigmentation (pink/red/flesh-colored), or a symmetric papular or nodular appearance are reported more commonly than in adult melanoma. Cordoro et al. [26] found that the most common prebiopsy diagnosis in this age group was pyogenic granuloma.

3 Initial Clinical and Pathologic Workup

Recognizing the relatively non-specific presentation and the rarity of pediatric melanoma, the potential for delay in diagnosis is quite high. Suspicious pigmented lesions in childhood should ideally be biopsied and evaluated by a dermatopathologist with expertise in evaluating these cases. Clinical history, including history of a congenital nevus or other precursor lesion in the area biopsied, patient age, extent of biopsy (complete excision, shave biopsy, partial excision/punch), patient demographics, color and size of the lesion, and a photograph of the lesion, can all be helpful to the pathologist, emphasizing the value of a close collaboration between clinician and pathologist in dealing with pediatric pigmented lesions of all types. Not uncommonly in our experience, skin lesions in children are initially considered to be warts and thus may be treated with a variety of topical agents prior to being referred for biopsy, and information about this can also be potentially helpful to the pathologist.

The preferred biopsy method is complete excision with a narrow margin of normal skin, which allows for more complete pathologic evaluation of the lesion, including its relationship to neighboring skin and subcutis. Formalin fixation is sufficient for all routine and specialized specimen evaluation methods, including FISH and CGH, the latter two of which are increasingly being utilized as adjuncts in the evaluation of pediatric melanocytic lesions, as discussed subsequently.

Initial histopathologic evaluation of biopsy specimens, especially those demonstrating histologically challenging, ambiguous melanocytic proliferations, may include a variety of commercially available immunohistochemical stains. Commonly used stains include assessment of proliferative activity, either using proliferation index with Ki-67 [78] or assessing mitotic count with phosphohistone H3 [21, 78]. Melanocytic maturation can be demonstrated by progressive loss of HMB-45 staining as dermal depth of melanocytes increases in benign and Spitz nevi compared to melanoma [68]. Complete loss of p16 expression by immunohistochemistry indicates homozygous (biallelic) deletion of *p16/CDKN2A* and may be seen in either atypical Spitz tumor or melanoma, but only rarely if at all in Spitz nevi [25, 65, 128]. Loss of BAP-1 expression has been demonstrated in a subset of histologically challenging, spitzoid-appearing benign and malignant melanocytic proliferations that may occur sporadically or in inherited form [124]. Recently, the presence of kinase fusions involving ALK, ROS-1, NTRK-1, BRAF, or RET has been found in up to 40 % of lesions with spitzoid histology, but has not yet been shown to be indicative of the malignant potential of these lesions [123].

4 Pathologic Classification

4.1 Spectrum of Melanocytic Neoplasia

There is a broad spectrum of melanocytic neoplasia in children, ranging from congenital to acquired, dysplastic, Spitz, blue, and deep penetrating nevi, pigmented epithelioid melanocytoma, and melanoma. Across this spectrum, there are lesions which do not neatly fit into any one diagnostic category, and these lesions have been given a variety of appellations, including borderline tumors, melanocytic tumors of uncertain malignant potential (MELTUMP), spitzoid tumors of uncertain malignant potential (STUMP), and atypical Spitz tumor. Multiple observational, retrospective, and prospective studies have sought to evaluate the natural history of these atypical neoplasms [11, 22, 28, 38, 66, 74, 107], but significant uncertainty remains and diagnostic agreement between even expert dermatopathologists is far less than 100 % [37]. For the purposes of this chapter, we refer to these diagnostically challenging lesions as "atypical melanocytic neoplasms."

Of these, the atypical spitzoid neoplasms are the most common. The term spitzoid refers to lesions with some but not all of the features of a typical (benign) Spitz nevus. It is often difficult to identify spitzoid lesions with the potential for recurrence and distant metastasis, as no consistent, distinctive factors have been identified that categorize malignant potential.

Multiple studies have attempted to identify tumor markers to characterize the malignant potential of atypical melanocytic neoplasms. CGH and FISH have been most consistently used when some but not all of the features of either melanoma or a benign lesion like a Spitz nevus are present in a given case [82]. Initial FISH results using probes targeting chromosomes 6p25 (the locus of gene *RREB1*), 6q23

(*MYB*), Cep6 (the centromere of chromosome 6), and 11q13 (*CCND1*) showed a sensitivity of 86.7 % and specificity of 95.4 % in diagnosis of melanoma compared to benign nevi, although false-positive diagnoses in tetraploid cases were an issue [39]. The second-generation FISH test targets 6p25, 11q13, 9p21 (*CDKN2A*), and 8q24 (*cMYC*) and has a higher accuracy with histologically unequivocal melanocytic neoplasms [38]. However, when used in the setting of diagnostically challenging spitzoid melanocytic proliferations, the sensitivity is less than 70 % [66, 79], so this test is not reliable as the sole arbiter of a malignant or benign diagnosis. It may be useful as a diagnostic adjunct: in one 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* [38].

CGH assesses for gains and losses of portions of genetic material across the entire spectrum of 23 chromosome pairs. In one series, while 96 % of melanomas had chromosomal gains or losses, only 13 % of atypical melanocytic neoplasms had abnormalities. While most benign nevi have normal karyotypes, 15 % of Spitz nevi showed an increase in copy number of chromosome 11p at the *HRAS* locus, versus 70 % of atypical spitzoid neoplasms [12]. In contrast, melanoma in pediatric and adult cases rarely shows an *HRAS* mutation. Loss of *BAP1* on 3p21 is associated with the development of melanocytic tumors with spitzoid features, and a recent screening of a database of ambiguous melanocytic tumors showed that 6.7 % of cases had 3p21 loss [129]. Kinase fusions involving ALK, ROS-1, NTRK-1, BRAF, and RET are found in up to 51 % of melanocytic tumors with spitzoid morphology. Although the presence of a fusion protein is not informative about the biologic potential of the lesion, some may confer sensitivity to tyrosine kinase inhibitors [16, 123]. There are further studies investigating the role of epigenetics and hypermethylation as biomarkers of melanoma and treatment response. Mutations of the *TERT* promoter, which increase telomerase activity, were recently found in 4 of 58 atypical spitzoid tumors, and all 4 cases with a *TERT* mutation developed metastases and died of disease [59]. Most recently, microRNA studies have been conducted and may show promise as adjuncts for evaluating histologically ambiguous lesions [43, 58].

Involvement of lymph nodes draining the site of an atypical lesion could potentially indicate its malignant nature; patients with diagnostically challenging lesions may be offered a sentinel lymph node biopsy for this purpose (see Sect. 4.3).

4.2 A Proposed Nomenclature for Categorization of Pediatric Melanocytic Neoplasia

Compounding the difficulty making a firm diagnosis of benign or malignant lesions is the lack of a standard terminology so that clinicians can understand exactly what the pathologist is trying to convey about the nature of the lesion in question. This in turn makes it difficult for clinicians to communicate to the patient or patient's family about the nature of the lesion, the risk for metastasis and death, and the

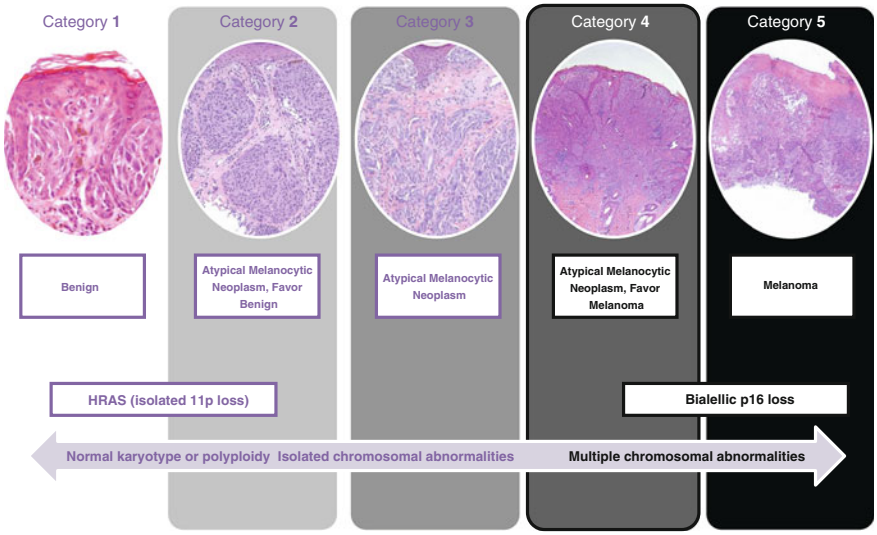

Fig. 2 Spectrum of melanocytic neoplasms in children. We have adopted a 1–5 scale that reflects the histologic appearance of the primary lesion (depicted) as well as molecular/genetic information derived from comparative genomic hybridization or fluorescence in situ hybridization, and can also reflect the findings of sentinel node biopsy in appropriate cases. Only a few molecular abnormalities, however, definitively characterize as lesion as likely benign (isolated 11p loss) or malignant (biallelic p21 loss). This numerical scale facilitates communication not only between the pathologist and the clinician, but also between the clinician and the patient and family. Importantly, the categorization can evolve as additional clinical, pathologic, and molecular information becomes available. (Modified from Sreeraman Kumar et al. [108].)

available treatment options. In an effort to add a degree of objectivity to this process, we have adopted a five-point system for categorizing melanocytic lesions from clearly benign at one end of the spectrum to clearly malignant at the other (Fig. 2). This system is derived from the original "BiRADS" reporting system for categorizing the results of mammography [30] and is similar to a proposal for categorizing dysplastic nevi [91]. We have found this system useful in our conversations between pathologist and clinician and between clinician and patient/family, and also for conveying the process whereby the initial uncertainty about a lesion can lessen or even resolve entirely as additional pathologic material is analyzed or new clinical details emerge [106].

4.2.1 Category 1: Benign

Lesions in this category possess classic histopathologic features of an unequivocally benign lesion. In the pediatric age groups, examples include Spitz nevi, pigmented spindle cell nevi of Reed, blue nevi, deep penetrating nevi, CMN, proliferative nodules in congenital nevi, melanocytic nevi, dysplastic melanocytic nevi, and speckled lentiginous nevi. There is no additional evaluation needed, but to

prevent recurrence complete excision is generally warranted, if not already achieved with the initial biopsy.

4.2.2 Category 2: Atypical Melanocytic Neoplasm, Favor Benign

Lesions in this category possess most but not all of the classic histopathologic features of one of the unequivocally benign lesions mentioned above. Some non-typical features are seen, but not to the extent that the pathologist feels that the lesion may represent a melanoma. Examples of such features include focal areas of proliferation/mitoses, focal increases in cellularity, or isolated foci of cellular atypia. At times, an unequivocal diagnosis cannot be made due to an incomplete biopsy that does not allow full evaluation of the lesion. Hence, these lesions should all be completely excised and the re-excision specimen evaluated to ensure that no more concerning features are seen in areas of the lesion not sampled in the initial biopsy material, but beyond that no further evaluation or management is generally warranted.

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

These are lesions with atypical features indicating possible metastatic potential, but which lack features that allow the pathologist to definitively classify the lesion as most likely malignant or benign. Many different terms have been proffered to describe these lesions, such as STUMP, spitzoid atypical melanocytic proliferation of uncertain significance (SAMPUS), and MELTUMP. However, these terms—while adequately capturing the inherent uncertainty of behavior—do not convey to the clinician whether there are any features that are more or less suggestive of malignancy. There are also some melanocytic lesions that are recognized diagnostic entities but for which the likelihood of malignancy is simply unknown, such as pigmented epithelioid melanocytoma, atypical cellular blue nevus, and some BAP-1 deleted melanocytic neoplasms (seen in patients with germline deletions of *BAP1*). CGH and/or FISH can be particularly helpful in these lesions. For example, an atypical spitzoid lesion in Category 3 by histopathologic criteria that had a single chromosomal aberration in chromosome 11p might be appropriately categorized as an atypical Spitz nevus, favor benign (Category 2), while an identical appearing lesion with multiple chromosomal gains and losses and FISH abnormalities in a high percentage of cells would be considered very concerning for melanoma, potentially more appropriately reported as atypical spitzoid lesion, favor spitzoid melanoma (Category 4).

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

4.2.4 Category 4: Atypical Melanocytic Neoplasm, Favor Malignant

These are lesions with substantial atypical features indicating the possibility of metastatic potential, but which lack sufficient features that allow the pathologist to definitively classify the lesion as malignant. As indicated above, there may be overlap between lesions in this category and those mentioned in Category 3, hence our feeling that simply labeling all these as "lesions of uncertain malignant potential" fails to adequately convey to the clinician a high enough degree of concern. Examples include Spitz-like neoplasms with high dermal cellularity, deep dermal or subcutaneous extension, high mitotic rate in the deep dermis, asymmetry and/or necrosis [118], or atypical cellular blue neoplasms that are large, with necrosis and/or increased mitoses >2/mm^2 [9]. These are lesions with metastatic potential, and there are well-described cases of such lesions eventually leading to recurrence, metastasis, and death (and of course ultimate reclassification into Category 5). Excision to negative margins should always be performed, and these lesions should be treated in an identical manner to an unequivocal melanoma of similar depth. For us, this includes sentinel node biopsy for most Category 4 lesions 1 mm or thicker. CGH and/or FISH can be helpful, and if markedly abnormal may provide sufficient evidence for the pathologist to render an outright malignant diagnosis (Category 5). Similarly, in most cases of Category 4 neoplasms, findings of lesional cells in the sentinel node, especially in the nodal parenchyma or growing in an expansile fashion, should be considered to represent evidence that the lesion is indeed malignant.

4.2.5 Category 5: Melanoma

Lesions in this category possess classic histopathologic features of an unequivocal melanoma. A greater percentage of melanomas in the pediatric population are spitzoid or nevoid in appearance, which adds to the difficulty in making an outright diagnosis of malignancy. Desmoplastic, lentigo maligna, and subungual melanomas are less common in children than in adults (Table 2) [8].

4.3 Further Evaluation and Reclassification of Atypical Melanocytic Neoplasms

It is not uncommon that additional information becomes available regarding a lesion that could not be categorized unequivocally as either benign or malignant on initial biopsy, and in some cases this new information allows for a definitive diagnosis. Virtually all lesions in Category 2, 3, or 4 should be completely excised to negative margins, and the re-excision examined by an experienced dermatopathologist for additional diagnostic clues unavailable in the initial biopsy specimen. As discussed above, further investigation with CGH and/or FISH as well as sentinel node biopsy should be considered in selected cases, and at times can allow a definitive diagnosis. Finally, long-term follow-up can result in reclassification of a benign or atypical

Table 2 Distribution of histologic subtypes of pediatric melanoma as reported in several large single-institution series

Author (number of cases)						
Histologic subtype	Paradela [87] (n = 128)	Livestro [61] (n = 73)	Aldrink [2] (n = 136)	Han [44] (n = 62)	Cordoro [26] (n = 60)	Total (n = 461)
Superficial spreading	48 %	62 %	49 %	47 %	9 %	45 %
Nodular	34 %	12 %	21 %	23 %	30 %	25 %
Acral lentiginous	4 %	1 %	4 %	0	0	2 %
Spitzoid	Not separately reported[a]	Not reported	2 %	4 %	13 %	3 %
Other/NOS/unclassified	14 %	25 %	24 %	26 %	48 %	5 %

Only cases deemed to be melanoma are included; cases of atypical melanocytic neoplasms, if reported in that series, are excluded. This could lead to an underestimation of some histologic subtypes, particularly spitzoid melanomas, which are often characterized as "atypical" rather than unequivocally malignant

Abbreviation: *NOS* not otherwise specified

[a] 36 % of cases had Spitzoid cytologic features

lesion to malignant based on the development of regional or distant spread or death from melanoma. Whenever management decisions are made based on an initial biopsy specimen, especially when that specimen represents a less-than-complete sampling of the lesion, the possibility that subsequent information will alter the diagnosis should be kept firmly in mind. Patients and families need to understand the uncertainties involved with the diagnosis of pediatric melanocytic lesions, and the possibility that a lesion initially felt to be most likely benign can subsequently prove to be malignant. Conversely, they as well as their physicians should also understand that a malignant diagnosis is not synonymous with death from melanoma: most patients with unequivocal melanoma diagnosed before age 21 are in fact cured with appropriate treatment.

5 Diagnostic and Treatment Paradigms for Pediatric Melanoma and Atypical Melanocytic Neoplasms

5.1 Preoperative Staging Workup

In patients diagnosed with unequivocal melanoma at initial biopsy, further evaluation begins with a thorough physical examination, including an assessment of the presence of any residual pigmented lesion at the primary site and examination of the regional lymph nodes. In patients with enlarged or difficult to examine regional lymph nodes, ultrasonography can be helpful, and if appropriate, ultrasound-guided fine needle aspiration can be carried out in an effort to establish the diagnosis of stage III melanoma preoperatively. Because of the risks associated with ionizing

radiation in children and adolescents [70, 89], CT or PET/CT scans should be used preoperatively only for well-defined indications: patients with clinically positive lymph nodes in whom biopsy establishes a diagnosis of stage III melanoma and those with signs or symptoms suspicious of metastatic disease should generally have further radiologic evaluation prior to surgery, while most other cases should not. For patients with atypical lesions (Category 2, 3, or 4), outside of a careful evaluation of the regional lymph nodes that may include ultrasonography in selected cases, preoperative radiologic imaging is not indicated. Routine use of laboratory tests is not indicated in pediatric patients with atypical or malignant lesions, except as needed to evaluate symptoms or ensure the safe conduct of planned surgery.

5.2 Wide Excision

Surgery is the mainstay of treatment for localized cutaneous melanoma and for atypical melanocytic lesions of all histologic types and in all categories of suspicion. If the initial biopsy of a Category 1 or 2 lesion has positive margins, complete excision is recommended. For Category 4 or 5 lesions (suspected or diagnosed melanoma), and likely for most Category 3 lesions, wide excision is indicated even if the initial biopsy had negative margins. The optimum margin of excision for pediatric melanoma has never been established, as children were excluded from randomized trials evaluating margin width in cutaneous melanoma. Pediatric melanoma seems to have a lower risk of local recurrence when compared with adult melanoma of the same thickness [61]. For older children, we advocate wide excision of the primary site utilizing standard adult guidelines for excision margin widths, namely 1 cm margins for lesions ≤1 mm in thickness at all sites, for tumors 1–2 mm in thickness in areas where a wider margin would require a skin graft or result in severe deformity, and for all tumors on the head and neck or distal extremities, and 2 cm margins for most thicker lesions. In children younger than 14, we utilize a 1 cm margin for melanomas of all thicknesses and in all primary sites and have not seen local recurrences with that approach [44, 126]. For Category 2 and 3 lesions, a maximum 1 cm margin is taken regardless of thickness or age. Whatever the initial excision margin employed, the goal of surgery is to achieve a final negative histologic margin. In those rare cases where a re-excision specimen is found to have residual neoplasm at the excision margin, further re-excision is indicated. If narrow re-excision of a Category 2 or 3 lesion uncovers residual tumor diagnostic of melanoma, wider excision may be warranted.

5.3 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 allows for surgical staging and can inform further

treatment decisions. The majority of pediatric patients with melanoma are node negative and have an excellent prognosis [8, 42, 49, 60, 74, 83, 87]. These patients can be followed with routine surveillance and are at low risk of recurrence, and the reassurance value of a negative sentinel node biopsy should not be underestimated. In many cases, however, the sentinel lymph node or nodes contain cells identical to the primary tumor—in fact, the incidence of a positive sentinel node is similar in patients with pediatric melanoma and atypical melanocytic neoplasms and higher than in adults with melanomas of similar thickness [95]. Conversely, the prognosis of sentinel node-positive pediatric cases appears to be substantially better than that for adults. We will address the role of sentinel lymph node biopsy in pediatric melanoma and atypical melanocytic neoplasms separately.

5.3.1 Indications for Sentinel Node Biopsy in Pediatric Melanoma

As in adults [73, 127], there is a strong argument for sentinel lymph node biopsy as a prognostic tool for pediatric melanoma, as recurrence and death are more likely to occur in sentinel node-positive cases [8, 14, 19, 44, 49, 71, 72, 75, 116]. The long-term consequences of removal of one or a few lymph nodes from a basin in a child are relatively few, albeit not zero [84]. In cases of pediatric melanoma ≥1 mm in thickness, well over 30 % of patients with clinically negative nodes will be found to have at least one positive sentinel lymph node (Table 3), and we routinely advocate the use of sentinel lymph node biopsy in pediatric patients with melanomas ≥1 mm in thickness in the absence of specific contraindications. As in adults [40], the indications for sentinel lymph node biopsy in thin melanoma (<1 mm) remain unclear. Lesions thicker than 0.75 mm, those with ulceration, and those with mitotic activity (mitotic rate ≥1/mm^2) are most commonly considered for sentinel node biopsy in adults with thin melanoma [45, 127], and we employ these same criteria for older children with thin melanoma. Thin melanomas are rarely diagnosed in younger children [109], which further limits our knowledge about relative indications for sentinel node biopsy, and we employ sentinel node biopsy only very selectively for children under 14 with melanomas <1 mm.

5.3.2 Indications for Sentinel Node Biopsy in Pediatric Atypical Melanocytic Neoplasms

Recent editorials advocated for a limited role for sentinel lymph node biopsy in the absence of a definite diagnosis of melanoma, given the unclear prognostic value of a positive finding and the potential for overtreatment [21, 24, 50]. It can be difficult to differentiate metastatic melanoma from benign nodal nevus cells because lesional cells from benign melanocytic neoplasms such as Spitz and cellular blue nevi can also be found within regional lymph nodes. Patients with unequivocally benign nevi can have benign collections of nodal melanocytes (termed “nodal nevi”) up to 22 % of the time. However, in patients with atypical melanocytic neoplasms, the collections of melanocytes are often seen in the parenchyma of the lymph node, similar to melanoma. Although it is generally considered that multiple positive

Table 3 Results of sentinel lymph node biopsy in pediatric patients with clinically node-negative melanoma as reported in several large single-institution series

Author	# of patients undergoing sentinel lymph node biopsy	% positive sentinel lymph node biopsies	% of sentinel node-positive cases undergoing completion lymphadenectomy	% of completion lymphadenectomy cases with positive non-sentinel nodes	Median follow-up	Overall survival	Notes
Gibbs [42]	2	100 %	100 %	0	62 months	100 %	No local or distant recurrence
Pacella [83]	4	50 %	100 %	0	14 months	100 %	All patients received adjuvant interferon
Toro [116]	12	25 %	100 %	33 %	11.7 months	92 %	1 death in the patient with positive non-sentinel nodes. There were no other recurrences
Butter [19]	4	50 %	50 %	0	Not reported	75 %	1 death in a node-negative patient who developed nodal metastasis at 8 months, underwent chemotherapy and interferon and died at 26 months

(continued)

Table 3 (continued)

Author	# of patients undergoing sentinel lymph node biopsy	% positive sentinel lymph node biopsies	% of sentinel node-positive cases undergoing completion lymphadenectomy	% of completion lymphadenectomy cases with positive non-sentinel nodes	Median follow-up	Overall survival	Notes
Ferrari [35]	4	50 %	100 %	Not reported	122 months	Not reported	
Roaten [97]	15	33 %	100 %	Not reported	33 months	100 %	
Shah [103]	10	60 %	100 %	33 %	26 months	100 %	5 patients received adjuvant interferon, 1 patient developed recurrence and is alive
Livestro [61]	16	44 %	100 %	14 %	5.4 years	94 %	1 node-positive patient developed a recurrence and died of disease
Aldrink [2]	18	39 %	100 %	29 %	8.5 years	100 %	4 patients lost to follow-up; no recurrence rate reported
Howman-Giles [49]	55	25 %	93 %	15 %	60 months	Overall: 94.1 % Node negative: 100 % Node positive: 79 %	3 deaths in the node-positive deaths, 1 node-negative patient alive with recurrence at 51 months

(continued)

Table 3 (continued)

Author	# of patients undergoing sentinel lymph node biopsy	% positive sentinel lymph node biopsies	% of sentinel node-positive cases undergoing completion lymphadenectomy	% of completion lymphadenectomy cases with positive non-sentinel nodes	Median follow-up	Overall survival	Notes
Berk [14]	10	20 %	100 %	50 %	24.5 months	90 %	1 node-positive patient developed nodal recurrence and liver metastases
Paradela [87]	69	45 %	74 %	10 %	45.4 months	Overall: 91 % Node negative: 90 % Node positive: 93 %	4 distant recurrences resulted in death: 2 node-positive patients and 2 node-negative patients
Tcheung [115]	4	50 %	100 %	Not reported	9.9 years	100 %	
Moore-Olufemi [72]	57	35 %	Not reported	Not reported	4.64 years	Overall: 88 % Node positive: 68 % Node negative: 94 %	7 deaths: 2 with positive CLND, 2 in patients with negative SLNB and 3 with positive SLNB and negative CLND

(continued)

Table 3 (continued)

Author	# of patients undergoing sentinel lymph node biopsy	% positive sentinel lymph node biopsies	% of sentinel node-positive cases undergoing completion lymphadenectomy	% of completion lymphadenectomy cases with positive non-sentinel nodes	Median follow-up	Overall survival	Notes
Han [44]	62	29 %	78 %	14 %	60 months	Overall: 85.5 % Node positive: 72 % Node negative: 91 %	Node-positive: 8 patients with recurrence: 4 locoregional and 1 distant and 1 unknown Node-negative: 5 patients with recurrence: 2 locoregional, 2 distant, and 1 unknown
Hung [50]	7	57 %	75 %	0 %	84 months	100 %	1 patient with positive SLNB developed an in-transit metastasis. All patients with positive SLNB received adjuvant interferon therapy

(continued)

Table 3 (continued)

Author	# of patients undergoing sentinel lymph node biopsy	% positive sentinel lymph node biopsies	% of sentinel node-positive cases undergoing completion lymphadenectomy	% of completion lymphadenectomy cases with positive non-sentinel nodes	Median follow-up	Overall survival	Notes
Mu [75]	244	25 %	78 %	Not reported	34 months	87 %	
Paradela [86]	69 (44 non-spitzoid, 25 spitzoid)	39 % (non-spitzoid 30 %, spitzoid 56 %)	Not reported	Not reported	Not reported	Not reported	
Parida [88]	29	41 %	100 %	Not reported	21.5 months	Node negative: 100 % Not reported for node positive	None of the SLNB negative patients had nodal recurrences
Averbook [8]	180	30 %	91 %	37 %		97 %	
Total (n)[a]	691	33 % (227)	66 % (151)	9 % (15)	–	94 %[b] (588)	

Only cases deemed to be melanoma are included; cases of atypical melanocytic neoplasms, if reported in that series, are excluded
Abbreviation: *CLND* completion lymph node dissection; *SLNB* sentinel lymph node biopsy
[a]Total provided for studies with all available information, excluding the Averbook registry data due to potential duplication of case reporting
[b]Excludes patients without available follow-up data

nodes, expansile tumor deposits, and the presence of necrosis or nodal effacement support a diagnosis of malignancy, there have been no studies that define a threshold of nodal involvement that is diagnostic for malignancy. Moreover, clinical studies have shown few or even no recurrences for atypical melanocytic neoplasms with positive sentinel nodes, at median follow-up intervals of 2–4 years (Table 4) [18, 20, 36, 41, 62, 64, 66, 71, 76, 102, 113, 120], and some small series of atypical melanocytic neoplasms managed with excision alone had no evidence of recurrent disease [22]. All these facts argue for a cautious approach to sentinel node biopsy in pediatric atypical melanocytic neoplasms, but a contrary case can also be made.

In fact, we have encountered numerous cases where patients with pediatric atypical neoplasms developed recurrence and even died of metastatic malignancy, often many years or even decades after initial diagnosis. Even in unequivocal pediatric melanoma, many of the recurrences and deaths from disease occur more than five years after initial diagnosis (Fig. 3) [44], so studies with relatively short (and often incomplete) follow-up must be viewed with a healthy degree of skepticism. Perhaps the strongest argument in favor of sentinel node biopsy for pediatric atypical neoplasms is the uncertainty associated with the diagnosis itself. It is well recognized that experienced pathologists will disagree in a substantial portion of cases in which at least one pathologist has rendered a diagnosis of atypical melanocytic neoplasm. Importantly, even cases with documented fatal outcomes have been called atypical or benign by at least some experienced pathologists when shown blinded cases [10, 37]. Hence, some cases that represent melanoma are not identified as such based on the initial biopsy. While the significance of atypical cells in the sentinel node is not always clear in these patients, there are cases where the presence of expansile nodules of tumor cells reveals a diagnosis of malignancy that might otherwise have been missed. Conversely, as alluded to previously, the finding of a negative sentinel node or nodes can help reassure the patient and family that—despite uncertainty about whether the lesion may be melanoma—everything possible has been done to make a diagnosis and the patient has been treated appropriately if the diagnosis is in fact melanoma. Recurrences in the nodal basin and distant metastatic disease are very uncommon in patients with pediatric atypical neoplasms after negative sentinel lymph node biopsy (see Table 4), and most such patients can be safely observed without any additional surgical or adjuvant therapy [46, 71].

5.4 Surgical Management of the Sentinel Node-Positive Nodal Basin

The management of the pediatric melanoma patient with a positive sentinel lymph node is contentious, and key principles are largely drawn by analogy to the adult literature. Completion lymphadenectomy, by definition a radical lymph node dissection after a positive sentinel node biopsy, is the current standard of care

Table 4 Results of sentinel lymph node biopsy in pediatric patients with clinically node-negative atypical melanocytic neoplasms as reported in several large single-institution series

Author	# of patients undergoing sentinel lymph node biopsy	% positive sentinel lymph node biopsies	% of sentinel node-positive cases undergoing completion lymphadenectomy	% of completion lymphadenectomy cases with positive non-sentinel nodes	Median follow-up	Overall survival/recurrence	Comments
Lohmann [62][a]	10	50 %	100 %	20 %		100 %	
Su [113]	12	50 %	100 %	17 %	12 months	100 %	
Gamblin [36]	10	30 %	100 %	33 %	Node negative: 28.1 months Node positive: 49 months	100 %	All node-positive patients received interferon
Urso [120]	5	40 %	50 %	100 %	5 months	100 %	
Murali [76]	9	55 %	100 %	0	10.7 months	100 %	
Ludgate [64]	57	47 %	100 %	3.4 %	Node positive: 43.8 months Node negative: 28.6 months	100 % in patients undergoing SLNB	89 % of node-positive patients received interferon
Busam [18]	11	55 %	Not reported	Not reported	47 months	100 %	

(continued)

Table 4 (continued)

Author	# of patients undergoing sentinel lymph node biopsy	% positive sentinel lymph node biopsies	% of sentinel node-positive cases undergoing completion lymphadenectomy	% of completion lymphadenectomy cases with positive non-sentinel nodes	Median follow-up	Overall survival/recurrence	Comments
Ghazi [41][a]	27	22 %	66 %	0	Node negative: 14 months Node positive: 31 months	100 % in patients undergoing SLNB	1 death in patient who had clinically positive nodes
Sepehr [102]	2	0	Not applicable	Not applicable	30 months	100 %	
Mills [71]	24	29 %	86 %	17 %	4.1 years	100 %	
Total (n)	167	40 % (67)	97 % (65)	9 % (6)	–	100 %	

Only cases deemed to be atypical are included; cases of melanoma, if reported in that series, are excluded. This could lead to an underestimation of the outcome for cases initially characterized as "atypical" rather than malignant, because some cases might subsequently be reclassified as malignant and excluded from analysis

Abbreviation: *SLNB* sentinel lymph node biopsy

[a]Includes some patients >21 years of age

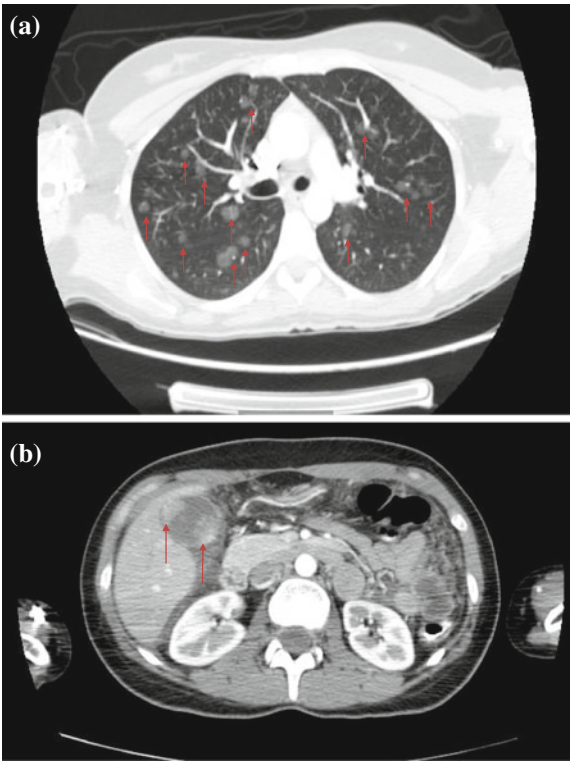

Fig. 3 Late recurrence of melanoma initially presenting in childhood. This patient was initially diagnosed at age 14 with a 3.4 mm ulcerated melanoma on her back. One sentinel lymph node in the ipsilateral axilla had a microscopic focus of metastatic disease. Twelve years later, she returned with abdominal pain and a new cutaneous lesion. **a** CT scan of the thorax demonstrated multiple pulmonary metastases, some of which are denoted with *red arrows*. **b** CT scan of the upper abdomen demonstrated mass lesions in the gallbladder (*arrows*), biopsy proven to represent metastatic melanoma. She subsequently developed brain metastases and died of disease nearly 14 years after her original biopsy

recommendation for adult patients [127], although involved non-sentinel nodes are found on histologic examination in only about 10 % of lymphadenectomy specimens (see Table 3) [67, 77, 98]. Only limited data are available on the rates of non-sentinel node involvement in pediatric melanoma, but what data are available suggests that the rate may [49, 61, 103, 116] or may not [119] be lower than that in adults. Virtually, no data are available on the in-basin recurrence rates for pediatric patients who do not undergo completion lymphadenectomy.

In our experience, the rates of lymphedema are lower for pediatric patients undergoing radical lymphadenectomy compared to adults, and dysesthesias and numbness that can be troublesome in adults are rarely consequential in children. However, the increased risk of infection that accompanies lymphadenectomy can be a problem, particularly for younger children, and younger patients likely are also

at some increased risk for motor nerve injuries that can have lifelong consequences. On the other hand, teenagers and young adults can be non-compliant with the close follow-up that is usually recommended for sentinel node-positive patients who do not undergo completion lymphadenectomy. Hence, our recommendation for completion lymphadenectomy is individualized based on a number of factors: the number and site(s) of sentinel nodes involved with tumor, the extent of tumor involvement within those nodes, the findings on the preoperative lymphoscintigraphy (which may presage the likelihood of non-sentinel node involvement [131]), and particularly the age of the child. For a very young child, even a few years of delay in performing a lymphadenectomy can decrease the short- and long-term consequences of that procedure, as long as the patient has been carefully followed and treated promptly after recurrence is manifest. Teenagers and older patients need to be carefully assessed to be sure they will be compliant with a close follow-up regimen, and if not, they may be best served by a completion lymphadenectomy. All patients who are observed without completion lymphadenectomy after a positive sentinel node biopsy in our practice are recommended to undergo ultrasound surveillance of the positive basin at least two to three times per year for the first several years, and then every six to twelve months thereafter for a minimum of five years, and are counseled to return promptly if they develop lymphadenopathy or other evidence of recurrence.

5.5 Surgical Management of the Clinically Node-Positive Nodal Basin

In contrast to patients with micrometastatic disease in a sentinel node, pediatric patients with clinically detectable lymph node involvement should undergo radical lymphadenectomy of the involved basin(s) unless there is clear evidence of distant metastatic disease. In general, identical surgical principles are utilized in children and adults to determine the extent of the lymphadenectomy, and like in adults, the relative indications for pelvic ("deep") node dissection in inguinal node-positive cases remain unclear. The only absolute indication for pelvic node dissection in pediatric melanoma is pathologic or radiologic evidence of involvement of one or more iliac or obturator nodes, but deep node dissection should be considered for cases with large or multiple involved inguinal nodes even in the absence of abnormal pelvic nodes on preoperative scanning. Most adult studies indicate that inclusion of the external iliac and obturator nodes with an inguinofemoral node dissection does not increase long-term morbidity [33, 100], and our experience in pediatric patients supports this.

5.6 Adjuvant Systemic Therapy

While systemic adjuvant therapy has been widely used in the adult melanoma population for stage III and even selected high-risk stage II patients [55], there is a dearth of information in the pediatric population, given both the rarity of the disease and the exclusion of children from most melanoma clinical trials.

5.6.1 Interferon-α2b

Three single-institution studies have retrospectively evaluated the feasibility of using high-dose interferon-α2b in stage III resected pediatric melanoma [23, 80, 103]. Patients were noted to tolerate the therapy well, requiring fewer dose modifications than typically reported in adult studies. In one study involving five patients with resected stage III disease, dose modification was required during the induction phase in two patients due to myelosuppression and during the maintenance phase in two patients for abnormal liver function tests, while depression and major mood change were observed in two other patients [103]. A prospective study of high-dose interferon in 15 sentinel node-positive patients (eight of whom were initially diagnosed with atypical melanocytic neoplasms but subsequently reclassified as melanoma) found that all 15 patients were able to complete induction therapy, and only one patient failed to complete maintenance therapy due to toxicity (coming off therapy five weeks before scheduled completion). Two patients developed recurrent disease during maintenance, one of whom was resected to a disease-free state and continued on therapy. The other patient as well as one patient who recurred after the end of therapy died of metastatic melanoma [80].

Although interferon-α2b is well tolerated in children, subcutaneous injection of the medication three times weekly is inconvenient. Pegylated interferon-α2b (peginterferon) can be administered once a week and has pharmacokinetic and pharmacodynamic properties more favorable for maintenance therapy than standard interferon [27]. It has been approved for use in the adjuvant therapy of node-positive melanoma [31, 32, 48]. However, the approved regimen involves five years of therapy, which limits patient acceptance. We have successfully substituted peginterferon for standard maintenance interferon, administering it once weekly at 3 mcg/kg for 48 weeks after a "standard" one-month IV induction phase. A current pediatric clinical trial (NCT00539591) is comparing the pharmacokinetics, feasibility, and quality-of-life impact of subcutaneous peginterferon 1 mcg/kg/week for 48 weeks with that of conventional interferon during maintenance therapy. Results favoring the use of peginterferon once weekly would certainly increase the convenience of therapy in children.

Recently, cooperative group phase III studies investigating the role of adjuvant interferon in patients with node-positive melanoma have begun including children under 18 years of age. SWOG trial S0008 (NCT00006237), ECOG E1697 (NCT00003641), and E1609 (NCT012734338) are examples. No results specific for pediatric patients have as yet been presented from any of these studies, but they

hold promise to increase our knowledge base about adjuvant interferon in pediatric melanoma.

5.6.2 Other Adjuvant Therapy Agents Under Evaluation

New agents for treating unresectable metastatic melanoma (see Sect. 5.7 below) merit evaluation as adjuvant therapy in an effort to improve on the risk–benefit ratio of interferon in adults and children. E1609 compares high-dose interferon to two doses of ipilimumab (monoclonal antibody blocking CTLA-4) and includes children age 15 and older. This will likely provide the first opportunity to evaluate new agents in the adjuvant therapy of melanoma.

5.7 Metastatic Disease

5.7.1 Systemic Therapy

Pediatric patients with metastatic melanoma should strongly consider enrollment in a clinical trial given the limited knowledge specifically about this patient population. There are currently several trials evaluating drugs that have been proven to increase survival in the adult stage IV melanoma population, such as ipilimumab, vemurafenib or dabrafenib (BRAF inhibitors), or anti-PD1 antibodies. Like with adult melanoma, knowing the *BRAF* mutation status of the melanoma is paramount to making decisions about treatment for stage IV disease. The overall distribution of *BRAF* mutant melanomas in the pediatric melanoma population is not known, but it appears that adolescents and young adults with histologically conventional melanoma have a higher rate of *BRAF* V600E mutations than seen in the adult melanoma population [69]. Melanomas in children, especially those arising in congenital nevi, predominantly lack *BRAF* mutations and hence are currently not candidates for molecularly targeted therapy [63]. As in adults, immunotherapy is appropriate first-line therapy for pediatric melanoma patients whose tumor lacks a *BRAF* mutation and even for some *BRAF* mutant melanoma cases with relatively low tumor burden and few or no symptoms [53]. Interleukin-2, ipilimumab, and the anti-PD1 inhibitors pembrolizumab and nivolumab are currently commercially available, but there is little or no published experience regarding safety and efficacy of any of these agents in children under 16.

5.7.2 Palliative Radiation

Radiation therapy in the pediatric population is reserved for palliation of metastatic disease, particularly brain metastases, or rarely for the treatment of unresectable regional disease. Advances in radiation techniques such as image guidance, stereotactic radiation therapy, intensity-modulated radiation, and proton beam radiation have allowed for more conformal treatment, allowing for increased sparing of normal tissue that likely has particular value in the pediatric population [110]. Fractionated techniques have been shown to be safe in children [122],

suggesting that with modern techniques, radiation therapy can be used on a case-by-case basis as an effective method of palliation of metastases in children.

6 Prognosis and Follow-up

While there are no established follow-up guidelines specifically for pediatric melanoma, early detection of recurrence may allow for surgical intervention and/or a more favorable outcome, and of course sun protection and screening for second primary cutaneous malignancies is important in melanoma patients of all ages.

6.1 Follow-up

A study comparing pediatric patients with positive and negative sentinel lymph nodes found that recurrence occurred only in patients with node-positive disease and could occur more than five years from diagnosis due to the long natural history of the disease [44]. To date, there are no specific recommendations or guidelines for the follow-up of pediatric melanoma patients after surgery.

6.2 Prognosis of Pediatric Melanoma Based on Stage of Disease

Stage of disease is one of the primary determinants of overall survival in pediatric melanoma just as in adults, with localized disease having a more favorable prognosis. Available evidence suggests that prognosis is likely better for pediatric melanoma patients diagnosed when prepubertal versus postpubertal [35, 57], but this is not reflected in current staging systems.

6.2.1 Stage I–II: Localized Disease

Early-stage, localized pediatric melanoma portends an excellent prognosis with multiple series reporting from 94 to 100 % overall survival over 10 years for stage I disease and from 79 to 100 % for stage II disease, with a disease-free survival of more than 70 % [8, 34, 57, 109]. Ulceration and increase in tumor thickness are associated with a less favorable prognosis and a higher local recurrence rate and a decreased overall survival, as in adult melanoma.

6.2.2 Stage III: Regional Metastatic Disease

Metastatic disease to regional lymph nodes is associated with decreases in overall survival and disease-free survival in comparison with localized disease. Pediatric melanoma patients have a more favorable prognosis than adults with similar staged disease, with 70–77 % overall survival at 10 years [8, 34, 57].

6.2.3 Stage IV: Distant Metastatic Disease

Distant metastases are associated with a poor prognosis, with 40 % overall survival at 5 years and 0 % at 10 years reported in a large registry series [8].

6.3 Prognosis of Atypical Melanocytic Neoplasms

Atypical melanocytic neoplasms, as described in Sects. 4.1 and 4.2 above, are diverse and heterogeneous both histopathologically and molecularly and likely in terms of their prognosis as well. While most patients with atypical melanocytic neoplasms have an excellent prognosis, deaths from melanoma have occurred in children whose initial lesion could not—even in retrospect—be characterized as clearly malignant. Atypical lesions with certain specific high-risk features are more likely to develop recurrent or metastatic melanoma. Prior studies have shown that atypical melanocytic neoplasms with diameter greater than 1 cm, extension into the subcutaneous tissue, ulceration and higher numbers of mitoses per high-powered field, and those arising in children greater than 10 years of age are associated with increased risk of metastases [107]. In addition, recent studies show that lesions with 9p21 deletions have an increased risk of recurrence and metastasis [38]. However, the prognostic significance of sentinel lymph node biopsy remains controversial in these atypical neoplasms, as described in Sect. 5.3.2 above.

7 Future Directions and Challenges

Our understanding of the natural history and epidemiology of pediatric melanoma is limited by the relatively small number of patients, variations in pathologic diagnosis, and incomplete data about the cases that do occur. While one multicenter patient registry has been published [8], most studies are single-institution studies with small patient numbers. Unresolved questions about the utility of sentinel lymph node biopsy, completion lymphadenectomy, adjuvant therapy, and treatment of advanced disease will only be better elucidated with greater national and international collaboration and a commitment to prospective evaluations and clinical trials. For pediatric patients with unresectable disease or metastasis, access to the latest biologic treatments is limited by their age. As the incidence of pediatric melanoma continues to rise, the need for improved prognostication and age-specific treatment and follow-up guidelines are sorely needed.

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