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Melanoma in children and adolescents

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Abstract

Childhood and adolescent melanoma is rare, accounting for only 1.3% for all cases of cancer in patients under the age of 20 years. However, in 15–19 year olds, melanoma accounts for up to 7% of all cancers. Review of reported cases in this age group reveals that predisposing 'paediatric' conditions such as a giant congenital melanocytic naevi or xeroderma pigmentosum are rarely present. Furthermore, inactivating germ-line mutations of the gene *CDKN2A* have only been reported in 1.5% of cases of early onset melanoma. Epidemiological studies suggest that interactions between solar exposure, development of naevi, pigmentary traits, and a family history of melanoma are the main determinants of melanoma development during the first 20 years of life. As yet, there are no available staging or treatment strategies for this group of patients so treatment recommendations are based on the adult experience. To improve our understanding of the natural history of melanoma and to identify the most appropriate therapies for young patients with this disease, practising physicians are encouraged to enroll their patients, especially those with advanced stage disease, in cooperative group trials which incorporate newer staging systems and promising therapies.

Keywords: Melanoma; Paediatric; Adolescents; Interferon; Naevus; Children's Oncology Group

1. Epidemiology

The incidence of melanoma in the white population and in developed countries has risen steadily for most of the past century with annual age-standardised increases of 3–7% in many countries [1,2]. An epidemiological study from the Scottish Melanoma Group conducted over a 19-year period demonstrated an increase in the age-standardised incidence of melanoma of 303% for men and 187% for women [3]. In Queensland, Australia, the estimated lifetime risk of developing invasive melanoma in 1997 was 1 in 16 men and 1 in 24 women [4], whilst in the United States (US), the risk is estimated to be 1 in 58 for men and 1 in 82 for women [5]. Furthermore, in the US, melanoma is the most common cancer afflicting females between the ages of 25 and 29 years of age. Despite increasing rates of melanoma over the past several decades, a stabilising or declining trend in the incidence and mortality rates among younger people has been recently documented in some countries [2].

Cutaneous melanoma is rare under 20 years of age, particularly before puberty. From 1973 to 1996, the Surveillance, Epidemiology and End Results Section of the National Cancer Institute (SEER) identified 53 365 cases of newly-diagnosed cutaneous melanoma of which only 698 (1.3%) occurred in patients under the age of 20 years [6]. Among patients younger than 15 years of age, melanoma accounts for only 0.9% of all cancers, but the incidence of the disease rises steeply with age. It accounts for 7% of all cancers among patients aged 15–19 years (Fig. 1) [7] and, in the SEER report, the most dramatic increase in the annual percent incidence of melanoma (2.6% per year during the observation period) was also seen in this age group. Similar trends in the age-specific distribution of paediatric melanoma have been reported by the Swedish Cancer Registry. Only 43 of 287 (1.5%) registered cases of melanoma under the age of 20 years occurred in prepubertal patients [8]. The estimated annual incidence rate per million in US patients aged 15–19 years is 14.1, similar to that reported by investigators in The Netherlands, but lower than that reported from the UK [9]. These epidemiological observations reveal important differences in the distribution of melanoma between adoles-

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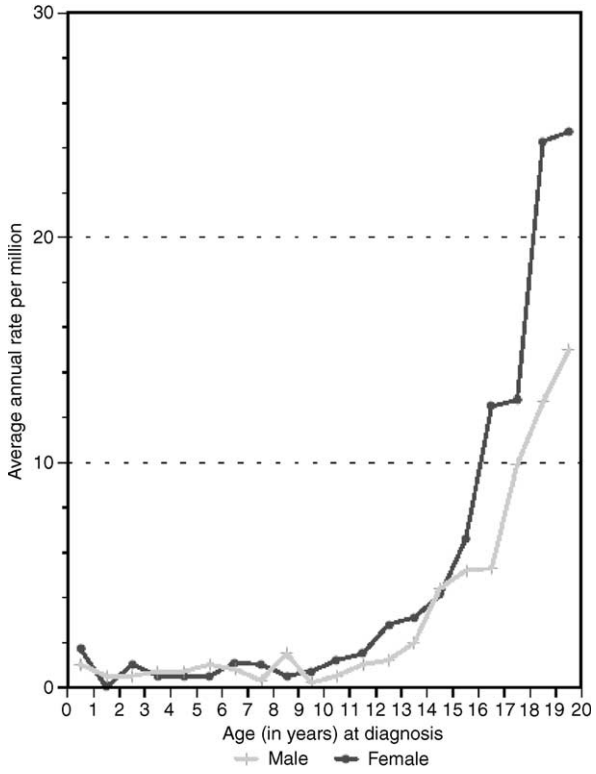


Fig. 1. Malignant melanoma. Age-specific incidence rates by gender. Source: SEER 1976–1984 and 1986–1994. SEER, Surveillance, Epidemiology and End Results.

cents and young adults and other age groups. They also highlight the need to study systematically this and other diseases that preferentially affect this age group which has traditionally been underrepresented in clinical trials and whose cancer survival rates have lagged behind those seen in younger patient populations [10].

2. Risk factors

A number of risk factors known to predispose to the development of adult melanoma, as well as some conditions associated with this tumour in childhood, have been reviewed in detail [1–21].

Prepubertal melanoma, which comprises cases of melanoma diagnosed prior to the attainment of sexual maturity, is extremely rare [11]. Prepubertal melanoma can be divided into three categories based on the age at which the melanoma is diagnosed: congenital (in utero to birth), infantile (birth to the first birthday), and melanoma of childhood (first birthday to the onset of puberty). Among 23 cases of congenital or infantile melanoma, 11 were present at birth and 12 developed within the first year of life. Only 3 cases of maternal origin transplacentally-acquired melanoma were reported in this series. Disease arising from medium-sized and large congenital naevi was seen in 13 cases (57%). One-third of these cases arose in the scalp area. The remaining 7 cases arose either *de novo* ($n=1$) or from smaller cutaneous naevi [11].

3. Xeroderma pigmentosum

Xeroderma pigmentosum (XP) is a rare autosomal recessive disorder characterised by increased cutaneous light sensitivity, and a greater than a 1000-fold increase in the frequency of sun-induced skin cancers. Neurological abnormalities are present in 20–30% of patients [22,23]. XP results from a defect in DNA excisional repair mechanisms. To date, eight different 'complementation groups' (each group (A–G and a variant) represents a different gene that if mutated will cause XP) have been described). Groups A, C and D may be associated with neurological abnormalities including microcephaly, progressive mental deterioration, ataxia, sensorineural deafness and impaired reflexes [24]. In patients with XP the median age at diagnosis of skin tumours is 8 years. Squamous and basal cell carcinomas are most commonly reported. Melanoma occurs in approximately 5% of the patients with a median age at diagnosis of 19 years. Melanomas most commonly involve the face, head and neck [25,26]. Avoidance of sun exposure is the mainstay of prevention, but administration of retinoids has been found to decrease the incidence of cutaneous neoplasms [25]. Due to the rarity and complexity of the disease, genetic and social counselling, as well as careful clinical advice directed at prevention and early detection of tumours, is essential for the 'best management' of these patients.

4. Immunosuppression

Patients with inherited immunodeficiencies have a 3–6-fold increased risk of malignant melanoma. Recipients of organ transplantation have up to a 4-fold increase in the risk of developing melanoma compared with the general population and in paediatric practice these patients account for up to 15% of all post-transplantation skin cancers [27]. Melanomas in this population preferentially affect patients with a light complexion and a tendency to freckle [12,28].

The number of observed to expected cases of melanoma after the use of conditioning regimens that incorporate total body irradiation (TBI) prior to allogeneic bone marrow transplantation has been reported to be as high as 5 to 1 and the relative risk of developing melanoma after high-dose TBI is as high as 8.2 [29]. Recently, there have been a number of reports describing the occurrence of melanoma and the presence of an increased number of naevi <5 mm in diameter in HIV-infected individuals [30–33]. Several authors have also noted that survivors of childhood leukaemia, when

compared with controls, have higher naevus counts, increased naevus densities, and a larger number of melanocytic naevi >6 mm [34–36]. These findings underscore the importance of host immunity in the development of benign and malignant melanocytic lesions during childhood and should encourage prompt diagnostic and therapeutic interventions in children with pigmented lesions who are or have been immunosuppressed.

5. Familial melanoma

Familial cases account for approximately 10% of malignant melanomas. Inactivating mutations of the *CDKN2A* gene, which encodes the two unrelated tumour suppressors, p16 and p14ARF, have been found in 20–40% of families with three or more affected first-degree relatives and in around 15% of individuals with multiple primary melanomas [37]. The penetrance of *CDKN2A* germ-line mutations varies with geographical location and the degree of ultraviolet (UV) exposure. For example, by age 80 years, the age-specific penetrance estimates for individuals in Europe was 0.58, whereas the estimates for patients in the United States and Australia were 0.76 and 0.91, respectively [38,39]. Inactivating mutations of other genes such as *CDK4* (a target of p16) have also been described [40]. Since early onset of the disease is one of the features of a genetic cancer syndrome, three separate groups of investigators have analysed the frequency of germline *CDKN2A* mutations in early onset melanoma [41–43] and found that only 4 of 257 (1.6%) patients studied had these abnormalities. These findings suggest that environmental as well as other as yet unidentified genetic factors are responsible for the development of early-onset melanoma. However, based on the available information presented here, routine testing for *CDKN2A* mutations in early onset or multiple primary melanoma is not warranted.

6. Naevus phenotype and environmental factors

Small congenital melanocytic naevi are present in up to 1% of newborns, but their potential for malignant transformation is uncertain. When malignant transformation is reported, postpubescent children are most commonly affected. In two recent studies comprising a total of 462 patients, no melanomas were noted to arise within small or medium-sized congenital naevi [44,45].

Acquired melanocytic naevi often appear after infancy, are prone to increases in size after early childhood and puberty and are frequently located in sun-exposed areas. There is substantial evidence to relate the risk of developing melanoma to the number of melanocytic naevi acquired during childhood. Therefore, it is important to review some of the epidemiological studies that have examined the association between environmental and constitutional factors and the development of naevi and melanoma during childhood and adolescence. In a study of over 3000 Italian schoolchildren, subjects who burned easily after their first sun exposure and those who did not tan easily had higher naevus densities. The naevus density increased with the number of recorded episodes of sunburns and 21% of individuals studied had at least one naevus of >6 mm in diameter. Factors associated with the development of larger naevi included the presence of light pigmentary traits (fair skin, blue eyes, blond hair) and a propensity to sunburn easily [36]. In another study from Queensland, Australia, 111 schoolchildren aged 12–13 years were followed for up to 5 years to determine their annual naevus counts and to determine the factors associated with the development of melanocytic naevi. In this study, male gender and increasing age were the two most important factors predicting the development of naevi during adolescence. The degree of shoulder freckling correlated with increased naevus counts and appeared to be an important surrogate indicator of protection habits such as sunscreen use. This study also showed that habitual sun exposure in an area of high solar exposure, such as Queensland, is a more important risk factor for the development of naevi in adolescents than periods of concentrated sun exposure [46]. Two case–control studies from Australia have also examined factors associated with the development of melanoma in children and adolescents. In one study, Youl studied factors influencing the development of melanoma in 250 adolescents aged 15–19 years identified by the Queensland Cancer registry between 1987 and 1994 [42]. In this study, patients with melanoma had higher numbers of naevi 2 mm or larger when compared with controls and over 50% of melanoma patients had 100 naevi or more, when compared to 13% of controls. In addition, a higher number of naevi larger than 5 mm were also associated with cases of melanoma compared with controls. The authors reported a 34-fold increased risk of developing melanoma in patients with 100 or more naevi and the presence of 10 or more large naevi was associated with a greater than 15-fold increased risk. In univariate analysis, ability to tan, propensity to sunburn, skin type, density of facial freckling, hair and eye colour, a history of a first-degree relative with melanoma, increased number of blistering sunburns, and lack of use of sunscreen under the age of 5 years were all associated with an increased risk of developing melanoma. In multivariate analysis, however, only number of naevi >2 mm, eye colour, tanning ability, facial freckling, and family history of melanoma were associated with an increased risk of developing melanoma suggesting that in this population, genetic susceptibility

is a primary determinant. In the other study, Whiteman and colleagues, also working in Queensland, reported factors associated with the development of melanoma in 61 children who were less than 15 years of age [47]. Risk factors in this population were remarkably similar to those reported in the Youl study and included the presence of multiple large naevi, sun-sensitive phenotype (facial freckling, inability to tan), and a family history of melanoma. No measures of acute or chronic UV exposure were associated with an increased risk of melanoma. These studies reinforce the notion that the risk for developing melanoma in younger patients might be the result of an interaction between genetic and environmental factors in individuals with a 'susceptible' pigmentary trait or a family history of melanoma. These results are also in accord with a recent adult melanoma study in which there was no obvious association between sun exposure and the development of melanoma within families known to have an increased genetic susceptibility to the disease [4].

Dysplastic naevi or clinically atypical moles affect 5–10% of the US population, are potential precursors of melanoma and define a population 'at risk' for early onset disease. In a case–control study of 716 patients with melanoma, the risk for developing the disease was highly related to the number of dysplastic naevi. One clinically dysplastic naevi conferred a 2-fold increase in the risk of melanoma whereas 10 or more conferred a 12-fold increased risk [48]. In a study of 33 families comprising 844 subjects with two or more members with invasive melanoma, the authors recorded 86 new cases of melanoma among 37 individuals over a follow-up period of 2–25 years. Fifty-one melanomas were found to have a precursor lesion of which 32 were clearly defined as dysplastic naevi [40]. In an earlier study by the same authors, 37% of children of melanoma-prone families had dysplastic naevi and the cases of paediatric melanoma only occurred in those individuals with this type of naevi. The age at diagnosis of melanoma was younger than average, with 9% of cases developing before the age of 20 years. There was also a statistically significant reduction in the age at diagnosis of melanoma in successive generations, from 50 years in the first generation to 12 years in the fourth generation [49]. These findings could potentially result from either increased surveillance and/or genetic anticipation.

6.1. Spitz naevus

The distinction between Spitz naevus and melanoma, particularly among patients aged 10–12 years, is controversial and difficult. Some authors advocate the term 'atypical Spitz tumour' to describe controversial melanocytic lesions which resemble Spitz naevi, but raise the diagnostic possibility of melanoma [50]. Furthermore, these lesions may be classified as being at 'high-risk' for aggressive behaviour based on the presence of ulceration, large size, asymmetry, deep extension, hypercellularity, cytological atypia, and prominent and atypical mitosis [50]. In a survey of dermatologists in the US, over 90% of the responding dermatologists stated that they would perform biopsy of a lesion suspected of being a Spitz naevus and 43% favoured a complete excision. Most respondents selected a 1–2 mm margin of excision and 69% recommended complete re-excision in cases where the lesion was initially incompletely excised. However, only 8% of respondents to this survey recalled ever seeing cases of metastatic melanoma arising from lesions designated as Spitz naevus [51]. The role of sentinel node biopsy in controversial melanocytic lesions such as Spitz naevus is still unanswered, but it is interesting to note that in a study of 10 patients with an indeterminate diagnosis, 5 had 'tumour' deposits in the sentinel lymph node, yet all patients are alive and free of disease at a mean of 34 months from diagnosis. It is clear that more studies are needed before we understand the natural history of these controversial melanocytic lesions [52].

7. Clinical presentation of childhood and adolescent melanoma

As in adults, changes in the appearance of a pigmented lesion should alert the physician to the possibility of melanoma. In a report by Boddie, the most common clinical presentation of paediatric and adolescent melanoma included increasing size of a mole, bleeding, colour change, itching, palpable adenopathy and a palpable subcutaneous mass [53]. In another study by Saenz, 85% of patients presented with symptoms attributable to the primary skin lesion and included recent growth, pain, bleeding, ulceration, and colour change [54]. Since the diagnosis of melanoma is often unsuspected in children and adolescents with pigmented lesions, delays in diagnosis or misdiagnosis have been reported to occur in 50–60% of patients [54,55].

In a SEER report of 698 cases of cutaneous melanoma in patients under 20 years of age, female gender predominated (female to male ratio of 1.6) and when compared with adult melanoma cases, there was a slightly lower proportion of Caucasians [56]. In this same series, 89% of patients presented with localised disease. The most common primary site was the trunk, but, compared with older populations, a higher proportion of cases had primary tumours in the head and neck region. There was also a slightly higher incidence of melanoma in patients reported in the Southern registries. Table 1 summarises the clinical characteristics, associated clinical conditions, and outcome of 322 children and adolescents with melanoma reported in eight

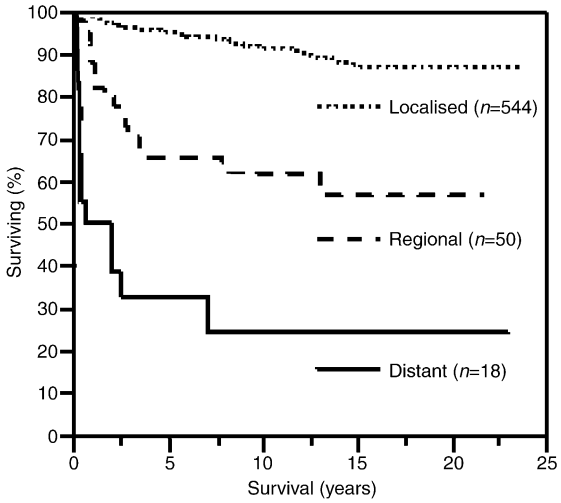
Table 1
Clinical characteristics and outcome in published series of paediatric and adolescent melanoma

Year/author [Ref.]	No. of pts	Age (years)	Gender	Primary site	Stage	Predisposing conditions	Outcome/comments
2002/Schmid-Wendter [87]	36	$<14=5$ $\geqslant14=31$	M = 17 F = 19	Trunk = 12 Extremity = 16 Head and neck = 7 Unknown = 1	Localised = 27* Nodal metastases = 8 Distant metastases = 1	Congenital naevus = 8 Acquired naevi = 9	Relative 5-year survival 87.5%. Survival correlated with tumour thickness and stage.
2000/Gibbs [88]	27	12 = 1 $\geqslant12=26$	M = 17 F = 10	Trunk = 14 Head and neck = 3	Localised = 26 <0.76 mm = 12 0.76–1.49 mm = 7 1.5–4.0 mm = 4 >4 mm = 1 Nodal spread = 1	Congenital naevus = 3 Dysplastic naevus = 7 Family history = 5	23/27 (85%) alive. Median value of Breslow's thickness 0.75 mm, similar to that observed in adults. Nodal spread developed in 4 of 11 pts with <1 mm lesions. 6/7 pts with nodal relapse were salvaged.
1999/Saenz [54]	40	$\leqslant12=11$ $>12=29$	M = 14 F = 26	Trunk = 10 Extremity = 23 Head and neck = 7	Localised = 23 Nodal spread = 16 Metastases = 1	Congenital naevus = 15	5-year survival 63%. 10/15 patients with melanoma arising in a congenital naevus died of their disease. Tumour thickness and stage of the disease correlated with survival.
1997/Milton [89]	32	$<12=19$	M = 15	Trunk = 13	Localised = 29	Family history = 1	23/32 (72%) alive. Breslow thickness <1.01 mm correlated with outcome.
		$\geqslant12=13$	F = 17	Extremity = 13 Head and neck = 6	Nodal = 3 Thickness, <1.5 mm = 20 1.5–4 mm = 4 >4 mm = 3		
1994/Davidoff [90]	85	$\leqslant14=23$ $>14=62$	M = 39 F = 46	Trunk = 29 Extremity = 37 Head and neck = 18 Ocular = 1 Unknown = 1	Localized = 79 Nodal spread = 6 Thickness <1.5 mm = 29 1.5–4 mm = 27 >4 mm = 10	Giant naevus = 2	5-year survival for localized disease 79%. Similar survival to that observed in adults but a higher incidence of nodal spread after definitive treatment.
1993/Tate [91]	48	$\leqslant14=14$ $>14=34$	M = 27 F = 21	Trunk = 15 Extremity = 23 Head and neck = 8 Other = 2	Localized = 34 Nodal spread = 4 Thickness <0.75 mm = 15 0.75–1.5 mm = 16 1.51–3 mm = 9 >3 mm = 4	Family history = 3 Giant naevus = 1 Albinism = 1 "Hormones" = 4	Overall 5-year survival 90% for 38 patients treated by the authors.
1991/Temple [92]	21	$\leqslant12=3$ $>12=18$	M = 5 F = 16	Trunk = 7 Extremity = 9 Head and neck = 5	Localised = 20 Metastases = 1	Dysplastic naevi = 2 Family history = 1 Congenital moles = 1	14/21 (67%) alive. Survival for localised patients correlated with Clark's level of invasion.
1990/Rao [58]	33	Median = 12	M = 23 F = 10	Trunk = 9 Extremity = 13 Head and neck = 7 Perineum 1 Unknown = 3	Localised = 23 Nodal spread = 9 Metastases = 1	Large naevus = 3 Prior malignancy = 4 Irradiation = 2	22/33 alive (67%). Prognosis is stage-dependent. Nodal involvement correlated with Breslow's and Clark's level.
Total	322	$\geqslant12$–14 = 213 <12–14 = 76	M = 157 F = 165	Trunk = 119 Extremity = 134 Head and neck = 55	Localised = 261 Nodal spread = 43 Metastases = 4	Overall = 72	74% >12–14 years. Similar M:F; Extremity sites (43%) and localised disease predominated (81%); 22% of pts had a predisposing factor.

pts, patients; M, male; F, female.

single-institution series since 1990. There was a similar distribution of cases of melanoma among females and males and nearly three-quarters of cases presented during the second decade of life. Primary tumours most commonly affected the extremities, followed by the trunk and head and neck regions. Of the children for whom adequate staging information was available, 85% presented with localised disease and 61% had lesions <1.5 mm thick. Metastatic disease at presentation was unusual and associated conditions such as pre-existing moles, and giant naevi were documented in only 22% of cases. These findings and those reported by SEER are similar to those noted in adults [57].

The outcome for children and adolescents with melanoma also appears to be similar to that reported for adults [57] and is dependent on the initial stage of the tumour. Fig. 2 depicts the survival for the 612 patients under the age of 20 years reported by the SEER and shows that patients with localised disease have an excellent outcome, whereas those with nodal and distant metastases have estimated 10-year survivals of only 60 and 25%, respectively. Further analysis of the 423 patients who survived 5 or more years from their initial diagnosis revealed that 27 of these patients subsequently died. Two-thirds of these deaths were attributable to melanoma. Table 1 shows that in single institution reports, outcome is also stage-dependent and that the thickness of the primary lesion correlates with the risk of nodal involvement and subsequent disease recurrence [58].



Multivariate proportional hazard survival analysis

	Chi square	*P* value
SEER stage	646.6	<0.0001
Year of diagnosis	2.3	0.31
Gender	0.8	0.34
Age at diagnosis	1.9	0.59

Fig. 2. Malignant melanoma. Survival in patients under 20 years of age by stage. Source: SEER 1973–1996 (reproduced with permission from *Pediatr Hematol Oncol* 2002, **19**, 309–317; Taylor and Frances Ltd: http://www.tandf.co.uk/journals). SEER, Surveillance, Epidemiology and End Results.

7.1. Staging

Comprehensive staging guidelines have not been established for patients with paediatric and adolescent melanoma. As depicted in Table 1 and in Fig. 2, most authors have 'simplified' this task by grouping patients into three broad categories: those with localised disease, nodal spread and distant metastases. In addition, most reports have failed to incorporate basic information regarding the characteristics of the primary tumour. The revised staging system developed by the American Joint Committee on Cancer (AJCC) provides a reproducible model which reflects the natural history of melanoma and incorporates a detailed description of important prognostic variables that are predictive of clinical outcome. For localised disease, there are new thresholds for melanoma thickness and recognition that ulceration is an important predictor of outcome. For patients with nodal spread, the new system recognises the importance of the number of lymph nodes involved, as well as the prognostic significance of ulceration and in-transit or satellite metastases. For patients with metastatic disease, the new staging system incorporates a description of the sites of metastases and the prognostic value of serum lactic dehydrogenase. The results of sentinel node biopsy are now being incorporated, to account for the reported differences in outcomes between series with pathologically- and clinically-involved nodes [59]. It is vital that future trials including paediatric and adolescent melanoma patients incorporate this staging system to facilitate the interpretation of results from different institutions and patient populations. In addition, given the scarce literature describing the use of sentinel node biopsy for the staging of paediatric and adolescent melanoma [60,61], these trials must mandate the routine use of sentinel node biopsy in order to determine the prognostic and therapeutic value of this procedure in young patients and to compare these results with those reported in the adult literature [62–64].

Comprehensive guidelines for the appropriate staging work-up for children and adolescents with melanoma have not been established. Although the adult literature does not advocate the routine use of computed tomography (CT) of chest or abdomen to stage patients with apparently localised melanoma [65], a study at St Jude Hospital identified clinically undetectable metastases in 25% of paediatric patients with thick localised melanomas or in patients with melanoma arising at an unknown primary site [66]. In the absence of symptoms, the routine use of magnetic resonance imaging (MRI) to assess the brain is not recommended. For patients with localised disease and whose lesions are <1.5 mm thick, a complete blood count, serum chemistries including liver function tests, and a chest radiograph seem to suffice.

Positron emission tomography (PET) has emerged as a useful imaging modality in patients with cutaneous melanoma. This technique is more sensitive than CT scanning in detecting melanoma metastases, but, in adults, sentinel node biopsy is far superior to PET imaging for detecting clinically-negative nodal disease. In patients with a known recurrence of their melanoma, PET imaging can identify additional, unsuspected sites of disease in up to 20% of cases when compared with CT scanning [67–69]. However, to date, there are no published studies using PET imaging to stage paediatric melanoma.

7.2. Treatment

7.2.1. Treatment of the primary tumour

Early detection and surgical removal of any suspicious pigmented lesion is the mainstay of therapy for paediatric and adolescent melanoma. Such lesions must always be submitted for pathological assessment. Reporting of various histological features known to be of prognostic significance such as the type of melanoma, the presence of ulceration, the thickness of the lesion, Clark's level of invasion, and the presence of microscopic satellites should be encouraged.

Recommended guidelines for the resection of paediatric and adolescent melanoma follow the same principles as those established for adult melanoma. Briefly, *in-situ* melanoma can be managed with simple excision; lesions thinner than 1 mm in depth can be resected with a 1-cm margin and those 1–4 mm in thickness with a 2-cm margin. At least 2-cm margins are recommended for lesions deeper than 4 mm [70,71]. Sentinel node biopsy has become a 'routine' staging procedure in adult melanoma and should be incorporated into the surgical management of younger patients. The indications for sentinel node biopsy in paediatric and adolescent melanoma are based on the adult literature and include the presence of lesions thicker than 1 mm and the presence of ulceration or a Clark's level of invasion of IV or V in patients with lesions <1 mm [59,72]. The prognostic and therapeutic implications of microscopic involvement in a sentinel node has not been studied in the paediatric and adolescent population, but therapeutic lymphadenectomy of the involved area is recommended in instances in which the sentinel node reveals melanoma deposits.

7.2.2. Therapy for localised and resected melanoma

There are currently no large prospective trials evaluating the value of non-surgical therapies in paediatric and adolescent melanoma, but in the adult literature there is substantial evidence to suggest that the use of adjuvant interferon alpha 2b improves both the relapse-free survival and overall survival of patients with 'high-risk' resected melanoma [73–76]. In the first Eastern Cooperative Oncology Group (ECOG 1684) trial, 287 patients with high-risk resected melanoma were randomised to observation or adjuvant interferon alpha 2b for 1 year. At a median follow-up of 7 years, a significant prolongation in overall survival and relapse-free survival were demonstrated for the interferon arm [75]. In the second ECOG trial (1690), an attempt was made to decrease the toxicity of interferon by delivering lower doses over a longer period of time. A total of 608 patients with high-risk resected melanoma were randomised to one of three arms (observation, low-dose interferon for 2 years, and high-dose interferon for 1 year as in ECOG 1684). At a median follow-up of 52 months, patients assigned to the high-dose interferon arm had significantly better relapse-free survival than those in the low-dose arm, but there was no effect on overall survival [76]. However, interestingly, patients who relapsed in the observation arm and who were subsequently treated with interferon had a postrelapse survival advantage when compared with patients who did not then receive interferon. In the third ECOG trial (E1694), 880 patients were randomised to high-dose interferon or a melanoma vaccine, formulated from the GM2 ganglioside antigen [74]. This trial was terminated early because of a highly significant advantage in both survival and relapse-free survival for patients in the high-dose interferon arm. These three trials demonstrate that adjuvant interferon is effective in patients with high-risk resected melanoma. Unfortunately, there have been no large prospective trials using this agent in patients under the age of 18 years. At St Jude Children's Hospital, 11 patients have been treated with a high-dose interferon regimen identical to that used in the ECOG 1684 trial. The drug was well tolerated during induction, with only two grade 4 haematological events and one grade 4 liver event (W.L. Furman, personal communication). The United States Children's Oncology Group (COG), as well as investigators from other collaborative paediatric groups, such as the UK Children's Cancer Study Group (UKCCSG) and the International Society of Pediatric Oncology (SIOP) have recognised the need to overcome the obstacles that have constrained the study of so-called 'rare tumours' in children and adolescents. COG is now actively pursuing collaborative efforts with adult cooperative groups so that younger patients can have uniform access to newer therapies.

7.2.3. Treatment of disseminated disease

Most reports describing the treatment of paediatric melanoma are from single institutions in which diagnostic criteria staging and pathological evaluation of the primary tumour have varied significantly. Studies of the single agent, DTIC, the most active agent in adult melanoma, identified encouraging activity in four children with melanoma treated at MD Anderson between 1975 and 1984 [77]. At St. Jude Childrens Research Hospital,

Hayes reported objective responses in 7 of 9 children with melanoma using a combination regimen of vincristine, actinomycin D and cyclophosphamide [78]. In a second trial from this institution, investigators reported one complete and one partial response among four children with advanced stage melanoma using alternating courses of cisplatin and etoposide with vincristine, actinomycin D and cyclophosphamide and a 12-week course of interferon alpha 2a [79]. Although Interleukin-2 (IL-2) has been used extensively in adult melanoma, with response rates of approximately 15–20% [80], few studies have evaluated this agent in children with melanoma [81,82]. The use of 'biochemotherapy' [83] comprising interferon, IL-2, DTIC, cisplatin and vinblastine has produced responses in nearly 50% of adults with metastatic melanoma and durable remissions have been documented in 14% of patients [83]. However, this treatment has not been prospectively investigated in children. The availability of investigational therapies, such as the use of vaccines, has been restricted to patients who are older than 18 years of age and no prospective trials in adolescents have been performed. Collaborative efforts, now under discussion between paediatric and adult cooperative groups, should help facilitate the enrollment of younger patients onto trials that use these and other experimental therapies.

7.2.4. Radiotherapy

Radiotherapy is rarely indicated in the management of primary paediatric melanoma. However, it should be considered in patients with head and neck melanomas at high risk for parotid or cervical metastases and in those who develop brain metastases. Brain metastases have been reported to occur during the course of the disease in up to 18% of children with melanoma [84].

7.3. Prevention

Treatment for malignant melanoma is most effective when the diagnosis is made early and treatment is started immediately. Thus, strategies that emphasise risk reduction (primary prevention) and early detection (secondary prevention) are of paramount importance in controlling the current melanoma epidemic. However, as described earlier, recent epidemiological studies suggest that pigmentary and hereditary traits determine the risk of developing early onset melanoma, therefore it is not yet clear that preventive strategies alone will influence the incidence of the disease in younger patients. On the other hand, adult melanoma has been clearly linked to solar exposure, so the children are a prime target for educational and behavioural modification strategies that could have a positive influence in later life. Public education programmes to raise awareness about sun exposure and skin cancer such as 'The Sun Wise' programme, aimed at teaching children how to protect themselves from overexposure to sunlight, should be further studied [85]. Healthcare providers should encourage risk-reduction strategies, such as avoidance of intense sunlight exposure, use of protective clothing, and the use of broad spectrum sunscreen. Unfortunately, despite efforts to increase awareness of the risks of unprotected UV exposure, a recent cross-sectional study from all 50 US states, comprising 10 079 boys and girls aged 12–18 years, revealed that the prevalence of sunscreen use in this population was only 34%. Another disturbing finding from this study was that 10% of all respondents used tanning beds and the percentage increased to nearly 25% among girls aged 15–18 years [86]. This study emphasises the need for continued and sustained efforts to educate the public, particularly in schools, about the risks of sun exposure and the need for tougher legislations that discourages the use of tanning beds.

To facilitate early diagnosis, treating physicians must be familiar with the conditions associated with the development of early onset melanoma and educated to recognise the clinical signs of melanoma (asymmetry, border irregularity, colour variegation, and diameter >6 mm). Finally, enrollment of all patients into cooperative group trials may help us to better understand the natural history of the disease, its responsiveness to therapy, and the genetic and environmental factors responsible for the development of early-onset melanoma.

8. Future directions

Recently, transgenic animal models are beginning to shed some light on the relationship between melanoma and UV irradiation. After a single neonatal dose of erythemal UV radiation, transgenic HGF/SF mice developed lesions reminiscent of human melanoma. Furthermore, genetically-deficient *INK4a/ARF* neonatal mice subjected to neonatal irradiation demonstrated significantly accelerated melanogenesis compared with untreated mice [93]. These findings confirm that the interaction between environment, phenotype and genetics are all important determinants of melanoma. These models should eventually help elucidate the different molecular pathways involved in paediatric and adult melanoma and, in turn, lead to improved therapeutic and preventive strategies for this disease.

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