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ORIGINAL ARTICLE

Pediatric/Craniofacial

An 18-year Study of Malignant Melanoma in Childhood and Adolescence

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Background: Malignant melanoma is rare in childhood and adolescence. Diagnostic uncertainty and misdiagnosis often lead to delayed treatment.
Methods: We evaluated children and adolescents under 20 years of age presenting with malignant melanoma at our institution over an 18-year period. Data were collected, analyzed, and interpreted, following which findings were compared with the existing literature.
Results: Twenty-four patients were included in the study with mean follow-up of 61.8 months. Males comprised 54% of cases. On presentation, 33% of children had melanoma of s thickness 2–4 mm and 34% had stage III disease. Younger children presented with thicker melanomas, differing subtypes, and more advanced stage disease compared with older children. Extremities were the most common sites affected (42%). Dissection of the draining lymph node basins was undertaken in 38% of cases. Overall survival was 92%.
Conclusions: Tumor subtype, biology, hormonal influence, and lymph node status are all important prognostic factors in malignant melanoma in childhood and adolescence. Compared with adults, children presenting with thicker melanomas and more advanced stage disease generally have more favorable outcomes and a better survival. Plastic surgeons, commonly encountering skin lesion in children, must maintain a high index of suspicion so that early excision and sentinel lymph node biopsy may be promptly offered to patients with melanoma. *(Plast Reconstr Surg Glob Open 2019;7: e2338; doi: 10.1097/GOX.0000000000002338; Published online 30 August 2019.)*

Malignant melanoma in childhood is a rare diagnosis with approximately 300 to 420 new cases reported per annum in the United States.[1] The incidence increased by 2.9% in children of all age groups between 1973 and 2001, and overall childhood melanomas account for 2% of all melanoma cases.[2,3] Data from the Surveillance, Epidemiology and End Results (SEER) US cancer registry between 2000 and 2010 estimated an incidence of 5.93 cases of melanoma per 1,000,000 children and adolescents.[4] In the aforementioned study of 1,185 children, younger children comprised a much lower proportion of overall diagnoses with 4% aged between 0 and 4 years, 7% between 5 and 9 years, and the vast majority, 89% aged between 10 and 19 years.[5] The average age at diagnosis is 13.3 years.[11] Cutaneous childhood melanomas are generally classified into those arising on a background of CMN or those unassociated with CMN.[6–8] The latter of these are particularly difficult to diagnose. Challenges include differentiating benign lesions such as spitz nevi from malignant spitzoid melanomas which they may closely resemble and clinically distinguishing melanoma from other benign lesions such as pyogenic granuloma or verrucae.[6] This may in part be attributed to the fact that up to 60% of young children and 40% of adolescents present with atypical features including amelanosis, bleeding, raised papulonodular primary lesions, lesions of uniform color; variable diameter, and de novo lesions.[2,6,9]

Due to previously mentioned diagnostic challenges, the definitive diagnosis of malignant melanoma in children and adolescents is often delayed. As is the case with adults, early surgical intervention with wide local excision leads to a more favorable prognosis. However, more frequently among children, advanced disease on presentation with thicker primary tumors and sentinel node metastases culminates in a poorer prognosis.[1,6,10]

Overall, there is a paucity of large series or reviews within the literature compared with adults.

Childhood melanoma has been proposed by some authors to be a distinct biological entity to melanoma in

From the Welsh Centre for Burns and Plastic Surgery, Swansea, United Kingdom.
Received for publication February 17, 2019; accepted May 8, 2019.
Presented at the World Congress of Melanoma, October 2017, Brisbane, Australia.

DOI: 10.1097/GOX.0000000000002338

Disclosure: *The authors have no financial interest to declare in relation to the content of this article.*

adults.[6–8] This is also supported by the fact that melanoma in childhood differs not only in terms of clinical presentation but also with regards to risk factors, etiology, natural history, and prognosis.[11] In adults, the demographics of melanoma are known to be age related with older patients more likely to be male, present with tumors of the head and neck and with lentigo maligna histology.[12–15]

Data in children are much more limited. The SEER population database reports that the incidence of melanoma among teenagers is higher in areas with greater UV exposure.[1] Additionally, the use of artificial tanning facilities is reported as high, up to 47%, among female teenagers in the United States. These factors indicate that UV exposure is likely to be an important etiologic agent in this adolescent age group.[16,17]

However, in younger children, the short duration of exposure to UV makes this theory less plausible and other factors are likely to be implicated. Studies have suggested that tumor biology may differ in young children compared with adolescents or young adults.[11]

Younger children with melanoma are more likely to have congenital melanocytic nevi or familial atypical nevus syndrome, and total body nevus count is thought to be an important risk factor as identified on previous twin studies.[12] Additional factors warranting consideration include syndromes predisposing to developing cancer such as xeroderma pigmentosum or acquired/congenital immunosuppression.[19]

Among adults, important prognostic factors include Breslow thickness, presence of ulceration, increasing age, nonextremity site of primary tumor, involvement of lymph nodes, satellite lesions or in-transit metastases, raised lactate dehydrogenase, and metastatic disease.[10] However, prognostic factors are much less well understood in children. Although Breslow thickness is the most important prognostic factor in adults, no studies have attributed the same significance among children. A large European registry of children identified that male sex and lesions on the trunk were associated with a worse prognosis.[20] Advanced stage disease has also been linked to worse prognosis in other pediatric studies.[21,22]

In published case series, the 5-year survival among pediatric patients has been reported to be between 74% and 80%.[19,20] However, the largest population-based study using the SEER database reported a survival rate of 91%. This study, due to its size, although it excluded in situ melanoma cases, is likely to be more representative due to less bias. This figure has improved by around 4% per year over the last 3 decades.[2] This may be due to earlier or improved diagnosis, early surgical intervention, and treatments previously offered to adults now being offered to children including sentinel lymph node biopsy (SLNB).

Plastic surgeons play a key role in the early identification and excision of melanoma or precursor lesions in children. Risks of malignant transformation of atypical or congenital melanocytic nevi are often discussed with parents. Usually children are treated with adult-based protocols. One legitimate concern may be that the application of these protocols to all children may result in greater morbidity if the clinical course in children were less aggressive than in adults.[6] Therefore, a greater understanding and characterization of melanoma in children is necessitated to offer more bespoke therapeutic protocols. Increased awareness is necessitated to improve early detection, treatment, and survival. We undertook a study evaluating our experience of cases of malignant melanoma in childhood and adolescence over an 18-year period. Our aim was to increase awareness of the incidence, diagnostic challenges, management strategies, and prognosis of childhood melanoma among plastic surgeons to treat and inform both patients and parents most effectively.

METHODS

Our aim was to undertake a review of all the cases of malignant melanoma in childhood and adolescence presenting at our institution over an 18-year period to characterize common presenting features, review histological subtypes, staging, treatment, and survival to aid future management. Data were collected from the Cancer Information System Cymru, Cancer treatment outcomes registry (CANTORIS), and the Welsh Centre for Burns and Plastic Surgery operative database. Those included presented with MM under the age of 20 years and between the period 1996 and 2015. Patients were grouped into age groups based on the World Health Organization categories.

RESULTS

A total of 24 patients were included in the study (Table 1). The average age at diagnosis was 15 years (range, 2–19 years). In total, 54% of patients were males. Most patients presented with primary cutaneous MM (96%), whereas 1 patient had a melanoma deposit with unknown primary on presentation.

The commonest subtype of MM at presentation was superficial spreading (n = 11). These were all in the adolescent group (10–19 years) (Fig. 1). Other common subtypes in adolescents were nodular (n = 4), nevoid (n = 3), and spitzoid (n = 3). Two children were in the childhood group (0–10 years) with their melanomas arising from CMN and spitzoid. The commonest anatomical sites affected were the lower limb and head and neck forming 42% and 38% of cases, respectively (Fig. 2). There was no significant difference in site among pre- and postpubertal patients or between male and female patients. One third of children presented with MM of Breslow thickness between 2 and 4 mm (Fig. 3). The commonest stage of disease at presentation was stage III with which 34% of patients presented (Fig. 4). No trend in incidence was identified year on year from the start to the end of the study (Fig. 5).

Overall survival in our study was 92%. The mean follow-up was 61.8 months (range, 2–168 months). Two patients died at the age of 13 and 18 years from metastatic disease. Local recurrence occurred in 3 patients and regional recurrence in 5 patients. Nine patients (38%) underwent lymph node clearance to the regional lymph node basins. In total, 9 patients (38%) received systemic treatment in the form of interferon or chemotherapy. At the time of the

Table 1. Demographics, Histological Subtype, Staging and Survival for Pediatric Melanoma Patients

Patient Number	Sex	Age	MM Type	Stage	Regional Surgery	Systemic Therapy	F/U	Recurrence	Survival
1	F	2	From CMN	IIIa	No	No	144	No	Yes
2	F	4	Spitzoid	IIIa	Neck dissection	Interferon	168	Yes	Yes
3	F	10	Superficial spreading	Ia	No	No	60	No	Yes
4	M	12	Spitzoid	IIIb	Groin dissection External iliac dissection X2 Para-aortic node excision	Interferon Dacarbazine	35	No	No
5	M	14	Superficial spreading	Ia	No	No	165	No	Yes
6	F	15	Nodular	IIIc	Neck dissection	Interferon	30	No	Yes
7	F	15	Nevoid	Ia	No	No	80	No	Yes
8	F	16	Superficial spreading	IIIc	Groin dissection	Interferon	12	No	Yes
9	M	17	Superficial spreading	Ia	No	No	60	No	Yes
10	M	17	Superficial spreading	IIIb	Groin dissection	Interferon	35	No	Yes
11	M	18	Superficial spreading	IIa	No	No	60	No	Yes
12	M	18	Nodular	IIa	Groin dissection	Interferon	131	No	No
13	F	18	Superficial Spreading	IIa	No	No	57	No	Yes
14	M	18	Superficial spreading	Ia	No	No	113	No	Yes
15	F	19	Superficial spreading	IIa	No	No	8	No	Yes
16	F	19	Nevoid	0	No	No	14	No	Yes
17	M	19	Unknown primary	IIIc	Radiotherapy neck Bilateral neck dissection	Interferon	7	N/A	Yes
18	M	19	Nevoid	IIa	No	No	60	No	Yes
19	M	11	Spitzoid	IIIb	Neck dissection	No	13	No	Yes
20	M	11	Spitzoid	Ib	No	No	47	No	Yes
21	F	19	Superficial spreading	IIIb	No	Chemotherapy, radiotherapy, bevacizumab	94	Yes	Yes
22	F	18	Superficial spreading	Ia	No	No	42	No	Yes
23	M	18	Nodular	IIb	Neck dissection	Interferon	45	No	Yes
24	M	19	Nodular	IIb	No	Interferon	2	No	Yes

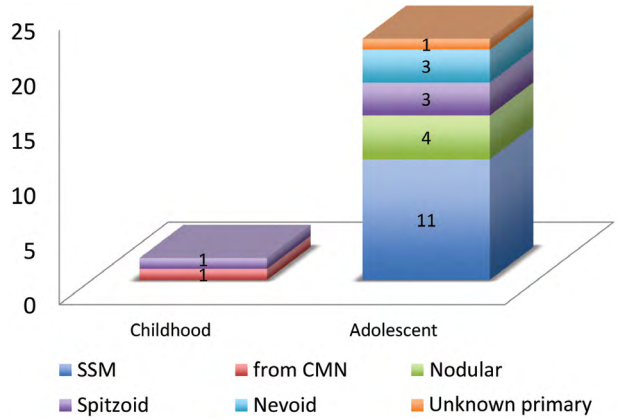

Fig. 1. Subtypes of melanoma on presentation according to age. Adolescent (13–20 years of age), childhood (1–13 years of age), congenital and infantile (<1 year of age).

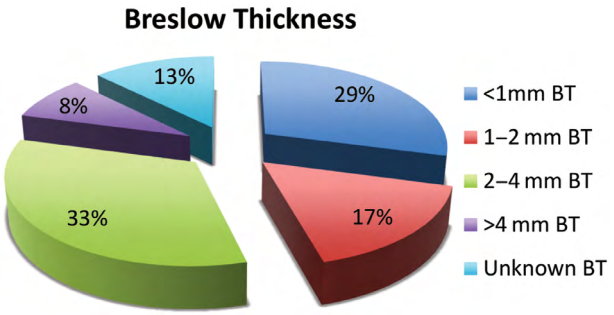

Fig. 3. Breslow thickness of malignant melanoma on presentation.

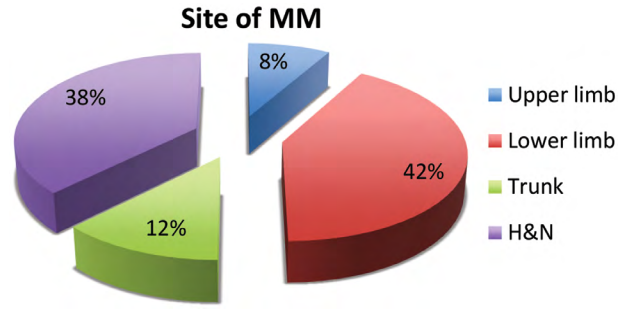

Fig. 2. Site of malignant melanoma on presentation.

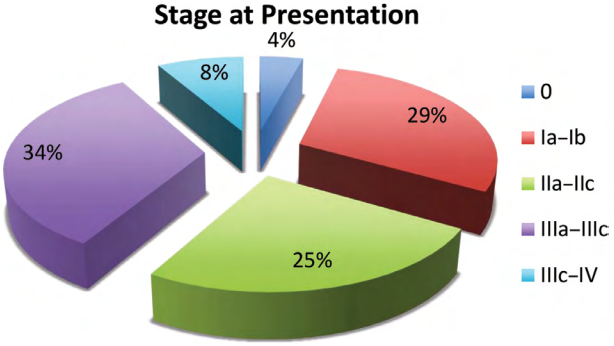

Fig. 4. Stage of malignant melanoma on presentation.

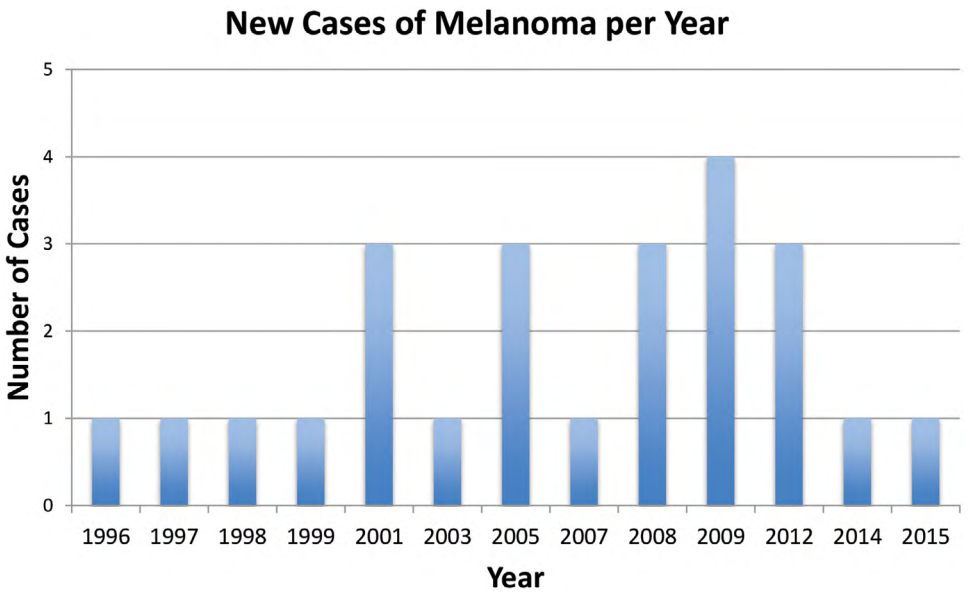

Fig. 5. Trends and number of new cases of childhood melanoma per year.

study, sentinel node biopsies were not routinely offered at the institution to children with malignant melanoma.

DISCUSSION

This is a series of childhood and adolescent melanoma cases published from the United Kingdom. A number of studies have been undertaken at institutions at other geographical sites (the United States,[2,23] Canada,[24] Sweden,[25] and Australia[22]) with several of these reporting increasing incidence of pediatric melanoma over time. Our study did not demonstrate this over the 18-year period. Half of the patients were diagnosed in the first 11 years (1996–2007) and the remaining half over the subsequent 8 years (2007–2015). There were no identifiable trends relating to the numbers of new cases diagnosed per year. As plastic surgeons we encounter a large number of skin lesions in children, and the overall incidence is extremely low (approximately 1 in 425,000 children).[24]

Previous studies have identified a female preponderance.[11,25–27] However, our study had a slightly greater proportion of male patients (54%) with no overall significant difference.

The majority of cases of malignant melanoma (92%) in our study were adolescents (10–20 years) with a much smaller proportion (8%) presenting in the childhood or congenital age groups (under 10 years).[11,28,29] This is in concordance with the literature with childhood melanomas accounting for 2% of pediatric melanoma cases and prepubertal accounting for 0.3%–0.4%.[30]

Older children/adolescents in our study presented most commonly with SSM (n = 11) followed by nodular melanomas (n = 4). This subtype predominance in adolescents is also highlighted within the literature.[1] Statistical comparison is not made with the young children group (under 10 years) due to the small numbers (n = 2). However, as highlighted in the literature, there is likely to be differences in pathogenesis among children of different age groups. UV exposure is hypothesized to be an important risk factor in older children/adolescents due to children undertaking outdoor activities for prolonged periods and some studies reporting an increase in use of artificial tanning facilities, particularly among female teenagers.[15,16] In younger children, genetic alterations are likely to be of greater importance and precursor lesions are often identified. In our 2 cases among younger children, one had a MM arising from a CMN and the other a spitzoid melanoma. Studies have demonstrated that large/giant congenital melanocytic nevi accounted for 57% of all reported cases of congenital or infantile melanoma.[30]

Trozak et al[31] and Quaba and Wallace[32] reported that a third of cases of melanoma (between 0 and 15 years) arose from congenital melanocytic nevi. In most cases, these were associated with widely disseminated metastatic disease. In our series, only 1 patient presented with melanoma following a congenital melanocytic nevus without associated metastatic disease. Melanoma in childhood may also arise de novo or from nevi. Wu and Lambert[33] reported out of 13 pediatric melanoma cases approximately 60% arose de novo or from other nevi or skin lesions.

It is thought that nevi or skin lesions that present in childhood are most likely to be congenital in nature. Characteristics vary from small melanotic nodules to protuberant pigmented masses. Some authors have reported a 3- to 21-fold increased risk of melanoma when these are present.[30]

Younger patients in addition are more likely have associated syndromes predisposing to malignancy such as xeroderma pigmentosum or have congenital or acquired immunosuppression.[1]

Regarding site, the lower limb was the most common location affected in our patients followed by the head and neck region. This is comparable to the study by Dean et

al[24] which identified the extremities as the most commonly affected anatomical site.

In our study, we identified that children presented on average with thick melanomas, with 33% of children presenting with tumors of Breslow thickness between 2 and 4 mm. Younger children in our group, 1 to 14 years of age, had thicker melanomas (median, 2.64 mm) compared with those over 14 years of age (median 1.5 mm). Lange et al[11] also found that younger children (1–14 years of age) were more likely to present with thicker melanomas than young adults/older teenagers.[11] This may be due to the inherently different tumor biology of melanoma in children and delayed diagnosis.[10] Additionally, although in adults tumor thickness is known to be the most important prognostic factor in children, it seems that this is not the case. Young children 1 to 19 years of age with thicker melanomas have been shown to have far better survival compared with adults.[10] The exact reason behind this is not known though differences in tumor biology, hormonal influence around puberty, genetics, and additional prognostic factors are likely to contribute.

In our study, around a third (34%) of patients had stage III disease on presentation. This is comparable to the literature. Lange et al[11] report regional disease in 25.5% of patients aged 1–4 years compared with 9.1% in those aged 20–24 years. One contributing factor is delay due to diagnostic uncertainty due to the condition being rare and difficult to diagnose clinically and histologically. Lesions in children may arise from a previous nevus or have atypical appearances on presentation that may be challenging to differentiate from benign lesions. If fact, as was the case in one of our patients, where the lesion caused a diagnostic discrepancies among multiple different pathologists, and a second case where a lesion was initially classified as benign and then only identified as malignant once it had recurred. On the other hand, some benign lesions may be incorrectly identified as malignant leading to potential overtreatment. Studies have shown that pediatric melanoma is misdiagnosed in up to 43% of cases.[21] Where uncertainty exists with these lesions, referral to a specialist histopathology center is advisable.

Overall, 5-year survival in our study was 92%, 2 children having melanoma-related deaths. These were both males aged 13 and 18 years. The former of these had a primary spitzoid melanoma on the lower limb and the latter a nodular melanoma on the trunk. Studies in the literature report generally poorer 5-year survival rates between 74% and 80% compared with our data.[19,20] Strouse et al,[2] however, reported a 5-year survival rate of 91%. The latter study is likely the most representative as it is population based. Offenmueller et al[34] reported even greater 5-year survival rates of 95.2%. Both children who died in our series were >10 years old. Ferrari et al[7] postulated improved survival outcomes in children <10 years compared with those ≥10 years of age. This again highlights the likely differing biological entities of melanoma among the 2 groups.

Limitations of our study include that our cohort of patients, when using the World Health Organization classification, in the childhood group (1–10 years) was small (n = 2); therefore, one cannot make wider inferences based on this data. There were also no data available relating to comorbidities and family history of patients. Additionally, data relating to surgical excision margins, details of surgical technique, and dosing of adjuvant therapies would have been beneficial to evaluate in relation to outcome. During the time of our study, SLNBs were not routinely offered to children with malignant melanoma. In adults, this forms a routine part of the diagnostic/staging algorithm alongside wide local excision. The incidence of positive SLNB has been shown to be higher in children compared with adults.[35,36] Despite this, young age, in the literature, is considered to be a favorable prognostic factor for melanoma, a finding which may reflect in part a difference in the strength of the immune system among the different age groups and thus an overall higher proportion on positive SLNB in young children.[35,37]

It has been postulated that surgical intervention and removal of lymph nodes may alter biological behavior of the tumor, leading to a more favorable outcome.[38,39]

Busam et al[37] have shown that a positive SLNB does not necessarily always correlate in children with a poorer outcome. Outcome is also closely linked to the tumor type and characteristics with atypical spitzoid melanocytic tumors having a much less aggressive course and outcome that unambiguous melanoma cases with positive SLNB. Therefore, in children, it is apparent that a number of factors including tumor subtype, lymph node involvement, stage, and hormonal factors interact together to influence long-term survival and prognosis.

CONCLUSIONS

Pediatric melanoma is rare, but as plastic surgeons commonly encountering skin lesions in children, a high index of suspicion is required. It should be noted that children often present with atypical features and early excision, and sentinel node biopsy should be offered. Children generally, compared with adults, present with thicker primary melanomas and with a more advanced stage of disease. However, despite this, their overall survival is better than adults, highlighting a likely important intrinsic difference in tumor biology, hormonal influences, or genetic factors. A national cancer registry across the United Kingdom will be greatly beneficial in reviewing a larger number of cases due to the rare nature of the diagnosis.

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DECLARATION OF HELSINKI

Statement of Conformity: This study was conducted in accordance with the Declaration of Helsinki.

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