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Paediatric malignant melanoma in Ireland: A population study and review of the literature☆

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Summary *Introduction:* Malignant melanoma is increasing in frequency worldwide; however, this disease is rare in children. As large-scale studies on paediatric melanoma are lacking, management is currently often based upon the understanding of the disease process in adults. The aim of this study was to characterise cases of paediatric melanoma diagnosed in the Republic of Ireland over a 21-year period.
Methods: This was a retrospective, multicentre study using national data provided by the National Cancer Registry of Ireland and individual practitioners.
Results: Twenty-four cases of melanoma treated in 11 different centres were included in the study. The median patient age at diagnosis was 15 years. The majority of cases arose on the limbs. The median Breslow thickness in patients of the pre-pubertal age group was 8.25 mm, while in children more than 13 years, it was 1.65 mm. Eight patients had disease recurrence and five patients died.
Conclusion: The diagnosis of melanoma remains rare in children. This study contributes to our current understanding of malignant melanoma in paediatric patients; however, further investigation of the disease characteristics in this group is necessary to achieve optimal management of these cases and therefore improve outcomes.

Introduction

Malignant melanoma is increasing in frequency worldwide[1]; however, the disease remains rare in children.[2-4] There is a relative paucity of literature in the area of paediatric melanoma and a number of issues exist when reviewing published data. The definition of 'childhood' varies widely

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amongst studies, and many publications on the topic include patients up to the age of 21, rendering interpretation of their findings to be difficult. This limits applicability of study conclusions to all paediatric patients. Furthermore, it is now widely accepted that the disease behaviour in younger, pre-adolescent children varies in a number of ways from those in the post-pubertal age group, in whom disease characteristics appear to be more akin to the adult population.[2,5,6] Therefore, published studies that fail to differentiate these two groups may give an inaccurate or misleading account of disease biology and outcomes in the paediatric population as a whole. An additional factor in existing literature related to paediatric melanoma is the uncertainty surrounding the behaviour and malignant potential of melanocytic lesions that do not fulfil the diagnostic criteria for malignant melanoma at presentation.[7] Some have an undetermined metastatic potential, such as atypical Spitzoid lesions and the so-called 'melanocytic tumours of uncertain malignant potential'. The inclusion or exclusion of patients with such lesions in the analysis of malignant melanoma in young patients may also give an inaccurate picture of the diagnostic and treatment modalities required to achieve optimal outcomes in this potentially fatal malignancy.

Because of the limited number of large-scale studies in paediatric melanoma, management is often based upon the knowledge extrapolated from our understanding of the disease process in adults. It is unclear, as yet, if this is appropriate.

It is known that disease stage at presentation is one of the single most important determinants of outcome in malignant melanoma.[8] As a result, the use of sentinel lymph node biopsy (SLNB) has now been widely accepted as an accurate prognostic indicator in lesions of intermediate and deep Breslow thickness in the adult population. However, little has been published about its use in children, and only in more recent years has it become a common place for use in the staging of melanoma in this group.[9-12]

Although in Ireland the incidence of childhood cancers has slowly risen in recent years,[13] the number of cases of malignant melanoma diagnosed annually in this group has not been previously studied. The National Cancer Registry of Ireland (NCRI) records all cancer cases diagnosed within the Republic of Ireland. Histopathological data are provided to the registry by all hospitals, which are then supplemented by demographic, radiological and mortality information assembled by a designated Tumour Registration Officer within each centre. The collation of information with histopathological reports and the registry's quality assurance protocols mean definitive data are not available for a minimum of 2 years following the diagnosis.[14]

To our knowledge, this is the first study to analyse malignant melanoma in a paediatric population in Ireland. Our primary aims were to identify all cases diagnosed in this group within the Republic of Ireland over a 21-year period and to characterise their disease course. Secondary aims included description of diagnostic and treatment modalities, the use of SLNB and the uniformity of histopathological reporting.

Methods

This was a retrospective, multicentre study using national data provided by the NCRI and individual practitioners.

The NCRI identified all cases of malignant melanoma diagnosed in children, up to and including the age of 16 between January 1994 and March 2015 inclusive. Sixteen years was chosen as the upper age limit included in the study as it is the maximum age at which children in Ireland can be admitted to a paediatric hospital. Because of the confidential nature of the information stored by the NCRI, the only data made available to the authors were related to the number of cases, the institutions in which they were diagnosed, and the overseeing consultant responsible for the management of each event.

With this information written request was then made on the authors' behalf to each of the consultants involved, inviting them to participate in the study. They were asked to provide demographic, clinical and histopathological data relating to each case.

All data analysis was performed using Stata (StataCorp, Texas, USA).

Results were tabulated and expressed as totals and/or percentages where applicable.

Results

The NCRI identified 40 database entries of malignant melanoma in children for the time period of the study. Review of the preliminary data resulted in the exclusion of 7 cases (2 duplications, 2 benign lesions, 1 patient outside the specified age range, 1 case with no patient details, and 1 case where the primary disease and recurrence were recorded as 2 separate episodes).

Requests were made to the overseeing consultant for clinical information regarding the remaining 33 patients. A response rate of 73% meant that data was available on 24 patients for analysis (Table 1). In 9 cases, incomplete clinical data meant they could not be included in the study.

Demographics

Patient demographics are summarised in Table 2. For the purposes of this study, all children aged 12 and under were characterised as pre-pubertal. They accounted for only 29% of cases (7/24), and the median age at presentation in this group was 6.3 years. Those aged 13 and older represent 71% of the patients, with a median age of 15.6 years at diagnosis. There were 15 females and 9 males.

Patients were treated in 11 different centres across the Republic of Ireland. Of the 7 children in the pre-pubertal group, 3 patients were ultimately managed in a tertiary referral paediatric hospital with dedicated paediatric plastic surgeons, dermatologists and oncological services. Of the remaining cases in this group, 3 were managed by plastic surgeons in a university teaching hospital and 1 was managed by a plastic surgeon in the private sector. With regard to the 17 patients in the adolescent group, initial management of 3 cases was at a tertiary referral paediatric

Table 1 Patient summary.

Year of Diagnosis	Gender	Age at Diagnosis	Presenting Symptom	Site	Histological Subtype	Breslow Thickness	Sentinel Node Biopsy	Sentinel Node Positive	Metastatic Disease	Death
1994	Female	15	New Lesion	Limb	Nodular	Not Specified	No	-	No	No
1996	Male	12	Change in Existing Lesion	Limb	Not Specified	In-Situ	No	-	No	No
1996	Female	12	Change in Existing Lesion	Limb	Not Specified	In-Situ	No	-	No	No
1998	Male	16	Change in Existing Lesion	Trunk	Malignant Melanoma in Cellular Blue Nevus	Not Specified	Not Specified	Not Specified	Yes	Not Specified
2000	Female	15	New Lesion	Limb	Nodular	1.8 mm	Yes	Yes	Yes	Yes
2000	Female	14	Change in Existing Lesion	Trunk	Superficial Spreading	In-Situ	No	-	No	No
2001	Female	13	New Lesion	Head and Neck	Nodular	2.8 mm	Yes	No	No	No
2002	Female	13	Change in Existing Lesion	Limb	Spitzoid	1.51 mm	Yes	No	Yes	Yes
2001	Male	1	New Lesion	Limb	Not Specified	2.3 mm	No	-	No	No
2001	Male	15	New Lesion	Limb	Atypical Spitzoid Melanocytic Lesion	In-Situ	No	-	No	No
2002	Female	15	Change in Existing Lesion	Limb	Superficial Spreading	1.25 mm	Yes	No	No	No
2004	Female	8	New Lesion	Head and Neck	Spindle Cell	19 mm	Yes	No	Yes	Yes
2006	Male	15	New Lesion	Limb	Nodular	2.18 mm	No	-	No	No
2010	Female	15	New Lesion	Limb	Superficial Spreading	In-Situ	Not Specified	Not Specified	Not Specified	No
2011	Female	15	Not Specified	Head and Neck	Superficial Spreading	0.4 mm	No	-	No	No
2011	Female	16	Not Specified	Unknown Primary	Not Specified	No primary found	No	-	Yes	Yes
2011	Female	15	Not Specified	Not specified	Not Specified	In-Situ	Not Specified	Not Specified	Not Specified	No
2011	Female	6	Change in Existing Lesion	Head and Neck	Not Specified	11 mm	No	-	No	No
2013	Female	14	Not Specified	Limb	Nodular	7.8 mm	Yes	Yes	Yes	No
2013	Male	15	Change in Existing Lesion	Trunk	Superficial Spreading	2.2 mm	Yes	Yes	Yes	Yes
2014	Male	5	New Lesion	Limb	Atypical Spitzoid Melanocytic Lesion	Not Specified	No	-	Yes	No
2014	Female	15	Change in Existing Lesion	Limb	Superficial Spreading	0.95 mm	Yes	No	No	No
2014	Male	3	New Lesion	Head and Neck	Spindle Cell	5.5 mm	No	-	Yes	No
2015	Male	15	New Lesion	Limb	Superficial Spreading	0.9 mm	Yes	No	No	No

Table 2 Patient demographics.

Gender	15 Female, 9 Male 1.7:1
Median Age at Diagnosis (Range)	15 years (1.82–16.6)
Pre-Pubertal Patients (12 years or younger)	7 (29%) Median age at diagnosis 6.3 years
Post-Pubertal Patients (13 years or older)	17 (71%) Median age at diagnosis 15.6 years

Table 3 Site of primary lesion.

Site	Number of patients
Lower Limb	8 (33%)
Upper Limb	6 (25%)
Head and Neck	5 (21%)
Trunk	3 (13%)
Unknown Primary	1 (4%)
Site not Specified	1 (4%)

hospital. Seven cases were managed in the private sector and nine cases were treated in public teaching hospitals.

Risk factors

None of the patients had a documented history of Xeroderma Pigmentosum, immunodeficiency or immune modulating medications prior to diagnosis. No family or personal history of melanoma was identified in any of the patients in the study group.

Site

The majority of cases arose on the limbs (Table 3). In the case of one patient, clinical information provided did not designate the site of the lesion.

In 11 cases, the lesion arose de novo while the presenting symptom was change in an existing lesion in 9 and a palpable subcutaneous mass in one. Details of symptomatology were not provided in 3 cases.

Histological

Subtype

Histological subtype was not specified in 6 patients. In the other 18 patients, superficial spreading melanoma was the most common subtype (39%), with nodular melanoma the next most frequently diagnosed (28%).

In the pre-pubertal group, 2 spindle cell melanomas and one Spitzoid melanoma were diagnosed. One lesion was originally reported as an atypical Spitzoid melanocytic lesion, but the patient later presented with recurrence in the regional lymph nodes and this case was therefore also included in the study.

In the post-pubertal group, 1 had a Spitzoid melanoma and 1 had a malignant melanoma in a cellular blue naevus.

Breslow thickness

Six patients were presented with melanoma in-situ. In patients with invasive disease, the pathology reports included the Breslow thickness in 14 cases ranging from 0.4 mm to 19 mm, with a median Breslow thickness of 2.19 mm (Table 4).

Multi-Disciplinary Team (MDT) discussion

Ten cases (42%) were discussed at a regional melanoma/oncological multi-disciplinary team meeting. In most, but not all cases, this was an adult MDT. In 3 cases, no discussion took place. All 3 of these cases were diagnosed before 2001. Information regarding MDT input was not provided in the remaining 11 cases.

Treatment

Wide local excision was the definitive treatment in 17 cases. In 2 patients, margins of excision from the original biopsy were deemed adequate, and therefore, further wide excision was not required. In 1 case, in which no primary was identified, systemic medical treatment was the definitive modality of treatment. Data relating to definitive treatment were not specified in 4 cases.

Sentinel lymph node biopsy

No patients presented in the 1990s underwent SLNB. From the year 2000 onwards, nine patients (38%) underwent SLNB. The median Breslow thickness in this cohort was 1.8 mm (range 0.9–19 mm). Three cases had a positive biopsy, and all 3 proceeded to completion lymphadenectomy.

Staging

Nineteen patients had stage I/II disease at presentation. Five patients presented with stage III disease; 2 had clinically obvious lymphadenopathy and 3 had positive sentinel lymph nodes. All 5 patients had imaging to assess for systemic metastases. Further 2 patients without nodal disease also had imaging. There was no evidence of systemic metastases in any case (Table 5).

Disease progression

Eight patients had disease recurrence. In 2 cases, this was in the regional lymph nodes and both patients were treated successfully with lymphadenectomy. Five patients developed systemic metastases, and ultimately, all succumbed to their disease. Four of the 5 patients that died had stage

Table 4 Disease course.

	Total	Pre-pubertal	Post-pubertal
Number of Cases	24	7 (29%)	17 (71%)
Median Breslow Thickness	2.19 mm	8.25 mm	1.65 mm
Nodal Disease at Diagnosis	5 (21%)	1	4
Disease Recurrence – Lymph Nodes	2 (8%)	2	-
Disease Recurrence – Systemically	6 (25%)	1	5
Mortality	5 (21%)	1	4

Table 5 Disease course by age grouping.

	Under 13*	13 or Older**
Number of Cases of Invasive Disease	4	10
Median Breslow Thickness (Range)	8.25 mm	1.65 mm
Number of Cases of In-Situ Disease	2	4
Number of Deaths	1	4
Nodal Recurrence	2	2
Metastatic at Diagnosis	1	4

* Under 13: one atypical melanocytic tumour, which later presented with regional nodal disease recurrence.

** Over 13: no details were provided regarding 2 and the patient in whom no primary was identified was in this group.

III disease at presentation. A further patient was recorded as having disease recurrence but was lost to follow-up after moving abroad.

The survival rate in the pre-pubertal group was 86% and in the post-pubertal group was 76%, and overall survival was 79%. If the figures are adjusted to include only patients with a minimum of 5 years follow-up (18 cases), then the overall survival is 78%.

International collaboration

In 6 cases, a second opinion was sought from the United Kingdom or North America regarding histological diagnosis or the role for adjuvant systemic therapy.

Discussion

Although the patient group examined in this study is small, the study offers valuable information to those involved in the diagnosis and treatment of malignant melanoma in the paediatric population. The demography of the study group is in keeping with other publications in this area, with a minority of cases diagnosed in children before teenage years (29%).

With regard to disease characteristics, the findings of this study are reflective of larger publications on the topic. Across a number of reports, the limbs and trunk have repeatedly been found, in recent years, to be the commonest site for melanoma to arise in paediatric patients.[15-19] Similarly, the histological subtypes most frequently reported in existing data for this patient group are superficial spreading and nodular.[3,15,16,20] However, the presenting symptoms in our study group differed somewhat from larger studies in the area of paediatric melanoma in that almost half of the patients presented with de novo lesions. In other published reports, the majority of patients were presented with symptoms related to an existing lesion such as growth, pain or bleeding.[17,20]

It is now widely considered that the biological behaviour of melanoma in pre-pubertal children is different from the one that arises in adolescents.[5,6] Therefore, arguably, the most meaningful studies in the area differentiate between the two patient groups.

The median Breslow thickness of the invasive cases analysed in this study was 2.19 mm. Although other publications vary widely in terms of the age profile of patients included, this figure is comparable to their results.[18] However, the finding of more advanced lesions in the group aged 13 and under was of interest to us. Several published reports have corroborated the view that melanoma is often more advanced at presentation when it occurs in infants and pre-pubertal children,[3,6,16,18,20] and yet, overall survival in this group appears to be better, even with lymph node positive disease.[21] Indeed, our results showed that, albeit in the context of a relatively short median follow up period, the overall survival rate in patients younger than 13 was better than in adolescents (86% vs. 76%).

Of the 24 cases analysed, patients' management took place across 11 centres nationally. Although this finding is suggestive that the diagnosis of melanoma in children is often unexpected, it may also be indicative that the treatment of paediatric cases is being undertaken in centres where cases of the disease are not encountered frequently. In a retrospective review of paediatric patients, Freemyer et al. demonstrated that when initial management of melanoma is undertaken at a specialist cancer centre, overall survival is improved, particularly in more advanced disease.[22] With imminent opening of a new children's hospital in Ireland due during the coming years, it is hoped that the management of rare diagnoses such as paediatric melanoma may become more centralised in this country. Although meaningful conclusions cannot be drawn regarding the differences in outcomes between patients initially managed by generalists versus those managed by melanoma specialists from such small study numbers, it is likely that the input of a specialist centre in such cases is preferential to centres with less experience in the disease.

MDT discussion of cases has become the gold standard in care for malignant melanoma.[23] Currently, in Ireland, there are 6 centres with multi-disciplinary teams managing

malignant melanoma in adults and several additional institutions that treat skin cancer and refer cases of melanoma to their local MDT. Only 10 of the 24 cases analysed in this study were discussed at a regional MDT meeting. Although some of these were diagnosed during the first decade of the study period, when MDT discussion was not a common place, this finding further supports the role for specialist centres in management of paediatric cases where access to MDT consensus opinion is routinely available and concentration of expertise relating to this rare presentation is likely. Failure to refer such cases may not only affect patient outcomes but, in the case of such a rare presentation as paediatric melanoma, it may also represent a missed opportunity to educate clinicians and other MDT participants about the disease.[24]

It is well known that young patients tend to develop sentinel node-positive disease more commonly than adults.[9,11,25] However, no formal guidelines exist relating to the use of SLNB for melanoma in the paediatric population. It is the interpretation of sentinel node positivity in this patient group that poses a difficulty and further supports the specialised management of these rare cases. A number of studies have shown that despite higher SLNB positivity rates than adults, children's overall survival from melanoma is better, even in the presence of nodal disease, and the rate of recurrence is lower.[5,18,25,26] It is also known that lymph node surgery for melanoma carries with it a risk of complication.[27] Given the value of completion lymphadenectomy following positive SLNB in adults has been questioned in recent times,[8,28] the optimal treatment for children with nodal disease is not clear at present. Our findings show that 2 patients with lesions of intermediate Breslow thickness did not undergo SLNB; however, the ability to elucidate reasons for this is unfortunately beyond the scope of this study.

In an analysis of the Surveillance, Epidemiology and End Results Database from the United States, Mu et al.[11] demonstrated that pre-adolescent children were more likely to undergo SLNB for melanoma than teenagers or young adults. However, in an effort to analyse the prognostic value of this procedure from a series of 327 paediatric patients with melanocytic lesions, Roaten et al.[25] revealed that several biopsies were performed for benign lesions. Indeed, this practice is described to aid diagnosis in the case of atypical melanocytic lesions, whereby the presence of sentinel node micro metastases will suggest a diagnosis of malignant melanoma.[29] Although the findings of our study do not take into account sentinel lymph node biopsies performed for benign disease, 1 lesion that was originally designated as an atypical melanocytic lesion recurred in the regional lymph nodes. Therefore, even if SLNB is performed for the purposes of confirmation of benign histology, there can be no certainty that a negative node at biopsy implies a lack of metastatic potential in the future.

This study includes patients treated during a 21-year period. Within that time-frame, a number of practices in the management of malignant melanoma changed.[30] Current guidelines for melanoma are based on disease stage at diagnosis.[31,32] It was, therefore, interesting to note that in 3 out of the 24 cases analysed in this study, no Breslow thickness was included in histological reports. Although it does not currently alter the course of treatment, histological subtype was also absent from reports on 2 patients. In 2014, the Royal College of Pathologists issued standards for histological reporting of primary cutaneous melanoma in which was a revision of the first dataset from 2002.[33] Before this, little standardisation existed regarding the reporting of melanocytic lesions, and although the number of patients in this study with an incomplete report is small, this finding is reflective of the experience of other regions during a similar time period.[34]

Knowledge of malignant melanoma is continually evolving, yet our understanding is mainly based on the disease process in adults. Management of both loco-regional and systemic disease has improved in recent years on foot of the developments in pharmacologic and immunotherapeutic agents that target melanoma at a cellular level. Our understanding of the genetic contribution to malignant melanoma in adults is now advanced, and tailored treatments to specific mutations in genes such as the B-Raf Proto-Oncogene (BRAF) have shown promise.[35] However, the relative rarity of melanoma in childhood has, to now, meant the ability to evaluate new treatments in this patient group has been limited. Furthermore, insufficient case numbers have precluded adequately powered clinical trials. Despite this, analysis of the genomics of paediatric melanoma has perhaps been the most important development in recent years in this area and has allowed more accurate prognostication and analysis of tumour aggression in this population.[36,37]

With this in mind, never before has the need for interdisciplinary and international collaboration been so pronounced. In 6 of the cases evaluated in this study, international expertise was sought to assist with diagnosis and treatment choices, but with recent advances, it is likely the level of inter-institutional involvement that will increase. Indeed since the completion of this study, it has now become routine for the only dedicated paediatric oncology centre in Ireland to send melanoma specimens for Telomerase Reverse Transcriptase(TERT) mutation analysis as part of the MDT discussion process. Alliances such as the Rare Tumor Committee of the Children's Oncology Group, Rare Tumors in Pediatric Age Project, and the European Cooperative Study Group for Pediatric Rare Tumors have already done much work with regard to furthering our understanding of rare cancers in young patients.[38] Their recognition of the fact that some childhood malignancies are underrepresented in major national and international cancer registries has given greater prominence to such rare diseases and is a positive step towards improving decision making in the management of melanoma in children. It is likely that the ability to work together with international colleagues will only enhance our ability to optimise outcomes.

Naturally, this study has limitations, and its retrospective nature means its findings are subject to the inherent biases of such a design. Our results were reliant on participation of individual clinicians. Retired consultants and resultant inaccessible medical records meant that a comprehensive overview of the characteristics of malignant melanoma in the Irish paediatric population over 2 decades could not be optimally completed, and some practitioners declined to participate, an occurrence which could not be circumvented by the authors. Furthermore, the small number of patients does not allow assessment of potential changes in overall disease outcome during the course of the 21-year study period. However, this merely endorses the need for

prospective data collection to formally assess the disease in this patient group in the future, which could also enable the inclusion of relevant patient history details such as ethnicity, sun exposure and family history. Inclusion of much of this type of information was precluded by the retrospective design of this study. Although much information is collated by the NCRI to aid with the process of disease analysis, it is likely that centralised management of cases of rare presentations such as paediatric malignant melanoma may allow for easier and more clinically pertinent data collection. Our inability to access the records of all reported cases of paediatric melanoma during the study period is an inherent consequence of the stringent, albeit appropriate, confidentiality with which the NCRI maintains all patient records, which makes the study of patient demographics and specific treatment regimens difficult. However, it allowed analysis of trends, and it was possible for the authors to exclude duplicate and irrelevant entries in the registry, using the data provided, with regard to paediatric melanoma for the purposes of this study. As information regarding puberty was not reported in the cases included in this study, differentiation was made between the two groups based on an assumption with regard to patient age. Substantial variability exists between gender, socio-economic group and race with regard to onset of puberty, and as a result, it was difficult in this study to choose a cut-off age at which we could reliably assume patients were either pre- or post-pubertal. We acknowledge this as a potential limitation of our findings; however, current literature on the topic is suggestive that in a Western population, it is reasonable to expect that at the age of 13 the onset of puberty will have commenced.[39]

The findings of this study suggest the diagnosis of malignant melanoma in children and adolescents remains rare. As treatment advances continue to evolve for this disease in adults, and incidence in this group continues to rise, it is likely that the need for knowledge of disease behaviour in paediatric patients will also be necessary to improve outcomes.

Though the patient cohort in this study is small, it represents the only report of this disease in children in the Republic of Ireland to date. While exact figures for and Irish population up to and including the age of 16 in Ireland for the exact years studied is not available, in 2016, children up to and including the age of 14 represented nearly one quarter of the country's population and yet our study showed a maximum of 4 cases annually over a 21-year period.[40] This suggests incidence rates here for paediatric melanoma are similar to those reported in larger publications.[2] It is hoped that not only will our findings increase awareness of this disease but also add to our understanding of its behaviour in this patient group. In pre-pubertal patients, despite deeper melanomas, the outcome was better than adolescent patients, and we therefore concur with larger studies, which suggest the disease process in younger patients differs from that of adolescent and adult patients. Future research should focus on further stratifying these groups to identify whether less aggressive treatment of melanoma in younger children than adults may result in similar outcomes. Although malignant melanoma in paediatric patients is unusual, at least 1 case has been diagnosed almost every year over the 21-year period reported here. The need therefore exists amongst clinicians who are likely to encounter this condition to optimise knowledge of the disease characteristics of which we are currently aware.

Conflict of interest statement

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