443 paediatric cases of malignant melanoma registered with the German Central Malignant Melanoma Registry between 1983 and 2011

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Abstract  Background: Malignant melanoma is a very rare paediatric tumour. This study was performed in order to understand clinical features and prognosis of malignant melanoma in children and adolescents.

Methods: 443 patients ≤18 years of age with malignant melanoma were prospectively registered with the German Central Malignant Melanoma Registry between 1983 and 2011. Cases were collected from 58 participating centres. 276 paediatric cases with a follow-up >3 months were evaluated for survival probabilities and prognostic factors by Kaplan–Meier method.

Results: Age of diagnosis ranged from 3 months to 18 years (median age 16 years). The male to female ratio was 0.8 (202 male, 240 female). Most melanoma were located at the trunk (n = 195) and the lower extremity (n = 114). Patients with >3 months of follow-up (median 55 months) showed an overall survival (OS) of 94.8% in 5 years. Survival according to tumour stage was 98.5% for stage I (n = 190), 91.1% for stage II (n = 39) and 53.0% for stage III/IV tumours (n = 11). Worse outcome was seen in patients with nodular melanoma (OS 77.9%, n = 42) compared to superficial spread histotype (OS 100%, n = 138) or other histotype (OS 96.9%, n = 88) (p < 0.0001), in case of thicker tumours (Clark level IV or V, OS 87.1%,...
1. Introduction

Though malignant melanoma is rare in children and adolescents there has been rising attention within the paediatric community about its occurrence. It has been estimated that in the United States (US) approximately 427 new cases of malignant melanoma are diagnosed in patients under the age of 20 each year [1]. In children under 15 years of age the incidence of malignant melanoma is found to be about 0.7–0.8/million [2–5]. Anyway, as melanoma incidence increases dramatically with age, the incidence in individuals aged 15–19 is reported to be more than 10 times higher (>10/million), already [2–5]. In other words, 1–4% of all new melanoma cases occur under the age of 20 years, and only 0.3% in children younger than 15 years [6]. Due to its rarity little is known about the biology and clinical behaviour of paediatric malignant melanoma. Therefore, clinical management is so far the same as in adults, despite of evidence that malignant melanoma may behave differently in young patients [7]. First of all, diagnosis is extremely difficult to establish. The borders between malignant melanoma and more benign lesions as Spitz nevi [8], atypical Spitz tumours, Spitzoid melanoma and melanocytic tumours of uncertain malignant potential (MELTUMP) are not sharply defined. These diagnostic problems may result in under- or overdiagnoses as well as false therapy decisions. Several authors report that prepuberal children present with relatively thick lesions and in advanced stages [9,10]. It is still unclear whether this observation is due to late diagnosis in children or possible differences in biology [7].

The prospective German Central Malignant Melanoma Registry (CMMR) records approximately 35–50% of all melanoma patients in Germany. It has been founded thirty years ago as voluntary network of dermatohistopathologists and has evolved into the leading resource of clinical data about melanoma cases in Germany. For the first time CMMR data have been screened to extract all paediatric cases in order to report clinical features and prognosis of malignant melanoma in children and adolescents.

2. Patients and methods

The present study includes 443 patients under the age of 19 years who were diagnosed with cutaneous melanoma and ocular melanoma (one patient) and were prospectively registered with the German Central Malignant Melanoma Registry (CMMR) between 1983 and 2011. The CMMR is a hospital based, prospective registry. As in Germany, the majority of melanoma patients are referred to the hospitals, and patients are cooperatively kept under surveillance by the hospitals and dermatologists in private practice, data from the CMMR can be considered as representative and information from approximately 35–50% of all melanoma patients in Germany is received. The incidence of cases observed over the years did not change substantially in the study period.

2.1. Data and patient management

Our study complied with the guidelines of the Declaration of Helsinki. As such, the institutional review board of the University of Tübingen approved the study. All patients had given their written informed consent to have their data on primary tumour and follow-up recorded within the CMMR. The histopathological diagnosis of malignant melanoma was established by the dermatohistopathologists of the cooperating centres. Lesions with atypical or uncertain behaviour were excluded from the analysis. No independent review process of the histopathologic reports was performed; however, there is a continuous medical education of dermatopathologist as organised by the German Dermatologic Society. Information about spitzoid versus non-spitzoid melanomas was only available in 78 patients from the University Hospital Tuebingen. Fifteen of these patients presented with spitzoid melanoma, 65 patients with non-spitzoid melanoma. Fifty-eight cooperating university dermatology departments reported paediatric patients to the registry. Staging investigations at diagnosis included a physical examination, lymph node ultrasound, abdomen ultrasound, chest X-ray and blood examination. Sixty-nine patients underwent sentinel lymph node biopsy. Tumour characteristics and case history were recorded in a standardised manner, and patients were examined regularly every 3–6 months for a period of 10 years. One hundred and twenty nine patients were initially operated in a hospital, 275 patients in an outpatient clinic. The histopathological diagnosis was established by the dermatohistopathologists of the cooperating centres.
Ulceration was diagnosed by histopathology and was defined as the absence of intact epidermis overlying the major portion of primary melanoma. Patients were treated with a relatively uniform approach. Surgery was the mainstay of treatment; adjuvant treatment was given only in a few cases. Follow-up of at least three months was available in 276 cases with a median follow-up of 55 months. Although follow-up information up to 226 months was available for single cases in the CMMR data, we cut follow-up time at a maximum of 10 years for the analysis, as patients usually participate in the follow-up programme for a maximum of 10 years; afterwards, only patients with progressive disease are regularly documented. Patients were classified according to Clark level [11] and Breslow thickness [12] and according to the 2009 American Joint Committee on Cancer (AJCC) Melanoma Staging and Classification System [13]. This classification was applied retrospectively for all patients diagnosed before 2009 and prospectively for all patients diagnosed thereafter. As in the 2009 staging system, mitotic rate was newly introduced for patients with tumour thickness <1.0 mm, further differentiation between T1a (without ulceration and mitosis <1/mm) and T1b (with ulceration or mitoses ≥1/mm) was not possible for patients diagnosed before 2009.

2.2. Analysis

Overall survival (OS) was estimated according to the Kaplan–Meier method for patients with a follow-up >3 months (n = 265). Patients were evaluated from the time of histologic diagnosis up to latest follow-up or death for overall survival (OS). The log-rank test was used to compare the survival curves in patient subgroups. P-values <0.05 from two-sided testing were considered as indicating statistical significance. In this exploratory analysis no adjustment for multiple testing was employed. The univariate analysis to ascertain the potential impact of prognostic factors could not be supplemented by a Cox regression approach incorporating simultaneously multiple prognostic factors due to a high amount of censored data (95%). All statistical analyses were performed with the statistic software package SAS.

3. Results

3.1. Patient and tumour characteristics

Patient and tumour characteristics are shown in detail in Table 1. The male to female ratio was 0.8 (202 male, 240 female). Age at diagnosis ranged from 3 months to 18 years, with a median age of 16 years, only 38 patients were <10 years of age. Three cases of infantile melanoma were identified (<1 year of age). Six patients (3.8%) had a family history of melanoma, eight patients (2.0%) presented with multiple melanoma at time of diagnosis and 10 patients (2.4%) with melanoma as second disease. Most melanoma were located at the trunk (n = 195, 44%) and the lower extremity (n = 141, 32%). Male patients mainly developed melanoma on the trunk (n = 102, 50.5%), while female patients mainly presented with melanoma at the lower extremities (n = 121, 50.4%). One patient with ocular melanoma was reported. Eight patients developed a melanoma on a congenital nevus, 110 patients (33.0%) presented with melanoma on nevus cell nevus. Approximately, half of the cases (n = 228) showed a histology of a superficial spread melanoma, 66 (15%) cases were classified as nodular type. Fifteen out of 78 patients from the University Hospital Tuebingen presented with spitzoid melanoma. None of the patients with spitzoid melanoma died, whereas seven out of 65 patients with non-spitzoid melanoma were noted to have a melanoma specific death. The median tumour thickness was 1.28 mm (range 0–11 mm); most children presented with thin lesions (Breslow thickness till 1.00 mm 60.3%, 1.01–2.00 mm 17.6%, >2.00 mm 16.5%) and Clark level I–III (Clark level I, II, III 63.9%, Clark level IV, V 29.3%). Most patients (n = 412) presented with local disease; only two patients showed in-transit metastases, three patients distant metastases and 25 patients spread into regional lymph nodes. According to the AJCC system, 310 patients (70.0%) were in stage I, 63 stage II (14.2%), 27 stage III (6.1%) and 3 stage IV (0.7%). For 40 patients no exact classification in stages was possible. In 330 patients the tumour could be primarily completely resected, 57 patients received incomplete resection (56 patients with unknown resection status). Sentinel lymph node biopsy (SLNB) was performed in 69 (16%, from 1996 onwards) patients by individual decision of the treating physician, but not routinely. Out of these patients 12 (17%) showed a positive sentinel lymph node (see Table 3). No increase of registered cases was seen over consecutive time periods.

3.2. Patient and tumour characteristics in case of melanoma on congenital nevus

Eight patients developed a melanoma on a congenital nevus. The female/male distribution was 1/1.7. One patient was 21 months old at the time of diagnosis, the other patients were between 14 and 18 years old. All tumours were located at the back, except one on the breast and one in the face. Tumour thickness was 0–1.0 mm for four patients, 1.01–2.00 mm for three patients; all patients were Clark level III, except one patient with Clark level IV; for one patient no information on tumour thickness and Clark level was available. All tumours could be resected completely; no lymph node involvement was seen. Three patients were lost to
follow-up; the other five patients are alive without disease (median follow-up: 113 months).

### 3.3. Patient and tumour characteristics in case of positive sentinel lymph node

Sentinel lymph node biopsy was performed in 69 patients. Out of these twelve patients 17% showed positive sentinel lymph nodes at the time of diagnosis and were classified as stage III melanoma. For characteristics of these patients see Table 3. Patients with a positive SLNB presented with thicker tumours compared to the whole group of patients (n.s.), most showed Clark level IV. All primary tumours could be resected completely. Most patients showed a single positive lymph node, one patient four positive lymph nodes and one patient 6. Half of the patients received a radical lymph node dissection. The median follow-up accounted for 15.3 months. Until now, one patient with a single positive lymph node and without lymph node dissection died 53 months after diagnosis and the patient with six positive lymph nodes died 11 months post melanoma diagnosis. Two patients with a single positive lymph node are alive after 21 and 99 months respectively. Unfortunately, the other seven patients with a single positive lymph node and the one patient with four positive lymph nodes were lost to follow-up.

### 3.4. Survival and prognostic factors

Overall survival (OS) at 5 years of all paediatric patients with melanoma was 94.8%. Univariate analysis is shown in Table 2. Because of the relatively small series and low number of deaths, the analysis was limited. 5-year OS was significantly lower in patients with nodular melanoma (OS 77.9%, n = 42), than in patients with superficial spread histotype (OS 100%, n = 138) or other histotype (OS 96.9%, n = 88) (p < 0.0001). OS was also worse in case of thicker tumours (Clark level IV or V, OS 87.1%, n = 84) than thinner tumours (Clark level I, II, III, OS 99.1%, n = 164) (p = 0.0008) and in case of ulceration (OS 65.6%, n = 17) compared to no ulceration (OS 99.2%, n = 182). Survival according to tumour stage was 98.5% for patients in stage I (n = 190), 91.1% for patients in stage II (n = 39) and 53.0% for patients in stage III/IV (n = 11) (see also Fig. 1). No significant difference in survival was seen for gender, age group and tumour site.
4. Discussion

We present the so far largest series on prospectively registered paediatric patients with malignant melanoma. Over a time period of nearly 30 years 443 paediatric patients were registered with the German Central Malignant Melanoma Registry (CMMR). At the same time a total number of 92,162 patients with invasive melanoma were reported to the registry. Therefore the paediatric cases account for 0.55% of registered patients.

Our series confirms the rarity of melanoma in childhood. In the United States malignant cutaneous melanoma under the age of 20 years account for approximately 1% of all melanoma cases, the incidence rate is reported to be 6.0/1,000,0000 [14]. Rates have been increasing significantly by 2–3% per year in adolescents and adults, but not in children <10 years, in Northern America and Europe over the last decades [5,14–16]. This trend was mainly seen for sun-exposed areas of the body (face and trunk for boys and lower limbs and hip for girls) and regions with high UV exposure [14]. Interestingly, very recent reports from Australia and Sweden could see a decrease of melanoma cases after the launch of sun protection education campaigns [3,17]. In our series no significant change in number of registered cases was seen over time.

Previous series on paediatric malignant melanoma report 5-year overall survival rates of 70–89% [7,18–23]. In contrast, in our study, overall survival after 5 years for 265 patients with adequate follow-up was 94.8% (compared to 90.8% 5-year SUR in adult patients, CRMM registry, unpublished data). Other than most previous reports published by paediatric oncologists, though, these patients were diagnosed and treated by dermatologists. Better survival rates in our series may be explained by differences in the clinical presentation of patients seen by dermatologists and large paediatric oncology centres worldwide. It can be suspected that children with diagnosis of advanced melanoma are more often seen in a Children’s University Hospital than young patients with small easily resectable melanomas, which are predominantly treated in dermatological outpatient settings. Therefore, an under-estimation of advanced paediatric melanoma, treated in paediatric haematooncological clinics could be present in the CRMM, favouring children with primary melanoma. Children with typical melanocytic lesions are probably referred to a dermatologist, while patients with...
atypical lesions mimicking for example pyogenic lesions or warts or patients with advanced disease might be primarily seen by paediatricians. As our patients were treated by dermatologists the tumour presentation is likely to differ from those seen in children’s hospitals.

Ferrari et al. estimate that only one in ten adolescents with melanoma are treated in paediatric oncology centres in Italy [24]. Brecht et al. recently published a series of rare paediatric tumours registered with the German Childhood Cancer Registry (GCCR) [25]. Between 2001 and 2010 a total number of 55 cases of paediatric melanoma were registered. We assume that this is a second smaller cohort of patients, who were treated by paediatric oncologists and registered with the GCCR, but not with the CMMR.

Several reports on paediatric malignant melanoma describe specific characteristics of childhood melanoma, especially for patients under the age of 10 years (e.g. thicker lesions, nodular histotype, advanced stage, amelanotic tumours) [7,10,24,26–28]. Cordoro et al. suggested modifying the commonly used ABCD detection criteria for malignant melanoma as it might be inadequate in childhood [28]. First analysis on childhood melanoma risk factors reports that the number of melanocytic nevi, a tendency to freckle, the presence of congenital nevi, immunosuppression, xeroderma pigmentosum and other cancer predisposition genes influence the occurrence of malignant melanoma [29,30]. Also survivors of childhood cancer, especially hereditary retinoblastoma, soft tissue sarcoma, Hodgkin lymphoma and gonadal tumours have an increased risk to develop malignant melanoma [31].

The distribution of the patient and tumour characteristics in our study showed no evident differences to adult melanoma patients as described as follows [32]. We report a male: female ratio of 0.84. The prominent anatomic site in male patients was the trunk (50.5%), while female patients mainly presented with melanoma of the lower extremities (50.4%). Most children presented with thin lesions (median tumour thickness 1.28 mm; 60.3% of all patients had a tumour thickness of less or equal than 1.00 mm) and Clark level I-III (Clark level I, II, III 63.9%). Superficial histotype was found in 51.5%, nodular histotype in 14.9% of cases. Most patients presented in stage I (70.0%). Though our series of paediatric patients cannot be compared with previous adult series statistically, these findings are consistent with earlier reports on characteristics of adult melanoma registered with the CMMR [33]. Therefore our study fails to detect differences between particular clinical features of paediatric melanoma.

Several prognostic factors like Breslow tumour thickness, Clark level and tumour stage reported for the adult population have been found to influence prognosis in children, too [9,20,24]. We could confirm a significant worse outcome in patients with thicker tumours, in advanced tumour stage, with ulceration of the tumour or nodular melanoma compared to superficial spread histotype or other histotype.

Our series does not give any evidence for the need of a different clinical approach in children than in adults. Sentinel lymph node biopsy (SLNB) was performed in 69 patients from 1996 onwards by individual decision of the treating physician, but not routinely. As we
identified only 12 patients with positive sentinel lymph node (17.3% of a total of 69 patients with SLNB), and the median follow-up time was no more than 15.3 months, no definite conclusion could be drawn in terms of SLNB. Recent reports stress the importance of sentinel lymph node biopsy in children, especially in case of thick lesions (≥1.00 mm) and ulceration [23,24]. Mu et al. found significantly more positive lymph node biopsies in these children with thick or ulcerated lesions than in adults [23]. Our series also gives the impression that we see thicker tumours in case of a positive sentinel lymph node (Table 3).

In conclusion, data of our large series on prospectively registered paediatric patients with malignant melanoma suggest using the same clinical approach in children as used for adults [34]. After clinical diagnosis the melanoma should be resected with one to two centimetre safety margins. For staging the AJCC system is used. Sentinel lymph node biopsy should be offered in patients with more than 1 mm in thickness. With the goal of gaining further evidence for the diagnosis and treatment of paediatric melanoma, a close cooperation between experts in adult melanoma (Center for Dermatooncology, Department of Dermatology and Central Malignant Melanoma Registry of the German Dermatological Society, University Hospital Tuebingen), reference pathologists of the German Society of Pediatric Oncology and Hematology and of the German Dermatological Society and paediatric oncologists (German Pediatric Rare Tumor Registry, STEP) has been set up in Germany. As histological diagnosis in children is difficult and borders between true malignant melanoma and MELTUMP are not sharply defined, yet, for all patients registered with STEP a reference pathology review and comparative genomic hybridisation (CGH) method are performed [35]. A joint data base was established with the goal of registration of all rare cases of paediatric malignant melanoma in Germany in future. Only an interdisciplinary approach can ensure to draw a realistic picture of the whole spectrum of paediatric malignant melanoma and avoid wrong conclusions because of selection bias.

Conflict of interest statement

None declared.

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References


