



# Children with malignant melanoma: a single center experience from Turkey

Çocuklarda malin melanom: Türkiye'den tek merkez deneyimi

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## The known about this topic

Malignant melanoma is very rare in childhood and it comprises 1–3% of all malignancies in children and adolescents. Adolescents 15–19 years of age account for 73.2% cases of pediatric melanoma. Because of its rarity in children, the approach to diagnosis and treatment in pediatric melanoma has been adopted from adult guidelines.

## Contribution of the study

In the literature there are few studies reporting treatment results in children with melanoma. In our study only patients <15 years of age were included and their demographic characteristics, pathological features, treatment details, response to treatment and follow up data were assessed. Albeit the limited number of patients, it is the largest malignant melanoma series reported in children in our country.

## Abstract

**Aim:** Malignant melanoma is the most frequent skin cancer in children and adolescents. It comprises 1–3% of all malignancies. In this study, we aimed to evaluate the clinical aspects, histopathologic features, and treatment outcomes of our patients with malignant melanoma.

**Material and Methods:** Patients aged <15 years who were treated between 2003 and 2018 for malignant melanoma were retrospectively analyzed.

**Results:** Seventeen patients (10 females, 7 males), with a median age of 7 years (range, 7 months–13 years) were evaluated. Five patients had congenital melanocytic nevi. All had cutaneous melanoma except one with mucosal (conjunctival) melanoma. The most frequent primary tumor site was the lower extremities (35%). Sentinel lymphoscintigraphy, sentinel node biopsy, and PET/CT were performed as the staging procedures at initial diagnosis. Localized disease was present in eight patients; nine had regional lymph node metastasis. The only treatment was surgery in localized disease; surgery and adjuvant interferon treatment was given in patients with regional lymph node metastasis. Three developed distant metastasis (bone, lung, brain) at a median of 9 months. A three-year-old patient received a BRAF inhibitor (vemurafenib), and a 13-year-old patient received a check point inhibitor (ipilimumab); both died of progressive disease. The median follow-up for all patients was 25 months. The 5-year overall survival was 76.6%.

## Öz

**Amaç:** Malign melanom, çocukluk çağının en sık cilt kanseridir. Çocuk ve ergen yaş grubu tüm kanserlerin %1–3'ünü oluşturmaktadır. Bu çalışmada merkezimizdeki malign melanom tanılı hastalarımızın klinik, histopatolojik özellikleri ve tedavi, izlem sonuçlarını değerlendirmeyi amaçladık.

**Gereç ve Yöntemler:** Kliniğimizde 2003–2018 yılları arasında malign melanom tanısı ile tedavi ve izlemi yapılan 15 yaş altı hastalar geriye dönük olarak incelendi.

**Bulgular:** On yedi hasta (10 kız, 7 erkek) değerlendirildi ve yaş ortalamaları 7 yaş (7 ay–13 yaş) idi. Beş hastada doğuştan melanositik nevüs vardı. Melanom tipi bir hasta (mukoza, konjontiva) dışında cilt melanomu idi. İlk yerleşim yeri en fazla (35%) alt ekstremitede idi. Tanıda nodal evreleme amaçlı sentinel lenfosintigrafi ve sentinel lenf nodu biopsisi ile sistemik değerlendirme PET/CT ile yapıldı. Tanıda sekiz hastada lokalize hastalık, 9 hastada bölgesel lenf nodu metastazı vardı. Bölgesel olgularda sadece cerrahi, bölgesel lenf nodu metastazlı hastalara ayrıca interferon tedavisi uygulandı. Üç hastada ortanca 9 ayda uzak metastaz (kemik, akciğer, beyin) görüldü. Bu hastalardan 3 yaşındakine BRAF inhibitör (vemurafenib) ve 13 yaşındakine “check point” inhibitör (ipilimumab) verildi, iki hastada ilerleyici hastalıkla kaybedildi. Tüm hastalar ortanca 25 ay izlendiler. Hastaların 5 yıllık genel sağ kalımı %76,6 bulundu.

Cont. ➔

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**Conclusion:** Although malignant melanoma is rare in children, prognosis is good if diagnosed early. Physicians should be aware of skin lesions and full-layer biopsy should be obtained in suspicious skin lesions. Patients with congenital melanocytic nevi should also be followed up cautiously.

**Keywords:** Children, immunotherapy, malignant melanoma

**Çıkarımlar:** Çocukluk çağı melanomları nadir olsa da erken tanıda sonuçlar iyidir. Klinisyenlerin cilt lezyonlarında uyanık olmaları ve şüpheli lezyonlardan tam kat biyopsi alınması önemlidir. Doğuştan melanositik nevüsü olan hastalar da melanom açısından dikkatli takip edilmelidirler.

**Anahtar sözcükler:** Çocuk; immunoterapi, malign melanom

## Introduction

Malignant melanoma (MM) primarily occurs in adults; approximately 2% of all melanomas occur in children and adolescents (1). Melanoma most commonly arises from the skin with only a small minority of patients designated as having ocular, mucosal surfaces, and visceral organs (2). Due to melanoma's rarity in children, the approach to diagnosis and treatment in pediatric patients has been adopted mostly from adult guidelines. Recently, several studies have focused on the clinical characteristics, pathologic features, systemic therapy, and survival rates of pediatric patients with melanoma in an effort to increase our knowledge (2–8).

In this study, our aim was to evaluate the demographic characteristics, treatment, and outcomes of children with MM in our center.

## Material and Methods

Seventeen children aged <15 years who were diagnosed as having and treated for MM between 2003 and 2018 were retrospectively evaluated. Their demographic characteristics, pathologic features, treatment details, response to treatment, and follow-up data were assessed.

Patients diagnosis, stage, and treatment were adopted from adult guidelines. The American Joint Committee on Cancer (AJCC) staging system was used (9). Sentinel lymphoscintigraphy, sentinel node biopsy, and positron emission tomography (PET/CT) were performed as the staging procedures at initial diagnosis. In localized disease, surgery was the only treatment. Sentinel lymph node biopsy or dissection was performed in patients either with positive or suspicious findings in lymphoscintigraphy or with Breslow thickness >1 mm or if positron emission tomography – computed tomography (PET-CT) revealed metastasis to the lymph nodes. High-dose interferon alfa 2b (IFN alfa2b) (nine million units/day, three days per week, subcutaneous) was used as adjuvant treatment in patients with positive sentinel lymph nodes, after local surgery and lymph node dissection. Patients with distant metastasis and patients who relapsed received systemic chemotherapy; they received immunotherapy if they had no response or had further progression with approval of the Ministry of Health for reimbursement.

**Table 1. Patients and tumor characteristics**

Number of patients	17
Number of patients	17
Sex, female/male	10/7
Age, median (year)	7
Body site	
Trunk	3 (17.6%)
Head/neck	4 (23.5%)
Upper extremities	4 (23.5%)
Lower extremities	6 (35%)
Congenital nevi	5 (29%)
Histopathologic features	
Breslow thickness (median), mm	3.4 (1.5–15)
Mitotic index (median)/mm <sup>2</sup>	4 (0.5–23)
Ulceration	10 (58.8%)
AJCC	
I	2 (11.8%)
II	6 (35.2%)
III	9 (53%)
IV	0

AJCC: The American Joint Committee on Cancer

The study was conducted in accordance with the principles of the Declaration of Helsinki. Approval was obtained for the study from the local ethics committee of our hospital (October 27, 2017; Decision number: 404098). Written informed consent was obtained from the parents of all patients.

## Statistical Analysis

All analyses were performed using the SPSS 21.0 software (SPSS Inc., Chicago, IL, USA). The Kaplan-Meier test was used to calculate overall survival (OS). Overall survival was defined as the time from the date of histologic diagnosis to death or the last follow-up.

## Results

Twenty children with MM were assessed, three patients who were only consulted and referred to other centers were excluded. Thus, 17 (10 females, 7 males) children were included in our analysis (Table 1). Sixteen had cutaneous melanoma and one had mucosal (conjunctival) melanoma. The median age was 7 years (range, 7 months–13 year), 10 patients were aged younger than 10 years and six were aged younger than four years.



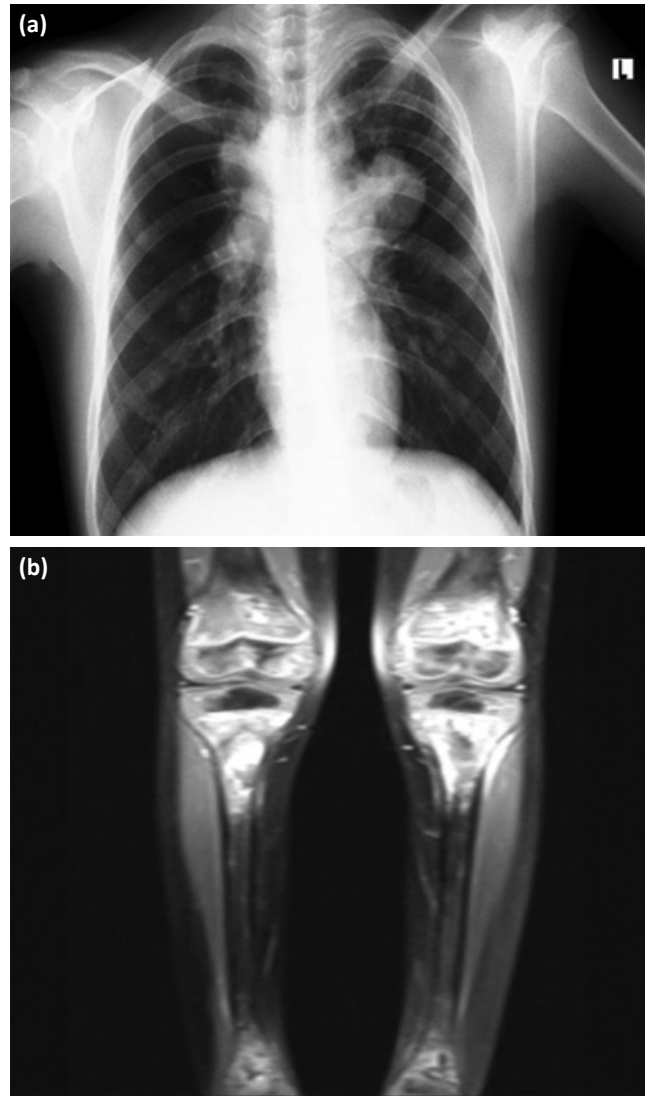
**Figure 1.** A patient with congenital melanocytic hairy nevus

The most frequent primary tumor site was the lower extremities (n=6, 35%) followed by the upper extremities (n=4, 23.5%), the head and neck (n=4, 23.5%), and the trunk (n=3, 17.6). Five patients (29%) had spitzoid melanoma and in five children developed MM in the site of the congenital nevus (Fig. 1).

The median Breslow thickness was 3.4 (range, 1.5–15) mm, and Clark level IV predominated (41%). Median mitotic index was 4 (range, 0.5–23) /mm<sup>2</sup> and ulcerated melanoma was found in 58.8% of lesions. Localized disease was present in eight patients; nine had regional lymph node metastasis at diagnosis. Three developed distant metastasis (bone, lung, brain) during follow-up (Fig. 2). According to the AJCC system, two patients (11.8%) were stage I, six (35.2%) were stage II, and nine (53%) were stage III at the initial diagnosis.

#### Treatment

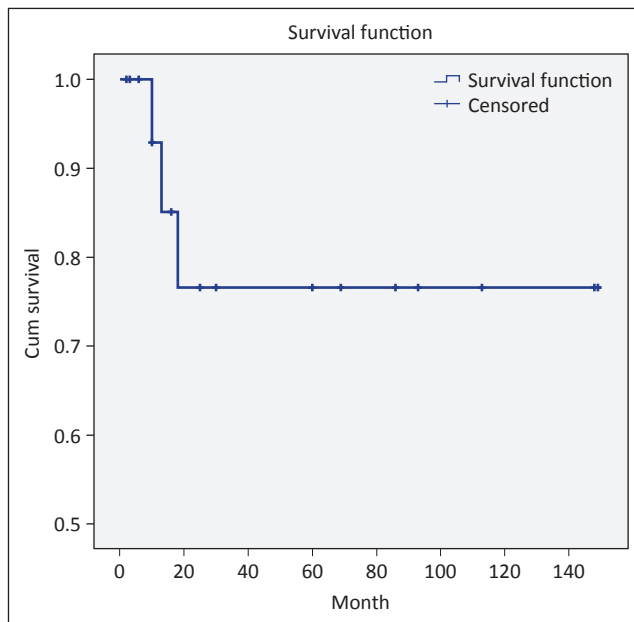
The only treatment was primary tumor resection with adequate safety margins in eight (47%) patients with localized disease. Local surgery with adequate safety margins and sentinel lymph node biopsy or dissection with adjuvant high-dose interferon (IFN) alpha 2b for one year was used in nine patients (53%) with regional lymph node metastasis. Adverse effects with IFN alpha 2b were fever



**Figure 2.** T Appearance of the lung metastasis on postero-anterior lung X-ray (a) and appearance of the multiple long bone metastasis on lower extremity magnetic resonance imaging (b)

and chills for one to two days following injection, and in one patient vitiligo was seen four months after the initiation IFN alpha 2b and continued during IFN treatment.

Despite adjuvant therapy with IFN alpha 2b, one patient whose MM had developed in the site of the large congenital hairy nevus, presented with regional lymph node metastasis 10 months after initiating IFN. This patient underwent local excision and temozolomide was initiated (200 mg/m<sup>2</sup>/dx5 days every 28 days); however, after six weeks he presented with multiple bone metastasis. His BRAF mutation testing was positive for V600K/E/R in the tumor and he was treated with vemurafenib. Upon approval of the Ministry of Health for reimbursement, vemurafenib therapy was started at a dose of 240 mg (375



**Figure 3. Overall survival rate of 17 children with malignant melanoma**

mg/m<sup>2</sup>) twice daily. One month later he died of progressive disease (10).

A patient with conjunctival melanoma who was under follow-up developed distant metastasis in the preauricular lymph nodes, bone, and lung, one year after diagnosis. His BRAFV600E mutation was negative. He was given temozolomide (200 mg/m<sup>2</sup>/dx5 days every 28 days) p.o as the first-line therapy; due to further progression he received immunotherapy (ipilimumab) as second-line upon receiving approval of the Ministry of Health for reimbursement, and palliative radiotherapy to some metastatic bone sites due to intractable pain. He died of progressive disease 19 months after diagnosis.

#### Overall survival

The median follow-up for all patients was 25 (range, 2–149) months. Three patients developed distant metastasis at a median of nine months after diagnosis and they died at a median of four months after metastasis. Two of the three patients who had distant metastasis were BRAFV600E mutation-negative. Two patients who died (age 7 months, age 3 years) due to distant metastasis had large congenital melanocytic nevus.

In all patients, the 3 and 5-year OS was 76.6%; in children aged ≥10 years, the 3 and 5-year OS was 83.3% (Fig. 3).

#### Discussion

Pediatric melanoma accounts for less than 3% of pediatric cancers during childhood and adolescence (11). The

low incidence of pediatric melanoma and the lack of classic melanoma criteria may be the reason for the delay in diagnosis (12). Due to its rarity, clinical experience of all pediatric patients with melanoma receiving treatment either as compassionate use or within a trial or multicenter experience should be reported such that our knowledge on the demographic characteristics and effect-adverse events of therapeutic characteristics accumulates.

In our study, there were more female patients (58.2%) than males. In previous pediatric series, in some there was female predominance (2, 3, 8, 13), in others a male predominance (4, 5).

In the literature, adolescents aged 15–19 years account for most cases of pediatric melanoma (73.2%); 17.3% were in patients aged 10 to 14 years, 5.7% were in children aged 5 to 9 years, and 1- to 4-year-old children accounted for only of 3.8% of cases (2). In our study, only patients aged <15 years were evaluated, patients ≥15 years of age were treated and followed up by medical oncologists (14).

In previous pediatric studies, congenital melanocytic nevi have been reported as constituting 1.5–16% of MM cases (3–5, 13). In our study, five (29%) patients had congenital melanocytic nevi. The lifetime risk for melanoma in giant congenital nevi is estimated to be between 5% and 10%, with most reported cases occurring during the first five years of life (15). The median age of our five patients with congenital nevi was 3 years (7 months–7 years). A study on the pathologic pattern of giant congenital nevi suggested that the presence of severely atypical epithelioid-shaped melanocytes with high mitotic count, such as >5 mitoses/mm<sup>2</sup>, with ulceration and partial chromosomal copy number changes by molecular studies, were features that should raise greatest concern for the possibility of developing melanoma (16). In two of the five patients with large congenital melanocytic nevus in our cohort, both of whom died, the median mitoses in the tumor was 22/mm<sup>2</sup> with ulceration (range, 20–23/mm<sup>2</sup>), in the other three with small congenital melanocytic nevus, median mitoses was 3 (range, 2–3)/mm<sup>2</sup>. In SEER data in adults, superficial spreading and nodular melanomas were common, none had a congenital nevus (17). Childhood melanoma may not behave biologically like its adult counterpart, so in clinical practice, dermatologists, pediatric oncologists, and plastic surgeons should be aware of congenital nevi appearance and pathologic features because they have significant predictive capabilities for patient prognosis and survival.

In most of our patients, the primary site was the extremities (58.8%), similar to other studies (3, 4). The trunk has

been reported as a more frequent site in patients aged >10 years (2, 8, 13). In adults, it is estimated that 84% of patients with melanoma present with localized disease (stage I-II), 9% with regional (stage III), and 4% with distant metastatic disease (18). According to the AJCC system, 47% of our patients presented with localized disease and 53% presented with regional disease without distant disease at initial diagnosis. According to the American National cancer database, it has been reported that young children have an increased incidence of advanced disease (2). Possible reasons include delayed diagnosis or age-related differences in biologic behavior that are not yet understood. The clinical and pathologic characteristics of melanoma in children can make diagnosis difficult (2).

In some reports, survival rates differed in childhood and adolescents. The 3 and 5-year OS in all patients in our study was 76.6%. The outcome in children aged  $\geq 10$  years was higher numerically than in younger patients (83.3% vs. 73%); however the number of patients was too limited for statistical analysis. In Ferrari et al. (5) Italian rare tumors project, the 5-year event-free survival (EFS) was worse in patients younger than 14 years than in older patients (64.6% vs. 94.7%). Lange et al. (2) also reported that in the American National cancer database, the OS of all stages was worse for children aged 1–9 years than for older patients (77% vs. 87%). However, other studies reported better outcomes of melanoma in childhood (aged <10 or <14 years) compared with adolescents (in the range of 92–100% vs. 89–94%) (3, 4, 8, 13). In adults, 5-year survival has been reported as more than 90% in localized disease, between 20–70% in stage III, and less than 10% in patients with metastasis (9). It is unknown whether age reflects a crude surrogate of declining immune competence, or other comorbidities, or differences in the biologic behavior of melanoma in patients of different age groups (19).

Surgery with adequate margins is the recommended treatment for patients with localized melanoma. Sentinel lymph node biopsy should be considered in patients with thin lesions ( $\leq 1$  mm) with ulceration, mitotic rate greater than  $1/\text{mm}^2$ , young age, and in patients with lesions larger than 1 mm with or without adverse features. If the sentinel lymph node is positive, the option to undergo a complete lymph node dissection should be discussed (20). In pediatric patients, adjuvant therapies have been adopted from adult guidelines (20). The National Comprehensive Cancer Network (NCCN) recommendation management options for completely resected stage III melanoma in adults are high-dose or PEGylated IFN or high-dose ipilimumab (21). In children and adolescents with surgically resected, histologically proven, stage III melanoma

involving regional lymph nodes receiving adjuvant IFN (high-dose and PEGylated) therapy, the survival and EFS at 20 months were reported as  $90.9 \pm 9.1\%$  and  $74.1 \pm 14.3\%$ , respectively, in one study (22) and three-year estimates of OS and EFS were  $95.2 \pm 5.8\%$  and  $91.3 \pm 7.5\%$ , respectively, in the other study (23). In our patients, adjuvant therapy with high-dose IFN was used in 47% of cases ( $n=8$ ).

Two of our patients received BRAF inhibitor or ipilimumab at recurrence. However, none had a response and they died of progressive disease. Although the safety of ipilimumab (anti-CTLA-4) (7) has been established in pediatric patients with melanoma, there was no objective response to ipilimumab in 12 patients with unresectable stage IIIc or stage IV pediatric melanoma in a phase I clinical trial, thus the authors suggested that there was no role for single agent ipilimumab in pediatric tumors and recommended further pediatric studies with a combination with other checkpoint inhibitors or immune-modifying agents (7). We observed no response in our patient with ipilimumab either. In a phase II study in adolescents with unresectable stage III or IV malignant melanoma, ipilimumab was found to be safe and the objective response was 28.26% (2/12) (24). This phase II study was closed prematurely because of slow recruitment based on the rare study population, availability of ipilimumab off-protocol, and competing trials with emerging therapies such as anti-PD-1 antibodies, which made single-agent ipilimumab treatment less desirable for the patients and treating physicians (24).

The NCCN panel considers single-agent BRAF inhibitor monotherapy with vemurafenib as appropriate first-line systemic treatment options for metastatic disease with any type of activating BRAF mutation (V600E, V600K, V600R, and others) in adults. Objective responses have been reported in 48–53% of cases (21). Some authors suggested that due to the challenges with new therapies (e.g., ipilimumab, nivolumab, vemurafenib, trametinib), adjuvant IFN for high-risk pediatric patients deserves consideration (23). However, in a prospective study with vemurafenib in pediatric patients aged 12–17 years with surgically unresectable, BRAF mutation-positive stage IIIc or IV melanoma, there was no objective tumor response (6); we also observed no response in our patient (10).

In adults, systemic combination treatments for metastatic cutaneous melanoma is recommended because there is some evidence that combined treatments work better than single treatments: anti-PD1 monoclonal antibodies, alone or with anti-CTLA4, improved progression-free survival compared with anti-CTLA4 monoclonal antibodies alone; Anti-PD1 monoclonal antibodies performed bet-

ter than anti-CTLA4 monoclonal antibodies in terms of OS, and a combination of BRAF plus MEK inhibitors was associated with better OS for BRAF-mutated melanoma compared with BRAF inhibitors alone (25).

The limitation of our study is that it is a retrospective, single-institution study with a limited number of pediatric patients aged <15 years. Despite the limited number of patients, it is the largest series reported in children in our country and region.

## Conclusion

Although MM is rare in children, prognosis is good if diagnosed early. Physicians should be aware of skin lesions and full-layer biopsy should be obtained in suspicious skin lesions. Patients with congenital melanocytic nevi or dysplastic nevi should also be followed cautiously. Regarding BRAF and checkpoint inhibitors in treatment of children with advanced stage melanocytic melanoma, further international multicenter studies that reach larger numbers of patients are needed.

**Ethics Committee Approval:** The study was conducted in accordance with the principles of the Declaration of Helsinki. Approval was obtained from Istanbul University Oncology Institute local ethics committee (27.10.2017/2017-509).

**Informed Consent:** Written consent was obtained from the parents of all patients.

**Peer-review:** Externally peer-reviewed.

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