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Second cranio-facial malignancies in hereditary retinoblastoma survivors previously treated with radiation therapy: Clinic and radiologic characteristics and survival outcomes

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Abstract ***Introduction:*** Hereditary retinoblastoma survivors have an increased risk for cranio-facial second primary tumours (SPT), especially after treatment with external beam radiotherapy (EBRT). This multicentre study evaluates the clinical and imaging characteristics and outcomes of cranio-facial SPTs in irradiated retinoblastoma survivors.
Patients and Methods: Clinical and radiological data of 42 hereditary retinoblastoma patients with 44 second and third malignancies were reviewed. Radiological data included anatomic location and computed tomography (CT) and magnetic resonance (MR) characteristics.

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Radiation induced tumours

Cox regression and likelihood ratio chi-square test were used to evaluate differences in patients' survival rates.

Results: Cranio-facial SPTs were diagnosed at a median age of 13 years. Histological types included osteosarcomas (43%), rhabdomyosarcomas (20%) (57% embryonal, 43% alveolar) and a variety of other types of SPT (37%). Predilection sites were: temporal fossa (39%), ethmoid sinus (23%), orbit (18%), maxillary sinus (16%) and intracranial dura mater (4%). Most of the osteosarcomas (78%) and rhabdomyosarcomas (80%) occurred in patients treated with EBRT in the first year-of-life. Treatment of SPTs with a microscopically complete surgical resection led to a significantly better 5-year overall survival (OS) ($P = 0.017$) and event-free survival (EFS) ($P = 0.012$) compared to patients treated without surgery or incomplete resection (OS: 83% versus 52%; EFS: 80% versus 47%).

Conclusions: Osteosarcomas and rhabdomyosarcomas are the most common cranio-facial SPTs in irradiated hereditary retinoblastoma survivors, which develop in specific locations and occur predominantly in patients irradiated in their first year-of-life. Microscopically complete surgical resection of SPTs is a major prognostic factor, suggesting the potential benefit of early detection by imaging.

1. Introduction

Hereditary Rb survivors are at greater risk of developing second primary tumours (SPTs)[1] because of *RB1*-gene germline mutation. In developed countries, SPTs are the leading cause of death in patients with hereditary Rb.[2–6]

The incidence of SPTs in hereditary Rb is 8.4% at 18-years and 36% at 50-years after diagnosis.[3,4,6–9] External beam radiotherapy (EBRT) increases the risk for subsequent malignant neoplasms, as up to 70% of SPTs in Rb patients develop inside or at boundaries of the irradiation field.[3,4,6,10–14] The age of Rb-diagnosis and subsequently age of irradiation is an additional risk factor: patients irradiated during the first year of-their-life develop two to eight times more SPTs than patients irradiated after one year.[15–17] The combination of EBRT and chemotherapy in hereditary Rb patients also slightly increases the risk for SPT development compared to EBRT alone.[4] Most common histological types of SPT in irradiation fields are osteosarcoma, rhabdomyosarcoma, leiomyosarcoma, other soft tissue sarcomas, meningioma[12,13,18,19] and rarely carcinomas.[8,9]

Prognosis of cranio-facial SPTs in Rb survivors is poor despite aggressive treatment. One major prognostic factor of these tumours is the feasibility of complete resection of the SPT[20] and therefore early diagnosis is crucial.

Computed tomography (CT)- and magnetic resonance (MR) imaging features of Rb are well documented. To our knowledge however, except for case reports,[18,19] there is only one study[16] describing the spectrum of imaging characteristics of cranio-facial SPTs in Rb survivors.

This multicentre study evaluates the clinical and imaging characteristics and outcomes of cranio-facial SPTs in irradiated hereditary Rb survivors.

2. Patients and methods

2.1. Study population

This retrospective study originated from an international partnership of five Rb-reference centres European Retinoblastoma Imaging Collaboration (ERIC) from Paris, Essen, Lausanne, Siena and Amsterdam in agreement with the recommendations of each local ethics committee or institutional review board. Patient records from 1989 and 2010 were reviewed and SPTs were included by both ophthalmologists and oncologists from the Rb-reference centres. The following inclusion criteria were set: (1) a cranio-facial second or third malignancy in a hereditary retinoblastoma patient (confirmed by ocular funduscopy, imaging or histopathology), (2) EBRT for retinoblastoma, (3) availability of adequate CT or MRI of the SPT. Patients with either metastatic tumour, retinoblastoma recurrence or trilateral retinoblastoma were not included in the present study. Forty-four second and third malignancies in 42 patients were included in this retrospective study. In the majority of patients the EBRT planning designs could not be retrieved from the medical records and were not digitally available, therefore a clear definition of the radiation fields and boundaries is lacking.

2.2. Clinical data and primary retinoblastoma treatment

Clinical records were evaluated for patients' age (at time of Rb-diagnosis, EBRT treatment and SPT-diagnosis), presence of *RB1*-mutation, treatment of Rb and radiation dose. Patients with bilateral Rb, a positive family history of Rb or a *RB1*-gene mutation were classified as "hereditary". Symptoms associated with SPT at first presentation, histopathological type of SPT and treatment for SPT were also recorded. Delay of SPT-diagnosis was calculated as the time elapsed from onset

of symptoms to confirmation of SPT-diagnosis (imaging or biopsy). Surgical treatment was categorised as complete or incomplete microscopic resection. The definition of microscopic complete resection was based on both pathological and surgical information. Microscopic complete resection was defined as if (macroscopically) the whole tumour was resected, with free resection margins at histopathology without macroscopic residual tumour on follow-up imaging. Time-intervals were calculated from EBRT to SPT-diagnosis, and SPT-diagnosis to death or last follow-up date. Clinical data of part of this patient-cohort were previously reported.[4,6]

2.3. Imaging data and analysis

Only pre-treatment images of SPTs were assessed to avoid treatment effects. Thirty-three MR scans were available for review including unenhanced T1-weighted images in all patients and post-contrast T1-weighted images and T2-weighted images. In addition, 22 CT-scans were available for review including 18 contrast-enhanced CT-examinations. In 11 out of 44 tumours both MR and CT were available.

Images were scored for location of SPT and involvement of bones and muscles in the cranio-facial area. Tumour location was afterwards categorised in predilection sites based on the presumed origin of the SPTs; an anatomical compartment or structure which contained the majority of the tumour mass. Additional parameters included regarding tumour spread into neighbouring anatomical compartments and structures (e.g. spread into the paranasal sinuses, orbit, intracranial, cavernous sinus and pterygopalatine fossa), perineural spread, invasion through the skullbase and vessel encasement or invasion.

MRI and CT characteristics for SPTs included tumour border (ill- or well-defined), enhancement (homo- or heterogeneous) and necrosis (yes/no). SPTs on MRI were also evaluated for signal intensity (SI) as compared to normal muscles on T1- and T2-weighted images (hypo-, iso- and hyperintense) and on CT (hypo-, iso- and hyperdense) for calcifications and density of the tumour.

2.4. Statistics

All data were statistically analysed using SPSS, version 15.0 (SPSS, Chicago III). Meningiomas were excluded from the survival analysis. For event-free survival analysis (EFS), an event was considered as if a relapse of the SPT (local recurrence or metastases) or cranio-facial third primary tumour occurred. Cox regression was used to evaluate differences in EFS and overall survival (OS) in patients treated with or without complete microscopic tumour resection by the likelihood ratio chi-square test. The 95% confidence intervals (CIs) at 5-year survival were calculated for the EFS and OS. The association between complete microscopic tumour resection and complete disease remission was analysed by the likelihood ratio chi-square test. Differences between histopathological subtypes and age at SPT-diagnosis were analysed using analysis of variance.

3. Results

3.1. Clinical characteristics

Patient and treatment characteristics are described in Table 1. All patients had hereditary retinoblastoma. EBRT was performed at a mean age of 11 months, and before 1-year of age in 69% of patients. Data regarding EBRT dose were available in all but two patients. A mean dose of 45 Gy (range 40–50 Gy) was delivered in 15–25 fractions of 2 or 3 Gy. Fourteen patients (33%) also received chemotherapy. Chemotherapy regimen included cyclophosphamide in 10, vincristine in 11, actinomycin in four, carboplatin in two, etoposide in two and cisplatin in two patients. In one patient chemotherapy data could not be retrieved.

SPTs were diagnosed at a median age of 13 years (range, 3–38 years). TPT (two patients) occurred at a median age of 15 years. Mean time-interval from EBRT to development of SPT was 15 years with a range of 3–37 years. In our study population, EBRT performed within the first year-of-life led to SPTs after a mean interval of 14 years compared to 17 years when performed after the first year-of-life.

Delay of diagnosis between onset of symptoms to confirmation of SPT was 56 days (mean 256 days, range 6–707 days). The most frequent presenting symptom was local swelling (60%). Other symptoms included: local pain (14%), headache (19%), sinus symptoms (epistaxis [7%] and persisting rhinorrhoea [5%]), not-fitting eye-prothesis (10%), symptoms of intracranial hypertension (5%) and ptosis (5%).

3.2. Treatment of SPTs

Forty patients underwent treatment for SPT which included chemotherapy in 35 patients (88%), surgery in 25 patients (64%) (out of which only seven patients showed a microscopic complete tumour resection), EBRT in four patients (10%) and brachytherapy in three patients (8%). Two patients received only palliative care because of extensive tumour spread.

3.3. Clinical and radiological characteristics according to histopathological subtypes

The 44 cranio-facial SPTs and TPTs were categorised in the following five groups: osteosarcomas (17 SPTs and two TPTs), rhabdomyosarcomas (nine SPTs), other

Table 1
Patient characteristics of retinoblastoma patients with SPT.

Characteristic	No. patients ($n = 42$)
Hereditary retinoblastoma	42
Median age Rb-diagnosis in M (mean, range)	8 (10, 0–36)
Median age EBRT in M (mean, range)	10 (11, 1–37)
Median age SPT in Y (mean, range)	13 (15, 3–38)
Sex	
Male	19
Female	23
Positive *RB1*-gene mutation	35
Treatment Rb	
Enucleation eye	28
EBRT	42
Unilateral	28
Bilateral	14
Chemotherapy	14
EBRT in first year-of-life	29

Rb = retinoblastoma, M = months, Y = years.

sarcomas, carcinomas and miscellaneous tumours (16 SPTs) (Table 2). Imaging characteristics for osteosarcomas and rhabdomyosarcomas are summarised in Table 3.

More osteosarcomas and rhabdomyosarcomas were found in Rb survivors treated with EBRT within the first year-of-life compared to EBRT after the first year-of-life although this difference was not significant ($P = 0.07$). The median age of occurrence of SPT was significantly younger for the two major histological types ($P = 0.008$ for osteosarcomas and $P = 0.003$ for rhabomyosarcomas) than for the others. In the subgroup of 14 patients treated with a combination of EBRT and chemotherapy, no significant correlations were found regarding histopathology, age at presentation or predilection sites of SPTs compared to patients treated for Rb with EBRT alone.

Table 2
Histopathology and age at diagnosis of 44 second and third primary tumours.

Histopathological subgroups	Number	Median age in years (mean, range)
Osteosarcoma	19	13 (14, 5–20)
Rhabdomyosarcoma	9	11 (11, 5–22)
Other sarcomas	8	22 (23, 15–36)
Leiomyosarcoma	2	
Undifferentiated sarcoma	5	
Liposarcoma	1	
Carcinomas	5	16 (19, 7–38)
Sebaceous gland carcinoma	1	
Undifferentiated spindle cell carcinoma	3	
Sinonasal neuroendocrine carcinoma	1	
Miscellaneous	3	11 (14, 3–28)
Meningeoma	2	
Esthesioneuroblastoma	1	

Table 3
Computed tomography (CT) and magnetic resonance (MR) imaging characteristics of osteosarcoma and rhabdomyosarcoma in %.

	Osteosarcoma	Rhabdomyosarcoma
Mean TV in cm^3(range)	107 (0.4–411)	91 (12–330)
Border		
Well-defined	88 (23)	100 (10)
Ill-defined	12 (3)	0
Necrosis		
Yes	65 (17)	50 (5)
No	27 (7)	50 (5)
NA	8 (2)	0
EP		
Homogeneous	4 (1)	15 (2)
Heterogeneous	86 (22)	75 (7)
NA	12 (3)	10 (1)
SI T1-W (MR)		
Hypointense	21 (3)	0
Isointense	71 (10)	100 (8)
Hyperintense	7 (1)	0
SI T2-W (MR)		
Hypointense	21 (3)	0
Isointense	7 (1)	25 (2)
Hyperintense	64 (9)	75 (6)
NA	7 (1)	0
Density (CT)		
Hypodense	17 (2)	50 (1)
Isodense	17 (2)	50 (1)
Hyperdense	25 (3)	0
NA	42 (5)	0
Calcifications (CT)		
Yes	50 (6)	50 (1)
No	33 (4)	50 (1)
NA	17 (2)	0

TV = tumorvolume, EP = enhancement pattern, SI T1-W = signal intensity on T1-weighted images SI T2-W = signal intensity on T2-weighted images, (absolute values in brackets), NA = not available.

Tumour origin was subdivided into five predilection sites; temporal fossa (39%), ethmoid sinus (23%), orbit (18%), superior maxillary (16%) and intracranial dura mater (4%).

3.4. Osteosarcoma

Osteosarcoma was the most frequent histological subtype (43%, 19/44), including two TPTs. Fourteen osteosarcomas (78%) developed in patients treated with EBRT within the first year-of-life. Median age for osteosarcoma diagnosis was 13 years (range, 5–20 years). The orbit (36%) (Fig. 2) and temporal fossa (36%) were the predilection sites in this group, Fig. 1. In patients with osteosarcomas with EBRT after the first year-of-life, the temporal fossa (50%) was mostly affected. All osteosarcomas in the maxillary sinus and 83% in the orbit were also present in this group. Nine out of 18 patients (50%) with osteosarcoma died (mean interval,

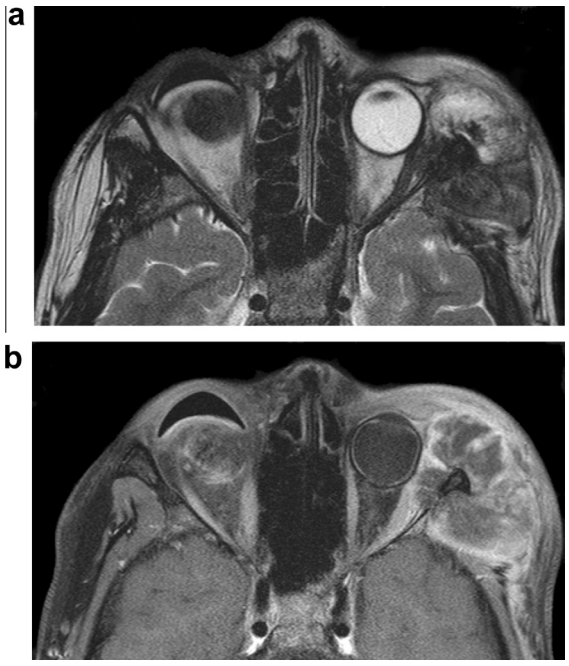

Fig. 1. Typical location of osteosarcoma originating from the lateral orbital wall (greater wing of the sphenoid) and temporal bone with extension into the temporal fossa in a 12 years-old girl with bilateral retinoblastoma. The tumour was treated with chemotherapy only after parental refusal for surgery. This girl died 3 years after diagnosis due to local disease progression.

65 months) and 10 patients are currently in complete remission (mean follow-up of 87 months).

3.5. Rhabdomyosarcoma

Rhabdomyosarcoma was the second most common SPT (20%, 9/44) including four embryonal and three alveolar subtypes (data not available for two patients). Median age of rhabdomyosarcoma was 11 years (range 5–22 years). Eight out of nine rhabdomyosarcomas were detected in patients irradiated in the first year-of-life, with the ethmoid (50%) (Fig. 2a and b) and temporal fossa (38%) as predominantly affected sites. Only one tumour developed in a patient irradiated after the first year; tumour occurred in the temporal fossa. In total, four out of nine rhabdomyosarcoma patients died after a mean follow-up of 77 months (range 5–154). Three patients died due to disease progression and one patient died 154 months after SPT-diagnosis from a TPT (osteosarcoma) occurring 6 years after rhabdomyosarcoma. Five patients are still in complete remission (mean follow-up, 68 months).

3.6. Other second primary tumours

A variety of other types of SPTs after irradiation were divided into; other sarcomas, carcinomas and miscellaneous tumours (Table 2). In eight patients with EBRT in the first year-of-life, five (63%) were other sarcomas, two (25%) carcinomas and one (12%) miscellaneous tumours. The temporal fossa (40%) and ethmoid sinus (40%) were the predilection sites for patients irradiated within their first year-of-life.

3.7. Survival

At the study time point, 20 patients were still alive (mean interval, 82 months; median, 73 months; range, 17–168 months) since SPT-diagnosis. Among these 20 patients, 19 were in complete remission (including three patients in second complete remission). One patient was disease free and lost to follow-up 1 month after complete microscopic tumour resection. Twenty-two patients died from disease progression (mean interval, 51 months; median, 32 months; range, 6 days–244 months) from diagnosis.

A significantly better 5-year OS ($P = 0.017$) (Fig. 3a) and EFS ($P = 0.012$) (Fig. 3b) were observed in patients with complete microscopic tumour resection and 5-year OS and EFS were respectively 83% (95% CI 54–100%) and 80% (95% CI 45–100%). Complete microscopic tumour resection also showed a statistically significant correlation with complete disease remission ($P = 0.036$) (Fig. 4). In patients with incomplete resection, the 5-year OS and EFS were 52% (95% CI 34–70%) and 47% (95% CI 29–64%) respectively. Tumour location ($P = 0.38$), histopathological subtype ($P = 0.33$) and age of EBRT (<1 year; >1 year) ($P = 0.53$) were not associated with a significant difference in survival.

4. Discussion

Osteosarcoma and rhabdomyosarcoma are the most common histopathological subtypes of cranio-facial SPTs in irradiated hereditary retinoblastoma patients, accounting for 64% of all SPTs in our study. Most osteosarcomas are primarily located in the orbit or temporal fossa and rhabdomyosarcomas in the ethmoid sinus or temporal fossa. Hereditary Rb-patients irradiated in their first year-of-life have a higher risk of SPTs since 79% of osteosarcomas, 89% of rhabdomyosarcomas and 63% of the other sarcomas develop in this group of children.[21]

In our study, the majority of the patients complained about a local swelling, sometimes combined with local pain as previously described.[20] The lymph nodes in the neck are usually not involved. Physicians should realise that otherwise innocent symptoms, such as a combination of chronic headache and sinus symptoms, may be potentially indicative for cranio-facial SPTs.[8] These (chronic) symptoms in irradiated hereditary Rb-patients should alert physicians to perform imaging without delay in order to detect SPTs at a potentially curative stage.

Radiologists should realise that cranio-facial SPTs in these patients occur in specific predilection sites. Most

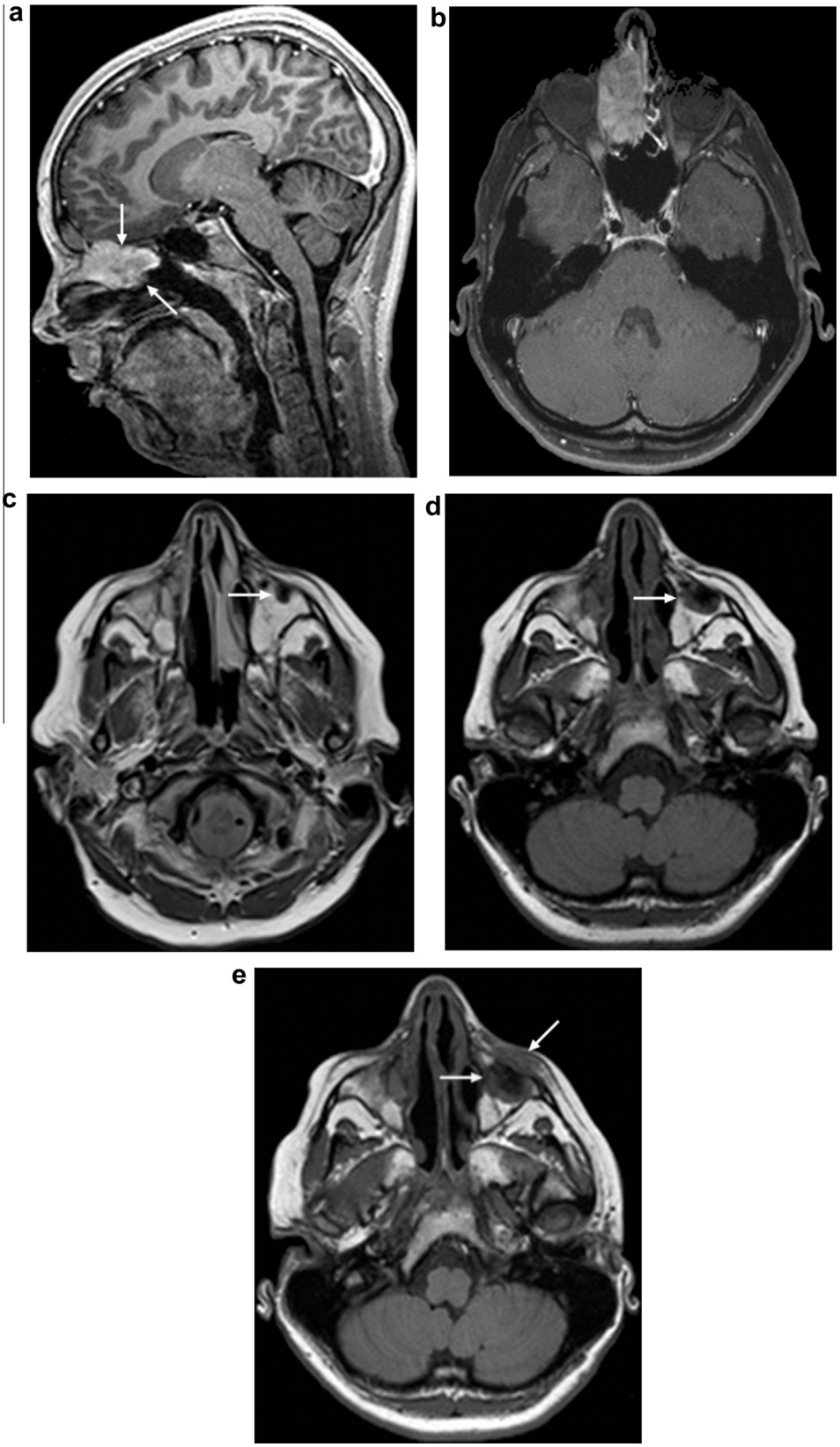

Fig. 2. A 13-year-old girl presenting with a second and third primary tumour after bilateral EBRT at 2 months of age. An embryonal rhabdomyosarcoma of the right ethmoid sinus (a and b) occurred at 13 years of age, which was treated with chemotherapy, surgery and brachytherapy. During follow-up for this second primary tumour, the patient complained about a painful swelling under the left eye and magnetic resonance imaging (MRI) demonstrated an osteosarcoma originating from the orbital floor with soft-tissue invasion (small arrow) (e). Retrospectively, this tumour could be observed 6 months and 2 months earlier without soft-tissue invasion (c and d). This third primary tumour was treated with chemotherapy, extensive surgery and brachytherapy. Both tumours were completely resected and this girl is still in second complete remission.

SPTs develop in the temporal fossa (39%), especially in patients treated with EBRT before 1 year-of-age. In the subgroup of 14 patients treated with a combination of EBRT and chemotherapy, no significant correlation was observed regarding histopathology, age at presentation or predilection sites of SPTs compared to patients treated for Rb with EBRT alone. Osteosarcomas frequently originated from the orbit and rhabdomyosarcomas from the ethmoid. Signal intensity or density is nonspecific for a specific histological type, although calcifications are present in at least 50% of osteosarcomas. Tateishi et al.[16] reported imaging characteristics (MRI or CT) of SPTs in the irradiated field in 15 patients, and only for osteosarcomas central calcification was found as important finding on CT. Therefore, any solid tissue mass should prompt to perform a biopsy for tumour identification without delay.

Prognosis of Rb patients with SPTs depends on possible treatment strategies. SPTs in the irradiated area, treated by a radical surgical approach in combination with chemotherapy and/or re-irradiation, show a better survival compared to cases without combined aggressive treatment.[22] Re-irradiation however, has an increased risk of complications due to post-radiation effects and might further increase the risk for a third or fourth primary tumour.[23] Therefore, in cases of small and resectable tumours in a previously irradiated area, surgery remains the modality of choice[24] and complete resection is important for an optimal outcome.[25] In some cases however, it is difficult to achieve clear surgical margins in this region.[20] Our study confirmed a significant better 5-year EFS (83%) and OS (80%) in patients treated with complete microscopic tumour resection. In this group, we saw significantly more patients with complete disease remission with a mean interval of 82 months. This stresses the need of early detection of SPTs in a stage where complete resection is possible. Additional pre-operative chemotherapy in combination with radical resection may increase the survival rate of patients treated for SPTs occurring after hereditary retinoblastoma.[20]

A diagnostic protocol based on clinical symptoms is important in Rb patients previously irradiated and specific information regarding these symptoms should be provided as warning signs for the patient of interest. However, symptoms are usually nonspecific and the most common is soft tissue swelling which may occur quite late in tumour development. For the same reason, a clinical depiction based on regular ENT examination would also probably be insufficient. In order to detect SPTs at an early and potentially resectable stage, an imaging screening programme could be suggested. According to our data, we would recommend to screen the population of all retinoblastoma patients treated with EBRT from an age of 5 years to approximately 20 years. Frequency of imaging is dependent of different factors including age and associated treatments, growth-

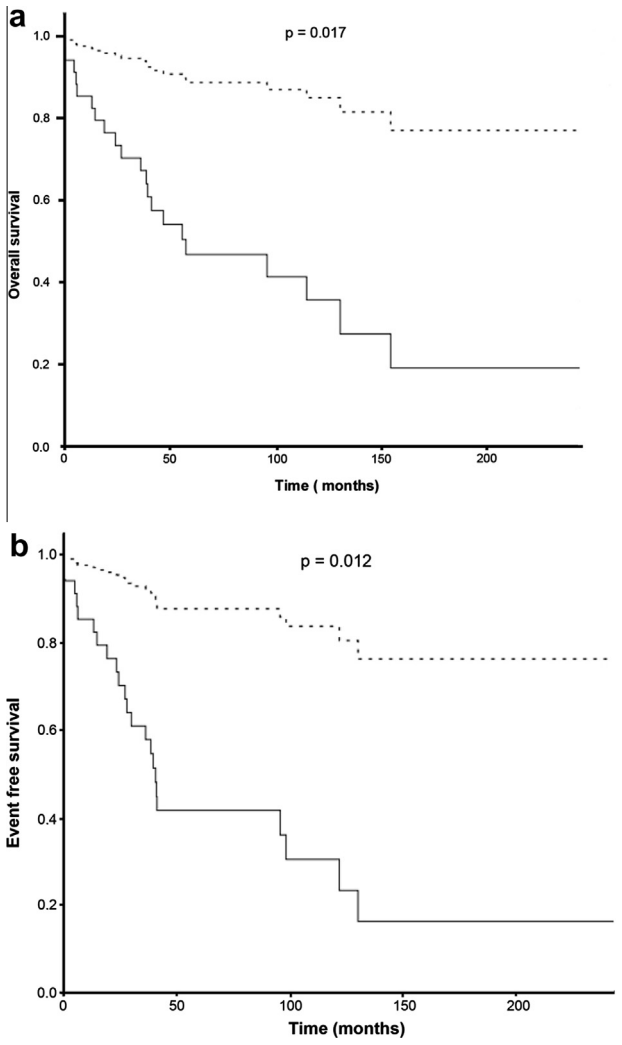

Fig. 3. Overall survival curve ($P = 0.017$) (a) and event-free survival curve ($P = 0.012$) (b) showing the effects of complete ($n = 7$, dotted line) and incomplete ($n = 33$, solid line) microscopic tumour resection in 40 retinoblastoma patients with second primary cranio-facial tumours.

rate of sarcomas, patients comfort and costs of imaging examinations. Although there is currently no consensus about the repetition time, a one year interval could be suggested. Because hereditary retinoblastoma patients are extra vulnerable for radiation damage to the DNA, CT-scans should be avoided, and MRI should be preferred.

The benefit of such an MR depiction programme in terms of survival is currently not evidence-based. Early diagnosis of SPTs should be balanced against patients' discomfort and anxiety related to repeated MRI examinations, and against potential false positive MR findings leading to unnecessary biopsies. Such a screening should only be performed through a scientific multicentre research protocol including informed consent and should assess screening-intervals, exact radiation dose at the tumour site, survival, accuracy, benefit, costs and tolerability of the method.

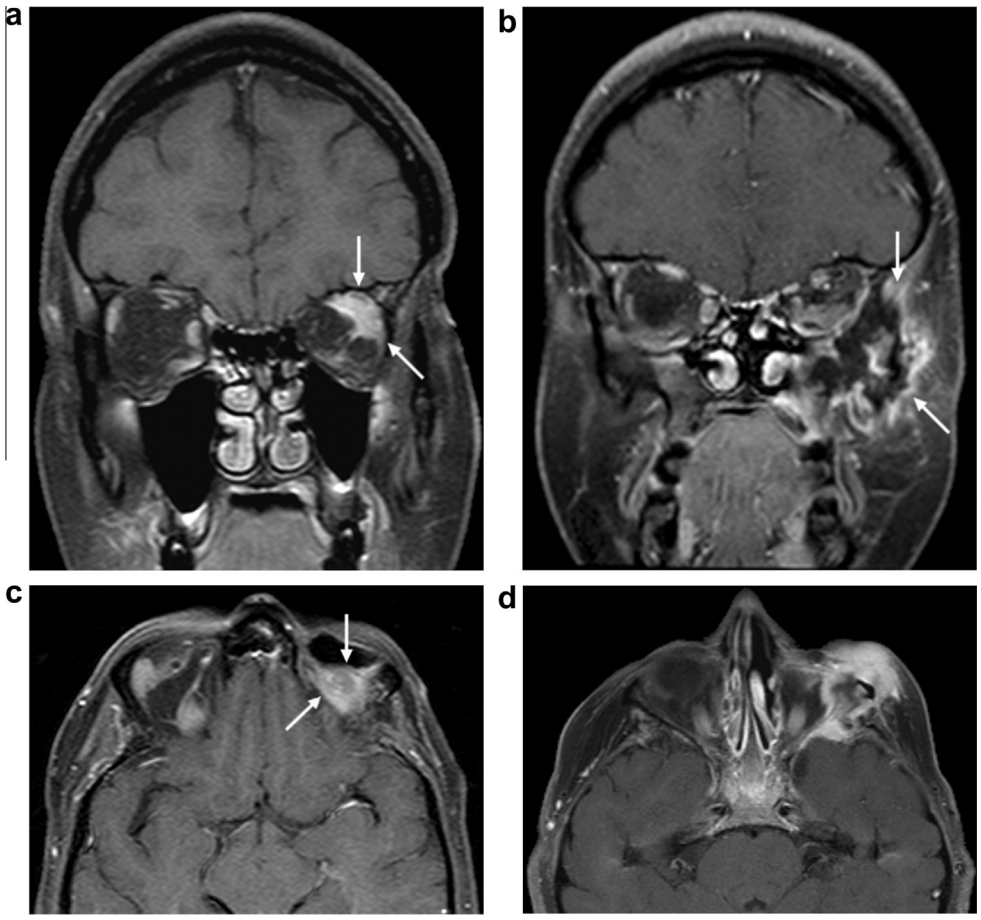

Fig. 4. Second primary tumours with complete (a and c) versus incomplete (b and d) microscopic tumour resection in the orbital region. Sebaceous gland carcinoma (a and c) in a 38 year old woman with invasion in intra-orbital fat treated with surgery and still under complete remission. Liposarcoma (b and d) in a 28 year old woman treated with chemotherapy and radiation therapy with tumour progression and death 3 years after diagnosis.

Precise comparison of the SPT location with the radiation fields was not possible in this study with the consequence that the exact dose at the tumour site could not be calculated. Furthermore, the small size of our patient-cohort was a study limitation for statistical issues.

In conclusion, osteosarcomas and rhabomyosarcomas are the major cranio-facial SPTs in irradiated retinoblastoma patients developing in specific locations, particularly in patients with EBRT in their first year-of-life. As complete surgical resection is a major prognostic factor, the diagnosis of SPT should be obtained as early as possible. Therefore, awareness about the risk factors and associated revealing symptoms, typical location and radiological patterns is important. An MRI-based screening programme could also prove value in detecting these tumours in an early and resectable stage to improve survival.

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Conflict of interest statement

None declared.

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