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Second primary tumors in retinoblastoma survivors: a study of 7 Asian Indian patients

Swathi Kaliki · Vijay Anand Reddy Palkonda

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Abstract
Purpose To assess the incidence, types, and outcomes of second primary tumors (SPT) in cases of retinoblastoma (RB) from a referral Tertiary eye care center
Methods Retrospective chart review of 7 cases
Results All 7 (100%) cases had bilateral RB at presentation. The mean age at diagnosis of RB was 16 months (median 7 months; range 5–72 months). Treatment of RB with intravenous chemotherapy was noted in 3 (43%) patients, 1 (14%) patient had received external beam radiotherapy (EBRT) to the orbit, 1 (14%) patient had received a combination of chemotherapy and orbital EBRT, while 4 (57%) patients had undergone primary enucleation of the worse eye and focal treatment of the better eye. The mean age at detection of SPT was 15 years (median 8 years; range 6–46 years). The mean time interval between diagnosis of RB and SPT was 13 years (median 7 years; range 1–41 years). The SPT's included osteosarcoma of long bone (n = 2), eyelid sebaceous gland carcinoma (n = 2), ventricular ependymoma (n = 1), orbital neuroblastoma (n = 1), and acute lymphoblastic leukemia (n = 1). All patients received treatment for the SPT with either surgical excision (n = 2), intravenous chemotherapy (n = 1), or a combination of surgery/chemotherapy/radiotherapy (n = 4). Over a mean follow-up period of 8 years (median 8 years; range 4–11 years), one (14%) patient died, while other 6 (86%) patients are alive and well.
Conclusion Though the incidence of SPT's in cases of RB is rare, life-long follow-up is mandatory in at-risk patients.

Keywords Eye · Tumor · Retinoblastoma · Second primary tumor · Second cancer

Introduction

Retinoblastoma (RB), the most common childhood ocular cancer, is life-threatening when left untreated. Over the years, advances in the management of RB have resulted in 92% to 98% chances of life salvage in children with RB[1–3]. Studies from various parts of the world have shown that the major cause of death in RB survivors is related to second primary tumors (SPT), occurring in those with heritable germline mutations [4,5].

The cause of SPT's in these patients with heritable RB is related to predisposing genotypic features [6,7]. There is an increased risk of development of SPT's in patients diagnosed with bilateral RB before the age of 1 year [6]; however, the type of RB

S. Kaliki (✉) · V. A. R. Palkonda
Operation Eyesight, Universal Institute for Eye Cancer (SK, VARP), L V Prasad Eye Institute, 500034 Hyderabad, India
e-mail: kalikiswathi@yahoo.com

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treatment is more important than the age of diagnosis [8]. Though radiotherapy is implicated in the increased risk of SPT's in genetically predisposed individuals [9,10], it has been shown that there is no statistically significant difference in the occurrence of SPT's in patients with bilateral RB treated with radiotherapy or chemotherapy[6]. Herein, in this study, we evaluate the incidence, presenting features, treatment, and outcomes of SPT's in Asian Indian RB survivors.

Methods

This is a retrospective study conducted at the Operation Eyesight Universal Institute for Eye Cancer, L V Prasad Eye Institute, Hyderabad, India. Institutional review board of L V Prasad Eye Institute, Hyderabad, India, approved the study. All patients with a diagnosis of RB during the study period January 2000–December 2019 were reviewed. Patients with histopathologically confirmed SPT were included in the study. All patients with no evidence of SPT, those with a second tumor due to RB metastasis, and those with inadequate data were excluded from the study.

The following data were extracted from the medical records: age at diagnosis of RB (months), laterality of RB, tumor classification/staging based on International Classification of Intraocular Retinoblastoma (ICIoR) [11] and International Retinoblastoma Staging System (IRSS) [12], treatment details of RB, age at diagnosis of SPT, time interval between diagnosis of RB and SPT, type of SPT, treatment details of SPT, and final outcome (alive/dead).

Results

Database search of 2292 RB records was done. The overall mean follow-up period was 40 months (median 25 months; range 0–233 months). There were 275 (12%) patients who had no follow-up after the first visit; 649 (28%) patients with a follow-up of less than a year; 403 (18%) patients with a follow-up period of 2 years; 362 (16%) patients with a follow-up period of 2–5 years; and 603 (26%) patients who had a follow-up period of more than 5 years. Including 2017 patients who had a follow-up of at least one year, seven (< 1%) patients were identified with SPT (Table 1, Fig. 1). The mean age at diagnosis of RB in these 7 cases was 16 months (median 7 months; range 5–72 months). There were 6 (86%) males and one (14%) female. There was no family history of RB in parents or siblings in any case. One patient had a daughter with RB who succumbed to the disease at the age of one year. All 7 (100%) cases had bilateral RB at presentation. Two patients had already undergone treatment of RB before presenting to us, and thus the tumors couldn't be classified. The remaining 10 eyes had group A (n = 1), group B (n = 1), group C (n = 2), group D (n = 3), or group E (n = 3) tumor at presentation. None of the patients had extraocular tumor extension at presentation.

The treatment details of RB included cryotherapy (n = 3 eyes), transpupillary thermotherapy (n = 5 eyes), xenon arc photocoagulation (n = 2 eyes), periocular chemotherapy (n = 2 eyes), intravenous chemotherapy (n = 4 patients), and external beam radiotherapy (EBRT) to the orbit (n = 4 eyes). Primary enucleation was performed in 4 eyes, and globe salvage was achieved in 10 (71%) eyes.

The presenting complaints of SPT included eyelid lesion (n = 2), leg pain (n = 2), headache (n = 1), proptosis (n = 1), and nasal bleeding (n = 1). The mean age at detection of SPT was 15 years (median 8 years; range 6–46 years). The mean time interval between diagnosis of RB and SPT was 13 years (median 7 years; range 1–41 years). The SPT's included osteosarcoma of long bone (n = 2), eyelid sebaceous gland carcinoma (SGC) (n = 2), ventricular ependymoma (n = 1), orbital neuroblastoma (n = 1), and acute lymphoblastic leukemia (n = 1). The mean time interval between diagnosis of RB and SGC was the longest at 31 years (median 31 years; range 21–41 years). Only one tumor (eyelid SGC) occurred in the field of prior irradiation.

The treatment details of SPT included systemic chemotherapy (n = 4), external beam radiotherapy to the affected area (n = 2), and/or surgical excision (n = 5). Over a mean follow-up period of 8 years (median 8 years; range 4–11 years), one (14%) patient died, while other 6 (86%) patients are alive and well. The patient who died had eyelid SGC and was doing well after surgical excision of the eyelid tumor. But the patient developed hematuria 4 years after treatment of SGC, and was detected to have a new urinary bladder cancer, and eventually died during the course of treatment of the same.

Table 1 Second malignancies in cases of retinoblastoma

Case	Age at detection of RB (months)	Laterality of RB	History of IVC	History of EBRT	Primary treatment of RB	Age at detection of SPT (years)	Time interval between RB and SPT detection (years)	Type of SPT	Treatment of SPT	Follow-up duration since treatment of SPT (years	Total follow-up duration (years)	Outcome
1	6	B/L	No	No	OD TTT + OS enucleation	6	6	Ventricular ependymoma	Excisional biopsy + EBRT	2	7	Alive and well
2	8	B/L	Yes	No	IVC	7	6	Neuroblastoma of paranasal sinuses and orbit	Systemic chemotherapy + EBRT	2	8	Alive and well
3	72	B/L	Yes	Yes	IVC	7	1	Acute lymphoblastic leukemia	Systemic chemotherapy	2	6	Alive and well
4	5	B/L	No	Yes	EBRT OU + xenon arc photocoagulation OS	21	21	OD Eyelid sebaceous gland carcinoma	Orbital exenteration	11	11	Alive and well
5	6	B/L	No	No	OD enucleation + xenon arc photocoagulation OS	46	41	OD Eyelid sebaceous gland carcinoma	Wide excisional biopsy	4	4	Dead*
6	7	B/L	Yes	No	IVC	10	10	Osteosarcoma of femur	Surgical excision + systemic chemotherapy	2	11	Alive and well
7	11	B/L	Yes	No	IVC	8	7	Osteosarcoma of tibia	Above knee amputation + systemic chemotherapy	1	6	Alive and well

RB Retinoblastoma, *IVC* intravenous chemotherapy, *EBRT* external beam radiotherapy. *B/L* bilateral, *TTT* transpupillary thermotherapy *OD* right eye, *OS* left eye, *OU* both eyes, * Died due to urinary bladder carcinoma

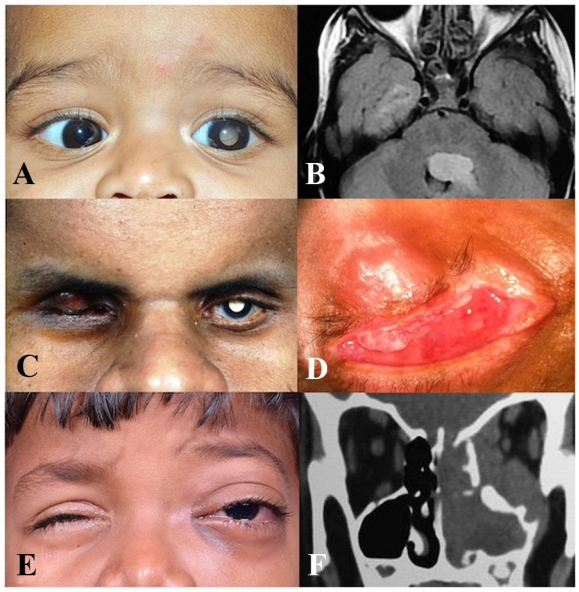

Fig. 1 Second cancers in retinoblastoma patients. **a** A 6-month-old child was diagnosed with bilateral retinoblastoma with group A tumor in the right eye and group E in the left eye. Treatment included transpupillary thermotherapy for the right eye and primary enucleation of the left eye. **b** Six years later, headache and projectile vomiting prompted brain imaging. Magnetic resonance imaging of the brain revealed an intracranial space occupying lesion in the 4th ventricle. Histopathology revealed a diagnosis of grade 2 ependymoma. **c** A 21-year-old male with a past history of bilateral retinoblastoma status post-enucleation of the right eye, xenon arc photocoagulation and cryotherapy to the left eye, and bilateral external beam radiotherapy at the age of 5 months presented with a right upper eyelid nodule. **d** Examination revealed nodular eyelid lesion involving the middle third of the right upper eyelid with associated loss of eyelashes. Histopathology confirmed the diagnosis of sebaceous gland carcinoma. **e** A 7-year-old boy with a past history of bilateral retinoblastoma status post-systemic chemotherapy at the age of 8 months presented with epistaxis and proptosis of the left eye. **f** Computed tomography of the orbit and paranasal sinuses revealed a diffuse ill-defined homogenous mass involving the left maxillary sinus, ethmoid sinus, medial and inferior orbits with associated bone destruction. Histopathology confirmed the diagnosis of neuroblastoma

Discussion

It has been well established that SPT's are a major concern in patients with hereditary variant of RB, with a further increased risk in patients receiving radiotherapy [13]. In our study, all cases had bilateral RB suggesting a heritable form of RB, and thus an increased risk of SPT's. The cumulative incidence of SPT's in a RB patient is 8% after 18 years of RB diagnosis, 16% at 20 years, 19% at 35 years[14], 36%–48% after 50 years of diagnosis of RB for hereditary variant versus 5% to 6% for nonhereditary variant[13,15]. In our study, the mean time interval between diagnosis of RB and SPT was 13 years.

The various SPT's described in RB cases include osteosarcoma (28%–37%), soft tissue sarcoma (7%–31%), brain and central nervous system (CNS) tumors (5%–11%), carcinomas (15%), melanoma (7%), fibrosarcoma (3%), chondrosarcoma (3%), other sarcomas (3%), leukemia (2% to 4%), sebaceous gland carcinoma (2%), and non-Hodgkin lymphoma (2%) [14,15]. The SPT's in our study included osteosarcoma ($n = 2$), sebaceous gland carcinoma ($n = 2$), brain tumor ($n = 1$), neuroblastoma ($n = 1$), and leukemia ($n = 1$).

Both radiotherapy and chemotherapy have been implicated in the increased risk of SPT's in RB survivors [8,13,16]. There is a threefold increased risk of SPT's in RB patients receiving radiotherapy and 1.8-fold increased risk in RB patients treated with chemotherapy [8,13]. While radiotherapy is associated with SPT's in the irradiated periorbital field, chemotherapy is associated with tumors elsewhere in the body [8]. In our study, history of radiotherapy was present in only 2 cases with only one case developing tumor in the irradiated field. Four cases had received systemic chemotherapy, while 2 patients had not received chemotherapy or radiotherapy. The

development of SPT's in these 2 cases could be related to genetic predisposition rather than the predisposition due to type of treatment.

Literature review of 676 SPT's by Woo et al. revealed that the median age at diagnosis of SPT is 13 years, with 3 years for CNS tumors, 6 years for leukemia, 13 years for sarcomas, 27 years for melanomas, and 29 years for carcinomas and neuroblastoma.[5] In our study, the median age at diagnosis of SPT was 15 years, with 6 years for CNS tumor, 7 years for neuroblastoma and leukemia, 9 years for sarcomas, and 34 years for carcinomas. Periocular sebaceous gland carcinomas had the longest time interval of 31 years between RB diagnosis and SPT detection. One tumor occurred in the irradiated field, and the other patient had no history of radiotherapy or chemotherapy.

The RB patients with SPT are also at risk of developing third, fourth, or fifth primary tumors during their lifetime [18]. The 5-year and 10-year incidence rate of third primary tumor in RB survivors is 11% and 22%, respectively. The median time to development of third primary tumor is 5.8 years after SPT. In our study, only one patient developed third primary tumor (bladder carcinoma) 4 years after SPT, at the age of 50 years. This finding is similar to the observation that there is an increased risk of epithelial cancers including breast, lung, and bladder cancers after 30 years of diagnosis of RB [17].

The cumulative mortality from SPT's at 50 years of RB diagnosis is 25% for patients with heritable RB versus 1% with non-heritable RB [19]. The survival rate of patients with RB has improved over the decades despite stable incidence of SPT's, and this could be related to advanced treatment strategies of SPT's [6]. In our study, only one patient died of third primary tumor (bladder carcinoma) and the remaining patients did well with appropriate treatment of SPT's.

Though there is a known risk of SPT's in heritable RB patients, there is no standard screening protocol recommendation. In a survey of cancer screening practices in RB survivors, it was noted that the frequency of computed tomography or magnetic resonance imaging, and testicular examination in males were significantly higher in heritable RB survivors compared to non-heritable form of RB [20]. However, pap screening and mammography in females was not significantly higher in the heritable RB group compared to non-heritable form of RB [20]. In our practice, we educate the parents and RB survivors about SPT's and investigations are performed only if there are any signs and symptoms of SPT.

The main limitation of our study is shorter follow-up duration, and thus these patients may go on to develop further tumors in future. The mean age of the 6 patients who are alive at last follow-up was 13 years (median 9 years; range 6–32 years). However, this is the largest case series on SPT's in Asian Indian RB survivors.

In conclusion, SPT's in RB survivors are rare. Patient education about SPT's in cases with heritable RB and awareness about signs and symptoms is the key to early detection of such tumors. Early detection and prompt treatment of SPT's allows improved life prognosis in RB survivors.

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Compliance with ethical standards

Conflicts of interest All authors declare that he/she has no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants or parents/guardians included in the study.

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