




Second Primary Malignant Neoplasms in Survivors of Retinoblastoma in a Single Ocular Oncology Practice

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Introduction: A retrospective review of patients treated for retinoblastoma who developed a non-pineoblastoma second primary malignant neoplasm (SPMN) was performed.

Methods: The demographics, clinical features and treatments for retinoblastoma, pathologic types of non-pineoblastoma second primary malignant neoplasm (SPMN), intervals between the retinoblastoma diagnosis and treatment and diagnosis of non-pineoblastoma SPMN, treatment provided for the SPMN, and the survival outcomes of the patients were evaluated.

Results: Of 550 patients treated initially for retinoblastoma, this series used the 15 (2.7%) that developed a non-pineoblastoma SPMN, 14 of which (93.3%) had been treated for bilateral retinoblastoma. All patients had carried a germline mutation in the *RBI* gene. The median time from retinoblastoma diagnosis to SPMN diagnosis was 19.0 years (extremes 3.4 and 39.4 years). Six of the fifteen patients died during the follow-up of their SPMN. The median interval between initial retinoblastoma diagnosis and death in the 6 patients who died of their SPMN was 18.8 years (extremes 6.2 and 34.6 years) and between diagnosis of the SPMN and death was 1.2 years (extremes 0.25 and 4 years).

Discussion: Of the patients who had been treated with External Beam Radiotherapy (EBRT), 13 developed a SPMN within the previously irradiated field.

Keywords: external beam radiotherapy, pediatrics, osteosarcoma, retinoblastoma, family history, second primary malignant neoplasm

Introduction

Retinoblastoma (RB) is the most common primary intraocular malignancy in pediatric patients. The two genetic situations are: 1 germline + 1 somatic variant versus two somatic variants of the *RBI* tumor suppressor gene located on chromosome 13q14.¹⁻³ Hereditary retinoblastoma is associated with an increased lifetime risk of second primary malignant neoplasms (SPMNs), most of which are either pineoblastoma (ectopic intracranial retinoblastoma) or sarcomas. SPMNs are the leading cause of death in individuals with hereditary RB. While RB-associated pineoblastoma tends to occur during early pediatric patients, most RB-associated sarcomas occur years or even decades after initial retinoblastoma diagnosis and treatment.^{4,5} SPMNs are significantly higher likelihood to occur patients with hereditary retinoblastoma who have loss-of-function variant mutations in *RBI*.⁶ The reported incidence of SPMNs in the published literature varies due to differing definitions of SPMNs, differing lengths of follow-up, referral practice biases, and differences in retinoblastoma treatment.⁷ For this cohort, we decided to classify pineoblastoma as ectopic retinoblastoma and not a secondary tumor. Some reports mention it as an extension of the primary tumor while others consider it to be secondary tumor. This is due to Pineoblastoma being histopathologically very similar to retinoblastoma and some consider them to be ectopic intracranial retinoblastoma. SPMNs are now the leading cause of death in patients with hereditary retinoblastoma in high-income countries.⁸

Because SPMNs often occur decades following the initial diagnosis of retinoblastoma, long-term follow-up is necessary to accurately determine the frequency of and risk factors for the development of such outcomes in retinoblastoma survivors. In a case review covering 9 reports, a study by Mahoney et al found that out of 82 patients with hereditary RB, SPMN were found in the field of prior irradiation in 4 out of 14 (28.6%) patients. While other reports such as Marees et al showed that 89% of SPMNs were found in hereditary RB patients treated prior radiation therapy, while 40% were in-field of of prior irradiation (specifically soft tissue sarcomas, cancer of the bone, or melanoma).⁹ Overall this study concluded that although there is a clear increase of SMNs in irradiated patients, it did not find a significant association between exposure to ionizing radiation and the incidence of SMNs.

Herein we report the demographic and historical features of a series of patients with non-pineoblastoma SPMNs, the clinical features and treatment for the retinoblastoma in these cases, the types of SPMNs that occurred in these patients, and the treatment outcomes of these patients following SPMN diagnoses over a forty-three-year period in a single referral ocular oncology practice.

Methods

The authors performed a retrospective chart review of all patients in the Augsburg ocular oncology practice with a history of retinoblastoma who developed a SPMN between 1975 and 2022. A SPMN was defined as a histopathologically distinct solid malignant neoplasm that occurred after the onset of the primary retinoblastoma. The study was performed with the approval of the Institutional Review Board of the University of Cincinnati College of Medicine for retrospective analysis of deidentified clinical information contained in the charts of human patients evaluated in the practice and generated as part of standard patient care.

The authors abstracted the following information from the charts: demographic information, family history of retinoblastoma, features of the affected eye(s), therapeutic interventions for retinoblastoma, the interval between initial diagnosis of retinoblastoma and detection-diagnosis of the SPMN, age at diagnosis of the SPMN, pathologic type of SPMN, location of the SPMN, treatment provided for the SPMN, duration of follow-up after retinoblastoma diagnosis and after SPMN diagnosis and treatment, and life status of the patient through most recent follow-up. Because genetic testing was not available for all patients, hereditary disease was defined by bilateral disease, a positive family history, and/or a germline *RBI* mutation detected on chromosomal/DNA analysis. Non-hereditary disease was defined by unifocal, unilateral disease, negative family history of RB, and/or chromosomal/DNA analysis that showed no evidence of a germline *RBI* mutation, these are additive terms and not exclusive to define a nonhereditary disease. Since radiation field size data was not available for most patients in this series, SPMNs occurring in the head/neck region were defined as “in the field” whereas those occurring in the body or extremities were defined as “out of the field” of radiation.

The cases in this series fell into two discrete groups: Group 1 consisted of patients whose baseline diagnostic evaluation was performed and at least some of their initial retinoblastoma treatment was provided in the Augsburg ocular oncology practice and collaborating pediatric oncology practice, and Group 2 consisted of patients whose baseline diagnostic evaluation was performed and retinoblastoma treatment was provided at an outside center prior to referral to the Augsburg ocular oncology practice. For Group 1, we could determine both the baseline prognostic group (for ocular preservation) of the intraocular retinoblastoma of each affected eye (using both the Reese-Ellsworth⁷ and Murphree [ABCDE]⁸ classification systems) and the baseline stage of the retinoblastoma (using the AJCC tumor-node-metastasis [TNM] staging system, 2017 version⁹). For Group 2, this information was generally not available (ie, not provided by the outside center where the patient’s baseline diagnostic evaluation had been performed) and could not be determined from records of the baseline evaluation obtained from those centers.

Statistical analysis was performed using Microsoft Excel (Microsoft Corp, Redmond, WA). Continuous numeric variables were described using the median and extreme values. Categorical variables were described using numerical counts and percentages.

Results

Of 550 pediatric patients with retinoblastoma encountered in this practice during the study period, our series used the 15 patients who developed a SPMN (2.7%), 2 of whom (patient 4 and 7) developed 2 distinct SPMNs. Patient 4 diagnosed with both a left temporal fossa rhabdomyosarcoma and a left orbital osteosarcoma, both inside the field of radiation. Patient 7 developed osteosarcoma of both the left proximal tibia and the right hip outside the field of radiation. The median age at retinoblastoma

diagnosis was 9.7 months (extremes 1.6 and 33.6 months). All 15 patients had a positive family history of retinoblastoma. Twelve patients were male (80%) and three were female (20%). Bilateral disease was present in 14 of the 15 (93.0%) patients, and the genetic nature of the one unilateral case (case 7, Table 1) was established by germline *RBI* mutation on genetic analysis.

Demographics and characteristics of each patient's retinoblastoma are presented in Table 1. Eleven patients received treatment prior to referral, including enucleation (11/30 eyes; 36.6%), and external beam radiation therapy (EBRT) (12/30 eyes; 40.0%). Following completion of their retinoblastoma treatment course, a total of 15/30 (50.0%) eyes were enucleated, and

Table 1 Demographics and Baseline Characteristics of Retinoblastoma

Case Number	Case Number Group Number ^{a,b}	Age (mo.) of Diagnosis	Gender	Laterality of Ocular Involvement	Eye (OD/OS)	Reese-Ellsworth Group	Murphree ABCDE Group	Initial Treatment	Secondary-Supplement Treatment (s)
1	1	1.9	M	Bilateral	OD ^c OS ^d	5A 3A	D B	EBRT ^e EBRT	PBT ^f ; Enucleation Cryotherapy
2	1	2.4	M	Bilateral	OD OS	5A 4A	D E	Enucleation EBRT	n/a n/a
3	1	11.8	F	Bilateral	OD OS	5B 5A	D E	EBRT Enucleation	n/a n/a
4	1	1.6	M	Bilateral	OD OS	5A 5B	E C	EBRT Enucleation	n/a n/a
5	2	8.1	F	Bilateral	OD OS	n/a n/a	n/a n/a	EBRT Enucleation	n/a n/a
6	2	2.2	M	Bilateral	OD OS	n/a n/a	n/a n/a	Enucleation EBRT	n/a n/a
7	2	33.6	M	Unilateral	OS	n/a	n/a	Enucleation	IVC ^g ; EBRT
8	2	2.2	M	Bilateral	OD OS	n/a n/a	n/a n/a	PBT Enucleation	Cryotherapy EBRT
9	2	9.1	M	Bilateral	OD OS	n/a n/a	n/a n/a	Enucleation EBRT	n/a n/a
10	2	14.8	M	Bilateral	OD OS	n/a n/a	n/a n/a	Enucleation EBRT	EBRT n/a
11	2	17.6	M	Bilateral	OD OS	n/a n/a	n/a n/a	Enucleation Enucleation	EBRT EBRT
12	2	8	M	Bilateral	OD OS	n/a n/a	n/a n/a	IVC IVC	TTT ^h TTT
13	2	21.3	F	Bilateral	OD OS	n/a n/a	n/a n/a	EBRT Enucleation	n/a n/a
14	2	1.8	M	Bilateral	OD OS	n/a n/a	n/a n/a	Enucleation EBRT	EBRT n/a
15	2	9.5	M	Bilateral	OD OS	n/a n/a	n/a n/a	EBRT Enucleation	n/a n/a

Notes: ^aGroup 1 = Initial evaluation and some of the initial treatment was provided by the Augsburg ocular oncology practice and collaborating pediatric oncology practice. ^bGroup 2 = Initial evaluation and some of the initial treatment was provided at an outside center prior to referral to the ocular oncology practice.

Abbreviations: ^cOD, Right eye; ^dOS, Left eye; ^eEBRT, External beam radiation therapy; ^fPBT, Plaque Brachytherapy; ^gIVC, Intravenous chemotherapy; ^hTTT, Transpupillary thermotherapy.

14/15 (93.3%) patients underwent EBRT. In 13 patients, retinoblastoma was diagnosed, and treatment was initiated prior to the adoption of carboplatin-etoposide-vincristine (CEV) and intravenous chemotherapy at our center (in 1995). All 15 patients were diagnosed and underwent treatment for their retinoblastoma prior to the availability of selective ophthalmic intra-arterial chemotherapy at our institution (in 2008). The 2 patients diagnosed after the introduction of primary systemic chemotherapy both received intravenous chemotherapy during their treatment course. None of the patients developed metastasis from retinoblastoma and no patient died of their retinoblastoma.

The characteristics of the SPMNs are reported in Table 2. Thirteen of the 14 patients (92.9%) who underwent EBRT developed their SPMN within the field of prior radiation. The histopathologic type of SPMN was osteosarcoma in 7,

Table 2 Second Primary Malignancy Characteristics

Case Number	Age (yrs.) at SPMN ^a Diagnosis	Interval (yrs.) Between RB Dx ^b -SPMN Dx	Body Location of SPMN	Pathologic Diagnosis of SPMN	Treatments Provided for SPMN	Life Status	Survival (yrs.) After Diagnosis of SPMN
1	8.75	8.6	R. Maxillary sinus and Orbit	Malignant fibrous histiocytoma	Exenteration, maxillectomy, IVC ^c	Living	n/a
2	19.4	19.2	L Orbit	Osteosarcoma	n/a	Deceased	1.3
3	13.5	12.5	L. Temporal lobe	Malignant astrocytoma	Resection, Radiation, IVC	Deceased	0.33
4	3.5	3.4	L. Temporal fossa; L Orbit	Rhabdomyosarcoma; Osteosarcoma	n/a	Living	n/a
5	37.5	36.9	R. Nasal cavity and Maxillary sinus	Osteosarcoma	Exenteration, Maxillectomy	Living	n/a
6	25.9	25.7	L. Maxillary	Osteosarcoma	Maxillectomy, IVC	Living	n/a
7	12	9.2	L. Proximal tibia; R. Hip	Osteosarcoma; Osteosarcoma	Above knee amputation, IVC; Arthroplasty and excision	Deceased	4
8	6.8	5.9	L. orbit	Osteosarcoma	n/a	Deceased	0.25
9	6.6	5.6	L. Temporal fossa	Rhabdomyosarcoma	Resection, IVC	Living	n/a
10	18.4	17.2	R. Temporal fossa	Rhabdomyosarcoma	Resection, radiation, IVC	Living	n/a
11	35	33.6	R. Ethmoid sinus and orbit	Malignant fibrous histiocytoma	Resection, radiation	Deceased	1
12	13	12.5	L. Parotid gland	Liposarcoma	Resection	Living	n/a
13	41.1	39.4	R. Orbit and paranasal sinuses	Malignant fibrous histiocytoma	Resection, radiation	Living	n/a
14	25.1	25	L. Ethmoid sinus and Orbit	Esthesioneuroblastoma	n/a	Deceased	0.5
15	31.75	31	R. Orbit	Leiomyosarcoma	Resection	Living	n/a

Abbreviations: ^aSPMN, Second primary malignant neoplasm; ^bRB Dx, Retinoblastoma Diagnosis; ^cIVC, Intravenous chemotherapy.

rhabdomyosarcoma in 3, malignant fibrous histiocytoma in 3, and a malignant astrocytoma, liposarcoma, esthesioneuroblastoma and a leiomyosarcoma in 1 case each. Treatment data for SPMN management was available for 11 of the 15 patients and included a combination of surgical resection in 11, intravenous chemotherapy in 6, and radiation therapy in 4. The median time from initial retinoblastoma diagnosis to development of SPMN was 19.0 years (extremes 3.4 and 39.4 years). The median time from retinoblastoma diagnosis to death in the 6 patients who died of their SPMN was 18.8 years (extremes 6.2 and 34.6 years), and the median interval between SPMN diagnosis and death from the neoplasm in these 6 patients was 1.2 years (extremes 0.25 and 4 years). In contrast, the median duration of follow-up after retinoblastoma in the 9 surviving patients was 32.0 years (extremes 12.5 and 39.3 years) and the median follow-up interval after diagnosis of the SPMN in these patients was 8.9 years (extremes 1.6 and 27.6 years).

Discussion

Following the advancement of therapeutic options for retinoblastoma, the survival rate for retinoblastoma is >95% in high-income countries.^{7,10} As the rate of mortality from retinoblastoma has decreased, SPMNs have become the leading cause of death for patients with hereditary retinoblastoma.⁸ The cumulative actuarial incidence of SPMNs in hereditary disease has been reported to be 15.7% at 20 years and around 30% at 40 years.^{7,11–13} At 60 years, a Danish cohort had a cumulative incidence of SPMNs of 51% for hereditary disease versus 13% for nonhereditary disease.⁸ The variance in published rates is due to a multitude of factors, including different lengths of follow-up, different definitions of SPMNs (some include pineoblastomas and non-melanoma skin cancers), different treatments provided for retinoblastoma, non-equivalent hereditary versus nonhereditary disease ratios, and use of national population-based studies versus tertiary referral center studies.⁷

Prior to the introduction of primary intravenous chemotherapy, EBRT was the predominant strategy for globe-salvaging therapy. EBRT for retinoblastoma has been associated with high rates of soft tissue and bony sarcomas in the field of radiation. In our study, 13 of 15 patients were diagnosed and treated prior to an effective and low toxicity CEV regimen of systemic chemotherapy, and all 15 patients were diagnosed and treated prior to the availability of selective ophthalmic intra-arterial chemotherapy at our center. This is reflected in the high rate of soft tissue and bony sarcomas in the field of radiation in our study (11 of 15 patients; 13 of 17 tumors). Additionally, 14 patients developed a SPMN in the head/neck region, 13 of whom had a history of prior EBRT.

Following the advent of an effective CEV intravenous chemotherapy as a treatment for retinoblastoma, there has been a change in patterns of SPMNs encountered. While hematologic SPMNs were rare prior to the introduction of chemotherapy, there has been an increased risk of hematologic SPMNs (most commonly acute myelogenous leukemia), especially in patients who received higher doses of chemotherapy.^{14–16} When used in combination with EBRT, chemotherapy may lead to higher rates of bone cancers and leiomyosarcomas in patients with hereditary disease compared to either treatment alone.¹⁷ Two patients in our study received intravenous chemotherapy during their treatment course. Patient 7 received both EBRT and a cyclophosphamide-based intravenous chemotherapy regimen, while patient 12 (the only patient that did not undergo EBRT) was treated with vincristine, etoposide, and carboplatin. Neither patient treated with systemic chemotherapy developed a hematologic SPMN.

Limitations of this study include its retrospective nature, the lack of follow-up information on the patients in the total group of 550 patients who did not develop a SPMN during available follow-up, the lack of baseline classification data on patients diagnosed and treated elsewhere prior to referral to the practice, the lack of information regarding the precise field of radiation, radiation dose, and fractionation schedule in most of the cases, and the referral bias of a single practice ocular oncology tertiary referral practice. An association of SPMNs with mutational status was not available in most cases in this series because genetic testing was not performed routinely during retinoblastoma management during the era of treatment for most patients in this cohort.

In conclusion, we describe our experience with non-pineoblastoma SPMNs in a tertiary referral practice. The vast majority of SPMNs in this series occurred in patients who had been treated by EBRT, and most occurred in the field of prior radiation. SPMNs occurred on average nearly two decades following the original diagnosis of retinoblastoma.

Human Studies and Informed Consent

The Institutional Review Board of the University of Cincinnati College of Medicine granted a waiver for informed consent in this retrospective chart review. All appropriate steps were taken.

Data Sharing Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Ethics Statement

This study complies with the Declaration of Helsinki.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

Maura Di Nicola consults for EyePoint Pharmaceuticals and reports personal fees from SpringWorks Therapeutics, outside the submitted work. Basil K Williams Jr consults for Alcon, Allergan/Abbvie, Alimera, Astellas, Castle Biosciences, EyePoint Pharmaceuticals, Genentech/Roche, Immunocore, and Regeneron; owns stock options of Lumata Health. Malcolm T Wiseman Jr, Jared J Ebert, James J Augsburger, Zelia M Correa, and James I Geller declare that they have no conflicts of interest in this work.

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