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

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Abstract

Background: To describe the clinical features and course of a series of survivors of retinoblastoma who developed a non-pineoblastoma second primary malignant neoplasm (SPMN). Methods: A retrospective review of patients treated for retinoblastoma who developed a SPMN was performed. The demographics, clinical features and treatments for retinoblastoma, pathologic types of SPMN, the 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 in this series had germline retinoblastoma. 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. Nine patients were still alive without active residual SPMN at the last follow-up. 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). Conclusion: A SPMN occurred in this series in 2.7% of retinoblastoma survivors, and all occurred in patients with germline retinoblastoma. All patients with SPMN who had been treated by EBRT developed the SPMN in the field of prior radiation.

Introduction

Retinoblastoma (RB) is the most common primary intraocular malignancy in pediatric patients. In most cases, it results from either a germline (hereditary) or somatic (non-hereditary) mutation of the *RB1*tumor suppressor gene located on chromosome 13q14.[1,2,3] 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. While RB-associated pineoblastoma tends to occur during early childhood, most RB-associated sarcomas occur years or even decades after initial retinoblastoma diagnosis and treatment. SPMNs are particularly likely to occur in patients with hereditary retinoblastoma who have nonsense mutations in*RB1* .[4] 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.[5] SPMNs are now the leading cause of death in patients with hereditary retinoblastoma in the developed world.[6] 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.

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 Augsburger 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 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 *RB1* 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*RB1* mutation. 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 Augsburger 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 Augsburger 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-Ellsworth[7] and Murphree [ABCDE][8] classification systems) and the baseline stage of the retinoblastoma (using the AJCC tumor-node-metastasis [TNM] staging system, 2017 version[9]). For Group 2, this information was generally not available (i.e., 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. Categorial variables were described using numerical counts and percentages.

Results

Of 550 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. 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 *RB1* 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 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, 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 the developed world.[5,10] As the rate of mortality from retinoblastoma has decreased, SPMNs have become the leading cause of death for patients with hereditary retinoblastoma.[6]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.[5,11-13]{Marees, 2010, Risk of third malignancies and death after a second malignancy in retinoblastoma survivors}At 60 years, a Danish cohort had a cumulative incidence of SPMNs of 51% for hereditary disease versus 13% for nonhereditary disease.[6] 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.[5]

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.[14,15,16] 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.

Despite the mortality rate associated with SPMN in survivors of hereditary retinoblastoma, imaging surveillance of asymptomatic patients has not been associated with decreased mortality and may lead to increased costs and false-positive results.[18] An expert consensus panel met in 2017 to evaluate follow-up recommendations for SPMNs and endorsed annual skin examinations for cutaneous melanoma screening but recommended

against radiographic screening of asymptomatic patients. The panel also recommended an annual history and physical examination and educating patients on the need for prompt evaluation of symptoms consistent with persistent sinusitis, skeletal tenderness, and pain.[18] As retinoblastoma treatment continues to evolve and long-term data on SPMNs related to intravenous chemotherapy and selective ophthalmic intra-arterial chemotherapy becomes available, screening guidelines may need to be updated.

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.

Conflicts of Interest Statement :

Maura Di Nicola consults for EyePoint Pharmaceuticals. Basil Williams consults for Allergan/Abbvie, Castle Biosciences, EyePoint Pharmaceuticals, Genentech/Roche, and Regeneron. No other authors have any conflict of interests.

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`20240101 Table 2 SPM (FINAL).docx` available at https://authorea.com/users/713562/articles/697866-second-primary-malignant-neoplasms-in-survivors-of-retinoblastoma-in-a-single-ocular-oncology-practice