Review of 676 Second Primary Tumors in Patients With Retinoblastoma

Association Between Age at Onset and Tumor Type

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Objective: To obtain a more accurate understanding of second primary tumors (SPTs) by analyzing a large number of SPTs from the published literature.

Methods: A literature search was performed to identify published cases of SPTs in patients with retinoblastoma. Patient age, radiation field, tumor location, and tumor type were analyzed for statistical association.

Results: The study included 676 SPTs in 602 patients. Median age at diagnosis of SPT was 13.0 years (range, 0.3-60.4 years) for all SPTs, 2.7 years for midline intracranial primitive neuroectodermal tumors, 13.0 years for sarcomas, 27.0 years for melanomas, and 29.0 years for carcinomas. The median age at which SPTs occurred inside the radiation field was younger than that for SPTs occurring outside the radiation field or in patients who did not undergo irradiation (P < .001). Sarcomas occurred more commonly inside the radiation field (P < .001). Melanomas, lipomas, leukemias, and lymphomas occurred more commonly outside the radiation field or in patients who did not undergo irradiation (P < .001).

Conclusions: Retinoblastoma patients pass through multiple windows of susceptibility to specific SPTs. This information will aid health care providers in monitoring this high-risk group, and it provides new insights for studying the underlying genetic predisposition to SPTs.

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A CENTURY AGO, RETINOBLASTOMA was almost uniformly fatal. However, improvements in diagnosis and treatment now allow most retinoblastoma patients in developed countries to survive their eye cancer and live into adulthood.1 Consequently, second primary tumors (SPTs) are now the leading cause of death in patients with heritable (or germline) retinoblastoma.2,3 Second primary tumors arise at a greatly increased rate in heritable retinoblastoma survivors compared with the general population. Osteosarcomas and soft tissue sarcomas are the most well-known SPTs in retinoblastoma survivors, particularly in younger individuals.4 However, as the life expectancy of these patients has improved in recent years, it has become apparent that they are susceptible to a much broader range of tumors. Thus, a greater understanding of these SPTs is important for understanding and managing this cancer predisposition syndrome.

Several previous studies have addressed the issue of SPTs in retinoblastoma survivors.2,3,5-7 Kleinerman et al2 reported that a risk of new cancers in patients with hereditary retinoblastoma were significantly higher than in those with the nonhereditary form and that radiotherapy also increased the risk. The importance of longer follow-up of the patients treated with chemotherapy was emphasized by Marees et al8 for the association of chemotherapy combined with the \textit{RB1} mutation with the risk of second solid malignancies. Fletcher et al7 revealed that survivors of hereditary retinoblastoma who were not exposed to high-dose radiotherapy had a high lifetime risk of developing a late-onset epithelial cancer. However, these have been single-institution studies, which may introduce bias as a result of differences in treatment and data collection from center to center. Furthermore, some studies have focused only on specific subtypes of SPTs.9-13

To maximize the utility of the large amount of published information, we col-
ected and analyzed data on 676 SPTs in 602 retinoblastoma patients from 128 published articles. To be able to monitor the retinoblastoma patients in long-term follow-ups, a systematic meta-analysis of published cases of SPTs was conducted. The purpose of this study is to document and analyze the spectrum of SPTs in this population. The incidence of SPTs in the whole population of retinoblastoma patients has been studied in the literature; it is not the object of our research.\textsuperscript{3,7,8} The results provide a comprehensive overview of SPTs and reveal important relationships between patient age, prior radiation treatment, tumor location, and histopathology.

**METHODS**

A MEDLINE search with key words retinoblastoma and second primary tumor, second neoplasm, second malignancy, second cancer, pinealoma, pinealoblastoma, or trilateral was conducted in the English literature between 1961 and 2006. The pertinent original articles were acquired and reviewed for data and additional references.

Inclusion criteria for articles used in the study included (1) documentation of 1 or more SPTs, and (2) availability of clinical information for individual patients. The data for this study were collected from 128 previously published articles. Because only published cases were included, institutional review board approval was not required. Patients described in more than 1 article were included only once. Information recorded included age at diagnosis, laterality, family history, treatment modalities, and radiation dose in cases of radiation therapy in patients with retinoblastoma; and age at diagnosis, histopathologic type, anatomic location, relationship to radiation field in those with radiation therapy, and treatment of SPTs.

All diagnoses for the retinoblastoma and SPTs were accepted as written in the literature. Midline primitive neuroectodermal tumors (PNETs), also called pinealoblastomas or trilateral retinoblastomas, were considered to be SPTs. The radiation field was defined as the tissues of the head or neck for each patient unless any specific remark on it was available in the article. Primitive neuroectodermal tumors were analyzed separately owing to frequent uncertainty about their relationship to the radiation field from the available information.

Statistical significance of comparisons between SPT subgroups was determined using the \( \chi^2 \) test. Spearman correlation test, and the Mann-Whitney test for continuous data. Statistical calculations and box plots were completed using MedCalc, version 9.2.0.2.

**RESULTS**

The study included 602 patients: 202 males, 196 females, and 204 individuals of unknown sex. Five hundred forty-one patients developed 1 SPT, 51 patients developed 2 SPTs, 7 patients developed 3 SPTs, and 3 patients developed 4 SPTs, for a total of 676 SPTs. Retinoblastoma was bilateral in 479 patients, unilateral in 82 patients, and unknown in 41 patients. Family history of retinoblastoma was present in 139 patients, absent in 176 patients, and unknown in 287 patients.

Germline mutations (507 cases [84.2%]) were regarded to be affirmative in cases with bilateral retinoblastoma or positive family history. Unilateral retinoblastoma with no family history occurred in 35 cases, unilateral retinoblastoma with unknown family history in 26 cases, unknown bilaterality with no family history in 14 cases, and unknown bilaterality and family history in 20 cases. Therefore, 60 patients (10.0%) had incomplete data for affirming germline mutation and only 35 patients (5.8%) developed SPTs without clinical evidence of germline mutation.

Year at diagnosis of retinoblastoma was available in 215 of 602 patients (35.7%). Eighty-nine of 215 patients were treated before 1960, 49 patients were treated in the 1960s, 50 patients in the 1970s, 24 patients in the 1980s, and 3 patients in the 1990s. Chemotherapy was carried out in 137 patients (n=395 [34.7%]) for the primary retinoblastoma; it was not performed in 258 patients; and chemotherapy status was unknown in 207 patients. Among 137 patients with chemotherapy, the chemotherapeutic agents were described in 115 patients. No chemotherapeutic agent showed any association with occurrence of SPTs (P >.05).

Radiation therapy was performed for retinoblastoma in 463 of 602 patients (76.9%), it was not performed in 73, and radiation statistics were unknown in 66 patients. The SPTs, excluding PNETs, occurred within the radiation field in 323 cases and outside the radiation field in 150 cases (unknown in 2 cases) in patients who underwent radiation for retinoblastoma. Seventy-two SPTs developed in the patients who had not received radiation therapy.

Median age at diagnosis of retinoblastoma was 0.8 years (mean, 1.2 years; range, 0-12 years). Median time from diagnosis of retinoblastoma to first SPT was 12.0 years (mean, 14.7 years; range, 0-59.0 years). Median age at diagnosis of first SPT was 13.0 years (mean, 15.3 years; range, 0.3-60.4 years); at second SPT, 26.0 years (mean, 27.0 years; range, 2.5-72.1 years); at third SPT, 34.7 years (mean, 34.3 years; range, 17.0-53.1 years); and at fourth SPT, 43.2 years (mean, 41.6 years; range, 32.0-49.7 years). The histopathologic tumor type was recorded for 635 (94%) SPTs, which included 351 (55%) sarcomas, 71 (11%) carcinomas, 68 (11%) midline intracranial PNETs, 43 (7%) melanomas, 23 (4%) lipomas, 21 (3%) leukemia/lymphoma, 20 (3%) central nervous system tumors (excluding PNETs), and 12 (2%) embryonal or undifferentiated tumors (Table). The SPTs that occurred in the patients’ first decade of life were Wilms tumor, midline PNET, leukemia/lymphoma, and rhabdomyosarcoma (median age, 1.2, 2.7, 6.2, and 7.0 years, respectively). In the second decade, osteosarcoma (median age, 12.2 years), chondrosarcoma (median age, 13.2 years), sebaceous carcinoma (median age, 13.3 years), Ewing sarcoma (median age, 13.6 years), embryonal and undifferentiated tumor (median age, 13.7 years), central nervous system tumors (median age, 14.5 years), other sarcoma (median age, 15.1 years), fibrosarcoma (median age, 15.3 years), other benign tumor (median age, 15.7 years), and malignant fibrous histiocytoma (median age, 17.0 years) developed. In the third decade, mucosaceous dermoid carcinoma (median age, 20.5 years), adenocarcinoma (median age, 23.5 years), leiomyosarcoma (median age, 26.0 years), melanoma (median age, 27.0 years), neuroblastoma (median age, 28.5 years), lipoma (median age, 28.5 years), and squamous carcinoma (median age, 29.3 years) were
present. Other carcinoma (median age, 32.0 years), basal cell carcinoma (median age, 41.1 years), and small cell lung carcinoma (median age, 41.5 years) occurred after the fourth decade.

**MIDLINE INTRACRANIAL PNETs**

For midline intracranial PNETs, the median age at diagnosis was 2.7 years (mean, 2.9 years; range, 0.3-11.0 years). They were diagnosed with imaging studies, including ventriculography, computed tomography, or magnetic resonance imaging, in 57 patients; identified with tissue diagnosis in 22 patients; and both in 18 patients.

Among patients with PNETs, 46 received radiation treatment for the primary retinoblastoma, 9 did not receive radiation treatment, and 13 had unknown radiation treatment status. The proportion of patients with other SPTs who received radiation treatment (46 of 55 [86.7%]; Spearman correlation, \( P < .001 \)) did not differ significantly from the proportion of patients with other SPTs who received radiation treatment (417 of 481 [86.7%]; Spearman correlation, \( P > .05 \)).

Chemotherapy was adopted only for 4 of 52 patients (7.7%) for the primary retinoblastoma, with 16 patients having unknown chemotherapy status. The chemotherapy rate for patients with retinoblastoma of the midline intracranial PNET is significantly low compared with that of the patients with other SPTs (134 of 343 [39%]; Spearman correlation, \( P < .001 \)).

**SPTs OUTSIDE THE RADIATION FIELD OR NO RADIATION THERAPY**

The median age at diagnosis for SPTs outside the radiation field (excluding midline intracranial PNETs) or in patients with no irradiation was 15.0 years (mean, 19.2 years; range, 4.0-55.0 years). The histopathologic diagnosis was available for 268 of 284 SPTs (94.4%) and included 138 (51.5%) sarcomas, 36 (13.4%) melanomas, 30 (11.2%) carcinomas, 23 (8.6%) lipomas, 21 (7.8%) leukemias and lymphomas, 3 (1.1%) central nervous system tumors, and 6 (2.2%) embryonal and undifferentiated tumors.

The 138 sarcomas included 95 (68.8%) osteosarcomas, 16 (11.6%) leiomyosarcomas, 10 (7.2%) Ewing sarcomas, 3 (2.2%) rhabdomyosarcomas, 3 (2.2%) fibrosarcomas, 3 (2.2%) malignant fibrous histiocytomas, 1 (0.7%) chondrosarcoma, and 7 (5.0%) other or unspecified histopathologic subtypes. Sarcomas occurred in the long bones of lower extremities in 86 (61%) cases, long bones of the upper extremities in 9 (6%) cases, bladder in 6 (4%) cases, various other locations in 26 (18%) cases, and an unspecified location in 11 (10%) cases.

The 30 carcinomas included 7 (23.3%) adenocarcinomas, 2 (6.7%) small cell lung carcinomas, 3 (10%) squamous cell carcinomas, 3 (10%) sebaceous carcinomas, and 15 (50%) other and unspecified histopathologic subtypes. Carcinomas occurred in the breast in 5 (15%) cases, lung in 5 (15%) cases, gastrointestinal tract in 3 (9%) cases, exocrine gland in 8 (24%) cases, and various other or unspecified sites in 9 (30%) cases.

Among 17 patients with leukemia, acute lymphocytic leukemia was present in 5 patients (median age, 4.8 years; range, 3.2-9.5 years), acute myelogenous leukemia (AML) in 10 patients (median age, 6.2 years; range, 1-27 years), and unknown subtype in 2 patients. Nine of the 10 AML patients (90%) had been treated with chemotherapy for retinoblastoma, whereas 3 of the patients with acute lymphocytic leukemia had not been treated with chemotherapy and the rest of them had unknown history (Mann-Whitney test, \( P = .004 \)). Among 9 AML patients, 6 underwent 3-drug chemotherapy, 2 patients had 2-drug chemotherapy, and 1 was treated with triethylene melamine. Modern schemas of chemotherapy were regarded to be an important relating factor in developing secondary AML.

Tumor subtypes tended to occur within specific age ranges, with the earliest tumors occurring in the following general order (from youngest to oldest age): Wilms tumor, central nervous system tumors, leukemia/lymphoma, rhabdomyosarcoma, osteosarcoma, Ewing sarcoma, embryonal tumors, and squamous carcinoma (Figure 1). Melanomas occurred as early as the second decade and continued to occur into the sixth decade of life. All except 2 (6%) melanomas occurred on sun-exposed areas of skin. Carcinomas begin to appear in the second decade, but they occupy a much larger proportion of SPTs as patients reach their fourth decade of life and beyond.

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<tr>
<th>Table. Relationship of SPTs and Radiation Field</th>
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<td><strong>Histopathologic Type of SPT</strong></td>
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<td>Sarcoma</td>
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<td>Carcinoma</td>
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<td>Midline intracrani al PNET</td>
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Abbreviations: CNS, central nervous system; PNET, primitive neuroectodermal tumor; SPT, second primary tumor.
The median age at diagnosis for SPTs inside the radiation field was 9.3 years (mean, 9.3 years; range, 1.3-15.7 years). The histopathologic diagnosis was available for 299 of 324 SPTs (92.3%) and included 213 (71.2%) sarcomas, 41 (13.7%) carcinomas, 7 (2.3%) melanomas, and 17 (5.7%) central nervous system tumors, 7 of which were meningiomas.

The 213 sarcomas included 102 (47.9%) osteosarcomas, 24 (11.3%) rhabdomyosarcomas, 18 (8.5%) fibrosarcomas, 18 (8.5%) leiomyosarcomas, 16 (7.5%) malignant fibrous histiocytomas, 5 (2.3%) chondrosarcomas, and 30 (14.1%) unspecified histopathologic subtypes. All of these sarcomas involved the bone or soft tissues of the orbit except for 14 cases of unspecified site.

The 41 carcinomas included 10 (24.3%) sebaceous cell carcinomas, 7 (17%) basal cell carcinomas, 4 (9.8%) adenocarcinomas, 9 (22.0%) squamous cell carcinomas, and 4 (9.8%) mucoepidermoid carcinomas, and 7 (17%) other and unspecified histopathologic subtypes. Carcinomas occurred on the eyelid and periocular skin in 25 (61.0%) cases, sinuses and/or nasopharynx in 6 (14.6%) cases, parotid gland in 6 (14.6%) cases, thyroid gland in 3 (7.3%) cases, and the tear duct in 1 (2.4%) case. All melanomas occurred on the eyelid and/or periocular skin.

Tumor subtypes tended to occur within specific age ranges, with sarcomas predominating throughout the first 2 decades of life and carcinomas predominating beyond the third decade (Figure 1). Melanomas occurred mostly in the third decade.

**STATISTICAL ANALYSIS**

The median age at diagnosis of midline intracranial PNETs was significantly younger than for other SPTs occurring inside or outside the radiation field ($P < .001$). The median age at diagnosis of SPTs occurring inside the radiation field (median, 14.0 years) was significantly younger than for those occurring outside the radiation field (median, 17.0 years; $P < .001$). Sarcomas were more common inside the radiation field ($P < .001$), whereas melanomas, lipomas, leukemias, and lymphomas were significantly more common outside the radiation field ($P < .001$) (Table and Figure 2).
The goal of this study was to identify relationships between patient age, radiation field, tumor location, and tumor type for SPTs in patients with retinoblastoma. This is the largest study to date analyzing SPTs in this high-risk population, and it provides important findings to aid health care providers in monitoring this high-risk group. The most important conclusion of this study is that retinoblastoma survivors traverse multiple windows of susceptibility to various but discrete types of SPTs throughout their lives.

Midline intracranial PNETs, also called pinealomas or trilateral retinoblastomas, were the earliest form of SPT to which retinoblastoma patients were susceptible, at a median age of 2.7 years. There was no significant difference in the rate of PNET between patients who did or did not receive radiation therapy, suggesting that these tumors are not causally related to radiation treatment. Shields et al suggested that chemotherapy for bilateral retinoblastoma may decrease the likelihood that an intracranial tumor will develop. A lower chemotherapy rate in those with midline PNETs for the primary retinoblastoma than in those who presented with other SPTs in this study suggests a possible preventive effect of adjuvant chemotherapy on the development of midline PNETs.

Sarcomas comprised a second major group of SPTs, with a median age at onset of 13.0 years. Median age at onset was youngest for rhabdomyosarcomas and osteosarcomas (median age, 7.0 and 12.2 years, respectively) and oldest for leiomyosarcomas (median age, 26.0 years). Melanomas occurred at a median age of 27.0 years, though there was a wide range, from 9.2 to 37.0 years.

Carcinomas generally occurred later than other SPTs (median age, 29.0 years), though there was a wide age range from 8.3 to 72.1 years. The chronologic pattern for carcinomas was sebaceous cell carcinomas of the eyelid (median age, 13.3 years), mucopidermoid carcinomas of the salivary glands (median age, 20.5 years), squamous cell carcinomas of the periocular skin and nasopharynx (median age, 29.3 years), adenocarcinomas (median age, 25.5 years), basal cell carcinomas of the eyelid and periocular skin (median age, 41.1 years), and small cell lung carcinoma (median age, 41.5 years).

Adenocarcinomas occurred inside the radiation field (eg, eyelid, lacrimal gland, and nasopharynx) and outside the radiation field (eg, thyroid, lung, breast, pancreas, cervix, prostate, and gastrointestinal tract). Interestingly, the age at onset for small cell lung cancer was significantly younger than for patients with the sporadic form of this cancer. Furthermore, the RB1 gene is frequently mutated in small cell lung cancer. Taken together, these findings suggest that RB1 mutations may predispose individuals to small cell lung cancer and that smoking should be strongly discouraged in this population.

Although secondary AML after retinoblastoma is a rare occurrence, there is a consensus that patients with retinoblastoma treated with chemotherapy are at increased risk of secondary AML. In this study, AML was significantly associated with a positive history of chemotherapy for retinoblastoma compared with the other leukemia patients. Specific leukemogenic agents, age at administration, and total dose of chemotherapy all may play a factor in increasing the risk of the secondary AML. The possible complication of secondary AML should be acknowledged and monitored for those who have chemotherapy for retinoblastoma.

Radiation treatment had a significant effect on the age at onset and histopathologic spectrum of SPTs. Within the radiation field, SPTs tended to develop at an earlier age (median, 14.0 years) than those outside the radiation field (median, 17.0 years). Sarcomas were more common inside the radiation field, especially chondrosarcomas, fibrosarcomas, and malignant fibrous histiocytomas. Conversely, melanomas and lipomas were more common outside the radiation field. Neoplasms such as leukemia, lymphoma, and Ewing sarcoma were seen only outside the radiation field.

RB1 gene mutations have been identified in many survivors after both retinoblastoma and other malignant tumors in childhood, suggesting that RB1 mutations play a role in the development of these tumors. However, the differing ages of susceptibility between these SPTs suggest that RB1 mutations may play distinct biological roles in different tumor types. For example, it has been suggested that RB1 mutation is rate-limiting for retinoblastoma, a few additional mutations may be required for childhood sarcomas, and perhaps many additional mutations are required for adult epithelial cancers. The findings of this study will be helpful in this important area of research.

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