# Second Tumors in Retinoblastoma Survivors after Ionizing Radiation

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Retinoblastoma (RB) is the most common ocular neoplasm in children, whose development depends on two mutational events that occur in both alleles of the retinoblastoma susceptibility gene (*RB1*). Regarding the nature of these mutational events, RB can be classified as hereditary if the first event is a germline mutation and the second one is a somatic mutation in retina cells or nonhereditary if both mutational events occur in somatic cells. Although the rate of survival of RB is significantly elevated, the incidence of second malignant neoplasms (SMNs) is a concern, since SMNs are the main cause of death in these patients. Furthermore, evidence confirms that hereditary RB survivors are at a higher risk for SMNs than nonhereditary RB survivors. This risk seems to increase with the use of ionizing radiation in some therapeutic approaches commonly used in the treatment of RB.

retinoblastoma | RB1 gene | ionizing radiation | second malignant neoplasms | hereditary cancer | radiation biology

## 1. Introduction

Retinoblastoma (RB) is the most common primary intraocular tumor in children. Its worldwide estimated incidence ranges from 1 in 15,000 to 1 in 18,000 live births, showing no racial, ethnic, or gender predisposition [1][2]. Retinoblastoma's survival rate can exceed 95% with early diagnosis and treatment. Thus, the survival rate in children diagnosed with RB in medically developed countries is significantly higher when compared to undeveloped countries due to the late diagnosis [3][4].

RB develops from the retinoblasts, precursors of retinal cells, and can be classified according to the disease's laterality: unilateral, if only one of the eyes is affected, or bilateral (20–30% of cases) if both eyes are affected. Regarding its genetic classification, it is clinically classified as hereditary, representing about 45% of the diagnosed cases, or nonhereditary. Tumor development is associated with the retinoblastoma susceptibility gene (*RB1*), a recessive tumor suppressor gene involved in cell growth and development, and it is reported that it only occurs when both alleles of *RB1* are lost or undergo deletion, inactivation, or mutation [3][4][5]. In 1971, Knudson et al. [6] proposed the "two-hit" hypothesis, stating that RB is caused by two complementary chromosomal mutations. Thus, nonhereditary RB is associated with two somatic mutations, whereas hereditary RB is related to a germline mutation that would be present in all body cells, followed by a mutation in somatic retina cells. The offspring of hereditary RB patients are predisposed to the disease with a penetrance of 80% [3][4][5]. All cases of nonhereditary

RB are associated with a unilateral tumor, whereas the hereditary form is mainly bilateral; however, in some cases, it can be unilateral. About 85% of unilateral RB result from somatic mutational events, and only 15% are related to hereditary RB [3][5]. However, the two mutational events that affect the *RB1* alleles seem to be insufficient for the formation of the malignancy, since a mutation in *RB1* first leads to retinoma, a benign precursor of RB [3][7]. In 2007, Corson and Gallie [8] stated that additional mutational events were required for the formation of a malignancy, supporting a “three-hit” hypothesis [9].

## 2. Risk of Second Tumor Incidence in Survivors of Retinoblastoma Treated with Radiation Therapy

The main cause of death among hereditary RB survivors remains to be the occurrence of subsequent malignant neoplasms (SMNs). SMNs are new tumors that develop after the incidence of a primary tumor. While some authors defend that an SMN is histologically independent from the first primary tumor, others state that trilateral RB has to be reported as an SMN. As already mentioned, all cells of hereditary RB patients carry a germline mutation in one allele of *RB1*, a tumor suppressor gene. On the other hand, nonhereditary RB is associated with mutations that occur only in retina cells. Therefore, survivors of hereditary RB seem to present a higher risk of developing SMNs compared to the general population as well as nonhereditary RB survivors [10]. Thus, this section aims to analyze some studies (**Table 1**) that have been performed to compare the incidence of SMNs between hereditary and nonhereditary RB and also to evaluate the risk of developing SMNs after treatment with RT in RB patients [10].

**Table 1.** Studies carried out to examine the risk of SMN incidence in survivors of RB when treated with radiation therapy.

| Authors | Sample Size | Treatment (# Patients) | Type of SMNs | Treatment Related to SMNs (# Patients) [a] | SMNs Location (# SMNs) [b] |
|---|---|---|---|---|---|
| Mohney et al. (1998) [11] | 180 patients:<br>- 82 hereditary<br>- 98 nonhereditary | Hereditary: RT (60); ChT (15); Unknown (7)<br>Nonhereditary: Not disclosed | Hereditary: 16 (6 soft tissue tumors, 4 bone tumors, 3 melanomas, 3 carcinomas—1 breast, 1 pancreas, and 1 thyroid)<br>Nonhereditary: 3 (1 benign soft tissue tumor and 2 carcinomas—cervical and breast) | Hereditary: EBRT (6); EBRT + CT (4); RA (3); EBRT + BT + RA (1); ChT (1); Unknown (1)<br>Nonhereditary: RA (1); Unknown (2) | Hereditary: In-field of irradiation (4); outside field of irradiation (10)<br>Nonhereditary: In-field of irradiation (1) |
| Kleinerman et al. (2005) [12] | 1601 patients: | Hereditary: Surgery (94); ChT (16); RT | Hereditary: 260 (75 bone, 34 connective and | Hereditary: RT (241); No RT (19) | Not disclosed |

| Authors | Sample Size | Treatment (# Patients) | Type of SMNs | Treatment Related to SMNs (# Patients) [a] | SMNs Location (# SMNs) [b] |
|---|---|---|---|---|---|
| | - 963 hereditary<br>- 638 nonhereditary | (466); RT + ChT (383); Unknown (4)<br>Nonhereditary: Surgery (480); ChT (40); RT (67); RT + ChT (47); Unknown (4) | soft tissue, 32 nasal cavities, 29 cutaneous melanomas, 17 eye and orbit, 10 brain, 10 female breast…)<br>Nonhereditary: 17 (7 female breast, 2 brain, 2 thyroid, 1 Hodgkin's lymphoma, 1 leukemia…) | Nonhereditary: Not disclosed | |
| Marees et al. (2008) [13] | 668 patients:<br>- 298 hereditary<br>- 370 nonhereditary | Hereditary: Surgery (70); ChT (16): RT (152); RT + ChT (58); Unknown (2)<br>Nonhereditary: Surgery (322); ChT (8): RT (22); RT + ChT (8); Unknown (10) | Hereditary: 62 (20 soft tissue, 16 bone tumors, 13 melanomas, 11 epithelial—4 bladder, 3 lung, 2 breast, and 2 non-Hodgkin lymphomas)<br>Nonhereditary: 12 (5 solid cancers, 3 soft tissue, 2 lung, and 2 leukemia) | Hereditary: EBRT (38); EBRT + ChT (17); Surgery (3); Laser coagulation (3); Unknown (1)<br>Nonhereditary: Surgery (12) | Hereditary: In-field of irradiation (22); outside field of irradiation (33)<br>Nonhereditary: In-field of irradiation (0); outside field of irradiation (0) |
| MacCarthy et al. (2013) [14] | 1927 patients:<br>- 806 hereditary<br>- 1121 nonhereditary | Not disclosed | Hereditary: 146 (33 leiomyosarcoma, 33 osteosarcomas, 14 melanomas, 15 brain/CNS, 9 female breast, 9 meningiomas, 8 bladder…) [c]<br>Nonhereditary: 23 (3 osteosarcomas, 4 brain/CNS, 3 meningioma, 2 female breast, 2 melanomas…) [c] | Not disclosed | Hereditary: In-field of irradiation (45); outside field of irradiation (70)<br>Nonhereditary: In-field of irradiation (6); outside field of irradiation (14) |
| Gregersen et al. (2020) [15] | 323 patients<br>- 133 hereditary | Hereditary: RT (31); RT + ChT (6); RT + ChT + | Hereditary: 25 (14 sarcomas, 6 melanomas, 3 carcinomas—2 | Hereditary: EBRT (13); No EBRT (12)<br>Nonhereditary: | Hereditary: In-field of irradiation (6); outside field of |

| Authors | Sample Size | Treatment (# Patients) | Type of SMNs | Treatment Related to SMNs (# Patients) [a] | SMNs Location (# SMNs) [b] |
|---|---|---|---|---|---|
| | - 190 nonhereditary | enucleation (13); RT + enucleation (93); ChT (2); ChT + enucleation (7); enucleation (171) Nonhereditary: RT (25); RT + ChT (6); RT + ChT + enucleation (11); RT + enucleation (75); ChT (2); ChT + enucleation (2); enucleation (12) | breast and 1 ovarian cancer—and 2 CNS) Nonhereditary: 13 (5 carcinomas—2 lung, 1 breast, 1 cervical cancer, and 1 thyroid cancer—4 sarcomas, 3 melanomas, and 1 CNS) | EBRT (0); No EBRT (13) | irradiation (7) Nonhereditary: In-field of irradiation (0); outside field of irradiation (0) |
| Schonfeld et al. (2021) [16] | 2052 patients: - 1128 hereditary - 924 nonhereditary | Hereditary: RT (550); RT + ChT (435); ChT (39); Surgery (90); Unknown (14) Nonhereditary: RT (101); RT + ChT (86); ChT (61); Surgery (636); Unknown (40) | Hereditary: 265 (89 soft tissue sarcomas, 80 bone tumors, 28 melanomas, 12 breast, 11 nasal cavity, 8 pineoblastoma, 6 CNS…) [d] Nonhereditary: 27 (8 breast, 3 melanomas, 3 gastrointestinal, 2 thyroid, 2 lung…) [d] | Not disclosed | Not disclosed |
| Zhao et al. (2021) [17] | 62 patients - 40 hereditary - 17 nonhereditary - 5 unknown | RT (35); Chemotherapy (17); Surgery (16); Unknown (5) [e] | Hereditary: 40 (37 sarcomas, 4 breast cancers, 3 adenocarcinoma, 2 meningiomas, 2 thyroid carcinoma...) Nonhereditary: 17 (11 sarcomas, 4 carcinomas...) | Hereditary: RT (27); No RT (10) Nonhereditary: RT (7); No RT (10) | Not disclosed |
| Sethi et al. (2013) | 86 patients | Proton therapy (55) | Proton therapy: 1 (osteosarcoma) | | Proton therapy: In-field of |

| Authors | Sample Size | Treatment (# Patients) | Type of SMNs | Treatment Related to SMNs (# Patients) [a] | SMNs Location (# SMNs) [b] |
|---|---|---|---|---|---|
| [18] | | Photon therapy (31) | Photon therapy: 4 (3 sarcomas—orbital, maxillary, temporal bone—and 1 glioblastoma multiforme) | | irradiation (0); outside field of irradiation (1) Photon therapy: In-field of irradiation (4); outside field of irradiation (0) |
| Mouw et al. (2014) [19] | 60 tumors [f] | PRT (60) [g] | Hereditary: 1 (osteosarcoma of the femur) Nonhereditary: 0 | | Hereditary: In-field of irradiation (0); outside field of irradiation (1) Nonhereditary: In-field of irradiation (0); outside field of irradiation (0) |

[a] Treatment approaches in patients who developed SMNs; [b] Location of SMNs in the irradiated group of patients. This classification between in-field and outside the field of radiation is based on the region where the SMNs develop (within the head and neck region is considered in-field of irradiation); [c] Among the hereditary group of patients, 146 SMNs were detected in 112 patients, whereas in the nonhereditary group of patients, 23 SMNs were detected in 20 patients; [d] Among the hereditary group of patients, 265 SMNs were detected in 239 patients, whereas in the nonhereditary group of patients, 27 SMNs were detected in 25 patients; [e] Data not disclosed regarding therapeutic approaches by hereditary/nonhereditary group; [f] Data show 60 tumors in 49 RB patients; [g] Among this group of patients treated with PRT, 25 patients had also received chemotherapy, and 43 tumors were treated with cryotherapy/laser; #: number; RT: radiation therapy (not specified); EBRT: external beam radiation therapy; BT: brachytherapy; RA: radium implants; ChT: chemotherapy; PRT: proton radiation therapy.


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