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Chapter

Secondary Malignancies in Adulthood and After Retinoblastoma Treatment in Childhood

Alena Furdova and Juraj Sekac

Abstract

Advances in retinoblastoma treatment in children nowadays and in the last decades lead to success and adulthood life without problems. Treatment modalities used in childhood to cure the retinoblastoma can affect health later. Some secondary malignancies in patients with retinoblastoma may be long-term side effects of radiation and chemotherapy. However, rates of second cancers in people treated for hereditary retinoblastoma are higher than in people who had sporadic retinoblastoma. The survivors of retinoblastoma in whom second malignant neoplasms develop are at a higher risk for the development of additional tumors than they were for the development of a second tumor. The standardized incidence rate of secondary malignancies is about 15% in inherited cases and about 1.5% in nonheritable retinoblastoma. However, today there is no clear consensus on what, if any, screening protocol would be most appropriate and effective.

Keywords: retinoblastoma, secondary malignancies, secondary tumors after radiotherapy, chemotherapy

1. Retinoblastoma and secondary malignancies

With major advances in retinoblastoma treatment in recent decades, most children treated for retinoblastoma are now expected to have a normal life [1]. Some of the treatment modalities used in childhood to cure the retinoblastoma can affect a child’s health later in life, so watching for health effects as they get older has become more of a concern in recent years [2]. The prognosis for survival is excellent. The current therapy includes an improved survival rate and decreased iatrogenic side effects [2–4].

The most common primary intraocular malignant tumor in children is retinoblastoma. Hereditary retinoblastoma with gene Rb1 has bilateral tumor infiltration most frequently. Also children with positive family history are presumed to have a germline Rb1 mutation [3]. Screening of mutations in the Rb1 gene can help to identify heritable retinoblastoma and contribute to clinical management and genetic counseling for affected families [5]. The main criteria in determining the result of a mutation is its location in the 3D structure. The altered 3D model structures of the Rb1 novel mutant proteins are also available today [6, 7].
Improvements in survival, from a 3-year survival rate of 76% in the 1970s to a 5-year survival rate of 97% since the mid-1990s, are due to advances in treatment [2, 8, 9]. But children who survive and have hereditary retinoblastoma have an increased risk for secondary malignant neoplasms (SMN). The most common subsequent malignancies are in bony tissues like sarcomas. Also secondary melanoma can develop most frequently [10, 11]. The authors of several studies in retinoblastoma survivors have reported an increased risk of SMN associated with previous treatment, particularly in radiotherapy (RT) which showed an increased risk when it was indicated in children under the age of 1 year [12–14]. In retinoblastoma survivors increased incidence of common epithelial cancers (especially in the lungs and breast) has been observed [15–18].

Young people treated in childhood for retinoblastoma are at risk, to some degree, for several possible late effects of their cancer treatment. The risk of late effects depends on a number of factors, such as the specific treatments used, the doses of treatment, the type of retinoblastoma (heritable or nonheritable), and the age of the patient when the therapy was used. The late effects of the retinoblastoma treatment are:

- Enucleation of the eye globe leads to loss of vision and cosmetic defects.
- Radiotherapy, especially external radiotherapy, of the affected eye leads to visual acuity loss or reduction and can lead also to deformities of the bony orbit.
- Kidney function reduction.
- Chemotherapy leads to heart problems.
- In children with retinoblastoma, generally, slowed growth and development are observed.
- In children with retinoblastoma generally changes in sexual development and ability to have children are observed.
- In survivors of retinoblastoma in adult age, an increased risk of SMN, especially in children with hereditary retinoblastoma, is present.

2. Secondary cancers after retinoblastoma treatment

Although the risk for a second retinoblastoma decreases significantly after 5 years of age, follow-up on all children after treatment is critical and particularly for those who carry the Rb1 mutation. Retinoblastoma survivors are at increased risk for local secondary complications after treatment, e.g., retinal detachment and cataracts, in later life because of the retinal changes caused by the cancer and therapy modalities. Although the general risk for secondary cancers associated with intravenous chemo-therapies is high, it's thought to be lower than the risk from radiation therapy.

2.1 Hereditary retinoblastoma (heritable)

Children with the heritable form of retinoblastoma have a much higher risk of developing other types of cancer throughout their lives. The most common secondary cancers among hereditary retinoblastoma survivors include:
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- Osteosarcoma
- Soft tissue sarcomas
- Malignant skin melanoma
- Lung cancer
- Lymphoma
- Bladder cancer
- Uterine cancer
- Breast cancer
- Brain tumors
- Cancers in the head region, mouth, or nose

The risk for these cancers is even higher in any parts of the body that got radiation during treatment for retinoblastoma in childhood. This is because each cell in the body has an abnormal Rb1 tumor suppressor gene, which, if it were normal, would help stop some of these cancers from forming. Most of these cancers are very treatable if detected early, which is why it's very important that these children (young people) are followed closely throughout their lives. Retinoblastoma survivors in adult age have the increased risk of SMN, and it is necessary to teach them and their relatives and speak with them about other factors that might increase their risk of secondary malignancies in adult age. Increased risk of skin melanoma may be due to higher sun exposure, and smoking can increase lung cancer risk. These young survivors have to avoid the risk factors. It is necessary to inform the relatives also about screening tests in adulthood of retinoblastoma survivors.

Children who got the heritable form of retinoblastoma also have a small risk of developing a tumor in the pineal gland within a few years. Magnetic resonance imaging (MRI) scans of the head in retinoblastoma survivors should be done regularly for several years after retinoblastoma treatment in childhood with the aim of detecting secondary tumors as soon as possible.

2.2 Sporadic retinoblastoma (nonheritable)

Patients with the nonheritable form of retinoblastoma who do not have the Rb1 gene change in all of their cells do not have such a high risk of secondary malignancies. Still, the risk of some types of secondary malignancies might be higher as a long-term effect of chemotherapy or external radiation therapy.

2.3 Follow-up

The whole long-life follow-up is necessary to retinoblastoma survivors. Long-term follow-up guidelines for survivors of childhood cancers and also retinoblastoma were invented by the Children's Oncology Group (COG). These guidelines are helpful for relatives but also doctors to send the patient regularly for screening tests, and they help to realize how late effects of, e.g., radiotherapy, can be treated [3].
In child’s healthcare team, it is very important to discuss possible long-term complications after treatment and to inform also parents and relatives, if these problems appear, how to treat them. The guidelines of COG are available for healthcare professionals, but also patients’ version is available (as “Health Links”) on the webpage as well.

2.4 Emotional and social issues

Even though most children with retinoblastoma are very young at the time of diagnosis, under the age of 4, they may have emotional or psychological problems that need to be addressed during the treatment and also after the treatment. Depending on the age of retinoblastoma, these children have some problems at school work due to visual acuity loss or reduction.

The factors can lead to problems in their life and they need help. Doctors, ophthalmologists, oncologists, and other members of the healthcare team like psychologists can recommend special support programs and services to help children during and after treatment and to avoid misdiagnosed secondary malignancies in adulthood. Parents and relatives can also be affected with the situation of primary retinoblastoma treatment and also secondary tumors which appear later. The family situation is worsened; financial stress and traveling to and staying near the cancer center are complicated for the family. Social programs and psychologists can help families deal with these problems. Oncology centers for patients with retinoblastoma may have programs to introduce new patients and their relatives to patients who have finished retinoblastoma therapy.

Loss of visual acuity is serious but enucleation leads to defect in the face. In patients with these problems, social groups and programs for the visually impaired can help. Most children treated for retinoblastoma can have good visual acuity in the unaffected eye, but it can happen that the surrounding tissues around the treated eye and the area of the orbit might have changes and later can lead to secondary malignancies. Such changes can be treated by reconstructive surgery. Early intervention can help to avoid psychological problems and also avoid secondary tumors in soft tissues in the orbit [3].

3. Secondary malignancies

In patients with retinoblastoma, secondary malignancies can be the result of the long-term side effect of radiation and chemotherapy. The incidence of secondary malignancies in children treated for hereditary retinoblastoma is higher than in children with sporadic retinoblastoma. In the study of MacCarthy et al. in 1927, retinoblastoma patients are diagnosed in Britain from 1951 to 2004; standardized incidence rate of secondary malignancies was reported: it was significantly higher in inherited retinoblastoma children—13.7% cases compared to 1.5% in nonheritable cases [19].

Osteosarcoma as the most frequent secondary malignancy following retinoblastoma treatment can be associated with the Rb1 gene and/or induced by radiotherapy. Studies have consistently demonstrated increased risks for bone cancers and soft tissue sarcomas among retinoblastoma survivors who received radiotherapy, but by investigations of chemotherapy, subsequent malignant neoplasm development has been limited. Previous reports among hereditary retinoblastoma survivors in studies have suggested that increased risks of bone cancers and soft tissue sarcomas are associated with chemotherapy [20, 21], but in the study of Wong et al., they were results of first comprehensive analysis of chemotherapy-related SMN risk [22].
In a study of 46 survivors of retinoblastoma who received triethylenemelamine and radiotherapy, 7 secondary malignancies were reported. This malignancies were sarcomas of the bones (femur and orbit), as well as other cancers of the brain, parotid gland, pineal gland, and cervix [23]. In other studies in 18 retinoblastoma survivors who developed a subsequent osteosarcoma, 7 and 6 survivors had received triethylenemelamine or cyclophosphamide, respectively [24].

In retinoblastoma survivors after receiving cyclophosphamide, secondary malignancy as osteosarcoma was frequently reported in other studies [25–27]. In a study of 25 survivors who received RT and developed subsequent soft tissue or bone sarcomas, they received cyclophosphamide, either alone or in combination with other agents [11]. Individual cases of bone cancers have also been reported in patients who received triethylenemelamine [28]. One study reported few secondary malignancies after retinoblastoma treatment with carboplatin, vincristine, and etoposide, but the mean follow-up time for hereditary survivors was only up to 7 years [29]. Additional follow-up in the future is needed to capture the typical age groups and intervals after retinoblastoma therapy for adults for SMN development.

In a study of 15 retinoblastoma survivors with secondary acute myelogenous leukemia, 12 of them had been treated with adjuvant chemotherapy, including topoisomerase II inhibitors, epipodophyllotoxins, and alkylating agents [30].

Studies of chemotherapy treatment for retinoblastoma and related SMN risks among retinoblastoma survivors are limited. But some results of previous studies reported CT-related risks of bone cancers among childhood cancer survivors. A case-control study of the UK National Registry of Childhood Tumors reported a nonsignificant 2.1-fold increased risk for bone cancers in the chemotherapy plus RT group relative to the group receiving RT only [26]. Childhood cancer survivors who had an alkylator score ≥ 3 and had received irradiation ≥1000 rad had a 1.6-fold increased risk for bone cancers as it was reported in another case-control analysis [31]. In both abovementioned studies, a supra-additive effect was observed when comparing the chemotherapy plus RT relative risk with the independent risks for RT and chemotherapy. There was a greater risk when survivors were treated with both as opposed to RT or chemotherapy alone [26, 27, 31]. The result in study of Wong et al. was limited to the small number of retinoblastoma survivors who were treated with chemotherapy but no RT, and there are no reported SMNs in this treatment group. But they were unable to estimate SMN risks associated with CT alone [22]. These studies also demonstrate a positive dose-response relationship for the alkylator score with bone sarcoma risk among childhood cancer survivors treated with chemotherapy only.

In studies among retinoblastoma survivors who received chemotherapy and RT, risk is increased for soft tissue sarcomas, especially leiomyosarcomas. A case-control analysis of a UK-based cohort of childhood cancer survivors reported a positive dose-response relationship for soft tissue sarcoma among survivors treated with alkylating agents [32]. Previous studies among retinoblastoma survivors have reported higher SMN risk with RT administered before the age of 1 year [12, 14, 33]. Although the alkylating agent-related risk estimate for leiomyosarcomas was higher for receipt of alkylating agents at age < 1 than for age ≥ 1 year, this difference was not statistically significant, and thus, it remains unclear whether treatment-related risks differ by age. Further research is needed to understand whether younger individuals may be more susceptible to alkylating agent-related SMNs. Other studies also noted a particularly elevated risk for leiomyosarcomas compared with other soft tissue sarcomas after retinoblastoma treatment, but those studies lacked data on retinoblastoma treatments [7, 15, 30, 31]. Loss of heterozygosity in Rb1 and in other major tumor suppressor genes, as well as deletions of chromosome 13, that contain the Rb1 gene has been reported in individuals who developed uterine
leiomyosarcomas. Future genetic studies in this population could elucidate the predisposition for leiomyosarcomas in patients with retinoblastoma [35, 36].

Children with the heritable form of retinoblastoma also have a very small risk to develop within a few years a tumor in the pineal gland; it is referred as a trilateral retinoblastoma. Tumors can start there, while the pineal gland can have cells similar to retina cells. That is why it is important to perform MRI of the head for several years after treatment of retinoblastoma to detect these tumors as early as possible. Trilateral retinoblastoma has been the principal cause of death from retinoblastoma in the United States during the first decade of life [37]. Yamanaka, Hayno, and Takashima analyzed 211 cases of trilateral retinoblastomas. The average latency period between the onset of retinoblastomas and trilateral retinoblastomas was 1.5 ± 1.8 years. Pineal tumors were found in almost 74% and sellar tumors in 22%. The overall median survival was 10.3 months, and the 5-year survival rate was 16%, while in patients receiving high-dose chemotherapy by stem cell transplantation, the survival time was significantly longer than with conventional chemotherapy. The authors conclude that trilateral retinoblastoma patients with an irradiation history had shorter survival than those without irradiation history for retinoblastoma, and high-dose chemotherapy should be considered as a potential treatment option for trilateral retinoblastomas [38].

Among patients with hereditary disease, treatment with radiotherapy in 95% was associated with a further increase in the risk of a subsequent cancer. After 30 years of follow-up, elevated risks of epithelial cancers (lung, bladder, and breast) were observed among survivors of hereditary retinoblastoma [18]. In the study of Wong et al., it was found that the incidence of secondary cancer after retinoblastoma treatment is higher due to the genetic predisposition. Genetic predisposition has a substantial impact on risk of subsequent cancers in retinoblastoma survivors, and radiation treatment increases it. A radiation dose-response relationship is demonstrated in all types of soft tissue sarcomas. Retinoblastoma patients should be examined for new cancers and followed into later life also in whole adulthood due to extraordinary secondary cancer risk [39].

The development of lung cancer is affected to a considerable extent by somatic mutations in the Rb1 gene in patients with an elevated risk for lung cancer. Higher risk of developing lung cancer is in patients undergoing chemotherapy and radiotherapy in retinoblastoma treatment [40, 41]. Some studies suggested there might also be an increased risk for lung cancer in non-irradiated patients [15].

Bladder tumors are distinguished between malignant and nonmalignant. In this case, there is only a small difference between them that is difficult to determine microscopically. The most common bladder cancer is papilloma and papillomavirus, which together account for about 90% of all tumors. The borderline between malignant and nonmalignant bladder tumors is very thin [42]. Study of Marees et al. significantly elevated risk of bladder cancer among hereditary retinoblastoma patients after prolonged follow-up, whose prevalence is mostly 30 years after retinoblastoma treatment [18]. Alterations in an Rb1 pathway have been established as a major contributor to bladder tumorigenesis, and carriers of an Rb1 mutation have an elevated risk of bladder cancer, when they reach the ages at which these malignancies occur in the population at large [43].

All available studies on the occurrence of secondary malignity after retinoblastoma treatment indicate that the most important risk factor remains the Rb1 gene mutation. Kleinerman describes in his study the risks of new cancers after radiotherapy in long-term survivors of retinoblastoma. Radiation increases the risk of another cancer in hereditary patients by 3.1-fold. Hereditary patients continue to have at significantly increased risk for sarcomas, melanoma, and cancers of the brain and nasal cavities [44].
3.1 Case report 1

Girl with bilateral retinoblastoma treated in 1989 in Bratislava by enucleation of the right eye and chemotherapy plus RT on the left side. Due to secondary complication, she underwent cataract surgery in 1993 and was aphakic and got glasses. In 2011 secondary tumor developed in the orbit region with infiltration to the brain. She underwent surgery three times by a neurosurgeon with adjuvant chemotherapy and high-dose RT due to verified leiomyosarcoma. In 2015 due to progression of the leiomyosarcoma, she underwent photon beam irradiation with gamma knife. Tumor masses infiltrating the orbit lead to exenteration of the orbit (Figures 1–3).

The risk of secondary malignancies after retinoblastoma treatment is high, but in contrast to bone cancers and leiomyosarcomas, chemotherapy was not associated with increased melanoma risk [10, 17]. The development of skin melanoma may be related to an underlying genetic predisposition associated with retinoblastoma rather than treatment modality. Major susceptibility genes for melanoma include CDKN2A and CDK4 which are both upstream from the Rb1 gene. In the future an additional investigation is necessary to understand the association between the development of melanoma and retinoblastoma treatment [45].

The leukemogenicity of certain chemotherapeutic agents is well established, and there are connections between alkylating agents and a range of development of solid tumors.
SMNs. Chemotherapy has also been associated with an increased risk for other types of malignancies, e.g., lung cancer after Hodgkin and non-Hodgkin lymphomas, stomach cancer after Hodgkin lymphoma in combination with high-dose abdominal RT, and colorectal cancer after childhood cancer [46, 47]. Increased sarcoma risk after childhood cancer is associated with anthracyclines therapy, especially after Hodgkin lymphoma or a primary sarcoma in childhood [48].

Hereditary retinoblastoma survivors who were treated with alkylating agents plus RT have a significantly higher risk of developing bone cancers and leiomyosarcomas than those treated with single RT. Excess risks of secondary cancers associated with alkylating agents plus RT persist for decades. Significantly higher incidence of leiomyosarcomas is diagnosed at a median age of 34 years. These risks are present during long-term follow-up of retinoblastoma survivors. Guide recommendations for future treatment protocols will define chemo-related SMN risk among retinoblastoma survivors, particularly in patients treated with chemotherapy without RT.

Current chemotherapy agents recommended for retinoblastoma include cyclophosphamide, ifosfamide, carboplatin, vincristine, etoposide, topotecan, and doxorubicin [49–51]. Most retinoblastoma survivors who received an alkylating agent received TEM, which is no longer used in clinical practice [52]. On the basis of the recently developed cyclophosphamide equivalent dose, TEM has substantially lower hematologic toxicity than agents used in current clinical practice. Generally there is the long latency period of SMN development and potentially different CT drug-related adverse effect. In the future studies have to evaluate SMN risk with long-term follow-up of patients with retinoblastoma treated with current agents. The cyclophosphamide equivalent dose can be easily calculated, facilitating its use for patient counseling. It is independent of the drug dose distribution of a particular patient population, a characteristic that will allow direct comparisons of outcomes among epidemiological cohorts. The use of the cyclophosphamide equivalent dose is promising in future research, assessing cumulative alkylating agent exposure [53].

Several limitations of certain studies dealing with SMNs should be taken into account. On reports of family history of retinoblastoma and laterality to define hereditary status, some unilateral retinoblastoma survivors could have had a germline Rb1 mutation and should have been included into analysis [17, 34].

Although some survivors in studies are lost to follow-up due to different reasons, SMN risk estimates are unlikely to be affected, because response was not related to
treatment received for retinoblastoma [54]. Due to results of Wong et al., although SMNs are more likely to be misclassified because histology is not specified, sensitivity analyses including 1-year versus 5-year survivors also yielded comparable results [22].

Skin malignancies are rare but usually are in the head region. Orbital malignancies are more frequent. In the study was presented a 22-year-old young man with history of bilateral retinoblastoma initially in childhood treated by enucleation of his left eye. The histopathology findings showed a moderately differentiated tumor with vitreous seeding. The patient received chemotherapy in addition to radiotherapy to his right eye. More than 20 years later, he got proptosis due to the right orbital tumor. The excisional biopsy of his orbital mass verified a spindle cell sarcoma with features of malignant fibrous histiocytoma [55].

3.2 Case report 2

Boy with unilateral retinoblastoma treated in 1988 in Bratislava with enucleation of the left eye globe and chemotherapy and RT. He got individual prosthesis.
without complications. In 2017 he developed “inflammation” of the right eye upper eye lid and was sent to an ophthalmologist for chalazion excochleation. By excisional biopsy was confirmed squamous cell carcinoma (Figures 4 and 5).

4. Conclusion

Retinoblastoma survivors as carriers of the retinoblastoma gene have a long life and increased incidence for secondary tumors. Ophthalmologists should always keep this in mind to be able to provide these patients with proper counseling, plan for close long-term follow-up, and update their knowledge in the therapy modalities of retinoblastoma current management and possible secondary malignancies in adulthood. A clear consensus on the form of a screening protocol would be most appropriate and effective in preventing future malignancies.

Conflict of interest

None of the authors has conflict of interest with this submission.
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Author details

Alena Furdova* and Juraj Sekac
Univerzita Komenského v Bratislave Lekárska fakulta Klinika oftalmológie LF UK Špitálska, Bratislava, Slovakia

*Address all correspondence to: alikafurdova@gmail.com

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