

VU Research Portal

Second primary tumors in patients with retinoblastoma: a review of the literature

Moll, A.C.; Imhof, S.M.; Bouter, L.M.; Tan, K.E.W.P.

published in

Ophthalmic Genetics

1997

DOI (link to publisher)

[10.3109/13816819709057880](https://doi.org/10.3109/13816819709057880)

document version

Publisher's PDF, also known as Version of record

[Link to publication in VU Research Portal](#)

citation for published version (APA)

Moll, A. C., Imhof, S. M., Bouter, L. M., & Tan, K. E. W. P. (1997). Second primary tumors in patients with retinoblastoma: a review of the literature. *Ophthalmic Genetics*, 18, 27-34.
<https://doi.org/10.3109/13816819709057880>

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal ?

Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

E-mail address:

vuresearchportal.ub@vu.nl

© Ophthalmic Genetics 0167-6784/97/
US\$ 12.00

Ophthalmic Genetics – 1997, Vol. 18,
No. 1 pp. 27–34
© *Aeolus Press*
Buren (The Netherlands) 1997

Accepted 7 August 1996

Second primary tumors in patients with retinoblastoma

A review of the literature

Annette C. Moll¹
Saskia M. Imhof¹
Lex M. Bouter²
Karel E.W. P. Tan¹

Departments of ¹Ophthalmology and ²Epidemiology and Biostatistics,
Vrije Universiteit, Amsterdam, The Netherlands

Abstract *Purpose:* The aim of this survey was to review the different studies regarding the occurrence of second primary tumors (SPT) among survivors of retinoblastoma. *Methods:* Ovid (Medline, Current contents life, Psychlit, Embase) was searched for the years 1966–1995 using the mesh headings: ‘retinoblastoma’, ‘second primary neoplasms’, and ‘multiple primary neoplasms’. The inclusion criteria were: the study should involve 50 patients or more and should not be limited to one specific SPT. A checklist with criteria regarding the study design and the results was applied to each study. *Results:* Eleven studies were identified which met the inclusion criteria. Thirty-five different types of SPT ($N_{\text{total}}=243$) were reported. Most of them were osteosarcomas (37.0%), followed by melanomas (7.4%), soft-tissue sarcomas (6.9%), brain tumors (4.5%), fibrosarcomas (3.3%), chondrosarcomas (3.3%), and sarcomas (3.3%). Less frequently reported were leukemias (2.4%), sebaceous cell carcinomas (1.6%), and non-Hodgkin lymphomas (1.6). Pineoblastoma, which in fact is a trilateral retinoblastoma and not an SPT, was found in 2.4%. Despite the differences, all 11 studies showed a higher incidence of SPT compared to the general population. Only 4 studies were judged to be free from selection bias, reporting a cumulative incidence of SPT of 8.4% 18 years after diagnosis, 15.7% at the age of 20 years, 19% at the age of 35 years, and a relative risk of 15.4 for SPT, respectively. *Conclusion:* SPT is a serious problem for the survivors of hereditary retinoblastoma and its importance should be recognized in (genetic) counseling of patients.

Correspondence to: A.C. Moll, M.D.
Department of Ophthalmology,
Free University Hospital,
De Boelelaan 1117, 1081 HV
Amsterdam, The Netherlands.
Tel. +31-20-4444795;
Fax. +31-20-4444745

Key words Retinoblastoma; second primary tumor; osteosarcoma; melanoma; pineoblastoma

Introduction Retinoblastoma is a malignant tumor of the retina in children. It can occur either unilaterally or bilaterally and may be familial or sporadic. Patients in whom the tumor is known to be familial and those with bilateral retinoblastoma have the hereditary form (30–40%). Patients with

unilateral retinoblastoma without a family history mostly have the nonhereditary form (60-70%).¹ In the hereditary form of retinoblastoma, a mutation of the *RBI* gene on chromosome 13q14 is present in all cells of the body, whereas in the nonhereditary form this mutation is only seen in the tumor cells of the retina.² Retinoblastoma is curable in most patients.³⁻⁵ However, hereditary retinoblastoma patients have a high risk of developing second primary tumor (SPT) in their childhood or adolescence. A high risk for SPT is also reported for adult hereditary retinoblastoma patients.^{6,7} This high risk for SPT in hereditary retinoblastoma patients is probably due to the germline mutation of the retinoblastoma gene (*RBI*) in all body cells. Consequently, the first step in the oncogenesis pathway is already present in all cells.⁸ Numerous articles have been published regarding the occurrence of SPT in retinoblastoma patients since the first publication by Reese et al.⁹ in 1949. These studies differ substantially in design and size, and partly for this reason there is a considerable variety in the reported incidence of SPT.

In (genetic) counseling of retinoblastoma patients or their parents, it is difficult to provide adequate information regarding the incidence of SPT based on the literature. Therefore, the aim of this review is to evaluate critically the different articles regarding SPT among survivors of retinoblastoma.

Methods A search was done in Ovid (Medline, Current contents life, Psychlit, Embase) for the years 1966-1995 using the mesh headings: 'retinoblastoma', 'second primary neoplasms', and 'multiple primary neoplasms'. The inclusion criteria were: the study should involve 50 patients or more and should not be limited to one specific SPT. Consequently, case reports and small case series were excluded. The references of the articles identified were checked. A checklist with criteria regarding the study design and the results was applied to each study. With respect to study design, the following issues were checked: origin of the patient group (clinic(s) and country), whether it was population-based or not, the primary retinoblastoma treatment, the number of patients included, whether it concerned a population with different types of retinoblastoma (percentage of the retinoblastoma types in terms of laterality or heredity), the follow-up period, the number of patients with completed follow-up, and the statistical method. Data extraction regarding the results concerned the cumulative incidence of SPT, death due to SPT, and the number of different types of SPT.

Results

RESULT OF THE SEARCH FOR ARTICLES Two hundred and six articles were identified in Ovid under the mesh headings: 'retinoblastoma', 'second primary neoplasms', and 'multiple primary neoplasms'. Fifteen articles fulfilled the inclusion criteria.^{6,10-23} However, seven of the 15 articles^{6,11-13,16-18} dealt with the same patient series: from these we selected the most complete versions for our review.^{6,16,18} One review article was found regarding SPT and retinoblastoma.²⁴ One hundred and ninety articles were excluded: these articles consisted of case reports, studies with less than 50 patients, and studies limited to one specific SPT. Furthermore, these 190 articles either dealt with SPT among relatives of retinoblastoma patients or reported not on the cumulative incidence of SPT, but on other aspects such as therapy of SPT, SPT in general, retinoblastoma in general, and detection of SPT.

Author	Clinic (country)	Period	n	Type RB	Follow-up		SPT			Stat
					Pat (%)	Mean period	n	Cum Inc	Death (%)	
Jensen & Miller ¹⁰	6 centers (USA)	1914-1969	1623	?	?	?	41	?	?	?
DeSutter et al. ¹⁶	Gent (Belgium)	1950-1984	110	40%bil	65	?	11	9.7%	100%	KM
	Essen (Germany)	1960-1984	515	66%bil	?	?	17	?	?	KM
Lueder et al. ¹⁴	Iowa City (USA)	1924-1985	50	100%her	?	?	7	30y:14%	71%	KM
Draper et al. ¹⁵	Centers (UK)	1962-1977	882	44%her	100	?	30	18y:8.4%	?	Act
DerKinderen et al. ¹⁸	Populat (Holland)	1945-1970	141	100%her	100	25y	17	35y:19%	71%	KM
Roarty et al. ¹⁹	AFIP (USA)	1922-1973	215	100%bil	?	7.2y	24	30y:26.1%	?	LT
Winther et al. ²⁰	Populat (Denmark)	1943-1984	175	34%her	87	24y	3	RR:15.4	?	RR
Smith et al. ²¹	Stanford (USA)	1954-1986	53	79%her	92	11y	8	30y:38%	50%	Act
Desjardin et al. ²²	Paris (France)	1922-1965	80	100%bil	30	31y	9	?	100%	?
Minoda et al. ²³	Populat (Japan)	1975-1982	409	100%her	?	?	15	20y:15.7%	47%	
Eng et al. ⁶	NY/Boston (USA)	1914-1984	1603	57%bil	91	17y	?	?	40y:26%	RR, KM

n, number of patients; AFIP, Armed Forces Institute of Pathology; NY, New York; y, years; SPT, second primary tumor; RB, retinoblastoma; bil, bilateral; her, hereditary; RR, relative risk in comparison to the population, populat, population-based; KM, Kaplan-Meier; LT, life table; Act, actuarial; pat, patients, Cum Inc, cumulative incidence for the total period at issue; death, case fatality rate of SPT; stat, statistical method; ?, was not stated in the publication and could also not be inferred or calculated.

STUDY DESIGN OF THE 11 STUDIES Table 1 shows an overview of the 11 studies^{6,10,14-16,18-23} we included that reported on the occurrence of SPT in retinoblastoma patients. These 11 studies differed substantially in design and population size. All 11 studies dealt with a historical cohort. The cohorts were identified within a single institution,^{14,19,21,22} in multiple centers,^{6,10,15,16} or in population-based registries.^{18,20,23} The reported periods occurred between 1914 and 1990. Two studies were restricted to bilateral^{19,22} and four to hereditary retinoblastoma, i.e. bilateral or unilateral with a positive family history.^{14,18,22,23} One study was unclear with regard to the laterality.¹⁰ The other studies included information regarding different mixed bilateral/unilateral^{6,14,16,19,22} or hereditary/nonhereditary^{14,15,18,20,21,23} retinoblastoma patient series. The proportion of patients with a complete follow-up was indicated explicitly in seven studies^{6,15,16,18,20-22} and the mean follow-up period ranged from 7.2 to 31 years. Only the median was given in three studies.^{6,19,21} In one series,⁶ the endpoint of follow-up was mortality due to SPT, in the other series^{10,14-16,18-23} the endpoint of follow-up was the diagnosis of SPT. The case fatality rate is given in seven series.^{6,14,16,18,21-23} In one series,⁶ the cumulative death due to SPT in hereditary retinoblastoma patients is given. Different statistical methods were used: actuarial methods,^{15,21} Kaplan-Meier,^{14,16,18} and life-table analysis¹⁹ are difficult to compare with relative risk.^{6,20}

One study¹⁴ also included pineoblastoma (trilateral retinoblastoma) as an SPT (n=3). Another study¹⁰ included three brain tumors, one of which was probably a pineoblastoma, as suggested by the authors. The other studies did not regard pineoblastoma as being an SPT.

TABLE 1. Overview of the literature regarding second primary tumors among survivors of retinoblastoma.

CONTENTS OF THE II STUDIES WITH RELATION TO SPT Jensen et al.¹⁰ reported that radiotherapy was associated with an increased risk of osteosarcomas, soft-tissue neoplasms, or carcinomas of the skin (n=30 radio-induced SPT), but they also reported 11 SPT which were considered not to be radiogenic.

The studies in Gent (Belgium) and Essen (Germany) by De Sutter et al.¹⁶ showed a cumulative incidence of second primary tumors ranging from 10% to 30% in a retinoblastoma population (40% had bilateral retinoblastoma), using a life-table analysis. They concluded that the incidence of SPT was independent of radiotherapy. In Gent, only six patients were treated with chemotherapy, so that the authors were not able to determine its influence on SPT. In Essen, chemotherapy did not seem to influence the risk of SPT.

In 50 hereditary retinoblastoma patients, Lueder et al.¹⁴ found a cumulative incidence of SPT of 6%, 14%, and 14% after 10, 20, and 30 years, respectively. Pineoblastoma was the probable cause of death in three of the five patients in this series¹⁴ who died of SPT. They did not find a (osteosarcoma).

Draper et al.¹⁵ found a cumulative incidence of 8.4% for all SPT in hereditary retinoblastoma patients 18 years after initial treatment; this figure was 6.0% for osteosarcoma only. Their results also suggested that the use of cyclophosphamide might increase the risk of SPT in hereditary retinoblastoma patients. The six pineoblastomas were not considered as SPT, but were reported separately in an article on ectopic intracranial retinoblastoma.²⁵ These authors¹⁵ also mentioned strong evidence for an association between retinoblastoma and malignant melanoma.

The Dutch population-based study¹⁸ showed a cumulative incidence of SPT of 19% in hereditary retinoblastoma patients at the age of 35 years.

Roarty et al.¹⁹ reported a cumulative incidence of SPT in patients with bilateral retinoblastoma of 4.4% ten years after diagnosis, 18.3% after 20 years, and 26.1% after 30 years, using the life-table method. They concluded that the cumulative incidence of SPT was higher (although not significantly) in patients who received radiation therapy (the cumulative incidence of SPT was 35.1% after 30 years).

A population-based study in Denmark by Winther et al.²⁰ found three SPT in 175 retinoblastoma patients (34% had hereditary retinoblastoma) and compared this risk with the risk in the general population. They reported a relative risk for SPT of 4.2 for all retinoblastoma patients, 15.4 for hereditary and 1.7 for nonhereditary retinoblastoma patients. These results, however, were based on one reported osteosarcoma, one Ewing sarcoma, and one anaplastic tumor only. One pineoblastoma was also found, but it was not incorporated into the study results.

Smith et al.²¹ described the incidence of SPT among 53 retinoblastoma patients (79% had the hereditary form) seen in Stanford. Fifty of these 53 infants received irradiation, and eight patients of this subgroup developed 11 SPT. The actuarial incidence of SPT was 6% ten years after diagnosis, 19% after 20 years, and 38% after 30 years. They reported one pineoblastoma, but excluded this tumor from the analysis.

Desjardin et al.²² was able to follow up 24 of the 80 bilateral retinoblastoma patients in Paris for more than 30 years and found nine SPT, six of which were potentially radiation-induced. They calculated a percentage of SPT between 18% and 68%, depending on the occurrence of SPT in the 24 patients lost to follow-up (32 deceased due to retinoblastoma).

The Japanese population-based study²³ found a cumulative incidence among the 409 hereditary cases of 0% at the age of 5 years, 4.8% at 10 years, and 15.7% at 20 years. They also reported two unilateral nonfamilial cases with SPT.

The large study by Eng et al.⁶ in 1603 retinoblastoma patients with a follow-up of 91% of the patients showed 96 deaths from SPT (relative risk of 30). With respect to the 919 bilateral retinoblastoma patients, the relative risk for SPT was 60 in comparison with that of the general population. After a 40-year follow-up, the cumulative mortality for all SPT combined was 26.0% for the bilateral group and 1.5% for the unilateral group in comparison with the general population.

DIFFERENT TYPES OF SPT IN PERCENTAGES The 11 reviewed articles^{6,10,14-16,18-23} reported a total of 243 SPT divided into 35 different types. Most of them were osteosarcomas (37.0%), followed by melanomas (7.4%), soft-tissue sarcomas (6.9%), brain tumors (4.5%), fibrosarcomas (3.3%), chondrosarcomas (3.3%), and sarcomas (3.3%). Less frequently reported were leukemias (2.4%), sebaceous cell carcinoma (1.6%), and non-Hodgkin lymphomas (1.6%). Ten different SPT types (squamous cell carcinoma, rhabdomyosarcoma, fibrous histiocytoma, Ewing sarcoma, liposarcoma, glioblastoma, anaplastic cell carcinoma, transitional cell carcinoma, meningioma, astrocytoma) were mentioned two or three times only. Fifteen different SPT types were found only once. A high number of SPT types were unknown (9.8%). Twice, a metastasis was qualified as SPT. Pineoblastomas, in fact a trilateral retinoblastoma and not an SPT, was found in 2.4%.

Discussion

STUDY DESIGN OF THE 11 STUDIES Only 11 articles^{6,10,14-16,18-23} on retinoblastoma and SPT fulfilled the inclusion criteria. The design of these studies, especially of those conducted in the past, was not very sophisticated. In the older studies, patients were drawn from the registries of one of a few departments of ophthalmology specializing in retinoblastoma, which probably led to an overrepresentation of complex patients. Difficult patients (mostly with hereditary retinoblastoma), possibly with a greater risk for SPT (due to the RBI mutation and/or excessive radiation therapy or chemotherapy), therefore, were more likely to be included in these studies, which may have caused a higher cumulative incidence of SPT. Population-based studies have the advantage of avoiding this type of selection bias. Three studies^{18,20,23} were nationwide and free of this kind of selection bias.

Documentation of the follow-up period varied from not indicated,^{10,14,19,23} to incomplete,^{6,16,20-22} to complete.^{15,18} The reasons for loss to follow-up were not given. An incomplete follow-up of the series may influence the cumulative incidence of SPT. The Japanese population-based study²³ covered the period 1975-1982 with a relatively short follow-up to 1990. Therefore, SPT such as melanomas, which occur in later life, were probably not found. Some studies did not clearly distinguish a metastasis from an SPT,^{16,20} which could also lead to an overestimation of the cumulative incidence of SPT. Eng et al.⁶ reported nine brain tumors, which were not specified further: possibly the brain tumors were pineoblastomas or late metastases from retinoblastoma. Another problem of this study was that the authors only reported on deaths

due to SPT. Therefore, they probably missed some nonfatal SPT and it is difficult to compare their results with others. Only the study of Winther et al.²⁰ presented relative risks in comparison with the general population. Despite the differences, all 11 studies showed an increased number of SPT compared with the general population. Four of the 11 studies were judged free from selection bias, reporting cumulative incidences of SPT of 8.4% 18 years¹⁵ after diagnosis, 15.7% at the age of 20 years,²³ 19% at the age of 35 years¹⁸ and a relative risk of 15.4 for SPT⁶ in comparison with the general population, respectively.

HEREDITARY VERSUS NONHEREDITARY RETINOBLASTOMA AND SPT It seems clear from the data reported that the high risk for SPT is virtually confined to those with the hereditary form of retinoblastoma. As mentioned in the introduction section, the high risk for SPT in hereditary retinoblastoma patients is probably due to the germline mutation of the *RB1* gene in all body cells. Consequently, the first step in the oncogenesis pathway is already present in all cells.⁸ Eng et al.⁶ reported in their series five SPT in 684 children with unilateral retinoblastoma; the overall risk was significant (RR=3.1; 95% CI=1.0-7.3). However, as they discussed, the increased risk was not entirely surprising, since a proportion of the patients with unilateral retinoblastoma could have in fact hereditary retinoblastoma, which placed them at a higher risk. The two unilateral nonfamilial retinoblastoma patients with SPT mentioned in the Japanese study²³ could also be hereditary cases with unilateral occurrence like other cases reported by Abramson et al.¹¹ and Hausmann and Stefani.²¹

DIFFERENT TYPES OF SPT All in all, 35 different SPT types were reported in the 11 studies. As was expected, most of the SPT types were osteosarcomas and soft-tissue sarcomas. Hereditary retinoblastoma patients harbor the somatic mutation in the *RB1* gene. This mutation also appears to play a pathogenetic role in a substantial proportion of osteosarcomas and soft-tissue sarcomas.²⁷⁻²⁹ Another important finding is the high incidence of malignant melanomas (7.4%) which do not appear to harbor *RB1* mutations.²⁷ In an overview of the literature regarding melanoma and retinoblastoma, Traboulssi et al.³⁰ reported that cutaneous malignant melanoma accounts for about 7% (range 4.2%-14.3%) of SPT. Pineoblastomas, trilateral retinoblastomas of the pineal gland,^{31,32} do not meet the definition of SPT, because pineoblastomas cannot be distinguished histologically from primary tumor retinoblastomas. Despite this, two studies regarded pineoblastoma as an SPT.^{10,14} Some authors only mentioned the finding of a pineoblastoma in their study.^{15,20,21} A valid cumulative incidence of pineoblastoma has not yet been reported in the literature. Holladay et al.³³ reported that 68% of the pineoblastoma patients had the familial hereditary form of retinoblastoma.

REVIEW Mitchell²⁴ gave a critical review of the literature of retinoblastoma and SPT, but discussed fewer patient series. He also concluded that the overall incidence of SPT is difficult to assess, because of the different methods and study groups, but that it is probably closer to 15% than to the 68% proposed by Abramson et al.¹³

CONCLUSION SPT is a serious problem for the survivors of hereditary retinoblastoma and its importance should be recognized in (genetic) counseling of retinoblastoma patients.

References

- 1 Vogel F. Genetics of retinoblastoma. *Hum Genet* 1979; 2: 1-54.
- 2 Knudson AG, Meadows AT, Nichols WW, Hill R. Chromosome deletion and retinoblastoma. *N Engl J Med* 1976; 6295: 1120-1123.
- 3 Abramson DH, Ellsworth RM, Grumbach N, Kitchen FD. Retinoblastoma: survival, age at detection and comparison 1914-1958, 1958-1983. *J Pediatr Ophthalmol Strab* 1985; 22: 246-250.
- 4 Kingston JE, Hungerford JL. Retinoblastoma. In: Plowman, Pinkerton, editors. *Paediatric Oncology, Clinical Practice and Controversies*. London: Chapman & Hall Medical 1992; Ch 14.
- 5 Shields JA, Shields CL. *Intraocular Tumors, a Text and Atlas*. Philadelphia: WB Sanders Company 1992; Ch 19, 390.
- 6 Eng C, Li FP, Abramson DH, Ellsworth RM, Wong L, Goldman MB, Seddon J, Tarbell N, Boice J. Mortality from second tumors among long-term survivors of retinoblastoma. *J Natl Cancer Inst* 1993; 85: 1121-1128.
- 7 Sanders BM, Jay M, Draper GJ, Roberts EM. Non-ocular cancer in relatives of retinoblastoma patients. *Br J Cancer* 1989; 60: 358-365.
- 8 DerKinderen DJ. A new concept of oncogenesis with an evaluation in retinoblastoma. Thesis, Utrecht 1987.
- 9 Reese AG, Merriam GR, Martin HE. Treatment of bilateral retinoblastoma by irradiation and surgery: report on fifteen years results. *Am J Ophthalmol* 1949; 32: 175-190.
- 10 Jensen RD, Miller RW. Retinoblastoma. Epidemiologic characteristics. *N Engl J Med* 1971; 285: 307-311.
- 11 Abramson DH, Ellsworth RM, Zimmerman LE. Nonocular cancer in retinoblastoma survivors. *Trans Am Acad Ophthalmol Otol* 1976; 81: 454-457.
- 12 François J, DeSutter E, Coppieters R, de Bie S. Late extraocular tumors in retinoblastoma survivors. *Ophthalmologica* 1980; 181: 93-99.
- 13 Abramson DH, Ellsworth RM, Kitchen FD, Tung G. Second nonocular tumors in retinoblastoma survivors. Are they radiation-induced? *Ophthalmology* 1984; 91: 1351-1355.
- 14 Lueder GT, Judisch GF, O'Gorman TW. Second nonocular tumors in survivors of heritable retinoblastoma. *Arch Ophthalmol* 1986; 104: 372-373.
- 15 Draper GJ, Sanders BM, Kingston JE. Second primary neoplasms in patients with hereditary retinoblastoma. *Br J Cancer* 1986; 53: 661-671.
- 16 DeSutter E, Messmer E, Hoepping W. Retinoblastoma: importance of time interval in onset of second tumors. *Bull Soc Belge Ophthal* 1986; 213: 27-40.
- 17 DerKinderen DJ, Koten JW, Beemer FA, Tan KEWP, Den Otter W. Non-ocular cancer in hereditary retinoblastoma survivors and relatives. *Ophthalmic Paediatr Genet* 1987; 8: 23-25.
- 18 DerKinderen DJ, Koten JW, Nagelkerke NJD, Tan KEWP, Beemer FA, Den Otter W. Non-ocular cancer in patients with hereditary retinoblastoma and their relatives. *Int J Cancer* 1988; 41: 499-504.
- 19 Roarty JD, McLean IW, Zimmerman LE. Incidence of second neoplasms in patients with bilateral retinoblastoma. *Ophthalmology* 1988; 95: 1583-1587.
- 20 Winther J, Olsen J, deNully Brown P. Risk of nonocular cancer among retinoblastoma patients and their parents, a population based study in Denmark, 1943-1984. *Cancer* 1988; 62: 1458-1462.
- 21 Smith LM, Donaldson SS, Egbert PR, Link MP, Bagshaw MA. Aggressive management of second primary tumors in survivors of hereditary

- retinoblastoma. *Int J Radiat Oncol* 1989; 17: 499-505.
- 22 Desjardin L, Haye C, Schlienger P, Laurent M, Zucker JM, Bouguila H. Second non-ocular tumours in survivors of bilateral retinoblastoma. A 30 year follow-up. *Ophthalmic Paediatr Genet* 1991; 12: 145-148.
- 23 Minoda K, The Committee for the National Registry of Retinoblastoma. Survival rate and risk factors for patients with retinoblastoma in Japan. *Jpn J Ophthalmol* 1992; 36: 121-131.
- 24 Mitchell C. Second malignant neoplasms in retinoblastoma, fact and fiction. *Ophthalmic Paediatr Genet* 1988; 9: 161-165.
- 25 Kingston JE, Plowman PN, Hungerford JL. Ectopic intracranial retinoblastoma in childhood. *Br J Ophthalmol* 1985; 69: 742-748.
- 26 Hausmann N, Stefani FH. Second nonocular tumors in cured unilateral retinoblastoma patients. *J Cancer Res Clin Oncol* 1991; 117: 4-5.
- 27 Benedict WF, Fung YK, Murphee AL. The gene responsible for the development of retinoblastoma and osteosarcoma. *Cancer* 1988; 62: 1691-1694.
- 28 Weichselbaum RR, Beckett M, Diamond A. Some retinoblastomas, osteosarcomas, and soft tissue sarcomas may share a common etiology. *Proc Natl Acad Sci USA* 1988; 85: 2106-2109.
- 29 Friend SH, Bernards R, Rogel S. Human DNA segment with properties of the gene that predisposes to retinoblastoma and osteosarcoma. *Nature* 1986; 323: 643-646.
- 30 Traboulsi EI, Zimmerman LE, Manz HJ. Cutaneous malignant melanoma in survivors of heritable retinoblastoma. *Arch Ophthalmol* 1988; 106: 1059-1061.
- 31 Jakobiec FA, Tso MO, Zimmerman LE, Danis P. Retinoblastoma and intracranial malignancy. *Cancer* 1977; 39: 2048-2058.
- 32 Bader JL, Meadows AT, Zimmerman LE, Rorke LB, Voute PA, Champion LAA, Miller RW. Bilateral retinoblastoma with ectopic intracranial retinoblastoma: trilateral retinoblastoma. *Cancer Genet Cytogenet* 1982; 5: 203-213.
- 33 Holladay DA, Holladay A, Montebello JF, Redmond KP. Clinical presentation, treatment and outcome of trilateral retinoblastoma. *Cancer* 1991; 67: 710-715.