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REVIEW

Trilateral retinoblastoma: A systematic review of 211 cases

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Abstract We conducted a systematic review of 72 studies to characterize trilateral retinoblastomas. Kaplan-Meier analysis was used to estimate survival, and statistical significance was assessed by using a log-rank test. We analyzed 211 cases of trilateral retinoblastomas. The average age of onset of retinoblastoma was 0.79 ± 1.38 years, and the average latency period between the onset of retinoblastomas and trilateral retinoblastomas was 1.49 ± 1.76 years. The brain tumors were found before the retinoblastoma diagnosis in 6 cases (3.1%), concurrently in 61 cases (32.1%), and after the retinoblastoma diagnosis in 123 cases (64.7%). Pineal tumors were found in 155 cases (73.4%) and sellar tumors in 46 cases (21.8%). The overall median survival was 10.3 months (95% CI, 8.5–13) and the 5-year survival rate was 15.7%. Central nervous system symptoms were variable and associated with shorter survival in univariate and multivariate analyses. The survival time in patients who received high-dose chemotherapy with stem cell transplant was significantly longer ($p = 0.0067$) than that of with or without conventional chemotherapy. Twelve long-term survivors were reported, and of these, six patients were treated with high-dose chemotherapy with stem cell transplant and six patients were treated with conventional chemotherapy. It is important that survivors continue to undergo regular medical surveillance in order to detect trilateral retinoblastoma at a potentially curative stage. Trilateral retinoblastoma patients with an irradiation history had shorter survival than those without irradiation history for retinoblastoma. High-dose chemotherapy should be considered as a potential treatment option for trilateral retinoblastomas.

Keywords Chemotherapy · High-dose chemotherapy with autologous peripheral stem cell transplant · Radiation therapy · Retinoblastoma · Total neuroaxis irradiation · Trilateral retinoblastoma

Introduction

Retinoblastoma (RB) is frequently occurring genetic diseases in the pediatric population with an incidence of one per 15,000–20,000 infants [24]. It is initiated by mutations in the *RB1* tumor-suppressor gene [32]. RB presents with bilateral disease in 40% of patients and unilateral disease in the remaining 60% [1]. Patients with a family history and/or bilateral RB or constitutional RB1 mutation are classified as having hereditary RB, whereas those with unilateral RB and a negative family history are classified as having non-hereditary RB. Patients with hereditary RB have a significant risk of developing a second malignancy due to mutation in the second copy of the *RB1* gene in other tissues [32]. Knudson proposed the "two-hit hypothesis" to explain the pathogenesis of heritable and non-heritable RB, namely that two mutations inactivating both copies of the *RB1* gene in the same cell are sufficient to initiate a tumor [49].

In 1977, Jakobiec et al. [37] first recognized the association of bilateral RB with intracranial tumors, which was subsequently termed trilateral RB by Brader et al. in 1980 based on the pineal gland's role as a "third eye" in lower vertebrates

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[7, 92]. Trilateral RB is now considered to be a syndrome of RB associated with primitive neuroectodermal tumors in the pineal gland, suprasellar region, or other midline brain structures [21, 31]. These tumors have an RB-like appearance with Flexner-Wintersteiner or Homer-Wright rosettes. Trilateral RB is found in approximately 0.6–12.7% of patients with unilateral or bilateral germline RB [11, 22, 61].

Recently, a few reports have attempted to further study cases of trilateral RB [21, 61]. Despite recognition that the occurrence of trilateral RB is an important problem, there are very few studies addressing the therapeutic management and outcomes of these patients following their diagnosis, which makes it difficult to define an optimal treatment strategy. In this review, we performed a meta-analysis on 211 patients with trilateral RB based on data from 72 studies that were published previously to clarify the characteristics, outcomes, and therapeutic management of trilateral RBs.

Methods

Literature selection process for studies included in the review

We conducted a systematic literature search for articles on "trilateral retinoblastoma" in the PubMed database through November 30, 2016. We used the following terms in combination in the search: "trilateral retinoblastoma," "pineoblastoma," "pineal region tumor," "sellar tumor," "sellar region tumor," and "retinoblastoma." The inclusion criteria were as follows: (1) full-text articles reporting data from individual cases of trilateral RBs written in English. (2) Trilateral RB was diagnosed by histology, magnetic resonance imaging (MRI), or computed tomography (CT). The exclusion criteria were (1) articles reporting a meta-analysis. The reference lists of all included articles were also investigated to identify other eligible papers.

We initially identified 24,491 articles concerning trilateral RB. After articles were excluded based on our present inclusion and exclusion criteria, finally 72 articles with a total of 211 patients were included in this review (Fig. 1) [2–6, 8–20, 22, 23, 26–29, 31, 33–42, 44, 46, 48, 50–60, 62–64, 67–83, 85, 86, 88, 89, 91, 93].

Several parameters were collected, including patient sex and age at RB diagnosis; family history and bilateral/unilateral lesion of RB; latency period from RB to the diagnosis of a brain tumor; treatment for RB; histopathology of the brain tumor; largest brain tumor diameter and its location and treatment; and overall survival (OS) time of patients with trilateral RB. We defined RB and trilateral RB diagnosed within 3 months as concurrent disease, and 3 months before as before RB, and 3 months after as after RB, respectively.

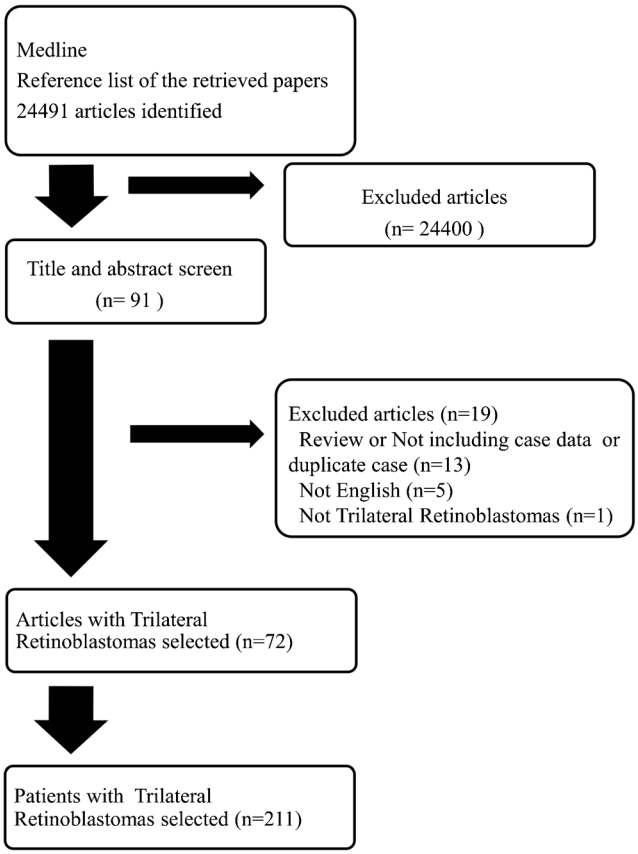

Fig. 1 Flowchart of the selection process for studies included in this systematic review

Statistical analyses

OS was defined from the date of diagnosis of trilateral RB to the date of death or last follow-up. Kaplan-Meier analysis was used to estimate the OS and the cumulative incidence for trilateral RB, and statistical significance was assessed using a log-rank test. We compared groups using hazard ratios and 95% confidence intervals (CI) obtained from a logistic regression model with respect to clinical variables that were assessed by both univariate and multivariate analyses with stepwise selection. All probability values were set at $P < 0.05$, two-sided. We used JMP software version 10 (SAS Institute Inc., Tokyo, Japan) for all statistical calculations.

Results

Trilateral retinoblastoma in the literature

During our review of the literature, we identified 211 (58 boys, 92 girls, and 61 unknown) cases of trilateral RB between 1977 and 2015 (Supplementary Fig. 1A). The average age of onset of RB was 0.79 ± 1.38 years (95% CI, 0.59–0.99). The majority (146, 76.8%) were diagnosed at less than 1 year of

age (Supplementary Fig. 1B). Bilateral RB affected 153 (72.5%), unilateral RB 22 (10.4%), and unknown 36 (17.0%). Enucleation of the eye was performed in 98 (46.4%), external-beam radiotherapy (EBRT) was delivered in 79 (37.4%), brachytherapy in 16 (7.5%), chemotherapy in 42 (19.9%), photocoagulation in 23 (10.9%), cryotherapy in 40 (18.9%), and hyperthermia in 2 (0.9%), respectively (Table 1). The average total irradiation (IR) dose delivered to the eye lesion was 46.7 ± 22.5 Gy (95% CI, 39.6–53.8).

The brain tumors were found to be pineal in 155 cases (73.4%), sellar in 46 cases (21.8%), and cerebellar in 2 cases (0.94%), respectively. Two cases (0.94%) had bilateral RB, a pineal tumor, and another primary sellar region tumor (Table 1). The average latency period between RB and the onset of trilateral RB was 1.49 ± 1.76 years (Supplementary Fig. 1C). The brain tumors were found before RB diagnosis in 6 cases (3.1%), concurrently in 61 cases (32.1%), and after RB diagnosis in 123 cases (64.7%), respectively (Supplementary Fig. 1D). The largest brain tumor diameter was ≥ 20 mm in 57 cases (27.0%) and < 20 mm in 30 cases (14.2%). Central nervous system (CNS) symptoms before trilateral RB diagnosis were identified in 66 cases (31.2%) and were not present in 49 cases (23.2%). Cerebrospinal fluid (CSF) dissemination at trilateral RB diagnosis was found in 34 cases (16.1%) and not found in 57 cases (27%) (Table 1).

Table 1 Characteristics of patients with trilateral retinoblastoma.

Characteristics	
Bilateral RB, *n* (%)	153 (72.5)
Familial RB, *n* (%)	48 (25.9)
Median age at RB diagnosis (year)	0.43
Median latency time RB to trilateral RB (year)	1.16
Gender, *n* (%)	
Male	58 (27.4)
Female	92 (43.6)
RB-brain tumor latency correlation	
After RB	123 (64.7)
Concurrent	61 (32.1)
Before RB	6 (3.1)
Treatment for intraocular RB *n* (%)	
Enucleation	98 (46.4)
EBRT	79 (37.4)
Brachytherapy	16 (7.5)
Chemotherapy	42 (19.9)
Photocoagulation	23 (10.9)
Cryotherapy	40 (18.9)
Hyperthermia	2 (0.9)
Brain tumor location	
Sellar	46 (21.8)
Pineal	155 (73.4)
Cerebellar	2 (0.94)
Sellar + pineal	2 (0.94)
Brain tumor size	
≧ 20 mm	57 (27.0)
< 20 mm	30 (14.2)
CNS symptoms	
Yes	66 (31.2)
No	49 (23.2)
CSF dissemination	
Yes	34 (16.1)
No	57 (27.0)

CNS central nervous system, *CSF* cerebrospinal fluid, *EBRT* external-beam radiotherapy, *RB* retinoblastoma

The latency period from retinoblastoma to the onset of trilateral retinoblastoma

A total of 123 cases (64.7%) of trilateral RB were diagnosed after RB. The median latency period between the diagnosis of RB and the diagnosis of trilateral RB was 1.49 ± 1.76 years (95% CI, 1.24–1.75) (Fig. 2a). There were no differences between latency periods grouped by bilateral or unilateral RB ($p = 0.0801$; Fig. 2b). There was a significant difference between latency periods grouped by with or without radiation treatment for RB ($p < 0.0001$, Fig. 2c). There was also a significant difference between latency periods grouped by with or without chemotherapy for RB ($p = 0.0002$, Fig. 2d). There was not a significant difference between latency periods grouped by with or without radiation plus chemotherapy for RB ($p = 0.5940$). There was a significant difference between latency periods grouped by with or without radiation treatment for RB within after Rb group (with IR vs without IR: $p = 0.0179$, Fig. 2e). There was not a significant difference between latency periods grouped by with or without chemotherapy for RB within after Rb group (with chemo vs without chemo: $p = 0.9042$, Fig. 2f). There was not a significant difference between latency periods grouped by with or without radiation plus chemotherapy for RB ($p = 0.6430$).

Prognostic factors

The median OS was 10.3 months (95% CI, 8.5–13) and the 5-year-survival rate was 15.7% (Fig. 3a). The patient outcomes were analyzed according to several potential diagnostic and prognostic factors. The median survival for patients with concurrent disease was 32 (95% CI, 14–not reached [NR]) months, with a 5-year survival rate of 47.0%. For patients with trilateral RB after RB diagnosis, the median survival was 9 (95% CI, 7–10) months, and the 5-year survival rate was 5.8% ($p < 0.0001$, Fig. 3b). The median survival for patients with a pineal tumor was 9.4 (95% CI, 8–13) months, with a 5-year survival rate of 15.5%. For patients with sellar tumors, the median survival was 12 (95% CI, 9–23) months, and the 5-year survival rate was 17.8% ($p = 0.4750$, Fig. 3c). The median survival for patients with CNS symptoms was 7 (95% CI,

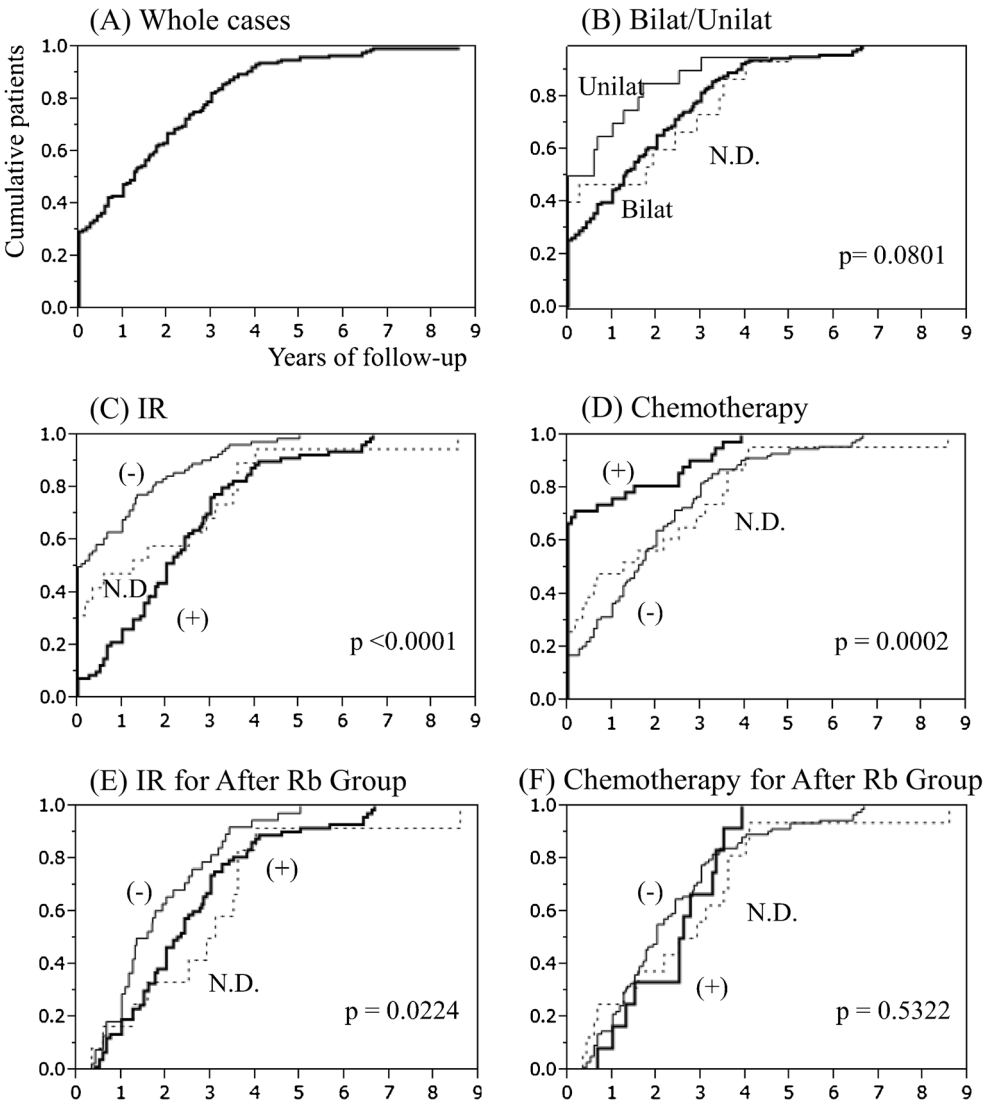

Fig. 2 Latency period from retinoblastoma to development of trilateral retinoblastoma. The *x*-axis represents the latency period (year) and the *y*-axis represents the cumulative patients. **a** Overall cohort. **b** Comparing groups classified as with bilateral [Bilat] or unilateral [Unilat] RB. **c** Comparing groups classified as combined with radiation therapy [IR (+)] for retinoblastoma or without radiation therapy [IR (−)] for retinoblastoma. **d** Comparing groups classified as combined with chemotherapy [(+)] for retinoblastoma or without chemotherapy [(−)] for retinoblastoma. **e** Comparing groups classified as combined with radiation therapy [IR (+)] for retinoblastoma or without radiation therapy [IR (−)] for retinoblastoma within after Rb group. **f** Comparing groups classified as combined with chemotherapy [(+)] for retinoblastoma or without chemotherapy [(−)] for retinoblastoma within after Rb group

6–8) months, with a 5-year survival rate of 0%. For patients without CNS symptoms, the median survival was 32 (95% CI, 11–NR) months, and the 5-year survival rate was 48.7% ($p < 0.0001$, Fig. 3d). The median survival for patients with brain tumor diameters ≥ 20 mm was 12 (95% CI, 8.3–21) months, with a 5-year survival rate of 13.5%. For patients with brain tumor diameters < 20 mm, the median survival was NR (95% CI, 13–NR) months, and the 5-year survival rate was 60.5% ($p = 0.0005$, Fig. 3e). The median survival for patients with CSF dissemination was 13 (95% CI, 9–19) months, with a 5-year survival rate of 11.7%. For patients without CSF dissemination, the median survival was 24 (95% CI, 12–NR) months, and the 5-year survival rate was 36.5% ($p < 0.0001$, Fig. 3f). Univariate analysis demonstrated that the RB-trilateral latency period, CNS symptoms, and CSF dissemination were significantly associated with OS. These variables were subsequently included in the multivariate analysis; however, CNS symptoms were the only significant variable retained in the model (Table 2).

Treatment results for trilateral retinoblastomas

Treatment outcomes were further analyzed in patients with trilateral RB (Fig. 4, Table 3). A total of 87 patients (41%) were reported after 2000 and 124 (59%) were reported before 2000. Histological verification was performed in 95 (45%) but not performed in 116 (54.9%). A subtotal or partial tumor resection was conducted in 35 patients and a biopsy in 19 patients. Cranial radiotherapy was performed in 84 patients, and total neuroaxis irradiation was performed in 18 patients. Chemotherapy using several agents was prescribed for 127 patients at the physician's discretion and high-dose chemotherapy with stem cell transplant (HDCT) was performed in 23 patients.

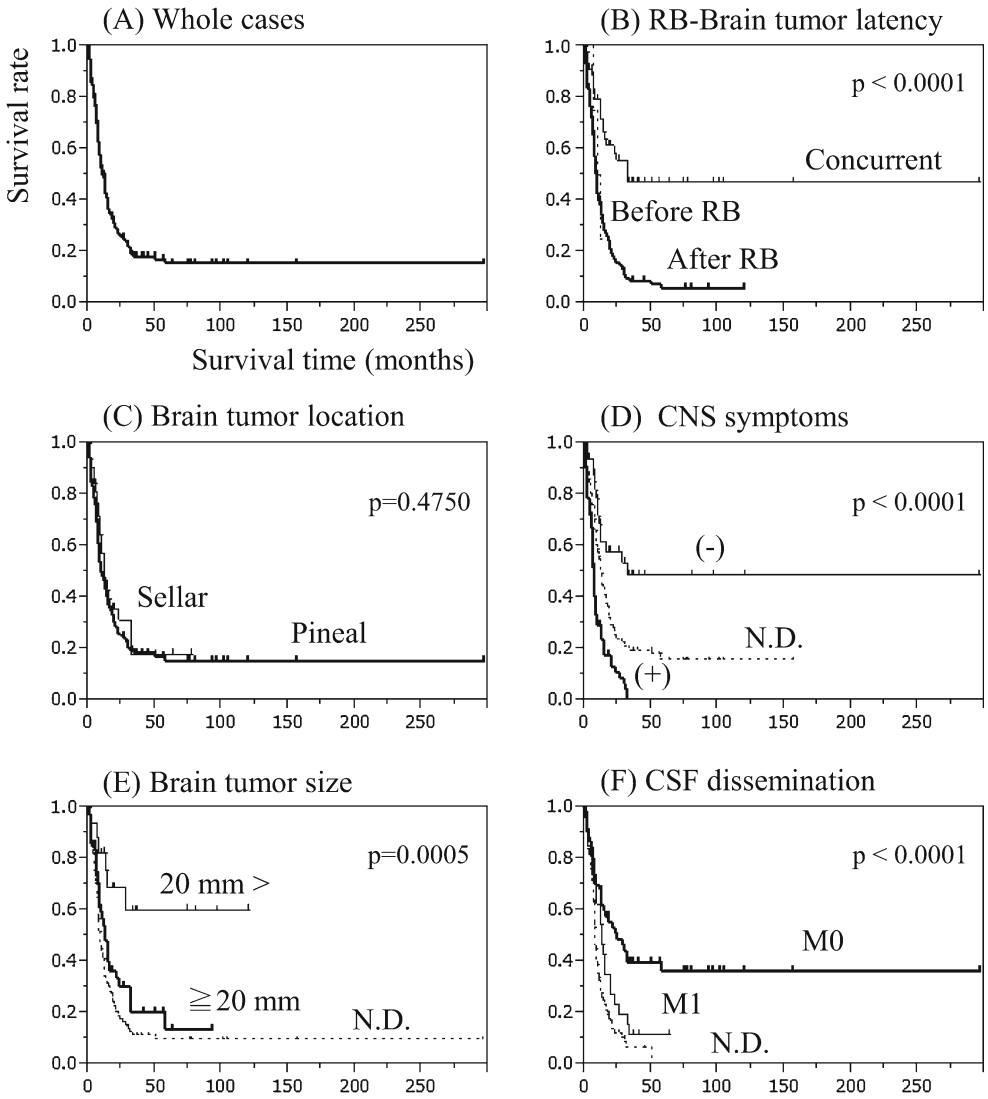

Fig. 3 Kaplan-Meier survival analysis in patients with trilateral retinoblastoma. The *x*-axis represents the survival time (month) and the *y*-axis represents the survival rate. **a** Overall cohort. **b** Comparing groups classified according to RB and brain tumor latency time as trilateral RB before RB [before RB], concurrent [concurrent], or after RB [after RB]. **c** Comparing groups of the brain tumor location as sellar [Sellar] or pineal [Pineal] region. **d** Comparing groups classified with CNS symptoms [(+)] or without CNS symptoms [(−)]. **e** Comparing groups classified based on the largest brain tumor diameter as smaller than 20 mm [< 20 mm] or larger than 20 mm [≥ 20 mm]. **f** Comparing groups classified based on presence [M1] or absence [M0] of cerebrospinal fluid dissemination

The median survival for patients reported after 2000 was 19 (95% CI, 13–33.6) months, with a 5-year survival rate of 31.5%. For patients reported before 2000, the median survival was 8 (95% CI, 6–9) months and the 5-year survival rate was 3.5% ($p < 0.0001$, Fig. 4a). The median survival for patients with histological verification was 10 (95% CI, 7–15) months with a 5-year survival rate of 12.0%. For patients who reported without histological verification, the median survival was 12

Table 2 Patient characteristics associated with overall survival

Variable	Univariate		Multivariate	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age	1.16 (0.16–5.07)	0.8618	4.04 (0.69–15.0)	0.1088
Gender	0.96 (0.66–1.39)	0.8569	0.86 (0.56–1.31)	0.4973
Brain tumor location	0.96 (0.66–1.45)	0.8766	0.77 (0.44–1.39)	0.3979
RB-brain tumor latency	5.31 (1.56–17.25)	0.0077	0.10 (0.001–8.88)	0.10489
CNS symptoms	2.82 (1.82–4.46)	< 0.0001	2.56 (1.53–4.40)	0.0003
Brain tumor size	1.68 (0.97–3.06)	0.062	0.92 (0.43–2.01)	0.8422
CSF dissemination	0.52 (0.32–0.87)	0.0139	0.70 (0.40–1.27)	0.2445

CI confidence intervals, *CNS* central nervous system, *CSF* cerebrospinal fluid, *HR* hazard ratio, *RB* retinoblastoma

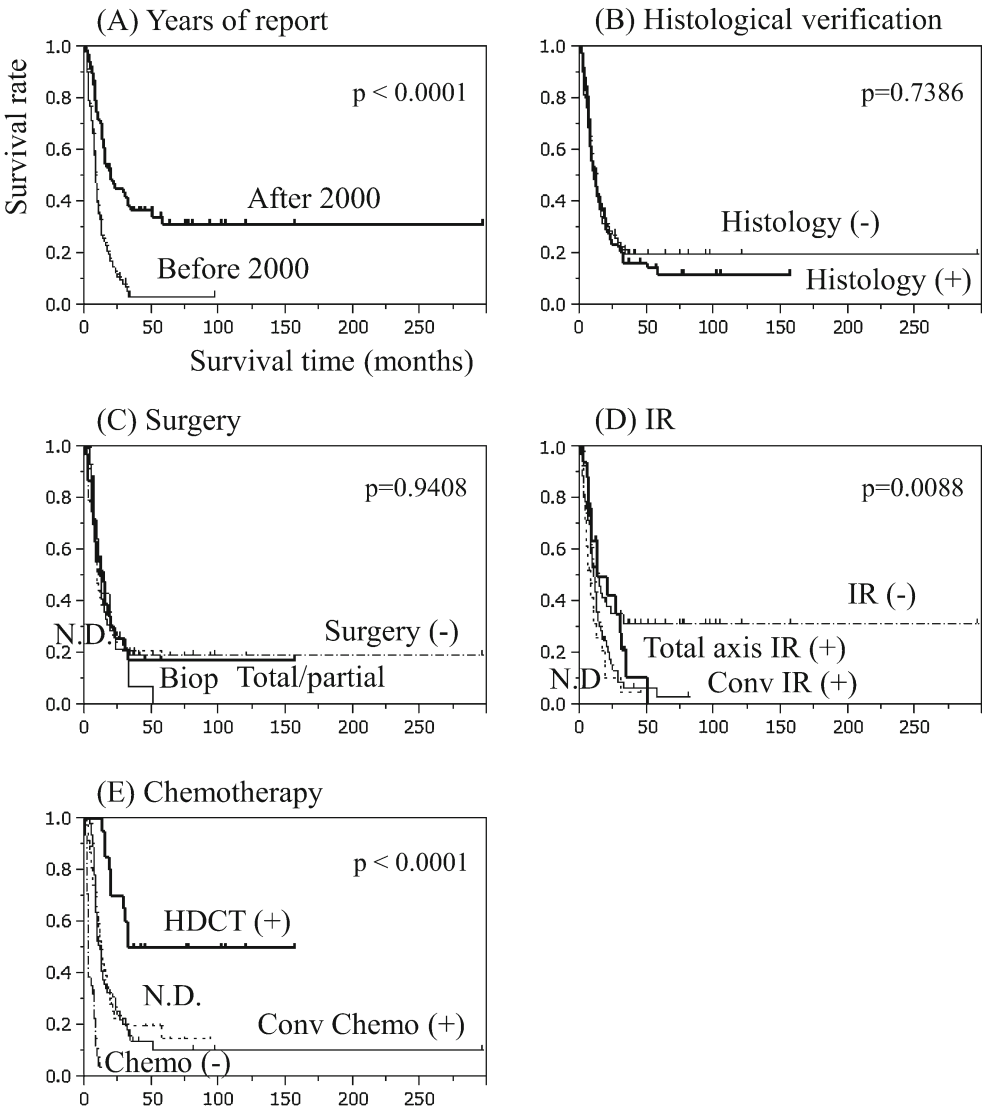

Fig. 4 Kaplan-Meier survival analysis in patients with trilateral retinoblastomas. The *x*-axis represents the survival time (months) and the *y*-axis represents the survival rate. **a** Comparing groups classified as either total/subtotal or partial resection [total/partial], biopsy [Biop], or without surgery [Surg (−)]. **b** Comparing groups classified as with [Histology (+)] or without [Histology (−)] histological verification. **c** Comparing groups classified as with conventional cranial irradiation [Conv IR (+)], total neuroaxis irradiation therapy [Total axis IR (+)], or without irradiation therapy [IR (−)]. **d** Comparing groups classified as with conventional chemotherapy [Conv Chemo (+)], high-dose chemotherapy with stem cell transplant [HDCT (+)], or without chemotherapy [Chemo (−)]

(95% CI, 8–14) months and the 5-year survival rate was 19.7% ($p = 0.7386$, Fig. 4b). The median survival for patients who underwent subtotal or partial tumor resection was 13 (95% CI, 7–19) months with a 5-year survival rate of 17.2%. For patients who underwent only biopsies, the median survival was 12 (95% CI, 4–23) months and the 5-year survival rate was 0% ($p = 0.9408$, Fig. 4c). The median survival for patients who underwent conventional cranial radiotherapy was 10 (95% CI, 7.5–12) months with a 5-year survival rate of 3.3%. The median survival for patients who underwent total neuroaxis radiotherapy was 12 (95% CI, 6–31) months with a 5-year survival rate of 0%. Patients who did not receive radiotherapy had a median survival of 13 (95% CI, 8–19) months with a 5-year survival rate of 31.8% ($p = 0.0088$, Fig. 4d). The

Table 3 Therapeutic modalities associated with OS

Variable	Univariate		Multivariate	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Surgery (total/partial vs biopsy or no surgery)	0.82 (0.42–1.64)	0.8488	0.52 (0.22–1.27)	0.1482
Radiation therapy (no IR therapy vs total axis IR)	0.73 (0.39–1.30)	0.0479	3.76 (1.66–9.60)	0.001
Chemotherapy (HDCT vs no chemotherapy)	3.49 (1.84–7.34)	< 0.0001	2.89 (1.32–7.11)	0.0067

CI confidence intervals, *HR,* hazard ratio, *HDCT* high-dose chemotherapy, *IR* irradiation therapy, *OS* overall survival

median survival in patients who received conventional chemotherapy was 11 (95% CI, 8.3–13) months with a 5-year survival rate of 10.5%, whereas patients who did not receive chemotherapy had a median survival of 2 (95% CI, 2–5) months with a 5-year survival rate of 0%. For patients who received HDCT, the median survival was NR (95% CI, 19–NR) months, with a 5-year survival rate of 50.0% ($p < 0.0001$, Fig. 4e). These variables were analyzed with multivariate analysis. HDCT and no radiation therapy were the strongest variables retained in the model ($p = 0.0067$ and 0.001, respectively, Table 3).

Long-term survivors

There were 12 patients with long-term (> 5 years) survival (Supplementary Table 1). Eleven cases were reported after 2000. The average age of RB diagnosis was 7.2 ± 5.8 months. Only one patient had CSF dissemination. Trilateral RB was diagnosed concurrently in 6 cases and after RB in 6 cases with an average latency time of 1.5 ± 1.5 year. The median survival time was 94.5 months (95% CI, 71.1–151.5). Six patients had been treated by HDCT and the other six patients were treated by conventional chemotherapy. In two cases, conventional chemotherapy consisted of vincristine, cyclophosphamide, and intrathecal methotrexate plus Ara C. For the other four cases, the conventional chemotherapy regimen was not described.

Discussion

A few articles have attempted to further study trilateral RBs; however, reports of trilateral RBs are limited [21, 61]. This series is the cohort of trilateral RBs with descriptions of individual patient data.

The pineal gland and retina both differentiate from the neuroectoderm. Trilateral RB is thought to result from the common photoreceptor origin of the pineal gland and the retina. In lower species, the pineal gland contains photoreceptor elements and a role lost in higher species [6, 92]. Some cells of the human pineal gland share with retinal cells the capacity to express the retinal S antigen [43]. In addition, ectopic photoreceptor cells are also present along the intracranial portion of the optic nerve [84].

Recently, early diagnosis and treatment of RB have improved the survival and vision of affected patients, and 90–95% of affected children become long-term survivors in developed countries [90]. In this series, 73 (34.5%) cases of trilateral RBs developed after IR therapy and 12 (5.6%) cases after chemotherapy. Radiation therapy is the most effective therapy to preserve eye function. However, for RB patients, especially in cases of hereditary RB, radiation therapy is a significant risk factor for secondary malignancies in the field exposed to radiotherapy [25, 87].

Since 2000, the treatment philosophy has altered from early enucleation of the affected eye to a conservative management approach. Cryosurgery and laser photocoagulation therapy are employed for a small tumor, and chemotherapy has been utilized for advanced tumors. Nowadays, many oncologists attempt to avoid the use of EBRT in advanced cases [24]. In this review, we found that patients who received ocular IR therapy for RB had a significantly longer latency period compared with that of patients without IR therapy. However, patients who received chemotherapy for RB had not a significantly longer latency period compared with that of patients without chemotherapy, The number of patients who had chemotherapy for RB is small ($n = 42$) compared to radiation therapy ($n = 89$), so there may be a bias.

A shorter RB-brain tumor latency time, CNS symptoms, and CSF dissemination were variables associated with shorter survival. Concurrent and before RB types were less likely to have CNS symptoms and CSF dissemination than the after RB type (Supplementary Table 2). Neuroimaging screening for brain tumors has become routine practice in the management of patients with trilateral RB and could improve the cure rate if patients are detected in an asymptomatic stage or when their tumors are 15 mm or smaller [47]. In our study, patients with trilateral RB who were asymptomatic at the time of diagnosis had a longer survival time. More than 90% of patients with trilateral RB developed a brain tumor within 4 years of the time of initial diagnosis of RB. Therefore, we recommend neuroimaging screening until 4 years of age for patients with bilateral and hereditary RB [47, 66]. Screening should be performed by the use of MRI, not by CT, to avoid radiation exposure. However, only a prospective trial can clarify the role of screening and its true effect on survival of patients with trilateral RB.

Trilateral RBs are difficult to treat, and death from leptomeningeal dissemination is common [47]. Leptomeningeal dissemination occurred in 51 (24.1%) cases after management of trilateral RB in this study. Surgical treatment and radiation therapy have no effect on patient survival in our analysis. Surgical management may be limited to biopsy. Craniospinal axis irradiation is dangerous for growth and cognitive and endocrine functions, particularly for children younger than 3 years of age [45, 65], and radiation therapy increases the long-term risk of secondary malignancies in long-term survivors of hereditary RB patients [30]. Treatment of trilateral RB with HDCT may avoid the need for surgical or radiation therapy. We believe that the role of HDCT should be evaluated in a prospective study.

There are limitations to this study as the data were obtained from retrospective case series treated using a variety of therapeutic management approaches. The data are not complete, since some studies did not report the size of the brain tumor, the presence of CSF dissemination or CNS symptoms, treatment methods, or survival time. Patients treated with chemotherapy have been diagnosed more recently. This bias may also affect the analysis on the benefit of HDCT because HDCT was only used more recently. Another bias that needs

to be considered when analyzing the benefit of HDCT is that only patients who respond well to the first course of chemotherapy to survive the first months of treatment receive HDCT. Patients with very advanced disease often die within a few weeks, so they never receive HDCT. However, our data support the benefit of HDCT for trilateral RB patients. Future studies need to focus on genetic profiling of trilateral RBs, in order to elucidate features for the development of targeted therapies.

Conclusion

The risk of trilateral RBs should be taken into account when treating and managing RB patients. In addition, it is important that survivors continue to undergo regular medical surveillance in order to detect trilateral RBs at a potentially curative stage. Moreover, HDCT should be considered as a potential treatment for trilateral RB patients. Extensive research on the molecular pathologies of trilateral RBs is warranted.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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Ethical approval The manuscript is a review article so it does not require authorization of ethical committee (ethical approval).

Informed consent The manuscript is a review article so it does not require authorization of ethical committee (ethical approval).

References

1. Abramson DH (1982) Retinoblastoma: diagnosis and management. CA Cancer J Clin 32:130–140
2. Amare P, Jose J, Chitalkar P, Kurkure P, Pai S, Nair C, Advani S (1999) Trilateral retinoblastoma with an RB1 deletion inherited from a carrier mother: a case report. Cancer Genet Cytogenet 111: 28–31
3. Amoaku WM, Willshaw HE, Parkes SE, Shah KJ, Mann JR (1996) Trilateral retinoblastoma. A report of five patients. Cancer 78:858–863
4. Andrade GC, Pinto NP, Motono M, Chojniak MM, Chojniak R, Bezerra SM (2015) Trilateral retinoblastoma with unilateral eye involvement. Rev Assoc Med Bras (1992) 61:308–310
5. Antoneli CB, Ribeiro Kde C, Sakamoto LH, Chojniak MM, Novaes PE, Arias VE (2007) Trilateral retinoblastoma. Pediatr Blood Cancer 48:306–310
6. Bader JL, Meadows AT, Zimmerman LE, Rorke LB, Voute PA, Champion LA, Miller RW (1982) Bilateral retinoblastoma with ectopic intracranial retinoblastoma: trilateral retinoblastoma. Cancer Genet Cytogenet 5:203–213
7. Bader JL, Miller RW, Meadows AT, Zimmerman LE, Champion LA, Voute PA (1980) Trilateral retinoblastoma. Lancet 2:582–583
8. Bagley LJ, Hurst RW, Zimmerman RA, Shields JA, Shields CL, De Potter P (1996) Imaging in the trilateral retinoblastoma syndrome. Neuroradiology 38:166–170
9. Bejjani GK, Donahue DJ, Selby D, Cogen PH, Packer R (1996) Association of a suprasellar mass and intraocular retinoblastoma: a variant of pineal trilateral retinoblastoma? Pediatr Neurosurg 25: 269–275
10. Bindlish R, LaRoche GR (1999) Successful treatment of neonatal trilateral retinoblastoma. J AAPOS 3:376–378
11. Blach LE, McCormick B, Abramson DH, Ellsworth RM (1994) Trilateral retinoblastoma–incidence and outcome: a decade of experience. Int J Radiat Oncol Biol Phys 29:729–733
12. Bomanji J, Kingston JE, Hungerford JL, Britton KE (1989) 123I-metaiodobenzylguanidine scintigraphy of ectopic intracranial retinoblastoma. Med Pediatr Oncol 17:66–68
13. Bonci GA, Rosenblum MK, Gilheeney SW, Dunkel IJ, Holodny AI (2013) Diffusion-weighted imaging to assess treatment response in a child with trilateral retinoblastoma. Pediatr Radiol 43:1231–1234
14. Brownstein S, de Chadarevian JP, Little JM (1984) Trilateral retinoblastoma. Report of two cases. Arch Ophthalmol 102:257–262
15. Bullitt E, Crain BJ (1981) Retinoblastoma as a possible primary intracranial tumor. Neurosurgery 9:706–709
16. Cho EY, Suh YL, Shin HJ (2002) Trilateral retinoblastoma: a case report. J Korean Med Sci 17:137–140
17. D'Elia G, Grotta S, Del Bufalo F, De Ioris MA, Surace C, Sirleto P, Romanzo A, Cozza R, Locatelli F, Angioni A (2013) Two novel cases of trilateral retinoblastoma: genetics and review of the literature. Cancer Genet 206:398–401
18. Dai S, Dimaras H, Heon E, Budning A, Doyle J, Halliday W, Drake J, Gallie BL, Chan HS (2008) Trilateral retinoblastoma with pituitary-hypothalamic dysfunction. Ophthalmic Genet 29:120–125
19. De Ioris MA, Fidani P, Munier FL, Serra A, Ilari I, Popovic MB, Natali G, Secco DE, Cozza R (2010) Successful treatment of trilateral retinoblastoma with conventional and high-dose chemotherapy plus radiotherapy: a case report. J Pediatr Hematol Oncol 32:e343–e345
20. De Ioris MA, Valente P, Randisi F, Buzzonetti L, Carai A, Cozza R, Del Bufalo F, Romanzo A, Angioni A, Cacchione A, Bernardi B, Mastronuzzi A (2014) Baseline central nervous system magnetic resonance imaging in early detection of trilateral retinoblastoma: pitfalls in the diagnosis of pineal gland lesions. Anticancer Res 34:7449–7454
21. de Jong MC, Kors WA, de Graaf P, Castelijns JA, Kivela T, Moll AC (2014) Trilateral retinoblastoma: a systematic review and meta-analysis. Lancet Oncol 15:1157–1167
22. De Potter P, Shields CL, Shields JA (1994) Clinical variations of trilateral retinoblastoma: a report of 13 cases. J Pediatr Ophthalmol Strabismus 31:26–31
23. Dimaras H, Heon E, Doyle J, Strahlendorf C, Paton KE, Halliday W, Babyn P, Gallie BL, Chan HS (2011) Multifaceted chemotherapy for trilateral retinoblastoma. Arch Ophthalmol 129:362–365
24. Dimaras H, Kimani K, Dimba EA, Gronsdahl P, White A, Chan HS, Gallie BL (2012) Retinoblastoma. Lancet 379:1436–1446
25. Draper GJ, Sanders BM, Kingston JE (1986) Second primary neoplasms in patients with retinoblastoma. Br J Cancer 53:661–671
26. Dudgeon J, Lee WR (1983) The trilateral retinoblastoma syndrome. Trans Ophthalmol Soc U K 103(Pt 5):523–529
27. Dunkel IJ, Jubran RF, Gururangan S, Chantada GL, Finlay JL, Goldman S, Khakoo Y, O'Brien JM, Orjuela M, Rodriguez-Galindo C, Souweidane MM, Abramson DH (2010) Trilateral retinoblastoma: potentially curable with intensive chemotherapy. Pediatr Blood Cancer 54:384–387

28. Ehlers N, Kaae S, Rasmussen K, Ratjen E (1983) Hereditary bilateral retinoblastoma, pinealoma and normal chromosomes. A case report. Acta Ophthalmol 61:838–843
29. Elias WJ, Lopes MB, Golden WL, Jane JA Sr, Gonzalez-Fernandez F (2001) Trilateral retinoblastoma variant indicative of the relevance of the retinoblastoma tumor-suppressor pathway to medulloblastomas in humans. J Neurosurg 95:871–878
30. Eng C, Li FP, Abramson DH, Ellsworth RM, Wong FL, Goldman MB, Seddon J, Tarbell N, Boice JD Jr (1993) Mortality from second tumors among long-term survivors of retinoblastoma. J Natl Cancer Inst 85:1121–1128
31. Finelli DA, Shurin SB, Bardenstein DS (1995) Trilateral retinoblastoma: two variations. AJNR Am J Neuroradiol 16:166–170
32. Friend SH, Bernards R, Rogelj S, Weinberg RA, Rapaport JM, Albert DM, Dryja TP (1986) A human DNA segment with properties of the gene that predisposes to retinoblastoma and osteosarcoma. Nature 323:643–646
33. Halperin EC (2000) Neonatal neoplasms. Int J Radiat Oncol Biol Phys 47:171–178
34. Helveston EM, Knuth KR, Ellis FD (1987) Retinoblastoma. J Pediatr Ophthalmol Strabismus 24:296–300
35. Holladay DA, Holladay A, Montebello JF, Redmond KP (1991) Clinical presentation, treatment, and outcome of trilateral retinoblastoma. Cancer 67:710–715
36. Ibarra MS, O'Brien JM (2000) Is screening for primitive neuroectodermal tumors in patients with unilateral retinoblastoma necessary? J AAPOS 4:54–56
37. Jakobiec FA, Tso MO, Zimmerman LE, Danis P (1977) Retinoblastoma and intracranial malignancy. Cancer 39:2048–2058
38. James SH, Halliday WC, Branson HM (2010) Best cases from the AFIP: trilateral retinoblastoma. Radiographics 30:833–837
39. Johnson DL, Chandra R, Fisher WS, Hammock MK, McKeown CA (1985) Trilateral retinoblastoma: ocular and pineal retinoblastomas. J Neurosurg 63:367–370
40. Jubran RF, Erdreich-Epstein A, Butturini A, Murphree AL, Villablanca JG (2004) Approaches to treatment for extraocular retinoblastoma: Children's Hospital los Angeles experience. J Pediatr Hematol Oncol 26:31–34
41. Judisch GF, Patil SR (1981) Concurrent heritable retinoblastoma, pinealoma, and trisomy X. Arch Ophthalmol 99:1767–1769
42. Jurkiewicz E, Pakula-Kosciesza I, Rutynowska O, Nowak K (2010) Trilateral retinoblastoma: an institutional experience and review of the literature. Childs Nerv Syst 26:129–132
43. Kalsow CM, Wacker WB (1978) Pineal gland involvement in retina-induced experimental allergic uveitis. Invest Ophthalmol Vis Sci 17:774–783
44. Kamaleshwaran KK, Shibu DK, Mohanan V, Shinto AS (2014) Rare case of trilateral retinoblastoma with spinal canal drop metastasis detected with fluorine-18 fluorodeoxyglucose positronemission tomography/computed tomography imaging. Indian J Nucl Med 29:115–116
45. Kiltie AE, Lashford LS, Gattamaneni HR (1997) Survival and late effects in medulloblastoma patients treated with craniospinal irradiation under three years old. Med Pediatr Oncol 28:348–354
46. Kingston JE, Plowman PN, Hungerford JL (1985) Ectopic intracranial retinoblastoma in childhood. Br J Ophthalmol 69:742–748
47. Kivela T (1999) Trilateral retinoblastoma: a meta-analysis of hereditary retinoblastoma associated with primary ectopic intracranial retinoblastoma. J Clin Oncol 17:1829–1837
48. Kivela T, Tuppurainen K, Riikonen P, Vapalahti M (2003) Retinoblastoma associated with chromosomal 13q14 deletion mosaicism. Ophthalmology 110:1983–1988
49. Knudson AG Jr (1971) Mutation and cancer: statistical study of retinoblastoma. Proc Natl Acad Sci U S A 68:820–823
50. Larsen S, Junewick J (2006) Trilateral retinoblastoma. Pediatr Radiol 36:82
51. Limn YS, Juraida E, Alagaratnam J, Menon BS (2011) Trilateral retinoblastoma. Med J Malaysia 66:156–157
52. Lueder GT (1992) Successful therapy for trilateral retinoblastoma. Am J Ophthalmol 114:646–647
53. Lueder GT, Judisch F, O'Gorman TW (1986) Second nonocular tumors in survivors of heritable retinoblastoma. Arch Ophthalmol 104:372–373
54. Malik RK, Friedman HS, Djang WT, Falletta JM, Buckley E, Kurtzberg J, Kinney TR, Stine K, Chaffee S, Hayes J et al (1986) Treatment of trilateral retinoblastoma with vincristine and cyclophosphamide. Am J Ophthalmol 102:650–656
55. Marks LB, Bentel G, Sherouse GW, Spencer DP, Light K (1993) Craniospinal irradiation for trilateral retinoblastoma following ocular irradiation. Med Dosim 18:125–128
56. Maugans T, Hochwalt C, Gonzales G, Geller J (2011) Progressive development of Chiari I malformation in a child with trilateral retinoblastoma and acquired growth hormone deficiency. Pediatr Neurosurg 47:464–465
57. McCormack S, Raftery R, Palmgren D, Leonard JC (1995) Pineoblastoma imaged during bone scintigraphy. Clin Nucl Med 20:1023–1024
58. Meadows A (1986) Trilateral retinoblastoma. Med Pediatr Oncol 14:323–326
59. Michaud J, Jacob JL, Demers J, Dumas J (1984) Trilateral retinoblastoma: bilateral retinoblastoma with pinealoblastoma. Can J Ophthalmol 19:36–39
60. Moll AC, Imhof SM, Bouter LM, Tan KE (1997) Second primary tumors in patients with retinoblastoma. A review of the literature. Ophthalmic Genet 18:27–34
61. Mouratova T (2005) Trilateral retinoblastoma: a literature review, 1971-2004. Bull Soc Belge Ophtalmol 297:25–35
62. Mukherjee M, Gothi R, Doda SS, Aggarwal SK (1991) Trilateral retinoblastoma. AJR Am J Roentgenol 157:198–199
63. Nelson SC, Friedman HS, Oakes WJ, Halperin EC, Tien R, Fuller GN, Hockenberger B, Scroggs MW, Moncino M, Kurtzberg J et al (1992) Successful therapy for trilateral retinoblastoma. Am J Ophthalmol 114:23–29
64. Nunna SV, Sharma R, Vashisht S, Berry M (1995) Trilateral retinoblastoma: CT evaluation. Indian J Ophthalmol 43:27–29
65. Palmer SL, Goloubeva O, Reddick WE, Glass JO, Gajjar A, Kun L, Merchant TE, Mulhern RK (2001) Patterns of intellectual development among survivors of pediatric medulloblastoma: a longitudinal analysis. J Clin Oncol 19:2302–2308
66. Paulino AC (1999) Trilateral retinoblastoma: is the location of the intracranial tumor important? Cancer 86:135–141
67. Pesin SR, Shields JA (1989) Seven cases of trilateral retinoblastoma. Am J Ophthalmol 107:121–126
68. Pham TT, Siebert E, Asbach P, Willerding G, Erb-Eigner K (2015) Magnetic resonance imaging based morphologic evaluation of the pineal gland for suspected pineoblastoma in retinoblastoma patients and age-matched controls. J Neurol Sci 359:185–192
69. Popovic MB, Diezi M, Kuchler H, Abouzeid H, Maeder P, Balmer A, Munier FL (2007) Trilateral retinoblastoma with suprasellar tumor and associated pineal cyst. J Pediatr Hematol Oncol 29:53–56
70. Provenzale JM, Gururangan S, Klintworth G (2004) Trilateral retinoblastoma: clinical and radiologic progression. AJR Am J Roentgenol 183:505–511
71. Provenzale JM, Weber AL, Klintworth GK, McLendon RE (1995) Radiologic-pathologic correlation. Bilateral retinoblastoma with coexistent pinealoblastoma (trilateral retinoblastoma). AJNR am. J Neuroradiol 16:157–165
72. Raizis AM, Van Mater D, Aaltonen LA, Lohmann D, Cheale MS, Bickley VM, George PM, Zhou Y, Rosoff PM (2013) Trilateral

retinoblastoma in a patient with Peutz-Jeghers syndrome. Am J Med Genet A 161a:1096–1100

73. Rodjan F, de Graaf P, Brisse HJ, Goricke S, Maeder P, Galluzzi P, Aerts I, Alapetite C, Desjardins L, Wieland R, Popovic MB, Diezi M, Munier FL, Hadjistilianou T, Knol DL, Moll AC, Castelijns JA (2012) Trilateral retinoblastoma: neuroimaging characteristics and value of routine brain screening on admission. J Neuro-Oncol 109: 535–544
74. Schwartz AM, Ghatak NR, Laine FJ (1990) Intrasellar primitive neuroectodermal tumor (PNET) in familial retinoblastoma: a variant of "trilateral retinoblastoma". Clin Neuropathol 9:55–59
75. Shah I, Baig A, Razzaq A, Faruqi A, Ali A, Khan FQ (2013) Trilateral retinoblastoma with unilateral eye involvement. J Pak Med Assoc 63:910–912
76. Shields JA, Pesin SR, Shields CL (1989) Trilateral retinoblastoma. J Clin Neuroophthalmol 9:222–223
77. Skrypnyk C, Bartsch O (2004) Retinoblastoma, pinealoma, and mild overgrowth in a boy with a deletion of RB1 and neighbor genes on chromosome 13q14. Am J Med Genet A 124a:397–401
78. Skulski M, Egelhoff JC, Kollias SS, Mazewski C, Ball WS Jr (1997) Trilateral retinoblastoma with suprasellar involvement. Neuroradiology 39:41–43
79. Srinivasan US, Pavai A, Sethumadhavan V (1998) Trilateral retinoblastoma–a case report. Ann Acad Med Singap 27:262–264
80. Stannard C, Knight BK, Sealy R (1985) Pineal malignant neoplasm in association with hereditary retinoblastoma. Br J Ophthalmol 69: 749–753
81. Stolovitch C, Loewenstein A, Varssano D, Lazar M (1992) Trilateral retinoblastoma. Metab Pediatr Syst Ophthalmol (New York, N.Y.: 1985) 15:57–59
82. Tarkkanen A, Haltia M, Karjalainen K (1984) Trilateral retinoblastoma. Pineoblastoma (ectopic intracranial retinoblastoma) associated with bilateral retinoblastoma. Ophthalmic Paediatr. Genet 4:1–6
83. Tasdemiroglu E (1999) Trilateral retinoblastoma. Acta Neurochir 141:893–894
84. Torczynski E, Jacobiec FA, Johnston MC, Font RL, Madewell JA (1977) Synophthalmia and cyclopia: a histopathologic, radiographic, and organogenetic analysis. Doc Ophthalmol 44:311–378
85. Towbin RB, Bisset GS (1986) Pediatric case of the day. Trilateral retinoblastoma Radiographics 6:1100–1104
86. Tsuruta T, Aihara Y, Kanno H, Kiyotani C, Maebayashi K, Sakauchi M, Osawa M, Fujii H, Kubo O, Okada Y (2011) High-dose chemotherapy followed by autologous and allogeneic peripheral blood stem cell transplantation for recurrent disseminated trilateral retinoblastoma. Childs Nerv Syst 27:1019–1024
87. Tucker MA, D'Angio GJ, Boice JD Jr, Strong LC, Li FP, Stovall M, Stone BJ, Green DM, Lombardi F, Newton W et al (1987) Bone sarcomas linked to radiotherapy and chemotherapy in children. N Engl J Med 317:588–593
88. Varan A, Akyuz C, Buyukpamukcu M (1998) A rare presentation of trilateral retinoblastoma. Tumori 84:515–516
89. Whittle IR, McClellan K, Martin FJ, Johnston IH (1985) Concurrent pineoblastoma and unilateral retinoblastoma: a forme fruste of trilateral retinoblastoma? Neurosurgery 17:500–505
90. Woo KI, Harbour JW (2010) Review of 676 second primary tumors in patients with retinoblastoma: association between age at onset and tumor type. Arch Ophthalmol 128:865–870
91. Wright KD, Qaddoumi I, Patay Z, Gajjar A, Wilson MW, Rodriguez-Galindo C (2010) Successful treatment of early detected trilateral retinoblastoma using standard infant brain tumor therapy. Pediatr Blood Cancer 55:570–572
92. Wurtman RJ, Moskowitz MA (1977) The pineal organ (first of two parts). N Engl J Med 296:1329–1333
93. Zimmerman LE, Burns RP, Wankum G, Tully R, Esterly JA (1982) Trilateral retinoblastoma: ectopic intracranial retinoblastoma associated with bilateral retinoblastoma. J Pediatr Ophthalmol Strabismus 19:320–325