Screening for Pineal Trilateral Retinoblastoma Revisited

A Meta-analysis

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Topic: To determine the age up to which children are at risk of trilateral retinoblastoma (TRb) developing, whether its onset is linked to the age at which intraocular retinoblastomas develop, and the lead time from a detectable pineal TRb to symptoms.

Clinical relevance: Approximately 45% of patients with retinoblastoma—those with a germline RB1 pathogenic variant—are at risk of pineal TRb developing. Early detection and treatment are essential for survival. Current evidence is unclear regarding the usefulness of screening for pineal TRb and, if useful, the age up to which screening should be continued.

Methods: We conducted a study according to the Meta-analysis of Observational Studies in Epidemiology guidelines for reporting meta-analyses of observational studies. We searched PubMed and Embase between January 1, 1966, and February 27, 2019, for published literature. We considered articles reporting patients with TRb with survival and follow-up data. Inclusion of articles was performed separately and independently by 2 authors, and 2 authors also independently extracted the relevant data. They resolved discrepancies by consensus.

Results: One hundred thirty-eight patients with pineal TRb were included. Of 22 asymptomatic patients, 21 (95%) were diagnosed before the age of 40 months (median, 16 months; interquartile range, 9–29 months). Age at diagnosis of pineal TRb in patients diagnosed with retinoblastoma at 6 months or younger versus older than 6 months were comparable (P = 0.44), suggesting independence between the ages at diagnosis of intraocular retinoblastoma and pineal TRb. The laterality of intraocular retinoblastoma and its treatment were not associated with the age at which pineal TRb was diagnosed. The lead time from asymptomatic to symptomatic pineal TRb was approximately 1 year. By performing a screening magnetic resonance imaging scan every 6 months after the diagnosis of heritable retinoblastoma (median age, 6 months) until 36 months of age, at least 311 and 776 scans would be required to detect 1 case of asymptomatic pineal TRb and to save a single life, respectively.

Conclusions: Patients with retinoblastoma are at risk of pineal TRb developing for a shorter period than previously assumed, and the age at diagnosis of pineal TRb is independent of the age at diagnosis of retinoblastoma. The GRADE (Grading of Recommendations Assessment, Development and Evaluation) level of evidence for these conclusions remains low. Ophthalmology 2019;1:1–7 © 2019 by the American Academy of Ophthalmology

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Trilateral retinoblastoma (TRb) refers to retinoblastoma presenting with a midline intracranial neoplasm resembling an embryonal tumor of the central nervous system. Patients with TRb—of whom three quarters have pineal TRb (pineoblastoma) and one quarter have suprasellar or parasellar TRb—are carriers of a germline RB1 pathogenic variant who typically also will have bilateral intraocular retinoblastoma. Trilateral retinoblastoma is an important cause of death among patients with heritable retinoblastoma.

The incidence of pineal TRb, according to our recent systematic review and meta-analysis, is 3.2% (95% confidence interval, 1.4%–5.6%) of all patients with heritable retinoblastoma (bilateral and unilateral tumors with family history or a germline RB1 pathogenic variant) and 2.9% (95% confidence interval, 1.9%–4.2%) of patients with bilateral retinoblastoma.1 Because 45% of all retinoblastomas are heritable2 and approximately 8000 new patients are expected globally each year,3 should all of them survive, TRb is predicted to affect approximately 125 children annually, in 90 of whom pineal TRb would develop.

Unlike nonpineal TRbs, pineal TRbs often are diagnosed after the intraocular tumor is diagnosed (metachronous).4 The often metachronous diagnosis of pineal TRb raises the question whether, and at which frequency, neuroradiologic
screening should be adopted for a child with a germline \textit{RB1} pathogenic variant. In practice, most centers follow the recommendation to perform brain magnetic resonance imaging (MRI) for children with retinoblastoma at diagnosis.\textsuperscript{1--8} However, some centers repeat the MRI for children up to 5 years of age,\textsuperscript{9} although the benefit from this practice is unclear.\textsuperscript{10} Whether screening for pineal TRb is useful is unclear even today. The objective of this study was to contribute to solving this problem by answering 2 previously unanswered questions: (1) Until which age are patients with heritable retinoblastoma at risk of pineal TRb developing? and (2) Does pineal TRb develop earlier if a patient is diagnosed with retinoblastoma at an early age (\textless{}6 months)?

**Methods**

**Search Strategy, Study Selection, and Data Extraction**

We performed this study according to the Enhancing the Quality and Transparency of Health Research reporting guidelines, including the Meta-analysis of Observational Studies in Epidemiology.\textsuperscript{11} This study adhered to the tenets of the Declaration of Helsinki. The ethics committee at VU Medisch Centrum approved this study with a waiver of informed consent.

We updated our literature search of the English, Dutch, and German literature for patients with TRb as performed for the 2014 systematic review and meta-analysis by de Jong et al.,\textsuperscript{12} with a new search (PubMed and Embase) performed on February 27, 2019 (performed by M.C.d.J. with 9 years of experience in conducting systematic reviews and meta-analyses; Appendix A, available at www.aaojournal.org). To ensure sensitivity, the search strategy included only terms describing the target disease (Appendix A).

Two authors (M.C.d.J. and A.C.M.) independently reviewed all articles for inclusion, and 2 authors (M.C.d.J. and W.A.K.) independently extracted data from the included articles. We extracted all data as described previously\textsuperscript{4} to update our entire TRb database. If TRb was diagnosed within 3 months of diagnosis of intraocular tumor, we considered the tumors synchronous. Patients were included if they were identifiable as unique and if at least the age at which the TRb was diagnosed was available.Overlap between patients was identified using all available data in included studies (such as age at diagnosis, gender, and hospital where patient was treated); if uncertainty remained, the most recently published case was excluded. Discrepancies were resolved by consensus.

Authors of articles published in 1995 or earlier were contacted via e-mail (in October 2017 and February 2019) for additional information relevant to the research questions (whether there was a screening program for TRb in place, whether TRb was detected during screening of after development of symptoms, and whether and when previous scan showing negative results was performed); however, none responded.

**Risk of Bias and Study Quality**

Risk of bias and methodologic quality of each article were assessed with a checklist proposed by Murad et al.\textsuperscript{12} Checklist items 5 and 6 were not included because they are relevant only to adverse drug events. Two authors (M.C.d.J. and R.W.J.) independently scored all included articles according to the checklist. Discrepancies were resolved by consensus.

**Overall Level of Evidence**

We graded the level of evidence of the 2 research questions stated in the introduction according to the GRADE system.\textsuperscript{13}

**Statistical Analysis**

We used IBM SPSS Statistics (Armonk, NY) software version 22. The cumulative frequency of TRb by age at diagnosis and by the time from intraocular retinoblastoma was plotted. The Mann–Whitney \textit{U} test was used to compare subgroups. Spearman’s \textit{r} was used to calculate a correlation between 2 continuous variables. \textit{P} values less than 0.05 were considered statistically significant. All tests were 2 sided. For the main analyses, the data of patients diagnosed in 1995 or later were included (see prior publications\textsuperscript{14,15}). We consider that this period, beginning with the introduction of chemotherapy to the routine management of retinoblastoma, most accurately corresponds to management today in terms of diagnostic methods and treatment for both intraocular retinoblastoma and TRb. We used data from patients diagnosed before 1995 to check the robustness of our analyses in the event that sample sizes were small.

**Results**

**Included Studies and Patients**

Our updated search resulted in 185 PubMed and 336 Embase hits (Appendix B, available at www.aaojournal.org). After excluding 52 duplicates, we reviewed 469 titles and abstracts for eligibility and excluded 451 articles. Eighteen articles were eligible, and we reviewed their full text. One article\textsuperscript{16} included only previously published patients. Six articles\textsuperscript{17--22} did not provide the data at diagnosis of TRb, 2 articles\textsuperscript{22,23} reported on patients with a TRb but without an intraocular tumor, and 3 articles\textsuperscript{24--26} did not report on patients with TRb at all and were excluded. The 6 remaining articles\textsuperscript{27--32} provided 15 new patients. Together with 174 patients from our earlier systematic review,\textsuperscript{4} we compiled data from 189 patients with TRb (Appendix C, available at www.aaojournal.org).

Of all patients, 138 (73\%) had a pineal TRb; 42 (22\%) had a suprasellar, parassellar, or ventricular TRb; and 3 (2\%) had both a pineal and a nonpineal TRb.\textsuperscript{3,35} In the remaining patients (3\%), the location of the TRb was unspecified. Of the 183 patients with a TRb in a known location, 73 (40\%) were diagnosed in 1995 or later, of whom 50 (68\%) had a pineal TRb, 21 (29\%) had a nonpineal TRb, and 2 (3\%) had both tumors; 37 (51\%) of them were synchronous, 28 (38\%) were metachronous, 1 was diagnosed before the intraocular tumor, and in 7 (11\%) patients, the sequence was unspecified. Restricting to pineal TRb, of the 50 patients diagnosed in 1995 or later, 18 (36\%) had synchronous tumors, 26 (52\%) had metachronous tumors, and in 6 (12\%) patients, this was unspecified.

**Risk of Bias and Study Quality**

Of the 96 included articles, 74 (71\%) did not fulfill the first criterion in the quality checklist (Appendix D, available at www.aaojournal.org), indicating that they likely reported patients who were interesting and did not necessarily present the entire experience the authors had with TRb. In 17 studies (18\%), 1 or more false-positive diagnoses could not be entirely ruled out (e.g., patient 151 in Appendix C received no follow-up and had a small presumed cystic pineal TRb of 11 mm).
Cumulative Frequency of Having Pineal Trilateral Retinoblastoma Diagnosed

We stratified the cumulative frequency of pineal TRb according to the presence or absence of symptoms (Fig 1). The distribution of the ages at which pineal TRb was diagnosed differed significantly between the groups (P = 0.0026, Mann–Whitney U test). The 2 cumulative frequency curves were separated by approximately 1 year, which we interpret as the lead time from a pineal TRb detectable on MRI to the onset of symptoms. The median largest diameter of an asymptomatic versus a symptomatic pineal TRb was 13 mm (interquartile range [IQR], 11–16 mm) versus 29 mm (IQR, 22–36 mm; P = 0.0004, Mann–Whitney U test).

No correlation between the age at diagnosis of a pineal TRb and its diameter was observed (including patients diagnosed before 1995, whether the intracranial tumor was asymptomatic or among 44 symptomatic ones (P = 0.49, Spearman) or among 44 symptomatic ones (P = 0.33).

Of 22 patients with an asymptomatic pineal TRb, all but 1 patient (95%) were diagnosed before 40 months of age (median, 16 months of age; IQR, 9–29 months of age; 1 outlier at 56 months of age; Fig 1). Also, the slope of the cumulative frequency curve for both asymptomatic and symptomatic pineal TRb is nearly consistent, suggesting that the likelihood of being diagnosed with pineal TRb within the period at risk is approximately constant and unassociated with age.

We found no difference in the age at which an asymptomatic pineal TRb was diagnosed in 11 patients before 1995 (median, 14 months; IQR, 10–36 months) compared with 22 patients in 1995 and later (median, 16 months; IQR, 9–29 months; P = 0.49, Mann–Whitney U test). The same was true of a symptomatic pineal TRb (median, 34 months [IQR, 24–39 months] vs. 36 months [IQR, 22–45 months], respectively; P = 0.81). The age at which a pineal TRb was diagnosed also was similar for patients whose intraocular retinoblastoma was diagnosed at the age of 6 months or earlier versus those with a later diagnosis, whether analyzing all, asymptomatic, or symptomatic patients (P = 0.44, P = 0.94, and P = 0.57, respectively; Fig 2; Appendix F , available at www.aaojournal.org).

The cumulative frequency curve of the interval from diagnosis of an intraocular retinoblastoma to pineal TRb showed that patients diagnosed with intraocular retinoblastoma after 6 months of age demonstrated pineal TRb after a shorter interval than those diagnosed at a younger age, whether considering all, asymptomatic, or symptomatic patients (Fig 3; P = 0.0004, P = 0.011, and P = 0.045, respectively, Mann–Whitney U test). Including in the analysis of patients diagnosed with pineal TRb before 1995 or restricting analysis to that period produced similar results (Appendix G, available at www.aaojournal.org). When comparing the age at diagnosis of an asymptomatic pineal TRb versus an asymptomatic nonpineal TRb, the cumulative frequency curves overlapped (Fig 4; P = 0.38, Mann–Whitney U test). Patients with bilateral and unilateral retinoblastoma were diagnosed with pineal TRb at comparable ages (including patients diagnosed before 1995), whether the intracranial tumor was asymptomatic (P = 0.52, Mann–Whitney U test) or symptomatic (P = 0.83; Appendix H, available at www.aaojournal.org).

Prior Treatment and Metachronous Pineal Trilateral Retinoblastoma

To evaluate the potential effect of previous systemic chemotherapy on the interval from intraocular retinoblastoma to pineal TRb, we
compared patients who were diagnosed with metachronous tumors either before or from 1995 onward. Restricting analyses to the latter period yielded a small sample size for no chemotherapy because chemotherapy was prevalent from 1995 onward. Patients who did not receive prior chemotherapy were diagnosed with pineal TRb similarly to those who did receive chemotherapy (Appendix I, available at www.aaojournal.org; $P = 0.38$, Mann–Whitney $U$ test). Patients who did not receive prior external beam radiotherapy were diagnosed with pineal TRb similarly to those who did receive such radiotherapy (Appendix J, available at www.aaojournal.org; $P = 0.65$, Mann–Whitney $U$ test).

**Potential Implications for Screening**

A lead time of approximately 1 year (with growth in that time from a median diameter of 13 to 29 mm; and a decrease in 5-year survival from 50% to 21% when diameter exceeds 15 mm)$^4$ suggests that a screening program should include scans more frequently than once yearly. Assuming that patients with known heritable retinoblastoma are screened every 6 months until the age of 36 months regardless of age at diagnosis of the intraocular tumor, this results in a screening MRI scan at the ages of 1, 1.5, 2, 2.5, and 3 years. An additional scan at 6 months of age is needed for familial retinoblastoma screened from birth and for other neonatal or early diagnoses.$^{34}$ These scans also would capture any rare metachronous nonpineal TRbs.

Given that 50% of pineal TRbs are diagnosed at the baseline MRI scan$^1$ and that 5% of pineal TRbs would be diagnosed after the age of 36 months (assuming that the patient diagnosed with an asymptomatic pineoblastoma at 38 months would have been diagnosed through MRI performed at 36 months), we estimate a metachronous pineal TRb incidence of 1.6% during the screening period. Assuming a sensitivity of 100% for MRI to detect an asymptomatic pineal TRb and no symptomatic ones emerging between scans, we would need to screen $1/0.016 = 62.5$ patients.

![Figure 3](image_url)

**Figure 3.** Cumulative frequency plots showing the interval between diagnosis of intraocular retinoblastoma and pineal trilateral retinoblastoma in patients diagnosed with intraocular retinoblastoma at 6 months of age or younger and older than 6 months of age (A) for all patients, (B) for asymptomatic patients, and (C) for symptomatic patients.
cases. Risk of toxic adverse effects, including death reported in 1 of 41 mortality. High-dose chemotherapy with stem cell rescue carries a risk unnecessary treatment with its associated morbidity and Also, the possibility of overdiagnosis (false-positive result) would sensitivity of MRI and any symptomatic interval pineal TRb. ¼ 4 program would be able to save 1 life for every 310.5 / 0.5 with MRI to diagnose 1 asymptomatic metachronous pineal TRb. Assuming an even distribution of diagnoses during the screening interval from 6 to 36 months (i.e., 0.2 positive scan every 6 months), we would require 62.5 scans in the first round and 62.3, 62.1, 61.9, and 61.7 subsequent rounds, amounting to 310.5 MRI scans in total. With a survival rate of approximately 50% for asymptomatic and 10% for symptomatic patients, the screening program would be able to save 1 life for every 310.5 / 0.5 × 5 / 4 = 776.25 MRI scans. These numbers will increase with a lower sensitivity of MRI and any symptomatic interval pineal TRb. Also, the possibility of overdiagnosis (false-positive result) would risk unnecessary treatment with its associated morbidity and mortality. High-dose chemotherapy with stem cell rescue carries a risk of toxic adverse effects, including death reported in 1 of 41 cases. 35–37

Overall Level of Evidence
Appendix K (available at www.aaojournal.org) outlines the GRADE (Grading of Recommendations Assessment, Development and Evaluation) level of evidence. The overall level of evidence is of low quality, that is, this research provides some indication of the likely effect. However, the likelihood that it will be substantially different (a large enough difference that it might have an effect on a decision) is high.

Discussion
We found that the age at which intraocular retinoblastoma and pineal TRb are diagnosed are unassociated with each other. This suggests independent development of intraocular retinoblastoma and pineal TRb, a conclusion strengthened by the fact that the age at diagnosis of pineal TRb also was unassociated with the laterality of the intraocular retinoblastoma that may reflect varying penetrance and expressivity of the germline RB1 pathogenic variant during retinal development. We found no association between prior chemotheraphy or radiotherapy for intraocular retinoblastoma and the interval to detection of pineal TRb. Consequently, prior treatment probably can be ignored when considering a screening strategy to detect metachronous TRb.

Previously, it was found that nonpineal TRb is diagnosed earlier than pineal TRb. This may be explained in part by a longer lead time bias in the diagnosis of symptomatic pineal TRb; however, pineal tumors are detectable at baseline MRI less frequently than nonpineal TRbs.

The retinoblastoma community currently agrees that a baseline brain MRI is standard of care to detect a synchronous TRb when intraocular retinoblastoma is diagnosed. Most question the benefit of performing additional imaging given the rarity of metachronous TRb. Our results do suggest that, should screening be opted for, it should be independent of age at which intraocular retinoblastoma is diagnosed. They also suggest that a screening program may be required only until the age of 36 to 40 months and that no specific age bracket exists that would require a variable screening approach (e.g., more or less frequent screening).

With an estimated incidence of metachronous pineal TRb of less than 2% in patients with heritable retinoblastoma, any screening program would require hundreds of MRI scans to detect 1 patient with an asymptomatic pineal TRb, and thus should undergo a thorough cost-benefit scrutiny.

Study Limitations
As noted in the previously published meta-analysis, our study is limited similarly by the heterogeneity of included patients. The problem of potential publication bias is illustrated by the checklist that showed that up to 71% of studies presented case reports or small case series, suggesting that the cases may not represent the entire experience of the center. Furthermore, in 18% of studies, the possibility cannot be excluded that at least 1 of the patients in a particular series did not represent a false-positive diagnosis, either because of deficient follow-up or because normal pineal glands sometimes may be difficult to differentiate from a small pineal TRb. However, the age at diagnosis of pineal TRb did not differ significantly in the group of patients with versus without confirmation.

Ideally, our research question and protocol would have been solved and published earlier. However, the research question emerged from a recent unpredicted diagnosis of a metachronous pineal TRb by the coauthors from Toronto, Canada (B.G., S.E.S., F.S., and H.D.), which led to contact with the authors of the previous meta-analysis on survival after TRb. As a result, the prior meta-analysis protocol was adapted to provide the required answers.

In conclusion, age at diagnosis of heritable intraocular retinoblastoma and pineal TRb likely are independent. Age at diagnosis of an asymptomatic nonpineal TRb and an asymptomatic pineal TRb are similar and are unassociated with the age at diagnosis and laterality of the intraocular
retinoblastoma. The lead time from a detectable pinealoblastoma on MRI to development of symptoms is approximately 1 year. Prior systemic chemotherapy or radiotherapy for intraocular retinoblastoma is not associated with the age at diagnosis of pineal TRb. Ninety-five percent of patients with an asymptomatic pineal TRb are diagnosed before the age of 40 months, which can be considered the period at risk of a pineal TRb developing. During this period, the risk of having a pineal TRb diagnosed is approximately constant over time. The GRADE level of evidence for these results remains low.

References


**Footnotes and Financial Disclosures**

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No animal subjects were included in this study.

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Abbreviations and Acronyms:

GRADE = Grading of Recommendations Assessment, Development and Evaluation; IQR = interquartile range; MRI = magnetic resonance imaging; TRb = trilateral retinoblastoma.

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