Journal Pre-proof

Screening for pineal trilateral retinoblastoma revisited: a meta-analysis

Marcus C. de Jong, MD, PhD, Wijnanda A. Kors, MD, Annette C. Moll, MD, PhD, Pim de Graaf, MD, PhD, Jonas A. Castelijns, MD, PhD, Robin W. Jansen, MD, Brenda Gallie, MD, Sameh E. Soliman, MD, Furqan Shaikh, MD, Helen Dimaras, PhD, Tero T. Kivelä, MD

PII: S0161-6420(19)32215-8
DOI: https://doi.org/10.1016/j.ophtha.2019.10.040
Reference: OPHTHA 10991

To appear in: Ophthalmology

Received Date: 26 March 2019
Revised Date: 19 October 2019
Accepted Date: 28 October 2019


This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2019 Published by Elsevier Inc. on behalf of the American Academy of Ophthalmology
Screening for pineal trilateral retinoblastoma revisited: a meta-analysis

1 Marcus C. de Jong1, MD, PhD
2 Wijnanda A. Kors2, MD
3 Annette C. Moll3, MD, PhD
4 Pim de Graaf4, MD, PhD
5 Jonas A. Castelijns5, MD, PhD
6 Robin W. Jansen1, MD
7 Brenda Gallie5,7, MD
8 Sameh E. Soliman4,5, MD
9 Furqan Shaikh6, MD
10 Helen Dimaras5,7,8,9, PhD
11 Tero T. Kivelä10, MD

Affiliations
1 Department of Radiology and Nuclear Medicine, Amsterdam UMC, Vrije Universiteit Amsterdam, Cancer Center Amsterdam, Amsterdam, The Netherlands
2 Department of Pediatric Oncology, Amsterdam UMC, Vrije Universiteit Amsterdam, Cancer Center Amsterdam, Amsterdam, The Netherlands
3 Department of Ophthalmology, Amsterdam UMC, Vrije Universiteit Amsterdam, Cancer Center Amsterdam, Amsterdam, The Netherlands
4 Faculty of Medicine, Department of Ophthalmology, University of Alexandria, Alexandria, Egypt
5 Department of Ophthalmology and Vision Science, The Hospital for Sick Children, Toronto, Canada
6 Department of Pediatrics, University of Toronto, Toronto, Ontario, Canada
7 Department of Ophthalmology and Vision Science, University of Toronto, Toronto, Canada
8 Child Health Evaluative Sciences Program, SickKids Research Institute, Toronto, Canada
9 Division of Clinical Public Health, Dalla Lana School of Public Health, University of Toronto, Toronto, Canada
10 Department of Ophthalmology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

Corresponding author:
Marcus C. de Jong, MD, PhD
Department of Radiology and Nuclear Medicine, Amsterdam UMC, Vrije Universiteit Amsterdam
PO Box 7057, 1007 MB Amsterdam
The Netherlands
Telephone: +31 20 4440814
Facsimile: +31 20 4442831
E-mail: mc.dejong@vumc.nl

Conflict of interest: No conflicting relationship exists for any author.

Running head: Screening for trilateral retinoblastoma

Funding: There was no specific funding source for this study

Abstract word count: 352 words

Manuscript word count: 2898 words

Figures: 4

Appendices: 11

References: 40
Key words: retinoblastoma, trilateral retinoblastoma, pineoblastoma, screening, MRI, lead time, period at risk

ABSTRACT

Topic: To determine until what age children are at risk for pineal trilateral retinoblastoma (TRb), 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: About 45% of patients with retinoblastoma – those with a germline RB1 pathogenic variant – are at risk for pineal TRb. Early detection and treatment is essential for survival. Current evidence is unclear on the usefulness of screening for pineal TRb and, if useful, until what age screening should be continued.

Methods: We conducted a study according to the MOOSE guideline 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 two authors, and two 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, interquartile range 9–29). Age at diagnosis of pineal TRb in patients diagnosed with retinoblastoma at ≤6 months versus >6 months of age were comparable (P=0.44), suggesting independency between the ages at diagnosis of intraocular retinoblastoma and pineal TRb. The laterality of intraocular retinoblastoma and its treatment were unassociated with the age when the pineal TRb was
diagnosed. The lead time from an asymptomatic to a 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 the age of 36 months, at least 311 and 776 scans would be required to detect one asymptomatic pineal TRb and to save one life, respectively.

**Conclusion:** Patients with retinoblastoma are at risk for pineal trilateral retinoblastoma for a shorter period than previously assumed and the age at diagnosis of pineal trilateral retinoblastoma is independent of the age at diagnosis of retinoblastoma. The GRADE level of evidence for these conclusions remains low.
INTRODUCTION

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

The incidence of pineal trilateral retinoblastoma according to our recent systematic review and meta-analysis is 3.2% (95% confidence interval [CI] 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% CI 1.9–4.2) of patients with bilateral retinoblastoma. Because 45% of all retinoblastomas are heritable, and approximately 8000 new patients are expected globally each year, should all of them survive trilateral retinoblastoma is predicted to affect around 125 children annually, and 90 of them would develop a pineal trilateral retinoblastoma.

Unlike non-pineal trilateral retinoblastomas, pineal trilateral retinoblastomas are often diagnosed after the intraocular tumor (metachronous). The often metachronous diagnosis of pineal trilateral retinoblastoma raises the question whether, and at which frequency, neuroradiologic screening should be adopted for a child with a germline \( RB1 \) pathogenic variant.

In practice, most centers follow the recommendation to perform a brain magnetic resonance imaging (MRI) for children with retinoblastoma at diagnosis. Some centers, on the other hand, repeat the MRI for children up to 5 years of age, although the benefit from this practice is unclear.
Whether screening for pineal trilateral retinoblastoma is useful is unclear until this
day. The objective of this article is to contribute to solving this problem by answering
two previously unanswered questions:

1. Until which age are patients with heritable retinoblastoma ‘at risk’ for pineal
   trilateral retinoblastoma?
2. Does pineal trilateral retinoblastoma develop earlier if a patient is diagnosed
   with retinoblastoma at an early age (≤ 6 months)?

METHODS

Search strategy, study selection and data extraction

We performed this study according to the EQUATOR (enhancing the quality and
transparency of health research) reporting guidelines, including meta-analysis of
observational studies in epidemiology a proposal for reporting (MOOSE). This study
adhered to the declaration of Helsinki. The ethics committee (METc VUmc) approved
this study with a waiver of informed consent.

We updated our literature search for English, Dutch and German literature for
patients with trilateral retinoblastoma as performed for the 2014 systematic review
and meta-analysis by De Jong et al.4 with a new search (PubMed and Embase)
performed on February 27, 2019 (Appendix A, performed by MCJ with 9 years of
experience in conducting systematic reviews and meta-analyses). To ensure
sensitivity the search strategy only included terms describing the target disease
(Appendix A). Two authors (MCJ and ACM) independently reviewed all articles for
inclusion and two authors (MCJ and WAK) independently extracted data from the
included articles. We extracted all data as previously described4 to update our entire
trilateral retinoblastoma database. If the trilateral retinoblastoma 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 trilateral retinoblastoma 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 papers published ≥1995 were contacted via e-mail (on October 2017 and February 2019) for additional information relevant to the research questions (whether there was a screening program for trilateral retinoblastoma in place, whether it was detected during screening or after development of symptoms, and whether and when a previous negative scan was performed), however, none responded.

Risk of bias and study quality
Risk of bias and methodological quality of each article was assessed with a checklist proposed by Murad et al. Checklist items 5 and 6 were not included because they are only relevant to adverse drug events. Two authors (MCJ and RWJ) 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 two research questions stated in the introduction according to the GRADE system.

Statistical analysis
We used IBM SPSS Statistics (version 22). The cumulative frequency of trilateral retinoblastoma by age at diagnosis and by the time from intraocular retinoblastoma
was plotted. The Mann-Whitney $U$ test was used to compare subgroups. Spearman's $\rho$ was used to calculate a correlation between two continuous variables. P-values <0.05 were considered statistically significant. All tests were two-sided.

For the main analyses, data of patients diagnosed in 1995 or later were included (see prior publication$^{14,15}$). 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 modalities and treatment for both intraocular retinoblastoma and trilateral retinoblastoma. We used data from patients diagnosed before 1995 to check the robustness of our analyses in case sample sizes were small.

RESULTS

Included studies and patients

Our updated search resulted in 185 PubMed and 336 Embase hits (Appendix B). After exclusion of 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$^{10}$ included only previously published patients. Six articles$^{16-21}$ did not provide the age at diagnosis of trilateral retinoblastoma, two$^{22,23}$ reported on patients with a trilateral retinoblastoma but without an intraocular tumor, and three$^{24-26}$ did not report on patients with trilateral retinoblastoma at all and were excluded. The six remaining articles$^{27-32}$ provided fifteen new patients. Together with 174 patients from our earlier systematic review,$^{4}$ we compiled data from 189 patients with trilateral retinoblastoma (Appendix C).

Of all patients, 138 (73%) had a pineal trilateral retinoblastoma, 42 (22%) had a supra- or parasellar or ventricular trilateral retinoblastoma, and 3 (2%) had both a
pineal and a non-pineal trilateral retinoblastoma,\textsuperscript{5, 33} in the remaining patients (3%), the location of the trilateral retinoblastoma was unspecified. Of the 183 patients with a trilateral retinoblastoma in a known location, 73 (40%) were diagnosed in 1995 or later of whom 50 (68%) had a pineal trilateral retinoblastoma, 21 (29%) had a non-pineal trilateral retinoblastoma, and 2 (3%) had both tumors; 37 (51%) of them were synchronous, 28 (38%) were metachronous, one was diagnosed before the intraocular tumor, and in 7 (11%) patients the sequence was unspecified. Restricting to pineal trilateral retinoblastoma, of the 50 patients diagnosed in 1995 or later, 18 (36%) had synchronous tumors, 26 (52%) 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), indicating that they likely reported patients that were interesting and did not necessarily present the entire experience the authors had with trilateral retinoblastoma. In seventeen (18%) studies one or more false positive diagnosis could not be entirely ruled out (e.g., patient 151 in appendix C had no follow-up and a small presumed cystic pineal trilateral retinoblastoma of 11 mm).

**Cumulative frequency of having pineal trilateral retinoblastoma diagnosed**

We stratified the cumulative frequency of pineal trilateral retinoblastoma according to the presence or absence of symptoms (Figure 1). The distribution of the ages at which pineal trilateral retinoblastoma was diagnosed differed significantly between the groups (\(P=0.0026\), Mann-Whitney \(U\) test). The two cumulative frequency curves
were separated by approximately 1 year, which we interpret as the lead time from a pineal trilateral retinoblastoma detectable on MRI to the onset of symptoms.

The median largest diameter of an asymptomatic versus a symptomatic pineal trilateral retinoblastoma 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 trilateral retinoblastoma and its diameter was observed in either among (including patients diagnosed before 1995 to ensure a larger sample size, because tumor size often was unreported; Appendix E) 31 asymptomatic patients (ρ=-0.11; P=0.56; Spearman) or among 44 symptomatic ones (ρ=-0.15; P=0.33).

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

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

The cumulative frequency curve of the interval from diagnosis of an intraocular retinoblastoma to pineal trilateral retinoblastoma showed that patients diagnosed with intraocular retinoblastoma after 6 months of age develop pineal trilateral retinoblastoma after a shorter interval than those diagnosed at a younger age whether considering all, asymptomatic or symptomatic patients (Figure 3, P= 0.0004, 0.011 and 0.045, respectively, Mann-Whitney U test). Including in the analysis patients diagnosed with pineal trilateral retinoblastoma before 1995, or restricting analysis to that period, produced similar results (Appendix G).

When comparing the age at diagnosis of an asymptomatic pineal trilateral retinoblastoma versus an asymptomatic non-pineal trilateral retinoblastoma the cumulative frequency curves overlapped (Figure 4, P =0.38, Mann-Whitney U test).

Patients with bilateral and unilateral retinoblastoma were diagnosed with pineal trilateral retinoblastoma 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).

Prior treatment and metachronous pineal trilateral retinoblastoma

To evaluate the potential effect of previous systemic chemotherapy on the interval from intraocular retinoblastoma to pineal trilateral retinoblastoma 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 trilateral
retinoblastoma similarly to those who did receive chemotherapy (Appendix I, P=0.38, Mann-Whitney U test).

Patients who did not receive prior external beam radiotherapy were diagnosed with pineal trilateral retinoblastoma similarly to those who did receive such radiotherapy (Appendix J, 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 mm 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 a year. 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 would also capture any rare metachronous non-pineal trilateral retinoblastomas.

Given that 50% of pineal trilateral retinoblastomas are diagnosed at the baseline MR scan,\(^1\) and that 5% of pineal trilateral retinoblastoma 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 trilateral retinoblastoma incidence of 1.6% during the screening period. Assuming a sensitivity of 100% for MRI to detect an asymptomatic pineal trilateral retinoblastoma and no symptomatic ones emerging between scans, we would need to screen \(1/0.016 = 62.5\) patients with MRI to diagnose one asymptomatic metachronous pineal trilateral retinoblastoma. 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 one 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 trilateral retinoblastoma. Also,
the possibility of overdiagnosis (false positive) would risk unnecessary treatment with
its associated morbidity and mortality. High dose chemotherapy with stem cell rescue
caries a risk of toxic adverse effects, including death reported in 1 of 41 cases.35-37

Overall level of evidence

Appendix K outlines the GRADE level of evidence. The overall level of evidence is of
low quality, i.e., 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 trilateral
retinoblastoma are diagnosed are unassociated with each other. This suggests
independent development of intraocular retinoblastoma and pineal trilateral
retinoblastoma, a conclusion strengthened by the fact that the age at diagnosis of
pineal trilateral retinoblastoma 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 chemotherapy or radiotherapy for intraocular retinoblastoma and the interval to detection of pineal trilateral retinoblastoma. Consequently, prior treatment probably can be ignored when considering a screening strategy to detect metachronous trilateral retinoblastoma.

Previously$^4, 38$ it was found that non-pineal trilateral retinoblastoma is diagnosed earlier than pineal trilateral retinoblastoma. This might in part be explained by a longer lead time bias in the diagnosis of symptomatic pineal trilateral retinoblastoma, however, not pineal tumors are less frequently detectable at baseline MRI than non-pineal trilateral retinoblastomas.

The retinoblastoma community currently agrees that a baseline brain MRI is standard of care to detect a synchronous trilateral retinoblastoma when intraocular retinoblastoma is diagnosed. Most question the benefit of performing additional imaging given the rarity of metachronous trilateral retinoblastoma. 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 might only be required until the age of 36-40 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 trilateral retinoblastoma of under 2% in patients with heritable retinoblastoma, any screening program would require hundreds of MRI scans to detect one patient with an asymptomatic pineal trilateral retinoblastoma, and thus should undergo a thorough cost-benefit scrutiny.
Limitations

As noted in the previously published meta-analysis, our study is similarly limited 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 one of the patients in a particular series was not a false positive diagnosis, either because of deficient follow-up or because normal pineal glands may sometimes be difficult to differentiate from a small pineal trilateral retinoblastoma. However, the age at diagnosis of pineal trilateral retinoblastoma did not significantly differ 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 trilateral retinoblastoma by the co-authors from Toronto, Canada, which led to contact with the authors of the previous meta-analysis on survival after trilateral retinoblastoma. As a result, the prior meta-analysis protocol was adapted to provide the required answers.

CONCLUSIONS

Age at diagnosis of heritable intraocular retinoblastoma and pineal trilateral retinoblastoma likely are independent. Age at diagnosis of an asymptomatic non-pineal trilateral retinoblastoma and an asymptomatic pineal trilateral retinoblastoma are similar, and unassociated with the age at diagnosis and laterality of the intraocular retinoblastoma. The lead time from a detectable pineoblastoma on MRI to
development of symptoms is approximately 1 year. Prior systemic chemotherapy or radiotherapy for intraocular retinoblastoma is unassociated with the age at diagnosis of pineal trilateral retinoblastoma. Ninety-five percent of patients with an asymptomatic pineal trilateral retinoblastoma are diagnosed before the age of 40 months, which can be considered the period at risk of developing a pineal trilateral retinoblastoma. During this period, the risk of having a pineal trilateral retinoblastoma diagnosed is approximately constant over time. The GRADE level of evidence for these results remains low.
REFERENCES


FIGURE LEGENDS

Figure 1. Cumulative frequency plot of age at diagnosis of a pineal trilateral retinoblastoma in asymptomatic versus symptomatic disease.

Figure 2. Scatterplot of age at diagnosis of intraocular retinoblastoma versus the age at pineal trilateral retinoblastoma diagnosis. Note the lack of patients diagnosed with pineal trilateral retinoblastoma before retinoblastoma (region in the lower right of the graph), which can be explained by our inclusion criteria: studies reporting on a ‘pineal trilateral retinoblastoma’ without intraocular retinoblastoma were excluded. Perhaps (some of) those patients did not survive long enough to develop intraocular retinoblastoma.

Figure 3. Cumulative frequency plots of the interval between diagnosis of intraocular retinoblastoma and pineal trilateral retinoblastoma in patients diagnosed with intraocular retinoblastoma at ≤ 6 months of age and > 6 months of age (a) for all patients, (b) for asymptomatic patients, and (c) for symptomatic patients.

Figure 4. Cumulative frequency plot of age at diagnosis of trilateral retinoblastoma for patients with pineal versus non-pineal trilateral retinoblastoma.
LIST OF APPENDICES

Appendix A. Search Strategy
Appendix B. Article inclusion flow diagram.
Appendix C. List of included trilateral retinoblastoma patients
Appendix D. Risk of bias and study quality checklist
Appendix E. Scatterplot of age at diagnosis of pineal trilateral retinoblastoma versus maximum tumor diameter.
Appendix F. Cumulative frequency plots of age at diagnosis of pineal trilateral retinoblastoma for intraocular retinoblastoma at ≤6 months versus >6 months of age.
Appendix G. Additional cumulative frequency plots of the interval between diagnosis of intraocular retinoblastoma and pineal trilateral retinoblastoma
Appendix H. Age at diagnosis of pineal trilateral retinoblastoma by laterality
Appendix I. Age at diagnosis of pineal trilateral retinoblastoma with and without prior chemotherapy
Appendix J. Age at diagnosis of pineal trilateral retinoblastoma with and without prior radiotherapy
Appendix K. GRADE level of evidence.
Age at diagnosis of pineal trilateral retinoblastoma (months)

Cumulative frequency

≈12 months

Clinical presentation

Asymptomatic

Symptomatic

0 12 24 36 48 60

100%

80%

60%

40%

20%

0%

Age at diagnosis of pineal trilateral retinoblastoma (months)

Clinical presentation

Asymptomatic

Symptomatic

=12 months

0% 20% 40% 60% 80% 100%
Interval between retinoblastoma and pineoblastoma (months) 
Cumulative frequency 
Age at retinoblastoma diagnosis 
≤ 6 months 
> 6 months 
0 12 24 36 48 60 
100% 
80% 
60% 
40% 
20% 
0%
Interval between retinoblastoma and pineoblastoma (months) 
Cumulative frequency 
Age at retinoblastoma diagnosis 
≤ 6 months 
> 6 months 
0 12 24 36 48 60 
100%
80%
60%
40%
20%
0%
Cumulative frequency

Age at retinoblastoma diagnosis

- ≤ 6 months
- > 6 months

Interval between retinoblastoma and pineoblastoma (months)
Patients with retinoblastoma are at risk for pineal trilateral retinoblastoma for a shorter time period than previously assumed and the age at diagnosis of pineal trilateral retinoblastoma seems to be independent of the age at diagnosis of retinoblastoma.