The incidence of trilateral retinoblastoma: a systematic review and meta-analysis

Marcus C de Jong, Wijnanda A Kors, Pim de Graaf, Jonas A Castelijns, Annette C Moll, Tero Kivelä
Purpose • To estimate the incidence of trilateral retinoblastoma in patients with retinoblastoma.

Design • Systematic review and meta-analysis

Methods • We searched Medline and Embase for scientific literature published between January 1966 and July 2015 that assessed trilateral retinoblastoma incidence. We used a random-effects model for the statistical analyses.

Results • We included 23 retinoblastoma cohorts from 26 studies. For patients with bilateral retinoblastoma the unadjusted chance of developing trilateral retinoblastoma across all cohorts was 5.3% (95% confidence interval [CI]: 3.3–7.7%); the chance of pineal trilateral retinoblastoma was 4.2% (95% CI: 2.6–6.2%) and the chance of non-pineal trilateral retinoblastoma was 0.8% (95% CI: 0.4–1.3%). In patients with hereditary retinoblastoma (all bilateral cases, and the unilateral cases with a family history or germline \(RB1\) mutation) we found a trilateral retinoblastoma incidence of 4.1% (95% CI: 1.9–7.1%), and a pineal trilateral retinoblastoma incidence of 3.7% (95% CI: 1.8–6.2%). To reduce the risk of overestimation bias we restricted analysis to retinoblastoma cohorts with a minimum size of 100 patients, resulting in adjusted incidences of 3.8% (95% CI: 2.4–5.4%), 2.9% (95% CI: 1.9–4.2%), and 0.7% (95% CI: 0.3–1.2%) for any, pineal and non-pineal trilateral retinoblastoma, respectively, among patients with bilateral retinoblastoma. Among hereditary retinoblastoma we found an adjusted trilateral retinoblastoma incidence of 3.5% (95% CI: 1.2–6.7%) and a pineal trilateral retinoblastoma incidence of 3.2% (95% CI: 1.4–5.6%).

Conclusion • The estimated incidence of trilateral retinoblastoma is lower than what is reported in previous literature, especially after exclusion of small cohorts that were subject to overestimation bias in this context.
INTRODUCTION

Until the age of about 7 years patients with hereditary retinoblastoma are at risk of having an intracranial midline primitive neuroectodermal tumor diagnosed, and among patients diagnosed since 1995 more than 95% has developed trilateral retinoblastoma before the age of 5 years. In histopathologic analysis these tumors look similar to corresponding retinal tumors. When uni- or bilateral retinoblastoma and a intracranial midline primitive neuroectodermal tumor both occur in a patient, this is referred to as trilateral retinoblastoma that can be found in the pineal gland (pineal trilateral retinoblastoma) in about three quarters of cases and in the remaining patients it develops in other midline brain regions (non-pineal trilateral retinoblastoma), usually the supra- and parasellar region, although other brain regions have been reported also.

In a recent meta-analysis we showed that survival has improved considerably in the last two decades from hardly any to almost half of all patients (see chapter 8). Favorable survival after pineal trilateral retinoblastoma depended strongly on early detection and small tumor size. The improved survival after trilateral retinoblastoma was highly associated with the use of (improved) chemotherapy regimens, especially high-dose chemotherapy with stem cell rescue.

Previous radiotherapy for retinoblastoma, especially before the age of 12 months, has been associated with a potentially higher incidence of pineal trilateral retinoblastoma in patients with hereditary retinoblastoma, even though the pineal gland is usually not (directly) within the field of radiation. Weather previous systemic chemotherapy is protective of developing trilateral retinoblastoma is still being debated.

There have been numerous reports on trilateral retinoblastoma incidence, but these studies are quite heterogeneous. Some are referral-based, others population-based. The only previously published study summarizing incidence data across studies reported an incidence of 5% to 15% among patients with bilateral retinoblastoma.

The objective of this study is to provide an overview, to critically analyze, and to provide pooled summary estimates of published incidence data for pineal and non-pineal trilateral retinoblastoma.

METHODS

We performed this systematic review and meta-analysis according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.

Search strategy

We searched Medline (PubMed) and Embase for English, Dutch, and German literature published from 1 January 1966 through 15 July 2015, evaluating trilateral retinoblastoma cases. We also considered alternatively found studies for inclusion (e.g., through checking references in included studies). The search was similar to the search we used in our systematic review and meta-analysis on survival of patients with trilateral retinoblastoma. To ensure a sensitive search, we included only keywords corresponding to the target condition, including: retinoblastoma, pineoblastoma, pineal, suprasellar, parasellar, sellar, ectopic, and brain, without any delimiters. For the detailed search see the appendix A.
### Table 1. Basic information about the retinoblastoma cohorts of all included studies that presented trilateral retinoblastoma incidence data

<table>
<thead>
<tr>
<th>Study</th>
<th>Inclusion period</th>
<th>Country</th>
<th>Cohort type</th>
<th>Type of Rb patients</th>
<th>Age at Rb diagnosis (months)</th>
<th>Patient follow-up from Rb diagnosis (months)</th>
<th>Unilateral Rb</th>
<th>Bilateral Rb</th>
<th>Familial Rb</th>
<th>Overlap with</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoaku et al.</td>
<td>1960-1994</td>
<td>UK</td>
<td>population</td>
<td>any</td>
<td>mean 6, range 0.75–17</td>
<td>64%</td>
<td>36%</td>
<td>38%*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antoneli et al.</td>
<td>1986-2003</td>
<td>Brasil</td>
<td>1 center</td>
<td>any</td>
<td>60%</td>
<td>40%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azur et al.</td>
<td>1975-2001</td>
<td>Australia</td>
<td>2 centers</td>
<td>any</td>
<td>mean 17.9 (b 22.6, u 3.5)</td>
<td>60%</td>
<td>40%</td>
<td>11%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bartuma et al.</td>
<td>2001-2011</td>
<td>Sweden</td>
<td>1 center</td>
<td>hereditary</td>
<td>mean 8, range 0–39</td>
<td>8%</td>
<td>92%</td>
<td>38%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blach et al.</td>
<td>1979-1990</td>
<td>USA</td>
<td>1 center</td>
<td>irradiated</td>
<td>median 7, range &lt;1–60</td>
<td>17%</td>
<td>83%</td>
<td>27%</td>
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</tr>
<tr>
<td>Chantada et al.</td>
<td>1988-2012</td>
<td>Argentina</td>
<td>1 center</td>
<td>bilateral</td>
<td>mean 13.9, range 0–114</td>
<td>100%</td>
<td>14%*</td>
<td>14%*</td>
<td>Moreno et al.</td>
<td></td>
</tr>
<tr>
<td>De Ioris et al.</td>
<td>1999-2009</td>
<td>Italy</td>
<td>1 center</td>
<td>any</td>
<td>median 10, range 0.5–73</td>
<td>58%</td>
<td>42%</td>
<td>14%</td>
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<td></td>
</tr>
<tr>
<td>De Potter et al.</td>
<td>1972-1992</td>
<td>UK</td>
<td>1 center</td>
<td>any</td>
<td>5.4%</td>
<td>46%</td>
<td>14%</td>
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</tr>
<tr>
<td>Duncan et al.</td>
<td>1990-1998</td>
<td>USA</td>
<td>2 centers</td>
<td>any</td>
<td>mean 44.8, range 0–139</td>
<td>≥63%</td>
<td>≤37%</td>
<td></td>
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</tr>
<tr>
<td>Helveston et al.</td>
<td>1967-1987</td>
<td>USA</td>
<td>1 center</td>
<td>any</td>
<td>u 23, b 10¶</td>
<td>59%</td>
<td>41%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jurkiewicz et al.</td>
<td>1996-2008</td>
<td>Poland</td>
<td>1 center</td>
<td>any</td>
<td>u median 22, b median 12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kingston et al.</td>
<td>1954-1983</td>
<td>UK</td>
<td>2 centers</td>
<td>any</td>
<td>31%</td>
<td>69%</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Klufas et al.</td>
<td>2006-2010</td>
<td>USA</td>
<td>1 center</td>
<td>treated with IAC</td>
<td>median 17.5, range 8–36</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lim et al.</td>
<td>2001-2009</td>
<td>Malaysia</td>
<td>1 center</td>
<td>any</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lim et al.</td>
<td>1997-2010</td>
<td>Singapore</td>
<td>1 center</td>
<td>any</td>
<td>mean 25.7, SD 19.9</td>
<td>median 36, range 0–156</td>
<td>35%</td>
<td>16%</td>
<td></td>
<td>Lueder et al.</td>
</tr>
<tr>
<td>Lueder et al.</td>
<td>1924-1985</td>
<td>USA</td>
<td>1 center</td>
<td>any</td>
<td>67%</td>
<td>33%</td>
<td>14%</td>
<td></td>
<td></td>
<td>Lueder et al.</td>
</tr>
<tr>
<td>Lueder et al.</td>
<td>1924-1989</td>
<td>USA</td>
<td>1 center</td>
<td>any</td>
<td>14%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lueder et al.</td>
</tr>
<tr>
<td>Moreno et al.</td>
<td>2000-2009</td>
<td>Argentina</td>
<td>population</td>
<td>any</td>
<td>u median 26 (IQR 13–42), b median 10 (IQR 5–19)</td>
<td>68%</td>
<td>32%</td>
<td></td>
<td></td>
<td>Chantada et al.</td>
</tr>
<tr>
<td>Popovic et al.</td>
<td>1990-2001</td>
<td>Switzerland</td>
<td>1 center</td>
<td>any</td>
<td>49%</td>
<td>51%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Provenza et al.</td>
<td>1985-2002</td>
<td>USA</td>
<td>1 center</td>
<td>any</td>
<td>52%</td>
<td>48%</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Rama. et al.</td>
<td>2000-2012</td>
<td>USA</td>
<td>1 center</td>
<td>any</td>
<td>mean 21, median 13, range 0–91</td>
<td>53%</td>
<td>47%</td>
<td>11%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scott et al.</td>
<td>1970-1990</td>
<td>USA</td>
<td>1 center</td>
<td>any</td>
<td>mean 15.8</td>
<td></td>
<td>52%</td>
<td>48%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shields et al.</td>
<td>1995-1999</td>
<td>USA</td>
<td>1 center</td>
<td>any</td>
<td>mean 14, median 8, range 1–87</td>
<td>mean 33, range 0–67</td>
<td>48%</td>
<td>52%</td>
<td>18%</td>
<td></td>
</tr>
</tbody>
</table>

Rb = retinoblastoma, u = unilateral, b = bilateral, IAC = intra-arterial chemotherapy, SD = standard deviation, IQR = interquartile range, Rama. = Ramasubramanian.

*As percentage of the patients with bilateral retinoblastoma.

¶Age at treatment, unknown if these are means or medians or some other measure.
Study selection and data extraction

Two authors (MCJ and ACM) independently reviewed article titles and abstracts for eligibility. Discrepancies were resolved by consensus. Subsequently the same two authors independently reviewed eligible full-text articles for inclusion in the systematic review and meta-analysis. Again, discrepancies were solved by consensus.

We included studies in the systematic review and meta-analysis if (1) the study mentioned the number of patients with trilateral retinoblastoma (can also be 0, as long as authors mentioned evaluating for trilateral retinoblastoma cases), if (2) articles reported details and size of the Retinoblastoma cohort in which patients with trilateral retinoblastoma were seen (e.g., number of patients with trilateral retinoblastoma diagnosed in a cohort of patients with retinoblastoma during a certain period), and if (3) the full-text article could be obtained. We excluded studies from the systematic review if (1) the article was a review or meta-analysis, and if (2) studies included overlapping incidence data. Two authors (MCJ and WAK) independently extracted incidence data. Discrepancies were resolved by consensus. We have defined hereditary retinoblastoma as patients with bilateral retinoblastoma, known familial retinoblastoma, or a detected germline mutation in $RB1$.

Data synthesis and statistical analysis

Ideally, we would present the cumulative incidence of trilateral retinoblastoma until a certain age (e.g., up to 5 years) in comparable retinoblastoma cohorts, however, most studies only provided the total number of patients with retinoblastoma and the number of trilateral retinoblastoma cases they found in their cohort. Therefore we are restricted to the calculation of a percentage of cases that developed trilateral retinoblastoma divided by total retinoblastoma cohort from certain time period. This method unfortunately does not take into account the effect of patients lost to follow-up, i.e., assuming that of all patients with retinoblastoma it is unequivocally known whether they developed trilateral retinoblastoma or not.

In addition to performing unadjusted analysis, we calculated adjusted estimates by including cohorts of at least 100 patients with retinoblastoma, to prevent overestimation bias. Most small cohorts published specifically after encountering at least one trilateral retinoblastoma and thus led to a report irrespective of how many patients without trilateral retinoblastoma had been seen (i.e., an arbitrary cohort of patients with retinoblastoma with a certain start
and end date will have been constructed around the patient(s) with trilateral retinoblastoma that were encountered. The limit of 100 patients was based on visual evaluation of a plot of the incidence of trilateral retinoblastoma against the total sample size across studies (figure 1). Typically, an unselected patient population contains 40% of bilateral retinoblastoma, and thus we considered also a cohort of at least 40 bilateral retinoblastomas to be large enough to guard for overestimation bias.

To assess the extent of this bias we compared data from developed versus developing countries, as one would expect follow-up to be more complete in developed countries (i.e., higher chance to find a trilateral retinoblastoma). This might lead to an underestimation of trilateral retinoblastoma incidence in the developing countries. Pooling data from different retinoblastoma cohorts also assumes comparability of these cohorts.

To evaluate changes in trilateral retinoblastoma incidence over time we used a cut-off at the year 1995. We chose this cut-off because around (or maybe even before) 1995 treatment of retinoblastoma started to shift from radiotherapy to chemotherapy. We used a random-effects model to calculate summary estimates of trilateral retinoblastoma incidence. A random-effects model is used for meta-analyses to account for heterogeneity between studies. For each analysis we calculated $I^2$ to evaluate heterogeneity among included studies; $I^2$ ranges from 0 to 100% with increasing heterogeneity. For the random-effects analyses we used MetaXL (version 2.1, EpiGear, Wilston, Australia) and SAS (Proc MIXED, version 9.3, Raleigh, NC, USA). The forest plots were created with Illustrator CS6 (Adobe, San Jose, USA).

Risk of bias and study quality assessment
Two authors (MCJ and TK) assessed the risk of bias with a modified checklist that was developed for prevalence studies by Hoy et al. With the checklist six items that could lead to bias were assessed (appendix B).

RESULTS
We identified 1865 unique studies from database searches. We excluded 1734 articles based on title and abstract (figure 2). We excluded 105 studies based on the full text; see figure 2 for reasons of exclusion. Twenty-six studies (3 pairs of studies had overlapping cohorts, but provided different data of interest and were therefore included, see table 1) met the inclusion criteria of this systematic review. Twenty-one studies (20 cohorts) were included in the meta-
Trilateral retinoblastoma incidence

Tables 2 and 3 show the incidence data as reported in each included study.

**Unadjusted estimates**

Twenty-six studies reported trilateral retinoblastoma incidence in 23 unique cohorts of patients with retinoblastoma, and in 15 studies (15 cohorts) bilateral could be distinguished from unilateral retinoblastoma (Table 2). Seven studies (6 cohorts) presented the trilateral retinoblastoma incidence in hereditary retinoblastoma, three studies (cohorts) reported trilateral retinoblastoma incidence after external beam irradiation for retinoblastoma, and five studies (cohorts) compared the incidence in patients with retinoblastoma with and without previous chemotherapy. Forest plots of the included studies (sorted by the midpoint of the study period) and the summary estimates are shown in figure 3.

For unilateral and bilateral retinoblastoma combined, the unadjusted chance of developing a trilateral retinoblastoma across all studies is 2.1% (95% confidence interval [CI]: 1.4–2.8%; 18 cohorts), the chance of developing pineal trilateral retinoblastoma is 1.7% (95% CI: 1.2–2.3%; 19 cohorts), and the chance of a non-pineal trilateral retinoblastoma is 0.4% (95% CI: 0.2–0.6%; 18 cohorts). For bilateral retinoblastoma the chance of developing a trilateral retinoblastoma is 5.3% (95% CI: 3.3–7.7%; 14 cohorts); restricting calculations to pineal trilateral retinoblastoma resulted in an incidence of 4.2% (95% CI: 2.6–6.2%; 15 cohorts) and restricting to non-pineal trilateral retinoblastoma gave an incidence of 0.8% (95% CI: 0.4–1.3%; 14 cohorts). In hereditary retinoblastoma we found a trilateral retinoblastoma incidence of 4.2% (95% CI: 1.6–7.7%; 5 cohorts), a pineal trilateral retinoblastoma incidence of 3.7% (95% CI: 1.8–6.2%; 6 cohorts), and we did not calculate the non-pineal trilateral retinoblastoma incidence as there were no cases in 5 retinoblastoma cohorts.

**Adjusted estimates**

We adjusted for potential overestimation bias by restricting the analysis to cohorts that included at least 100 patients with retinoblastoma (Figure 1). We found incidences of 1.7% (95% CI: 1.2–2.2%; 14 cohorts), 1.4% (95% CI: 1.0–1.7%; 15 cohorts), and 0.3% (95% CI: 0.2–0.6%; 14 cohorts), for any, pineal, and non-pineal trilateral retinoblastoma, respectively. In cohorts with only patient with bilateral retinoblastoma we found incidences of 3.8% (95% CI: 2.4–5.4%; 10 cohorts), 2.9% (95% CI: 1.9–4.2%; 11 cohorts) and 0.7% (95% CI: 0.3–1.2%; 10 cohorts), respectively. Among patients with hereditary retinoblastoma we found a trilateral retinoblastoma incidence of 3.5% (95% CI: 1.2–6.7%; 4 cohorts) and a pineal trilateral retinoblastoma incidence of 3.2% (95% CI: 1.4–5.6%; 5 cohorts).

**Period analysis**

To analyze changes over time we created 2 groups with the year 1995 as the cut-off year (depending on the midpoint of the study period). Before the year 1995 unadjusted trilateral retinoblastoma incidence for uni- and bilateral retinoblastoma combined was 2.5% (95% CI: 1.5–3.8%) versus 1.5% (95% CI: 0.9–2.2%) from the year 1995 onward (P=0.24). The incidence of pineal trilateral retinoblastoma before the year 1995 was 2.2% (95% CI: 1.3–3.4%) versus 1.2% (95% CI: 0.8–1.8%) from 1995 onwards (P=0.14).

Restricted to patients with bilateral retinoblastoma the unadjusted trilateral retinoblastoma incidence was 6.2% (95% CI: 3.2–9.9%) before the year 1995 versus 3.7% (95% CI: 1.4–6.9%) from the year 1995 onwards (P=0.44). The incidence of pineal trilateral retinoblastoma was 5.3% (95% CI: 2.7–8.8%) before the year 1995 versus 2.9% (95% CI: 1.3–5.1%) from the year 1995 onwards (P=0.38; figure 3).
Chapter 6

Effect of previous therapy

Four studies reported on trilateral retinoblastoma incidence in retinoblastoma cohorts who underwent previous systemic chemotherapy (table 3). In a single-center study with 4 trilateral retinoblastoma cases an inverse association between chemotherapy and the development of pineoblastoma was reported (P=0.014), with an incidence of 0.6% (1/180) and 8.6% (3/35) respectively for patients who did and who did not receive previous chemotherapy for their retinoblastoma.

In a single-center study from the same center, but different period, one pineoblastoma was found in 18 hereditary patients with retinoblastoma who did not undergo chemotherapy, compared to none in 99 patients who did undergo chemotherapy.

However, in another single center with 3 trilateral retinoblastomas this association was reversed with an incidence of 1.9% (3/159) versus 0.0% (0/38) respectively (P>0.99).

Three studies specifically looked at trilateral retinoblastoma incidence in cohorts of patients with retinoblastoma who underwent external beam radiotherapy (table 3). In a single-center study with 4 trilateral retinoblastomas a pineal trilateral retinoblastoma incidence of 1.7%...
Trilateral retinoblastoma incidence

A single-center study with 6 trilateral retinoblastomas found that patients with bilateral retinoblastoma who underwent irradiation as treatment for their retinoblastoma had a 6.2% (6/97) chance to develop trilateral retinoblastoma (5 pineal and 1 suprasellar); excluding the suprasellar tumor from the calculation resulted in a pineal trilateral retinoblastoma incidence of 5.2% (5/97).

Finally, in a single-center study with 5 cases a pineal trilateral retinoblastoma incidence of 5.7% (5/87) in patients with irradiated hereditary retinoblastoma was reported.

### Risk of bias and study quality assessment

Per-study scores on individual items of the risk of bias checklist (numbered from Q1 through Q6) can be found in appendix B showing quite some risk of bias in terms of how much the cohort is population like (Q1 and Q2) and the follow-up duration (Q4). To address assessment bias we compared trilateral retinoblastoma incidence in developed versus developing countries – the latter being potentially more prone to this type of bias, which would result in lower expected incidence numbers. This comparison indeed showed differences with unadjusted uni- and bilateral trilateral retinoblastoma incidences of 2.3% (95% CI 1.6–3.2%) versus 1.1% (95% CI 0.5–1.9%; P=0.32) and bilateral trilateral retinoblastoma incidences

<table>
<thead>
<tr>
<th>Study</th>
<th>Inclusion period</th>
<th>Treatment for retinoblastoma</th>
<th>Uni- and bilateral retinoblastoma</th>
<th>Bilateral retinoblastoma</th>
<th>Hereditary retinoblastoma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pineal</td>
<td>Non-pineal</td>
<td>Pineal</td>
</tr>
<tr>
<td>Bartuma et al.</td>
<td>2001-2011</td>
<td>systemic chemotherapy</td>
<td></td>
<td></td>
<td>0.0% (0/24)§</td>
</tr>
<tr>
<td>Chantada et al.</td>
<td>1988-2009</td>
<td>systemic chemotherapy</td>
<td>1.9% (3/159)</td>
<td>0.0% (0/159)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>no systemic chemotherapy</td>
<td>0.0% (0/38)</td>
<td>0.0% (0/38)</td>
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</tr>
<tr>
<td>Klufas et al.</td>
<td>2006-2010</td>
<td>intra-arterial chemotherapy</td>
<td>1.1% (1/89)</td>
<td>0.0% (0/89)</td>
<td>1.4% (1/70)</td>
</tr>
<tr>
<td>Rama. et al.</td>
<td>2000-2012</td>
<td>systemic chemotherapy</td>
<td>0.4% (1/252)</td>
<td>0.6% (1/180)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>no systemic chemotherapy</td>
<td>1.9% (3/156)</td>
<td>8.6% (3/35)</td>
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<tr>
<td>Shields et al.</td>
<td>1995-1999</td>
<td>systemic chemotherapy</td>
<td>0.0% (0/142)</td>
<td>0.0% (0/95)</td>
<td>0.0% (0/95)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>no systemic chemotherapy</td>
<td>1.4% (1/72)</td>
<td>5.9% (1/17)</td>
<td>0.0% (0/17)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>radiotherapy</td>
<td>4.3% (5/117)</td>
<td>5.2% (5/97)</td>
<td>1.0% (1/97)</td>
</tr>
<tr>
<td>Blach et al.</td>
<td>1979-1990</td>
<td>radiotherapy</td>
<td>4.7% (5/106)</td>
<td>0.0% (0/106)</td>
<td></td>
</tr>
<tr>
<td>Imhof et al.</td>
<td>1971-1993</td>
<td>radiotherapy</td>
<td>5.7% (5/87)</td>
<td>0.0% (0/87)</td>
<td></td>
</tr>
<tr>
<td>Rama. et al.</td>
<td>2000-2012</td>
<td>radiotherapy</td>
<td>2.8% (1/87)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Rama = Ramasubramanian.
The number of trilateral retinoblastoma patients divided by the size of the retinoblastoma cohort in parentheses. §24 patients received a full course of systemic chemotherapy, 1 was previously treated elsewhere and 2 did not receive (a full course of) chemotherapy; 1 of these latter 2 patients did develop TRb (location unspecified).

(3/179) was found in the group of patients with non-irradiated hereditary retinoblastoma and an incidence of 2.8% (1/36) was found in the irradiated group (P=0.5).8,21 A single-center study with 6 trilateral retinoblastomas found that patients with bilateral retinoblastoma who underwent irradiation as treatment for their retinoblastoma had a 6.2% (6/97) chance to develop trilateral retinoblastoma (5 pineal and 1 suprasellar); excluding the suprasellar tumor from the calculation resulted in a pineal trilateral retinoblastoma incidence of 5.2% (5/97).22

Finally, in a single-center study with 5 cases a pineal trilateral retinoblastoma incidence of 5.7% (5/87) in patients with irradiated hereditary retinoblastoma was reported.23
### Figure 3. Forest plots of trilateral retinoblastoma TRb incidence in cohorts of patients with (A) uni- and bilateral, (B) bilateral and (C) hereditary retinoblastoma. Incidence in percentages with a 95% confidence interval in parentheses.
### Trilateral retinoblastoma incidence

<table>
<thead>
<tr>
<th>Study</th>
<th>Incidence</th>
<th>Weight</th>
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<th>Weight</th>
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<td>Scott et al.</td>
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<td>*Ramasubramanian et al.</td>
<td>2.2 (0.4–6.2)</td>
<td>8.6</td>
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</tbody>
</table>

### Additional Data

- **Incidence**
  - Any location: 5.3 (3.3–7.7) (Q=38.39, P<0.01, I²=66%)
  - Pineal: 4.2 (2.6–6.2) (Q=37.58, P<0.01, I²=63%)
  - Non-pineal: 0.8 (0.4–1.3) (Q=7.62, P=0.87, I²=0%)

- **Weight**
  - Any location: 12.0
  - Pineal: 10.0 (2.1–26.5)
  - Non-pineal: 0.0 (0–11.6)

- **Unadjusted estimate**
  - Any location: 5.3 (3.3–7.7)
  - Pineal: 4.2 (2.6–6.2)
  - Non-pineal: 0.8 (0.4–1.3)

- **Adjusted estimate (*)**
  - Any location: 4.2 (1.6–7.7) (Q=8.51, P=0.07, I²=53%)
  - Pineal: 3.7 (1.7–6.5) (Q=11.34, P=0.05, I²=56%)
  - Non-pineal: 0.0 (0–11.6)

- **Adjusted estimate (**)**
  - Any location: 3.5 (1.2–6.7) (Q=5.45, P=0.01, I²=57%)
  - Pineal: 3.2 (1.4–5.6) (Q=8.17, P=0.09, I²=51%)
  - Non-pineal: 0.0 (0–11.6)
Chapter 6

6.0% (95% CI 3.5–9.2%) versus 2.6% (95% CI 0.4–6.2%; P=0.50) for developed and developing countries, respectively, though statistically not significantly different.

DISCUSSION

This systematic review gives an overview of studies on trilateral retinoblastoma incidence. Our summary estimates (especially the adjusted ones) of trilateral retinoblastoma incidence in bilateral or hereditary retinoblastoma are considerably lower than previously summarized by Kivelä², with an estimated incidence ranging from 5% to 15% in bilateral retinoblastoma, reflecting small cohorts in earlier studies. Even the unadjusted trilateral retinoblastoma incidence from this meta-analysis is lower and more precise (relatively narrow confidence intervals) than generally assumed in the literature; to test this we evaluated the trilateral retinoblastoma incidence mentioned in the introduction and discussion of articles included in the meta-analysis on survival after trilateral retinoblastoma³ (for obvious reasons we excluded articles that assessed trilateral retinoblastoma incidence), see appendix C.

The lower estimates for trilateral retinoblastoma incidence we calculated potentially reduce the cost-effectiveness of screening for trilateral retinoblastoma in patients with retinoblastoma beyond baseline imaging. More than 50% of trilateral retinoblastoma are diagnosed at the time of retinoblastoma diagnosis (with baseline magnetic resonance imaging of the eyes and brain), suggesting that baseline screening for trilateral retinoblastoma might indeed be useful.³

The few studies that published on prior use of systemic chemotherapy and risk of developing trilateral retinoblastoma have shown conflicting results with respect to a potential decrease of trilateral retinoblastoma risk in patients with retinoblastoma. Whether intra-arterial chemotherapy has an effect on the risk to develop trilateral retinoblastoma – theoretically improbable because systemic exposure to chemotherapy is very low – was only assessed in one relatively small cohort of 89 patients and does not allow for any conclusions on this issue.²⁴ Also the few studies that looked at prior radiotherapy did not allow for any meaningful meta-analysis. Should previous radiotherapy (commonly used before the year 1995) be inductive and previous chemotherapy (increasingly used since the year 1995) protective then we would expect to see a clear reduction of trilateral retinoblastoma incidence over time. The estimated incidences did slightly decrease after the year 1995, but the differences were not statistically significant (figure 3). Alternatively, larger cohort sizes in later studies could partially explain this difference.

There is much heterogeneity between the studies reporting trilateral retinoblastoma incidence. Some studies looked at incidence data in a population (3 cohorts from 3 studies, see table 1), but most are data from one or more (specialized) institutions which – due to referral bias – might have resulted in a higher trilateral retinoblastoma incidence, or maybe actually a lower incidence when children with trilateral retinoblastoma end up in different specialized pediatric neuro-oncology center (table 2). Also, some of the cohorts are from the same center. Other potential sources of heterogeneity are: the choice of start date and end date (year) of the retinoblastoma cohort at risk, and lost to follow-up of patients in the cohort. The estimates in
this study assume that of all patients with retinoblastoma in the cohort it is known whether they developed trilateral retinoblastoma, which might be considered appropriate because trilateral retinoblastoma develops relatively quickly (median interval 17 months) after retinoblastoma (since 1995 >95% are diagnosed with trilateral retinoblastoma before the age of 5 years).³

There is a risk that patients with asymptomatic trilateral retinoblastoma without histopathologic proof of disease might have been false-positive trilateral retinoblastoma cases (e.g., benign pineal cysts⁴) causing an overestimation of trilateral retinoblastoma incidence. On the other hand, patients with retinoblastoma, especially those from several decades back, might have died from central nervous system metastases that were not recognized as trilateral retinoblastoma (i.e., false negatives).

In summary the incidence of trilateral retinoblastoma is estimated to be substantially lower than previously reported in the literature concerning trilateral retinoblastoma, especially after adjusting for bias from small cohorts.
REFERENCES


