# Trilateral retinoblastoma: a systematic review and meta-analysis

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## Summary

**Background** About 5% of children with retinoblastoma from germline mutation of the *RB1* gene are at risk of developing trilateral retinoblastoma—intraocular retinoblastoma combined with a histologically similar brain tumour, most commonly in the pineal gland. We aimed to provide a systematic overview of published data for trilateral retinoblastoma, and to analyse how survival has changed.

**Methods** We searched Medline and Embase for scientific literature published between Jan 1, 1966, and April 14, 2014, that assessed trilateral retinoblastoma cases. We undertook a meta-analysis of survival with the Kaplan-Meier method and Cox proportional hazards regression, stratified on the basis of the original study, to account for between-study heterogeneity.

**Findings** We included 90 studies, with 174 patients with trilateral retinoblastoma. 5-year survival after pineal trilateral retinoblastoma increased from 6% (95% CI 2–15) in patients diagnosed before 1995, to 44% (26–61; p<0·0001) in those diagnosed from 1995 onwards. Before 1995, no patients with non-pineal trilateral retinoblastoma survived, but from 1995 onwards, 5-year survival was 57% (30–77; p=0·035). Hazard ratios (HR) adjusted for the presence of leptomeningeal metastases and trilateral retinoblastoma location, suggested that both conventional (HR 0·059, 95% CI 0·016–0·226; p<0·0001) and high-dose chemotherapy with stem-cell rescue (0·013, 0·002–0·064; p<0·0001) most strongly contributed to this improvement. Absence of leptomeningeal metastases (HR 2·13, 95% CI 0·98–4·60; p=0·055) were associated with improved survival. Non-pineal trilateral retinoblastomas were larger than pineal tumours (median 30 mm [range 6–100] *vs* 22 mm [7–60]; p=0·012), but both had similar outcomes since 1995.

**Interpretation** Our results suggest that improvements in overall survival are attributable to improved chemotherapy regimens and early detection of pineal trilateral retinoblastoma. As such, successful treatment of trilateral retinoblastoma should include screening at least at the time of retinoblastoma diagnosis and chemotherapy, which would preferably be a high-dose regimen with autologous stem-cell rescue.

**Funding** None.

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## Introduction

Patients with germline mutations in *RB1* have a risk of about 5% of developing intracranial midline primitive neuroectodermal tumours.[1] Such a tumour in a child who typically has unilateral or bilateral familial or sporadic hereditary intraocular retinoblastoma is known as trilateral retinoblastoma. This tumour type was first described in 1971, and was differentiated from cerebral metastases in 1977.[2] With rare exceptions,[3,4] trilateral retinoblastoma is located in the pineal gland or the suprasellar and parasellar region, and histopathologically, they resemble retinoblastoma.

A meta-analysis[2] published in 1999, showed that 88% of children with trilateral retinoblastoma did not survive for longer than 5 years. Of 94 children, only three survivors had been reviewed for long enough (≥5 years) to classify them as probably cured; all had asymptomatic pineal trilateral retinoblastoma no larger than 15 mm. Findings from another study[5] suggested that trilateral retinoblastoma might be curable with intensive chemotherapy, especially in patients without leptomeningeal metastases; however,

some tumours were resected, possibly confounding the effect of chemotherapy.

We did this study to provide a systematic overview and an updated meta-analysis of data for patients with trilateral retinoblastoma. In particular, we aimed to establish to what extent, if any, patients' survival has improved over time.

## Methods

### Search strategy and selection criteria

We undertook this study in accordance with the PRISMA statement.[6,7] We searched Medline (PubMed) and Embase for scientific literature written in English, Dutch, and German, published between Jan 1, 1966, and April 14, 2014, that assessed trilateral retinoblastoma cases. We also included alternatively sourced studies (eg, those from references in included studies). The search was formulated by MCJ, and reviewed by ACM and PG. To ensure sensitivity, we included only keywords corresponding to the target disorder—ie, retinoblastoma, pineoblastoma, pineal, suprasellar, parasellar, sellar, ectopic, and brain, without any delimiters (appendix).

See Online for appendix

### Study selection and data extraction

MCJ and ACM independently reviewed article titles and abstracts for eligibility, and solved discrepancies by consensus. Subsequently, these 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 if they reported one or more patients with an intraocular retinoblastoma and a primitive neuroectodermal tumour; if we could obtain the full-text article; if individual patients were identifiable; and if at least survival status (death due to trilateral retinoblastoma, death due to other cause, or alive) and follow-up data (age at diagnosis of trilateral retinoblastoma, and time of death or the last known time when still alive; this time could be 0 months) were available. We included articles that did not satisfy the final inclusion criterion if they provided additional information about a patient described in another included article. We excluded articles that were reviews or meta-analyses, and excluded patients (or articles when applicable to all patients) if it was uncertain whether they overlapped with already included patients.

MCJ and WAK independently extracted study data; discrepancies were resolved by consensus. In line with the meta-analysis by Kivelä,[2] if the largest trilateral retinoblastoma diameter was not reported, we estimated it from the published MRI or CT images to the nearest 5 mm. We contacted 44 investigators for further information, to which six investigators responded with additional data.

After completion of the database, TK reviewed all extracted data against those from his previous meta-analysis,[2] and from a subsequent database of published patients, and checked the present database for any missed studies. He also shared all updated patient information letters obtained from investigators in 1998 for his previous meta-analysis.

### Statistical analysis

We did statistical analyses with SPSS (version 20) and Stata (version 13). We did not use software specifically designed for meta-analysis, because such packages are mainly for assessment of summary statistics and our analysis was based on case-wise data. We analysed survival data with the Kaplan-Meier product-limit method. The numbers presented for survival are proportions for 5-year survival, with 95% CIs, with median survival times in months. We prospectively identified several groups of interest for comparative survival analysis (table 1). We focused on 5-year survival and the log-rank test instead of median survival times because many of the groups suffer from lead-time bias. For comparison of subgroups, p values were adjusted for various comparisons with Bonferroni correction. To assess the effect of improved treatment we chose 1995 as a cutoff for trilateral retinoblastoma diagnosis to create two groups, because around this time, treatment of intraocular retinoblastoma changed from simple surgery or external beam radiotherapy to other forms of treatment, particularly chemoreduction, and we postulated that the same development might be valid for trilateral retinoblastoma.[8]

For location, we differentiated pineal (pineoblastoma) from non-pineal trilateral retinoblastoma (midline intracranial primitive neuroectodermal tumour elsewhere). We defined retinoblastoma and trilateral retinoblastoma diagnosed within 3 months of each other as concurrent tumours. We defined long-term survivors as patients who were alive with no evidence of trilateral retinoblastoma at least 5 years after diagnosis. We considered treatment to be active if the article did not state that it was palliative or best supportive care.

To assess the effect of chemotherapy (none *vs* intrathecal or conventional systemic *vs* high-dose chemotherapy with stem-cell rescue), we used stratified Cox proportional hazards regression[9,10] to adjust for potential confounders: location of trilateral retinoblastoma (pineal *vs* non-pineal), age at diagnosis of trilateral retinoblastoma, symptoms (present *vs* absent), tumour size (≤15 mm *vs* >15 mm), leptomeningeal metastases or involvement of cerebrospinal fluid (present *vs* absent) at time of diagnosis. We verified the significance of all confounders by univariate regression.

In view of the number of events (58 to 97 events per model), we allowed no more than three predictors in the model and did not test interactions. We calculated hazard ratios (HRs) with their 95% CIs. The proportional hazards assumption was tested with the Schoenfeld residuals test.[11] To account for heterogeneity between studies we assigned each case with a unique identifier for stratification based on the original study. When more than one study reported the same patient, we assigned the case to the study with the most patients with trilateral retinoblastoma. We assigned single case reports to one of two strata, on the basis of publication date (<1995 and ≥1995) to keep the number of strata reasonable. We chose this cutoff to account for publication bias (initially almost all, and more recently only cases of interest could have been published—

| | Restriction | Additional stratification* |
|---|---|---|
| Year patients were diagnosed with trilateral retinoblastoma (<1995 *vs* ≥1995) | .. | Location |
| Trilateral retinoblastoma location (pineal, non-pineal) | .. | .. |
| Status of trilateral retinoblastoma at diagnosis (symptomatic, asymptomatic, or unknown) | Actively treated patients only | Year, location |
| Trilateral retinoblastoma size (≤15mm, >15mm, or unknown) | .. | Year, location |
| Concurrence of trilateral retinoblastoma with retinoblastoma (>3 months before, ≤3 months before or after, or >3 months after retinoblastoma) | Actively treated patients only | Year, location |
| Presence of metastatic disease at trilateral retinoblastoma diagnosis | Actively treated patients only | Year, location |

*p values adjusted with Bonferroni correction.

*Table 1*: Groups of interest for survival analysis

eg, surviving patients), and because it corresponded with our general study design. Use of three decade-long strata produced identical results (not reported).

To avoid effects from possible overdiagnosis of trilateral retinoblastoma, we compared survival after asymptomatic trilateral retinoblastoma with and without histopathological proof (if survival is better in the latter instance, overdiagnosis and resultant overestimation of subsequent survival should be suspected).

### Role of the funding source

There was no specific funding source for this study. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

### Results

Figure 1 shows the flow diagram for study selection. We identified 1769 articles of which 90 studies (including four from other sources[12–15] and one that was in press at the time of inclusion[16]), with 174 patients with trilateral retinoblastoma, qualified for inclusion (figure 1). The appendix shows all relevant data for each included patient, with bibliographic references; we merged data from patients who were included in more than one article. To confirm that these patients were the same individual, we matched them on the basis of patient characteristics (eg, same hospital or same age at diagnosis of trilateral retinoblastoma), and if the data were identical, we considered the cases identical. Some investigators specifically told us when a patient had been published previously.

Table 2 summarises characteristics of the included patients, by trilateral retinoblastoma location. Notably, patients with pineal trilateral retinoblastoma were substantially older at diagnosis of primitive neuroectodermal tumours than were those with non-pineal trilateral retinoblastoma. Non-pineal tumours were significantly larger than pineal tumours. Of 83 patients diagnosed before 1995, 44 (53%) were familial compared with 12 (32%) of 38 diagnosed after 1995 (p=0·032, Fisher's exact test); if no mention of family history is interpreted as no such history, the percentages are 45% (44 of 98 patients) versus 21% (12 of 58 patients; p=0·0031).

Table 3 summarises temporal changes in treatments for intraocular retinoblastoma (before diagnosis of trilateral retinoblastoma) and for trilateral retinoblastoma. We recorded a decline in use of radiotherapy and increasing use of chemotherapy for trilateral retinoblastoma since 1995. Use of high-dose chemotherapy with stem-cell rescue also increased, as did the proportion of actively treated patients with trilateral retinoblastoma. There was no clear trend for use of surgery.

Median survival after trilateral retinoblastoma diagnosis was 12 months (95% CI 10–14; IQR 6–33), and 5-year survival was 22% (95% CI 15–29; appendix). The longest
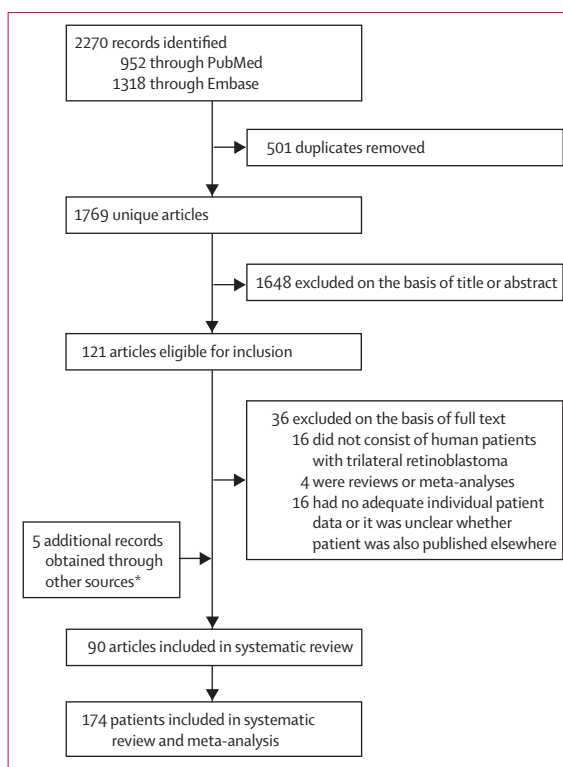


*Figure 1:* **Study flow chart**
*One article was in press at the time of inclusion, and we included one book.

time to death after a symptomatic pineal trilateral retinoblastoma was 59 months, compared with 32 months after symptomatic non-pineal disease (appendix). For asymptomatic trilateral retinoblastoma the longest time to death were 28 months for pineal disease and 33 months for non-pineal disease. Difference in the survival of asymptomatic patients with trilateral retinoblastoma, with and without histopathological proof, was not significant (p=0·29, log-rank test; appendix).

In view of a 5-year survival of 20% (95% CI 13–28), and a median survival of 11 months (7–15) for patients with pineal trilateral retinoblastoma, versus 34% (18–51) and 14 months (9–19), respectively, for those with non-pineal disease, we had insufficient evidence to conclude that either type of primitive neuroectodermal tumours would be associated with better survival (figure 2A). Two (1%) patients had both a pineal and a non-pineal tumour; both patients were excluded from this analysis.

Patients with trilateral retinoblastoma diagnosed during or after 1995 had better 5-year survival than those diagnosed before 1995 (48% [95% CI 33–61] vs 5% [2–13]), and a median survival of 24 months (95% CI incalculable) versus 8 months (6–10; figure 2B). We noted little difference in age at death between the two groups, showing that the difference in median median duration of survival is probably due to lead-time bias (appendix).

| | Any trilateral retinoblastoma (n=174)* | Pineal trilateral retinoblastoma (n=126) | Non-pineal trilateral retinoblastoma (n=40) | p value |
|---|---|---|---|---|
| Age at diagnosis of retinoblastoma (months) | 6 (0 to 120) | 5 (0 to 38) | 9 (1 to 120) | 0·0047† |
| Age at diagnosis of trilateral retinoblastoma (months) | 26 (1 to 144) | 31·5 (1 to 108) | 10 (1 to 144) | <0·0001† |
| Time interval between diagnosis of retinoblastoma and trilateral retinoblastoma diagnosis (months) | 17 (−60 to 103) | 24 (0 to 103) | 0 (−60 to 45) | <0·0001† |
| Age at death (months) | 38 (4 to 147) | 42 (17 to 109) | 22 (4 to 147) | <0·0001† |
| Size of trilateral retinoblastoma (mm) | 25 (6 to 100) | 22 (7 to 60) | 30 (6 to 100) | 0·012† |
| Patients diagnosed during or after 1995 | 57/148 (39%) | 38/111 (34%) | 19/37 (51%) | 0·080‡ |
| Men | 71/148 (48%) | 49/104 (47%) | 18/36 (50%) | 0·85‡ |
| Unilateral retinoblastoma | 27/163 (17%) | 17/117 (15%) | 10/38 (26%) | 0·14‡ |
| Familial retinoblastoma | 57/131 (44%) | 44/91 (48%) | 10/32 (31%) | 0·10‡ |
| Leptomeningeal metastases or CSF involvement at diagnosis of trilateral retinoblastoma | 35/113 (31%) | 22/81 (27%) | 7/24 (29%) | 1·00‡ |
| Patients who had active treatment | 134/156 (86%) | 95/112 (85%) | 33/36 (92%) | 0·41‡ |
| Asymptomatic trilateral retinoblastoma (all) | 53/142 (37%) | 36/100 (36%) | 17/34 (50%) | 0·16‡ |
| Asymptomatic trilateral retinoblastoma (<1995) | 17/79 (22%) | 11/58 (19%) | 6/14 (43%) | 0·16‡§ |
| Asymptomatic trilateral retinoblastoma (≥1995) | 27/47 (57%) | 18/29 (62%) | 9/17 (53%) | 1·00‡§ |
| Asymptomatic trilateral retinoblastoma (year unknown) | 9/16 (56%) | 7/13 (54%) | 2/3 (67%) | 1·00‡§ |
| Histopathological proof of trilateral retinoblastoma | 74/174 (43%) | 52/126 (41%) | 22/40 (55%) | 0·15‡ |
| Retinoblastoma diagnosed before trilateral retinoblastoma | 113/169 (67%) | 98/122 (80%) | 7/39 (18%) | <0·0001¶ |
| Concurrent diagnosis (within 3 months) | 53/169 (31%) | 24/122 (20%) | 27/39 (74%) | <0·0001¶ |
| Trilateral retinoblastoma diagnosed before retinoblastoma | 3/169 (2%) | 0/122 | 3/39 (8%) | <0·0001¶ |

Data are median (range) or n/N (%), unless otherwise indicated. *For six (3%) patients tumour location was unknown and two (1%) patients had more than one trilateral retinoblastoma; the appendix provides per-patient details. †Mann-Whitney U test, two-sided. ‡Fisher's exact test, two-sided. §Bonferroni correction for several comparisons. ¶Kruskal-Wallis test, two-sided.

*Table 2*: Patient characteristics by location of trilateral retinoblastoma

| | Period uncertain (n=18)* | <1995 (n=98) | ≥1995 (n=58) | p value |
|---|---|---|---|---|
| Previous chemotherapy for retinoblastoma | 2/13 (15%) | 4/87 (5%) | 6/50 (12%) | 0·17† |
| Previous chemotherapy for retinoblastoma‡ | 2/7 (29%) | 4/72 (6%) | 5/16 (31%) | 0·0088† |
| Previous radiotherapy for retinoblastoma | 2/8 (20%) | 53/81 (65%) | 5/47 (11%) | <0·0001† |
| Previous radiotherapy for retinoblastoma‡ | 2/5 (40%) | 53/66 (80%) | 4/16 (25%) | <0·0001† |
| Active treatment for trilateral retinoblastoma | 16/18 (89%) | 67/84 (80%) | 51/54 (94%) | 0·024† |
| Radiotherapy for trilateral retinoblastoma | 8/18 (44%) | 55/83 (66%) | 17/54 (31%) | 0·0001† |
| Surgery for trilateral retinoblastoma | 7/18 (39%) | 21/83 (25%) | 16/45 (36%) | 0·23† |
| No chemotherapy for trilateral retinoblastoma | 3/18 (17%) | 28/83 (34%) | 3/54 (6%) | <0·0001§ |
| Conventional systemic or intrathecal chemotherapy for trilateral retinoblastoma | 10/18 (56%) | 55/83 (66%) | 30/54 (57%) | <0·0001§ |
| High-dose chemotherapy with stem-cell rescue for trilateral retinoblastoma | 5/18 (28%) | 0/83 | 21/54 (39%) | <0·0001§ |

Data are n/N (%), unless otherwise indicated. *Excluded from the statistical tests. †Fisher's exact test, two-sided. ‡Includes only patients whose retinoblastoma was diagnosed 3 months or longer before trilateral retinoblastoma. §Kruskal-Wallis test, two-sided.

*Table 3*: Treatment according to period of diagnosis of trilateral retinoblastoma

Patients with pineal trilateral retinoblastoma had a 5-year survival of 6% (95% CI 2–15) before 1995, versus 44% (26–61) from 1995 onwards (figure 2C). Before 1995, none of the patients with non-pineal trilateral retinoblastoma survived, but from 1995 onwards, their 5-year survival was 57% (30–77; figure 2D).

Median survival of patients with asymptomatic trilateral retinoblastoma was 28 months (95% CI incalculable), versus 12 months (95% CI 9–15) for those with symptomatic disease. Median age at death did not differ between these patients, suggesting lead-time bias from earlier trilateral retinoblastoma diagnosis. However, the 5-year survival of asymptomatic patients was 45% (95% CI 30–60); better than the 11% (4–22) for patients with symptoms (log-rank p=0·0002; appendix).

We noted a large survival difference between asymptomatic and symptomatic patients who were actively treated only if the trilateral retinoblastoma was pineal
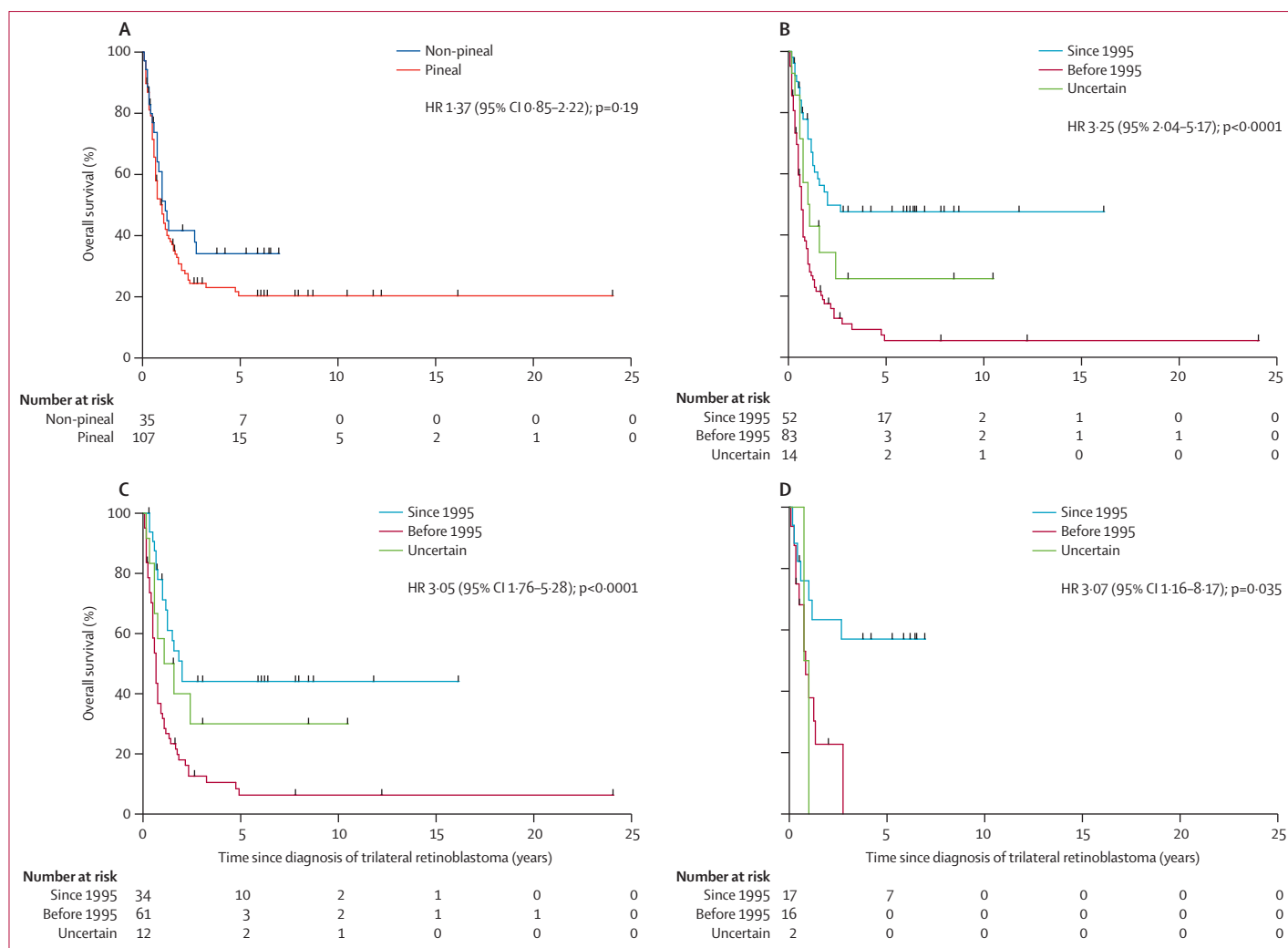
***Figure 2:*** **Kaplan-Meier curves showing survival after diagnosis of trilateral retinoblastoma for pineal versus non-pineal disease for all patients (A), trilateral retinoblastoma diagnosed before 1995 and from 1995 onwards for all patients (B), and stratified for pineal (C) versus non-pineal (D) disease**
Log-rank test, with Bonferroni correction in panels C and D, and hazard ratio (HR) from univariate Cox regression. Statistics exclude uncertain cases in panels B–D.

rather than non-pineal: 5-year survival was 50% (95% CI 31–67) for asymptomatic patients with pineal disease versus 4% (0–15) for symptomatic patients with pineal disease, and 33% (10–59) for asymptomatic patients with non-pineal disease versus 40% (15–65) for symptomatic patients with non-pineal disease (figures 3A, 3B).

Before 1995, asymptomatic patients with trilateral retinoblastoma had a 5-year survival of 20% (95% CI 5–42), compared with zero survival in symptomatic patients (figure 3C). Since 1995, 5-year survival of both asymptomatic (69%, 95% CI 43–85) and symptomatic (34%, 13–58) patients with trilateral retinoblastoma increased, although the difference in survival persisted (figure 3D).

Patients with concurrent trilateral retinoblastoma had a higher 5-year survival than those whose disease was diagnosed more than 3 months after retinoblastoma (51%

[95% CI 35–65] *vs* 11% [5–21]; HR 2·77, 95% CI 1·65–4·65; log-rank p<0·0001; appendix). Patients with a concurrent pineal trilateral retinoblastoma had a 5-year survival of 66% (95% CI 39–83), compared with 11% (5–22) for those with an antecedent ocular tumour (HR 4·46, 95% CI 1·90–10·44; log-rank p=0·0003; appendix). Patients with non-pineal disease had 5-year survival of 38% (95% CI 19–58) for those with concurrently diagnosed disease versus 40% (5–75; appendix) for those who did not. Stratification by period of diagnosis suggests improved survival curves for patients diagnosed from 1995 onwards (appendix).

Median size of pineal trilateral retinoblastoma diagnosed concurrently with retinoblastoma was smaller (13 mm, range 7–50) than the size of those diagnosed later (25 mm, 10–60; p=0·017, Mann-Whitney *U* test), unlike for non-pineal diseases, for which median sizes were 30 mm (6–100) and 30 mm (20–45), respectively.
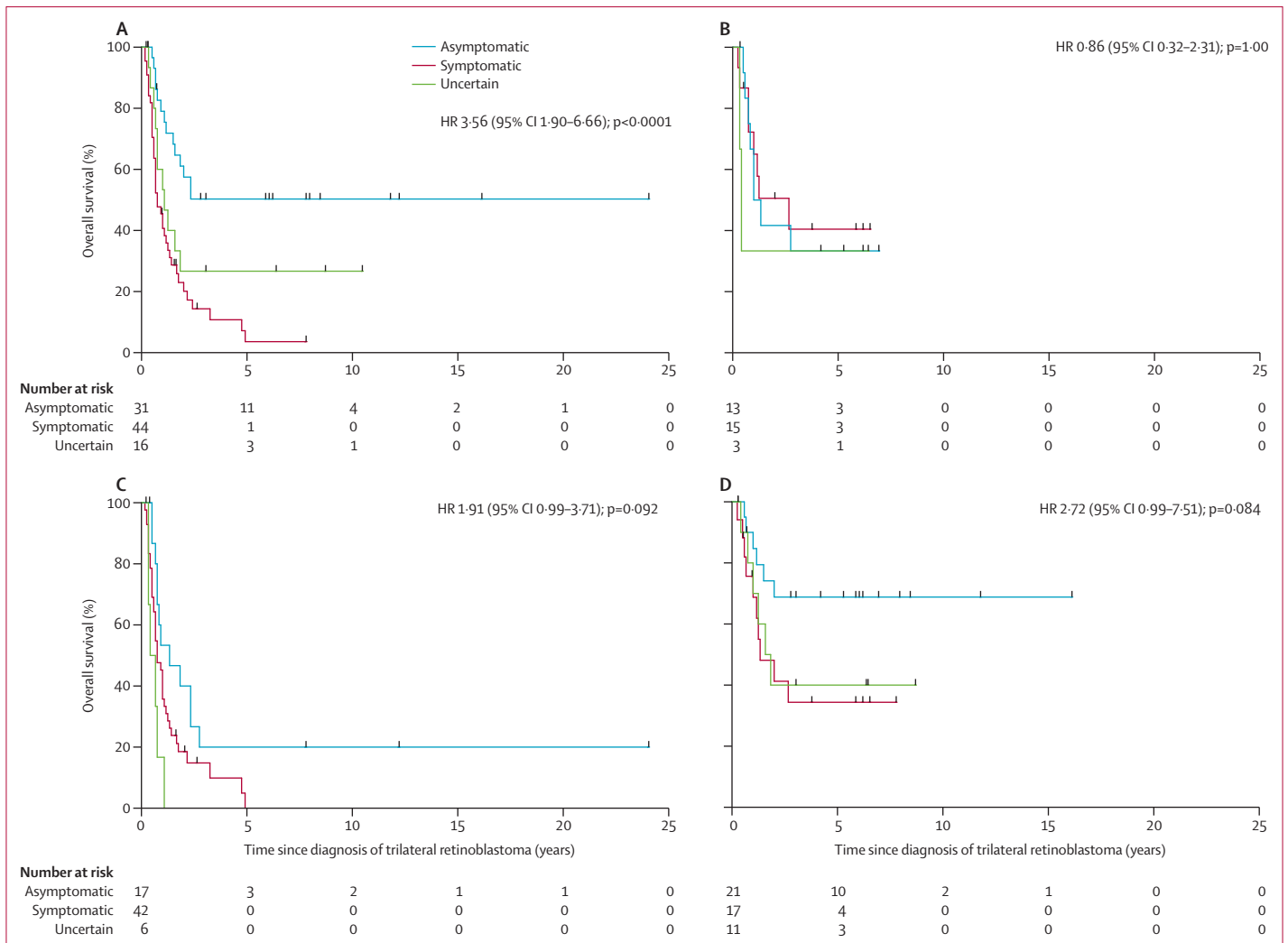
**Figure 3:** Kaplan-Meier curves showing survival after diagnosis of trilateral retinoblastoma for actively treated symptomatic and asymptomatic patients stratified by pineal (A) versus non-pineal (B) location, and period of diagnosis before 1995 (C) versus from 1995 onwards (D)
Log-rank test with Bonferroni correction, and hazard ratio (HR) from univariate Cox regression. Statistics exclude uncertain cases.

Of asymptomatic patients with pineal trilateral retinoblastoma, 12 (34%) of 35 were diagnosed at the baseline neuroimaging scan for retinoblastoma, another nine (26%) were diagnosed within the first year, and the remaining 14 (40%) were diagnosed within 4 years. Almost all non-pineal tumours in asymptomatic patients were detected at the same time as retinoblastoma (appendix). Of asymptomatic patients with pineal and non-pineal disease, a combined 26 (50%) of 52 were diagnosed at the baseline scan, and another 11 (21%) were diagnosed within 1 year.

Pineal trilateral retinoblastomas diagnosed before 1995, were significantly larger than those diagnosed later (median 30 mm [range 10–60] vs 17·5 mm [7–51]; p=0·0075, Mann-Whitney U test). Such a difference was not recorded in the size of non-pineal trilateral retinoblastomas that were a median of 30 mm (range 20–45) before 1995, versus 33 mm (6–100) thereafter (p=0·75).

5-year survival was 50% (95% CI 28–69) for patients whose trilateral retinoblastoma was 15 mm or smaller, versus 21% (11–33) when tumour size was greater than 15 mm (HR 2·02, 95% CI 1·05–3·90; log-rank p=0·029; appendix). When the analysis was restricted to pineal tumours, 5-year survival was was 53% (95% CI 29–72) and 11% (95% CI 3–24), respectively (figure 4A). One of three patients with a non-pineal trilateral retinoblastoma that was 15 mm or smaller survived for 5 years, compared with 39% (95% CI 20–58) of 28 patients with a larger tumour (figure 4B). There was no significant difference in overall survival based on tumour size in patients either diagnosed before or after 1995 (figure 4C and 4D).

Analysis according to the presence of leptomeningeal metastases or CSF involvement at the time of trilateral

retinoblastoma diagnosis for pineal versus non-pineal tumours, and for diagnosis before 1995 versus during or after 1995, showed survival differences similar to other surrogates of early detection, such as presence of symptoms and tumour size (appendix). Survival was worse in patients with pineal trilateral retinoblastoma with leptomeningeal spread than in those with a non-pineal tumour and no spread (HR 2·17, 95% CI 1·15–4·08; log-rank p=0·025).

The number of long-term survivors with a follow-up of at least 5 years after diagnosis of trilateral retinoblastoma rose from three (3%) of 98 patients (95% CI 1–9) before 1995, to 17 (29%) of 58 patients (18–43) from 1995 onwards (p<0·0001, Fisher's exact test). Of 18 patients whose year of diagnosis was uncertain, two (11%, 95% CI 1–35) were long-term survivors.

Table 4 summarises the characteristics and treatments of the long-term survivors with follow-up of 5 years or

more. Many long-term survivors did not receive radiotherapy or surgery, whereas all but one received chemotherapy. At least ten long-term survivors (six with pineal and four with non-pineal trilateral retinoblastoma) were treated with chemotherapy alone. 11 (73%) of 15 long-term survivors of pineal trilateral retinoblastoma presented without symptoms (one [7%] patient had symptoms, unknown in three [20%] patients). For non-pineal tumours, three (43%) of seven patients had no symptoms (three [43%] patients had symptoms, unknown in one [14%] patient).

Eight (36%) long-term survivors had histologically proven trilateral retinoblastoma, three (14%) had malignant cells in their CSF, eight (36%) with no histological confirmation showed treatment response on brain imaging, and for one (4%) patient there was no direct or indirect confirmation (appendix). Moreover, long-term survivors had similar proportions of histopathological
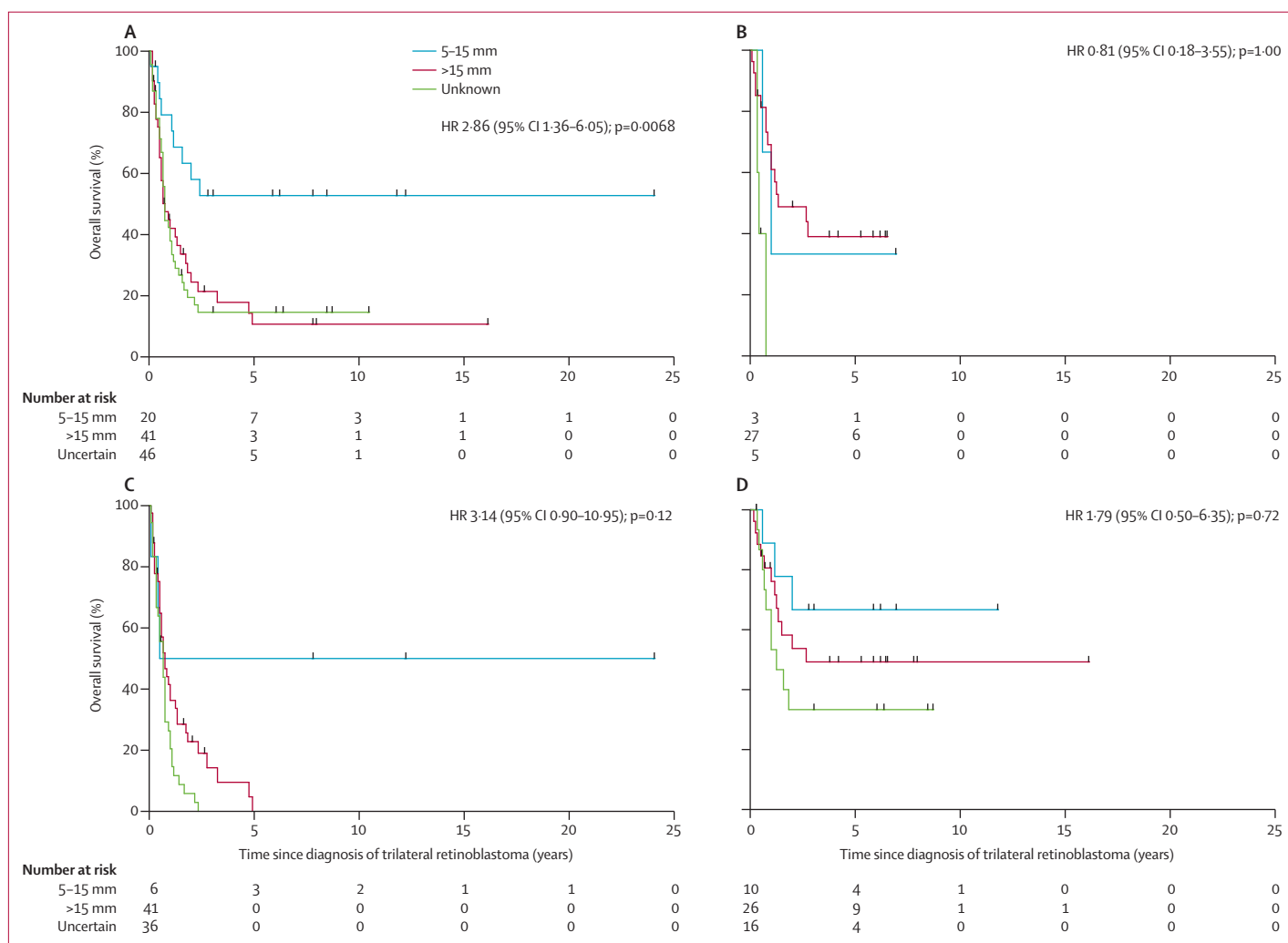


*Figure 4:* Kaplan-Meier curves showing survival after diagnosis of trilateral retinoblastoma for patients with a tumour size of 15 mm or smaller versus larger than 15 mm stratified by pineal (A) versus non-pineal (B) location, and by period of diagnosis before 1995 (C) versus from 1995 onwards (D)
Log-rank test with Bonferroni correction and hazard ratio (HR) from univariate Cox regression. Statistics exclude tumours of uncertain size.

| | Any trilateral retinoblastoma (n=22) | Pineal trilateral retinoblastoma (n=15) | Non-pineal trilateral retinoblastoma (n=7) | p value |
|---|---|---|---|---|
| Age at diagnosis of retinoblastoma (months) | 8 (0 to 72) | 7 (0 to 16) | 11 (5 to 72) | 0·14* |
| Age at diagnosis of trilateral retinoblastoma (months) | 12 (1 to 57) | 13 (1 to 57) | 10 (5 to 16) | 0·29* |
| Time interval between diagnosis of retinoblastoma and trilateral retinoblastoma (months) | 0 (–60 to 54) | 0·5 (0 to 54) | 0 (–60 to 2) | 0·030* |
| Size of trilateral retinoblastoma (mm) | 17 (6 to 100) | 14·5 (10 to 51) | 42 (6 to 100) | 0·10* |
| Size ≤15 mm | 8/17 (47%) | 7/10 (70%) | 1/7 (14%) | 0·050† |
| Unilateral retinoblastoma | 4/19 (21%) | 3/13 (23%) | 1/6 (17%) | 1·00† |
| Familial retinoblastoma | 1/15 (7%) | 1/10 (10%) | 0/5 | 1·00† |
| Leptomeningeal metastases or CSF involvement at diagnosis of trilateral retinoblastoma | 3/18 (17%) | 0/11 | 3/7 (43%) | 0·043† |
| Asymptomatic trilateral retinoblastoma | 14/18 (78%) | 11/12 (92%) | 3/6 (50%) | 0·083† |
| Histopathological proof of trilateral retinoblastoma | 9/22 (41%) | 6/15 (40%) | 3/7 (43%) | 1·00† |
| Trilateral retinoblastoma diagnosed ≥1995 | 17/20 (85%) | 10/13 (77%) | 7/7 (100%) | 0·52† |
| Radiotherapy | 5/22 (23%) | 3/15 (20%) | 2/7 (29%) | 1·00† |
| Surgery | 7/21 (33%) | 5/14 (36%) | 2/7 (29%) | 1·00† |
| No chemotherapy | 1/22 (5%) | 1/15 (7%) | 0/7 | 0·40‡ |
| Conventional systemic chemotherapy | 11/22 (50%) | 8/15 (53%) | 3/7 (43%) | 0·40‡ |
| High-dose chemotherapy with stem-cell rescue | 10/22 (45%) | 6/15 (40%) | 4/7 (57%) | 0·40‡ |
| Retinoblastoma diagnosed before trilateral retinoblastoma | 5/21 (24%) | 5/14 (36%) | 0/7 | 0·038‡ |
| Concurrent diagnosis (within 3 months) | 15/21 (71%) | 9/14 (64%) | 6/7 (86%) | 0·038‡ |
| Trilateral retinoblastoma diagnosed before retinoblastoma | 1/21 (5%) | 0/14 | 1/7 (14%) | 0·038‡ |

Data are median (range) or n/N (%), unless otherwise indicated. *Mann-Whitney U test, two-sided. †Fisher's exact test, two-sided. ‡Kruskal-Wallis test, two-sided.

*Table 4*: Characteristics of long-term survivors by trilateral retinoblastoma location

| | Hazard ratio (95% CI) | p value |
|---|---|---|
| **Chemotherapy for trilateral retinoblastoma** | | |
| None | Reference | .. |
| Conventional systematic or intrathecal | 0·059 (0·016–0·226) | <0·0001 |
| High-dose chemotherapy with stem-cell rescue | 0·013 (0·002–0·064) | <0·0001 |
| **Leptomeningeal metastases or CSF involvement** | | |
| No | Reference | .. |
| Yes | 2·13 (0·98–4·60) | 0·055 |
| **Trilateral retinoblastoma location** | | |
| Pineal | Reference | .. |
| Non-pineal | 1·09 (0·49–2·45) | 0·83 |

*Table 5*: Cox regression analysis

proof compared with other patients (tables 2, 4). These findings suggest that long-term survivors did not have benign pineal lesions misdiagnosed as trilateral retinoblastoma.

The importance of early detection of pineal trilateral retinoblastoma was shown by the finding that long-term survivors had fairly small tumours (median size 14·5 mm, range 10–51). Non-pineal tumours (median size 42 mm, range 6–100) have fundamentally different growth kinetics than pineal tumours, and are typically diagnosed simultaneously with intraocular retinoblastoma when already much larger than early diagnosed pineal tumours.

The appendix presents results from univariate regression of all modelled variables and from multi-variate models. All models fulfilled the proportional hazards assumption (appendix). Table 5 shows findings for the model that included tumour location, presence of leptomeningeal metastases or CSF involvement, and chemotherapy. Leptomeningeal metastases and CSF fluid involvement are determined with more precision than symptoms, which are always partly subjective, especially in young children; age is not entirely independent because pineal and non-pineal trilateral retinoblastoma present at different ages; and trilateral retinoblastoma size was the least significant in the corresponding model. Hence, we believe that lepto-meningeal metastases or CSF involvement is the clinically most useful model. In this model, conventional systemic or intrathecal chemotherapy and high-dose chemotherapy with stem-cell rescue were both strongly associated with improved survival after trilateral retinoblastoma. Other models with additional surrogates for early detection (ie, presence of symptoms, tumour size, and age at trilateral retinoblastoma diagnosis) showed similar strong associations of chemotherapy with survival (appendix).

When we restricted the analysis to either actively treated patients or to pineal trilateral retinoblastoma as a sensitivity analysis, the effect of chemotherapy remained (appendix).

## Discussion

Our findings show that survival of patients with pineal and non-pineal trilateral retinoblastoma has increased substantially since 1995 (panel). Early detection of smaller tumours predicted better survival for patients with pineal trilateral retinoblastoma, but early detection did not show a difference in survival for patients with non-pineal disease. We recorded a strong positive association between the use of chemotherapy, especially high-dose chemotherapy with stem-cell rescue, and improved survival.

The most notable differences between our findings and those of a previous meta-analysis[2] of trilateral retinoblastoma, in which the cutoff year was 1998, are the smaller size of pineal trilateral retinoblastoma compared with non-pineal tumours and the improved survival after both pineal and non-pineal disease since 1995. Our analysis clearly suggested that improved chemotherapy regimens, especially high-dose chemotherapy with stem-cell rescue, rather than changes in radiotherapy, the use of which declined, or surgery, which did not change in frequency or type, played a major part in the increased survival. Early detection also seems to have a role in the improved survival of patients with pineal trilateral retinoblastoma, on the basis of findings showing an increase in the proportion of asymptomatic pineal tumours, from 19% to 62%, and a decrease in the median size of pineal tumours, from 28 mm to 22 mm.[2] Some evidence shows that external beam radiotherapy before the age of 12 months might increase the risk of development of trilateral retinoblastoma.[17] Before 1995, patients with familial trilateral retinoblastoma were more likely to be irradiated before 12 months old for their retinoblastoma (as they were screened for ocular tumours), whereas since 1995, use of radiotherapy for retinoblastoma substantially decreased. Alternatively, early chemotherapy for familial retinoblastoma since 1995 might have cured some incipient trilateral retinoblastoma.

Non-pineal trilateral retinoblastoma develops earlier than pineal disease, and is therefore much more likely to be diagnosed concurrently with retinoblastoma.[2] Thus, screening for trilateral retinoblastoma at the time of diagnosis of retinoblastoma is mandatory. The benefit of later screening remains controversial. Our meta-analysis showed that 60% of asymptomatic pineal trilateral retinoblastoma, and almost all non-pineal tumours, were diagnosed within 1 year from retinoblastoma, arguing for regular screening for at least 1 year. Additional brain imaging would be needed to improve detection of pineal disease. Cystic pineal lesions can be identified at the time of retinoblastoma diagnosis, and follow-up of suspicious pineal cysts might help to diagnose pineal trilateral retinoblastoma when it is still asymptomatic.[17]

Survival after trilateral retinoblastoma has improved greatly since 1995. The improvement can partly be explained by early detection of pineal disease. However, survival of symptomatic patients has also improved. Moreover, no patients with non-pineal disease survived before 1995, but since then, use of high-dose chemotherapy has increased. All but one of the 22 long-term survivors received chemotherapy, and almost half underwent high-dose chemotherapy with stem-cell rescue. Regression analyses that adjusted for surrogates of lead-time bias (younger age, symptoms, smaller tumour, or absence of leptomeningeal metastasis) confirmed the importance of chemotherapy, especially the use of high-dose chemotherapy with stem-cell rescue, although conventional chemotherapy also had a significant effect. However, diagnosis before leptomeningeal spread has taken place might independently contribute to survival. We propose that treatment for trilateral retinoblastoma should include chemotherapy. This suggestion does not imply that additional radiotherapy or surgery should not be considered; in fact, intraocular retinoblastoma is seldom cured with chemotherapy alone, and successful treatment typically requires local consolidation.

There are several limitations to our study. We noted substantial heterogeneity in treatment for trilateral retinoblastoma. Chemotherapy regimens varied widely, as did the extent of surgery, from biopsy to total resection. Additionally, differentiation between surgery and biopsy was often difficult, because biopsy of a small tumour could have removed the entire trilateral retinoblastoma, whereas unspecified surgery might have led to only partial removal. To avoid over-analysis of such incomplete data, we did not estimate the effect of surgery and radiotherapy. Likewise, because only 13 patients underwent biopsy, its effect could not be analysed. In Cox regression analysis we focused on chemotherapy, because chemotherapy has become the most frequent type of therapy for trilateral retinoblastoma and regimens have improved greatly.

Median duration of survival and the log-rank test might have been affected by lead-time bias, because most categories in table 1 inherently signify diagnostic delay (eg, asymptomatic trilateral retinoblastoma is detected earlier than symptomatic disease, and presents with smaller tumours with no leptomeningeal metastases). Such bias was evident as a difference in age at trilateral retinoblastoma diagnosis in spite of a similar age at death between subgroups. Therefore, we focused on 5-year survival in the results. Lead-time bias was a concern especially with pineal trilateral retinoblastoma. Asymptomatic pineal disease was diagnosed much earlier than symptomatic disease, but the age at death was still similar. Given that the latest death to asymptomatic pineal trilateral retinoblastoma happened at 28 months, comparison of survival estimates at 5 years can be regarded as appropriate.

Whether, and in what form, publication bias might have introduced bias is hard to define. Various conceivable reasons exist why a case of trilateral retinoblastoma could be considered as interesting

**Panel: Research in context**

**Systematic review**

The appendix provides details of our search. We identified one similar meta-analysis[2] that included patients from 1966 to July, 1998, consisting of 106 children with trilateral retinoblastoma (with two patients from the author's institution). Trilateral retinoblastoma could be divided into two distinct types (pineal and non-pineal) with substantial differences in age at diagnosis and age at death.[2] Few patients survived, and the few who did survive had small asymptomatic tumours.

**Interpretation**

The greatest differences between findings from the previous and present meta-analyses are the significantly improved survival for both pineal and non-pineal trilateral retinoblastoma and the smaller size of pineal trilateral retinoblastoma diagnosed since 1995. Our results suggest that improved chemotherapy regimens, especially use of high-dose chemotherapy with stem-cell rescue, and early detection of pineal trilateral retinoblastoma are mostly responsible for the improved overall survival. As such, we believe that treatment of trilateral retinoblastoma should always include chemotherapy, preferably high-dose chemotherapy with autologous stem-cell rescue, with or without radiotherapy or surgery as adjuvant or consolidation treatments. Further research is needed to assess the added value of these treatment modalities. Early detection of pineal trilateral retinoblastoma can be achieved with brain imaging at the time of retinoblastoma diagnosis and, perhaps, by extended or targeted follow-up of suspicious pineal lesions.[16,17] The added value of follow-up after diagnosis of retinoblastoma, in terms of early detection, remains controversial and needs confirmation.

enough to publish. Cumulative survival might have been overestimated if, for example, a surviving patient with trilateral retinoblastoma is of more interest to report and, therefore, deceased patients might be under-represented among published cases. However, patients with trilateral retinoblastoma are increasingly sent to tertiary centres and about three-quarters of the long-term survivors were part of small consecutive series in which other patients died of trilateral retinoblastoma, which reduces the likelihood of publication bias.[5,12,18–23]

A scarcity of histopathological proof of trilateral retinoblastoma might have caused us to overestimate survival, because survivors without symptoms and a small tumour might have been false-positive cases. However, we did not identify any evidence of such bias, because the proportion of long-term survivors with histopathological proof was similar to that of the entire group, and all but one long-term survivor had direct or indirect confirmation of active trilateral retinoblastoma.

With due consideration to the unavoidable inherent limitations of this study, we regard the differences in survival large enough to reasonably conclude that the survival of patients with pineal and non-pineal trilateral retinoblastoma has improved over time, in addition to a reduction of radiotherapy and an increase of chemotherapy as treatment. Cox regression analysis supports the conclusion that chemotherapy, especially high-dose chemotherapy with stem-cell rescue, is the main treatment-related factor contributing to improvements in survival. This meta-analysis also shows the importance of early detection of small pineal tumours and we therefore recommend brain imaging at least at the time of retinoblastoma diagnosis. We could not show an improvement of survival in the typically early detection of non-pineal, mostly suprasellar or parasellar, trilateral retinoblastoma. Patients with sizeable symptomatic non-pineal trilateral retinoblastoma detected at baseline now have a similar chance of survival with chemotherapy as do patients with on average smaller pineal trilateral retinoblastoma.

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