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Adjuvant Chemotherapy Versus Radiotherapy Alone in Pediatric Intracranial Ependymoma: A Systematic Review and Meta-analysis

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Abstract

Background

Pediatric intracranial ependymoma remains a therapeutically challenging central nervous system tumor in which long-term outcomes depend primarily on maximal safe resection and postoperative focal radiotherapy (RT). Thus, the survival benefit of adjuvant chemotherapy remains uncertain. However, no meta-analysis has directly pooled survival outcomes comparing adjuvant chemotherapy vs. radiotherapy alone in pediatric intracranial ependymoma after maximal safe resection. To compare overall survival, disease control, and recurrence between chemotherapy plus radiotherapy and RT alone in pediatric intracranial ependymoma.

Methods

A systematic search, according to PRISMA guidelines, across PubMed, Scopus, Web of Science, and EBSCO was conducted from inception to April 2026. Included criteria were children with newly diagnosed intracranial ependymoma treated after maximal safe resection with postoperative adjuvant chemotherapy with or without radiotherapy compared with postoperative radiotherapy alone. The primary outcome was overall survival (OS). Secondary outcomes included disease-control survival and recurrence. Approximate Kaplan–Meier reconstructions were generated from extracted survival probabilities.

Results

From 495 records identified, 10 studies were included, representing 654 patients. Compared with RT alone, chemotherapy-containing postoperative strategies were associated with poorer overall survival (HR 1.99, 95% CI 1.21–3.28). Exploratory recurrence analysis showed no statistically significant difference between groups (RR 1.18, 95% CI 0.86–1.60). Better disease-control survival was associated with radiotherapy alone (median disease-control survival: 78.0 months vs. 36.0 months for chemotherapy-containing strategies).

Conclusions

These findings support postoperative focal radiotherapy as the therapeutic backbone for pediatric intracranial ependymoma and underscore the need for biomarker-driven prospective studies to identify the limited scenarios in which systemic therapy may provide meaningful benefit.

Introduction

Ependymoma represents the third most common cancer of the CNS in the pediatric age group. These tumors are midline tumors arising from the ependymal cells lining the ventricle and the central canal. (1, 2) Ependymomas are clinically challenging; long-term disease control depends on the interaction between surgical cytoreduction, tumor biology, anatomical location, and postoperative adjuvant therapy. (3, 4) Maximal safe resection remains a cornerstone of treatment, while focal radiotherapy has historically represented a major component of postoperative disease control. (2, 4–6) The current survival statistics for pediatric ependymoma are not very impressive with a 5-year overall survival (OS) and progression-free survival (PFS) estimates of 50% to 85% and 23% to 70%, respectively. (1) The role of chemotherapy, however, remains less clearly defined. (7, 8)

Chemotherapy has been used in several clinical contexts, including as part of multi-agent postoperative regimens, as a strategy to delay radiotherapy in younger children, and as an adjunct in patients considered at higher risk because of residual disease, metastatic presentation, or unfavorable clinical features. (5, 9, 10) Despite this rationale, the comparative survival benefit of adjuvant chemotherapy over radiotherapy-alone strategies remains uncertain. (3, 7, 10, 11) Nevertheless, available evidence is further complicated by heterogeneity in study design, treatment selection, extent of resection, radiotherapy protocols, follow-up duration, and outcome definitions. (9, 10)

Radiotherapy techniques have also evolved substantially, with contemporary series increasingly emphasizing involved-field, intensity-modulated, or proton-based radiotherapy approaches. (2, 4, 6) These developments raise an important clinical question: whether postoperative chemotherapy-containing strategies provide any measurable survival or recurrence advantage compared with radiotherapy-alone approaches in pediatric intracranial ependymoma. (12)

This systematic review and meta-analysis were designed to evaluate whether postoperative adjuvant chemotherapy-containing strategies improve outcomes compared with radiotherapy alone in children with newly diagnosed intracranial ependymoma after maximal safe resection. The primary outcome was overall survival. Secondary outcomes included disease-control survival and recurrence. To our knowledge, no previous quantitative synthesis has specifically compared postoperative chemotherapy-containing strategies with radiotherapy-alone approaches in newly diagnosed pediatric intracranial ependymoma using pooled time-to-event analyses.

Methods

Study Design and Reporting Standard

This systematic review and meta-analysis were performed in accordance with the PRISMA guidelines. The protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO 2026 CRD420261410267; available from https://www.crd.york.ac.uk/PROSPERO/view/CRD420261410267). The eligibility criteria, outcomes,

search strategy, and planned methods for study selection, data extraction, risk-of-bias assessment, and quantitative synthesis were prespecified. No major deviations from the registered protocol occurred.

The review question was structured using a PICO framework: Population—children 0–18 years with newly diagnosed intracranial ependymoma after maximal safe resection; Intervention—postoperative adjuvant multi-agent chemotherapy with or without focal radiotherapy; Comparator—postoperative radiotherapy alone; Outcomes—Overall survival, disease-control survival, recurrence/local control, treatment-related toxicity, and neurocognitive outcomes.

Eligibility Criteria

Studies were included if they evaluated outcomes of pediatric patients with newly diagnosed intracranial ependymoma treated with chemotherapy-containing postoperative strategies and/or radiotherapy-alone approaches after surgical resection. The quantitative synthesis focused on comparative studies. We excluded studies that involved only recurrent disease, adult-only populations, incorrect diagnoses, different publication types, or insufficient extractable outcome data.

Information Sources and Search Strategy

We carried out a systematic search of PubMed, Scopus, Web of Science, and EBSCO. We combined terms related to ependymoma, adjuvant chemotherapy, radiotherapy, and pediatric populations in our search strategy. The strategy for PubMed was based on the following Boolean framework:

("Ependymoma" [Mesh] OR ependymoma*[tiab]) AND ("Chemotherapy, Adjuvant" [Mesh] OR "Antineoplastic Combined Chemotherapy Protocols" [Mesh] OR adjuvant chemotherap*[tiab] OR multiagent chemotherap*[tiab]) AND ("Radiotherapy" [Mesh] OR radiotherap*[tiab]) AND ("Child" [Mesh] OR "Infant" [Mesh] OR "Adolescent" [Mesh] OR pediatric*[tiab] OR child*[tiab]) AND (randomized controlled trial [pt] OR cohort [tiab] OR comparative [tiab] OR multicenter [tiab]).

Study Selection

Study selection was performed according to PRISMA guidelines using Rayyan. Screening was performed by 3 independent reviewers, and conflicts were resolved by 2 additional reviewers. Titles and abstracts were screened first. The full text of studies considered potentially eligible was then reviewed. The full-text screening was done to verify population characteristics, intervention and comparator compatibility, postoperative treatment context, diagnosis, recurrence status, and outcome extractability. Articles were excluded at the full-text review stage if follow-up was inadequate, the clinical background was inconsistent, or outcome data were not usable. Figure 1

Data Extraction

Data were extracted into structured Excel templates and analyzed in Jupyter with Python. Six reviewers extracted domains, including study characteristics, country, year of publication, study design, sample size, definitions of intervention and comparator, chemotherapy regimen, radiotherapy details, duration of follow-up, survival estimates, rates of recurrence, Kaplan–Meier points, and risk-of-bias domains.

When available, data on survival were extracted as hazard ratios (HR) with 95% confidence intervals. Kaplan–Meier curves were digitized using WebPlotDigitizer; we extracted the study identifier, time (months), survival probability, treatment group, and number at risk (when available).

Outcomes

OS was the primary endpoint. Secondary outcomes were recurrence and disease-control survival defined descriptively as compatible EFS, PFS, DFS, or FFS when reported. Due to heterogeneity in the definition of disease control across studies, these results were summarized descriptively and with approximate reconstructed survival curves, rather than a single formal time-to-event endpoint.

Statistical Analysis

All analyses were performed in Python using pandas, NumPy, and matplotlib. For HR-based analyses, HRs were log-transformed, and standard errors were calculated from 95% confidence intervals using:

SE = (ln upper CI-ln lower CI)/3.92.

Random-effects meta-analysis was performed using inverse-variance weighting and Der Simonian–Laird estimation of between-study variance. Pooled HRs or RRs were back transformed from logarithm estimates. Heterogeneity was assessed using Q, I^2, and t^2. P values were calculated from the pooled log-effect estimate and its standard error.

Recurrence risk ratios were calculated from recurrence proportions and available group denominators. A random-effects model was used for the pooled RR estimation. Survival probabilities were obtained and used for descriptive Kaplan–Meier reconstructions. Pooled curves were generated only from compatible groups, and IQR bands reflected inter-study variability. The reconstructed curves were presented as visual summaries of descriptions and not as formal survival analyses of individual patient data.

Risk of Bias and Certainty of Evidence

Risk of bias was assessed through the domains of ROBINS-I adapted to the non-randomized comparative evidence included. We assessed the certainty of evidence for OS, recurrence, and disease-control outcomes using the GRADE framework. Risk of bias—Not downgraded Inconsistency—Not downgraded Indirectness—Not downgraded Imprecision—Not downgraded Publication bias—Not downgraded. **(Supplemental material)**

Results

Study Selection

The systematic search yielded 495 records: 241 from Scopus, 141 from PubMed, 87 from Web of Science, and 26 from EBSCO. We removed 168 duplicates and screened the titles and abstracts of 327 records. Figure 1 We excluded 310 studies due to incompatible populations, recurrent disease settings, inappropriate outcomes, unsuitable publication types, or incorrect diagnosis. Seventeen full-text articles were assessed for eligibility. Ten studies met the inclusion criteria and were incorporated into the qualitative synthesis. Seven full-text articles were excluded due to lack of follow-up, incompatible clinical backgrounds, or lack of extractable data. Figure 1

Study Characteristics

The 10 studies that were included 654 patients. Studies were published from 1996 to 2021. The evidence included was clinically heterogeneous, with variation in study design, chemotherapy regimens, timing and dosing of radiotherapy, inclusion of metastatic disease, extent of resection, duration of follow-up, and reporting of outcomes. Many of the studies were observational or mixed-design cohorts, and only a subset provided extractable comparative estimates that could be used for quantitative synthesis. Table 1

Overall Survival

Two studies had extractable HRs for OS and were included in the primary quantitative meta-analysis. Ten studies met the inclusion criteria for the systematic review; however, only two provided extractable hazard ratios suitable for the quantitative synthesis of overall survival. Pooling by random effects showed worse OS for patients who had postoperative strategies that included chemotherapy versus radiotherapy alone. The combined HR was 1.99, with a 95% confidence interval ranging from 1.21 to 3.28 ($p = 0.0068$). Figure 2 The statistical heterogeneity was low ($I^2 = 12.9\%$, $\tau^2 = 0.0207$).

The direction of effect favored radiotherapy alone. Showed worse survival in the chemotherapy-containing group compared to radiotherapy alone. These findings indicate that inclusion of chemotherapy was linked with significantly poorer OS than strategies based on radiotherapy alone.

Recurrence

Recurrence showed no significant difference in the risk of recurrence between chemotherapy-containing strategies and radiotherapy alone. The pooled RR was 1.18 (95% CI 0.86–1.60; $p = 0.296$); moderate heterogeneity was observed ($I^2 = 56.5\%$, $\tau^2 = 0.0555$). These studies suggest that chemotherapy-containing approaches did not significantly reduce risk of recurrence, although interpretation is limited by heterogeneity and incomplete reporting of outcomes. Figure 3

Disease-Control Survival

Approximate reconstructed median disease-control survival was 36.0 months for chemotherapy-containing strategies versus 78.0 months for radiotherapy alone. Figure 4 These reconstructed estimates should be viewed as descriptive summaries, not formal pooled time-to-event estimates, because disease-control endpoints were not consistently defined across studies.

The radiotherapy-alone group reached 120 months in the reconstructed OS analysis. Reconstructed survival curves consistently showed higher probabilities of survival for radiotherapy-alone cohorts over the follow-up periods studied. Figure 4

Risk of Bias

Nine non-randomized studies were assessed using ROBINS-1, whereas the single randomized trial was evaluated using the Cochrane RoB 2 tool. The non-randomized controlled studies showed predominantly moderate to serious risk of bias, mainly due to confounding, selection bias, and missing data, while the randomized trial was judged as having some concerns overall. **(Supplemental material)**

We judged the certainty of the evidence as low to very low across the evaluated outcomes using GRADE. The main reasons for the downgrade were risk of bias, methodological clinical heterogeneity, indirectness due to choice of treatment, and imprecision due to a small number of studies contributing to the quantitative estimates. **(Supplemental material)**

Discussion

Our study demonstrates that postoperative strategies that include chemotherapy do not result in better outcomes compared with radiotherapy alone for pediatric intracranial ependymoma. The strongest quantitative signal was observed for OS, with chemotherapy ± radiotherapy associated with inferior survival compared with radiotherapy alone. Figure 2 By contrast, recurrence risk did not differ significantly between groups, implying that the observed OS disadvantage may not be entirely explained by recurrence frequency alone. Figure 3

The rationale for chemotherapy in pediatric ependymoma has been based on the desire to omit or delay radiotherapy in very young children because of concern about the developing brain. Grundy et al. reported a primary postoperative chemotherapy strategy to avoid or delay radiotherapy in children less than 3 years old with intracranial ependymoma, while Massimino et al. similarly evaluated upfront chemotherapy with omitted or deferred radiotherapy in infants. (5, 10) This therapeutic rationale is clinically comprehensible, but the current pooled analysis fails to show a survival advantage for strategies that include chemotherapy. Figure 2

In our recurrence analysis, chemotherapy-containing strategies were not associated with a significant reduction in recurrence compared with radiotherapy. Figure 3 This suggests that recurrence outcomes may be influenced by differences in baseline risk, extent of resection, treatment protocols, and endpoint definitions; therefore, this finding should be considered exploratory. Consistent with the direction of the OS findings, reconstructed disease-control survival also favored radiotherapy alone, with an estimated

median of 78.0 months compared with 36.0 months for chemotherapy-containing strategies. Figure 4 However, disease-control endpoints combined related but non-identical outcomes, including every formal follow-up; these curves should be interpreted as visual summaries rather than formal pooled time-to-event, considering the missing data to complete a formal analysis. (3, 10)

Evans et al. found no improvement in long-term outcomes with adjuvant CCNU, vincristine, and prednisone added to craniospinal irradiation in childhood posterior fossa ependymoma (3, 4), reported outcomes in children with localized ependymoma treated with IMRT or proton-beam radiation therapy; and emphasized maximal resection and involved-field radiotherapy as central components of disease control. (4) Similarly reported postoperative radiotherapy outcomes in pediatric intracranial ependymoma, with gross total resection associated with improved survival outcomes. (6) These findings align with the direction of the present analysis, which did not identify a measurable advantage for chemotherapy-containing strategies over radiotherapy alone.

Nonetheless, the results suggest that radiotherapy-alone strategies were associated with longer disease-control survival and improved OS, whereas chemotherapy-containing strategies did not significantly reduce the risk of recurrence. (12) In most included studies, chemotherapy was preferentially administered to patients with unfavorable prognostic characteristics, including residual disease, metastatic presentation, or younger age, introducing substantial confounding by indication. (7, 12, 13) Therefore, the observed association between chemotherapy-containing strategies and poorer survival likely reflects baseline disease severity rather than a direct detrimental effect of systemic therapy. Individual patient data meta-analyses or harmonized prospective registries would greatly improve the ability to evaluate chemotherapy effects while accounting for prognostic imbalance.

Finally, current recommendations prioritize maximal safe surgical resection followed by focal radiotherapy whenever clinically feasible, while the role of chemotherapy remains comparatively limited and is generally confined to selected scenarios, including very young children in whom radiotherapy may be deferred and patients with biologically or clinically high-risk disease. (7)

Limitations

The main limitation of this analysis is the low number of studies contributing to formal quantitative synthesis. The recurrence analysis was exploratory and moderately heterogeneous. Data was taken by reconstructed extraction of Kaplan–Meier survival curves, giving major non-extracted data reported at quantitative synthesis of every study. Furthermore, some of the included cohorts were highly heterogeneous regarding age distribution, treatment intent, use of radiotherapy, chemotherapy protocol, disease setting, and definitions of endpoints. These limitations are reflected in the risk-of-bias and GRADE assessments. **(Supplementary Material)**

Conclusion

Across the available evidence, the overall direction of effect favored radiotherapy-centered treatment, whereas chemotherapy did not demonstrate a clear reduction in recurrence risk. These findings reinforce the need to define chemotherapy's role more selectively rather than broadly as routine adjuvant therapy. Future studies should prioritize prospective, molecularly stratified designs with standardized treatment definitions and harmonized survival endpoints to identify whether any specific subgroup may benefit from chemotherapy.

Declarations

Conflicts of interest/competing interests

None of the persons that are included in this case report have a conflict of interest.

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No funding was obtained or used for this study.

Author Contribution

All authors wrote part of the main manuscript. JS, DG, and JR review the main manuscript. AP, OO, and MM contributed to manuscript editing. JS does the analysis of data. JR register protocol and checklist. DG prepared figures and tables. AP, DG, MM, and JR conceptualized the study idea. All authors reviewed the final edition of the manuscript.

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Table

Table 1 is available in the Supplementary Files section.

Figures

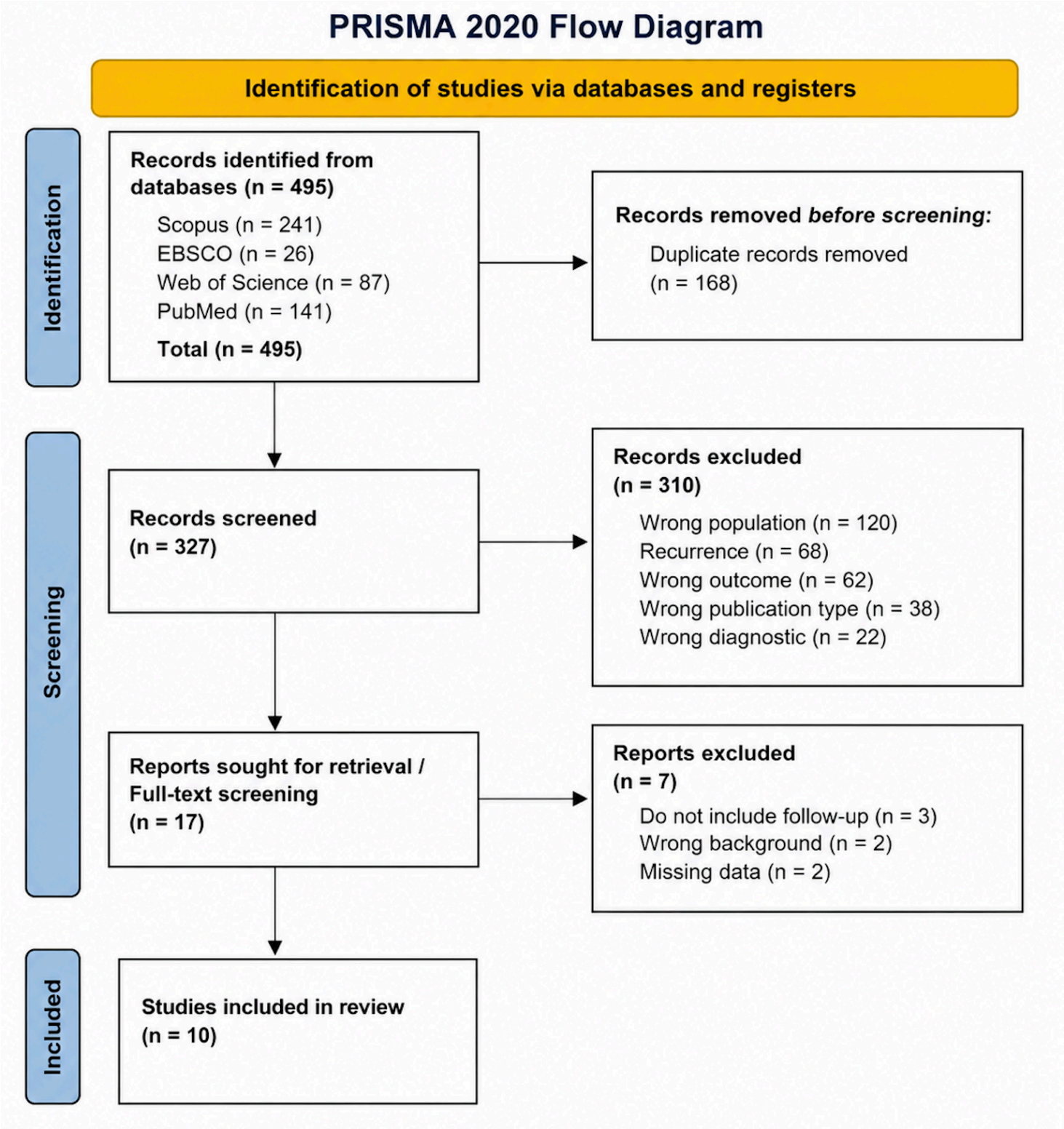


Figure 1

PRISMA Flow Diagram of Study Selection

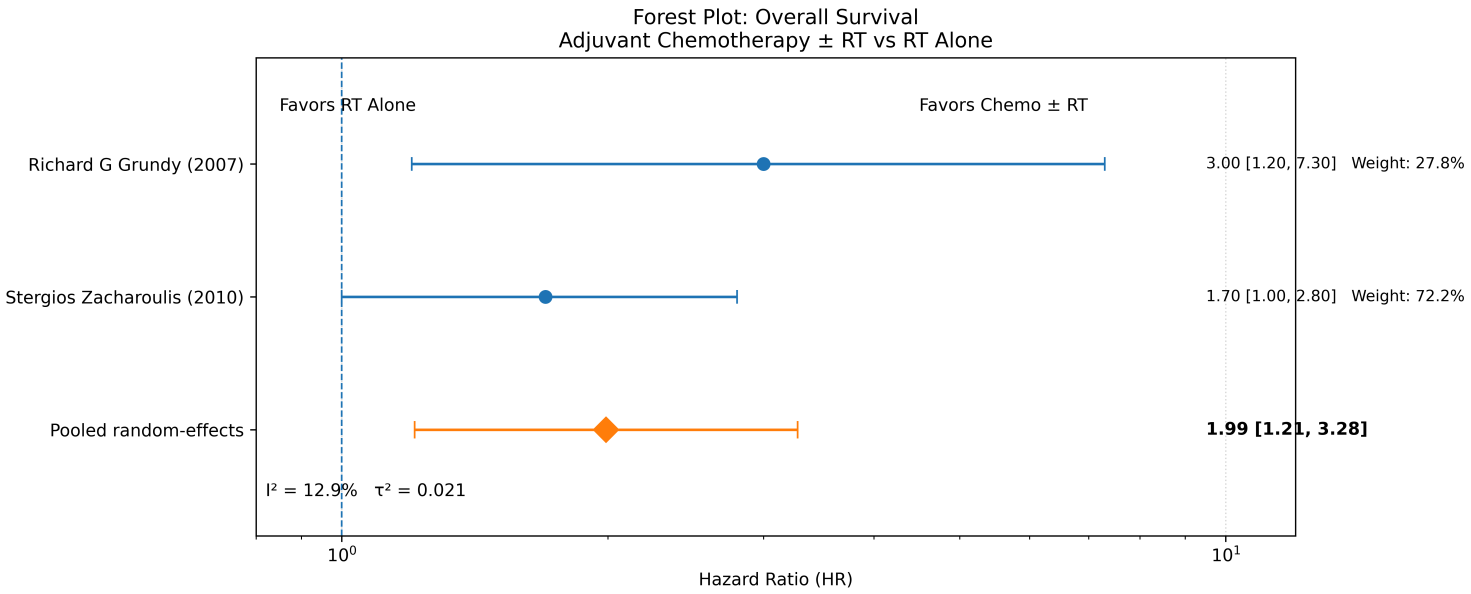


Figure 2

Forest Plot of Overall Survival

Footnote: Random-effects meta-analysis of extractable overall survival hazard ratios comparing chemotherapy-containing strategies to radiotherapy alone.

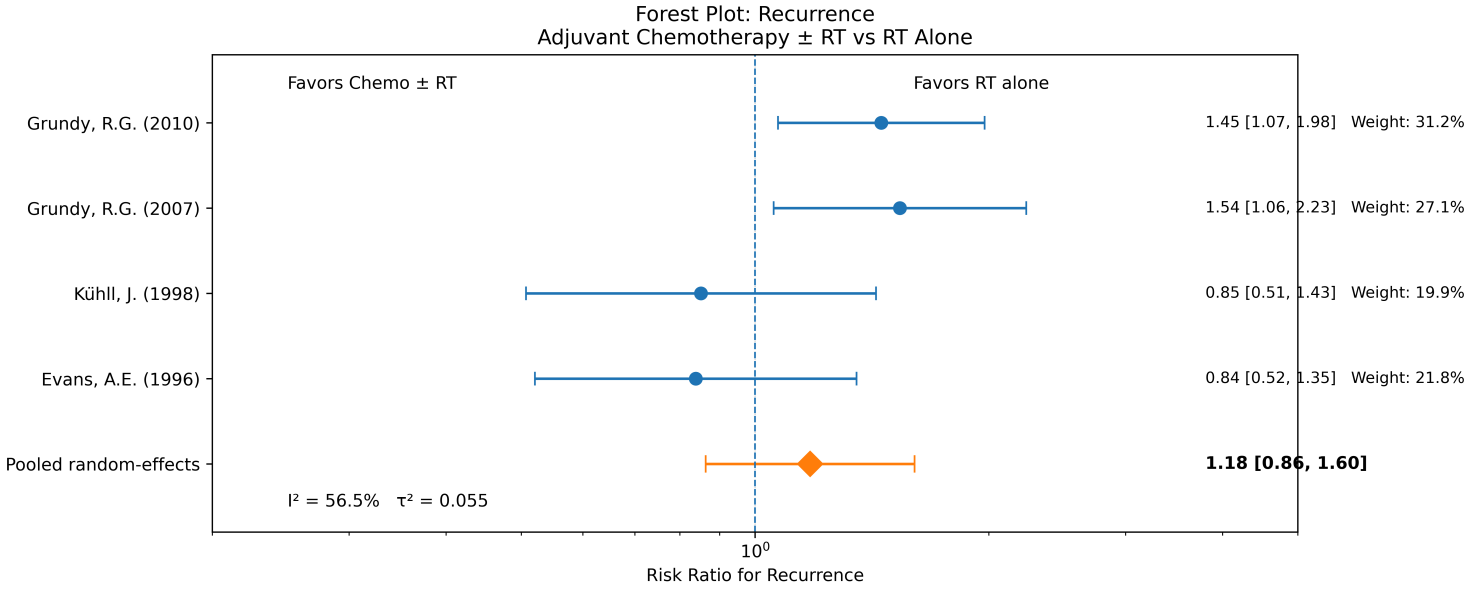


Figure 3

Forest Plot of Recurrence

Footnote: Random-effects meta-analysis of recurrence risk ratios for chemotherapy-containing strategies versus radiotherapy alone.

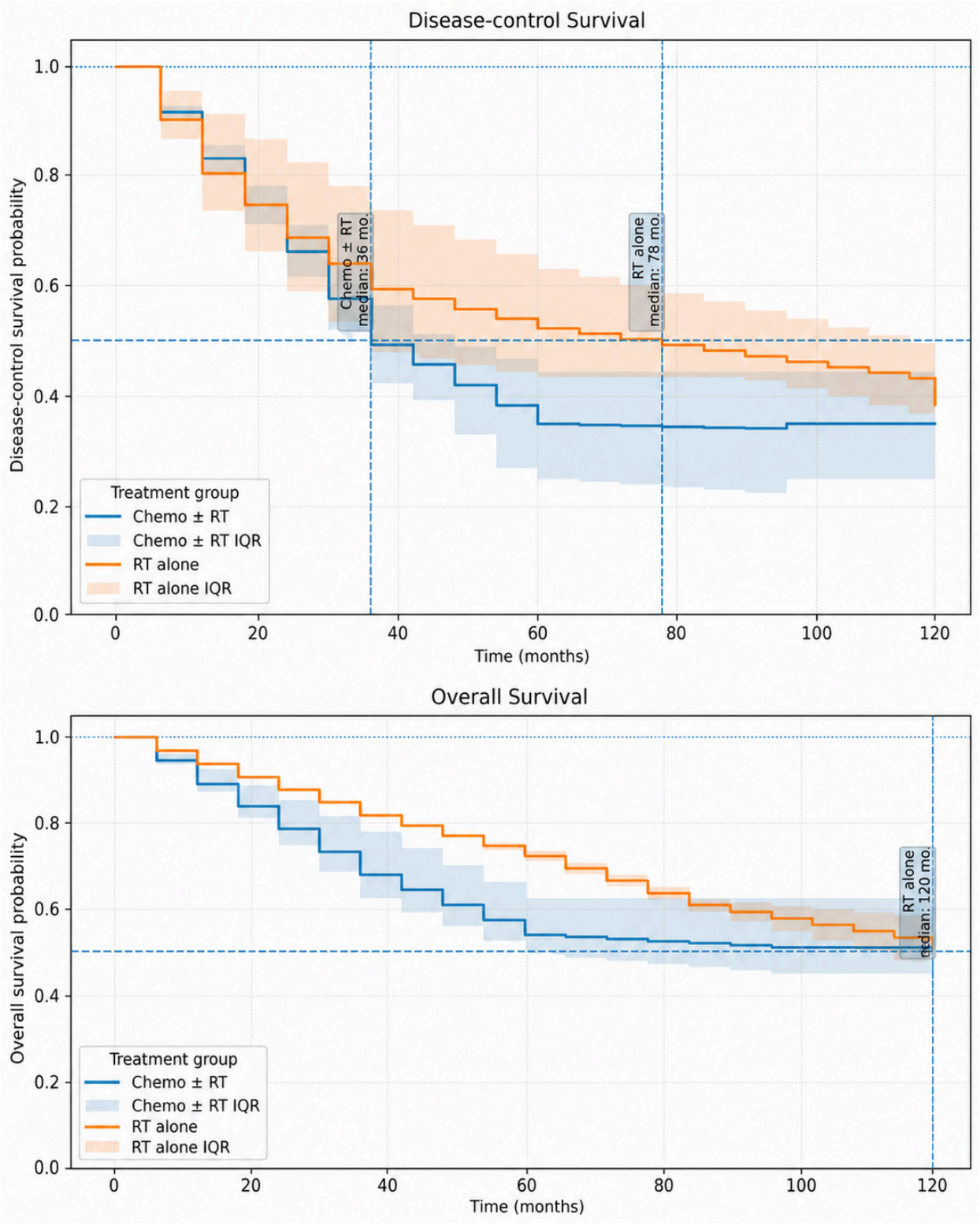


Figure 4

Reconstructed Kaplan–Meier Curves for Disease-Control and Overall Survival

Footnote: Estimated Kaplan-Meier curves: chemotherapy-containing strategies vs. radiotherapy alone for disease-control survival and overall survival.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1.Demographics.xlsx
- SupplementaryTable1.QuantitativeMetaanalysisandReconstructedSurvivalEstimates.xlsx
- SupplementaryTable2.GRADECertaintyofEvidenceAssessment.xlsx
- SupplementaryTable3.RiskofBiasDomainJudgments.xlsx
- Figure1.RiskofBiasAssessmentAcrossIncludedStudies.png