Adjuvant radiotherapy versus observation after gross total resection of WHO grade II ependymoma: a systematic review and individual-participant data meta-analysis

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Background: The role of adjuvant radiotherapy (RT) after gross total resection (GTR) of the World Health Organization (WHO) grade II ependymoma is controversial. Therefore, we aimed to compare the outcomes of adjuvant RT against observation after GTR of WHO grade II ependymoma. We also compared the outcomes of adjuvant RT against observation after subtotal resection (STR) of WHO grade II ependymoma and performed further subgroup analysis by age and tumor location.

Methods: PubMed and Embase were systematically reviewed for studies published up till 25 November 2022. Studies that reported individual-participant data on patients who underwent surgery followed by adjuvant RT/observation for WHO grade II ependymoma were included. The exposure was whether adjuvant RT was administered, and the outcomes were recurrence and overall survival (OS). Subgroup analyses were performed by the extent of resection (GTR or STR), tumor location (supratentorial or infratentorial), and age at the first surgery (<18 or ≥18 years old).

Results: Of the 4,647 studies screened, three studies reporting a total of 37 patients were included in the analysis. Of these 37 patients, 67.6% (25 patients) underwent GTR, and 51.4% (19 patients) underwent adjuvant RT. Adjuvant RT after GTR was not significantly associated with both recurrence (odds ratio =5.50; 95% confidence interval: 0.64–60.80; P=0.12) and OS (P=0.16). Adjuvant RT was also not significantly associated with both recurrence and OS when the cohort was analyzed as a whole and on subgroup analysis by age and tumor location. However, adjuvant RT was associated with significantly longer OS after STR (P=0.03) with the median OS being 6.33 years, as compared to 0.40 years for patients who underwent STR followed by observation.

Conclusions: Based on our meta-analysis of 37 patients, administration of adjuvant RT after GTR was not significantly associated with improvement in OS or recurrence in patients with WHO grade II ependymoma. However, due to the small number of patients included in the analysis, further prospective controlled studies are warranted.

Keywords: Brain tumor; ependymal tumors; individual-patient data; radiation; systematic review

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Introduction

Ependymomas are primary central nervous system tumors of neuroectodermal origin, with an annual incidence of approximately 0.43 patients per 100,000 population. Ependymomas have a strong predilection for the pediatric population and tend to be located infratentorially, in the posterior fossa or spinal cord (1,2). The classification of ependymomas has historically been histological, from Grades I to III according to the World Health Organization (WHO) classification system (3). However, as evident in the recent update to the WHO classification of central nervous system tumors in 2021, there is an increasing shift away from histological classification alone towards a classification system based on both histological and molecular characteristics (4-6), owing to the difficulty of applying the histological grading system in real-world clinical practice (3,7), the debatable prognostic utility of histological grading (3,7), and increasing recognition of the importance of molecular characteristics in the prognosis of ependymoma (3,5,8-10).

The cornerstones of management for ependymoma include surgery and radiotherapy (RT) (4,11). Specifically, treatment generally starts with maximal safe resection, with the aim being gross total resection (GTR) (11). This may then be followed with adjuvant RT in selected patients (11). The decision-making process behind the administration of adjuvant RT is complex, with a need to balance the oncological outcome against the functional outcome. While adjuvant RT may improve local control and overall survival (OS) in selected cases, there are also risks associated with RT, such as cognitive decline (12-17) and the development of secondary malignancies (18). The risk of developing secondary malignancies is especially relevant in the context of ependymoma as the majority of patients live beyond 10 years after diagnosis (2), providing ample time for secondary malignancies to develop (18).

Given the risks associated with RT (12-18), there is a need to ascertain its benefits so that the risks and benefits of adjuvant RT can be adequately weighed. To this end, it is generally accepted that adjuvant RT is beneficial for patients with incompletely resected or WHO grade III ependymoma (regardless of the extent of resection), in that it generally improves local control and OS (11).

However, significant controversy exists regarding the benefit of adjuvant RT for WHO grade II ependymoma, especially after GTR (11). Consequently, practices regarding the administration of adjuvant RT after GTR of WHO grade II ependymoma can be fairly variable across institutions (19). The benefit of adjuvant RT in this group has to be re-examined, for if it does not strongly improve OS or reduce recurrence rates, the risks from RT may outweigh the benefits.

Therefore, we performed an individual-participant data meta-analysis, comparing the outcomes of adjuvant RT against observation after GTR of WHO grade II ependymoma. We also compared the outcomes of adjuvant RT against observation after subtotal resection (STR) of WHO grade II ependymoma, and performed further subgroup analysis by age at the first surgery and tumor location. We present this article in accordance with the PRISMA reporting checklist (20) (available at https://cco.amegroups.com/article/view/10.21037/cco-23-136/rc).

Highlight box

Key findings

- Among patients with World Health Organization (WHO) grade II ependymoma, adjuvant radiotherapy (RT) was associated with significantly longer overall survival (OS) after subtotal resection (STR).
- However, adjuvant RT did not significantly impact OS and recurrence after gross total resection (GTR).

What is known and what is new?

- For WHO grade II ependymoma, it is generally accepted that adjuvant RT improves local control after STR.
- However, the role of adjuvant RT after GTR was hitherto unclear. Our meta-analysis found that adjuvant RT after GTR does not significantly improve local control and survival.

What is the implication, and what should change now?

- For patients who underwent GTR of WHO grade II ependymoma, adjuvant RT may not be necessary.
- However, given the small sample size of our cohort, further validation studies incorporating more patients are warranted.

Methods

Search strategy

PubMed and Embase were queried for studies published in the English language from the inception of the databases up to 25 November 2022. The search string used was (ependymoma*) AND (radio* OR radiation OR gamma knife OR cyber knife OR linear accelerator) within the title and abstract fields.

Table 1 Characteristics of the included studies

First author, year of publication	Number of patients with WHO grade II ependymoma	Adjuvant management, n (%)	Age at the first surgery (years), mean (SD)	Females, n (%)	Tumor located supratentorially, n (%)	GTR, n (%)	Number of criteria fulfilled in the STROBE checklist (out of 22)
Kawabata, 2005 (22)	15	Adjuvant RT: 9 (60.0) Observation: 6 (40.0)	28 (19.7)	11 (73.3)	9 (60.0)	12 (80.0)	19
Lundar, 2024 (23)	15	Adjuvant RT: 10 (66.7) Observation: 5 (33.3)	7.2 (4.2)	8 (53.3)	15 (100.0)	6 (40.0)	19
Sun, 2018 (24)	7	Adjuvant RT: 0 (0.0) Observation: 7 (100.0)	24.6 (11.9)	3 (42.9)	7 (100.0)	7 (100.0)	19

WHO, World Health Organization; SD, standard deviation; GTR, gross total resection; STROBE, Strengthening the Reporting of Observational studies in Epidemiology; RT, radiotherapy.

Study selection

Two authors (Y.Z. and S.H.O.) independently screened the titles and abstracts of the records retrieved from our search for potential inclusion in this study. Subsequently, the full texts of the identified studies were obtained and independently assessed by the same two authors (Y.Z. and S.H.O.) to determine their definitive inclusion in the study. Studies that reported individual-participant data on the treatments and outcomes of patients with WHO grade II ependymoma were included. Any uncertainties regarding study inclusion were resolved through consultation with the senior authors (V.D.W.N. and B.V.).

Data extraction

One author (Y.Z.) extracted and pooled together all reported individual-participant data of patients with WHO grade II ependymoma from each included study. The data of patients who received adjuvant chemotherapy or whose tumor WHO grade was unknown were not extracted.

Assessment of methodological quality

One author (Y.Z.) conducted the assessment of the methodological quality of the included studies using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist (21). The number of criteria fulfilled by each study was reported in *Table 1*.

Exposure and outcomes

The exposure for this study was whether adjuvant RT was administered. Specifically, the cohort was stratified into whether the patients received (I) surgery followed by observation, or (II) surgery followed by adjuvant RT. Adjuvant RT was defined as RT that was administered after the first resection. RT administered upon tumor recurrence or progression was not considered adjuvant RT.

The outcomes for this study were (I) recurrence, which was defined as radiologically significant tumor regrowth postoperatively as ascertained by the respective study authors, and (II) OS, which was defined as time to death from first surgical resection due to any cause during the follow-up period.

Statistical analysis

Descriptive statistics of the study population were reported, with the cohort stratified into whether patients underwent surgery followed by adjuvant RT or surgery followed by observation. Hypothesis testing against various patient characteristics was performed using Fisher's exact test, with a P value of lower than 0.05 considered statistically significant.

The association between the administration of adjuvant RT and OS and recurrence were investigated using the Kaplan-Meier method and univariate logistic regression modeling respectively, with a P value of lower than 0.05 considered statistically significant. For recurrence analysis, logistic regression modeling was used rather than Cox regression modeling as most of the studies included in the evidence synthesis did not report time-to-recurrence. Subgroup analyses were performed by the age at the first surgery (<18 or ≥18 years old), tumor location (supratentorial or infratentorial), and the extent of resection

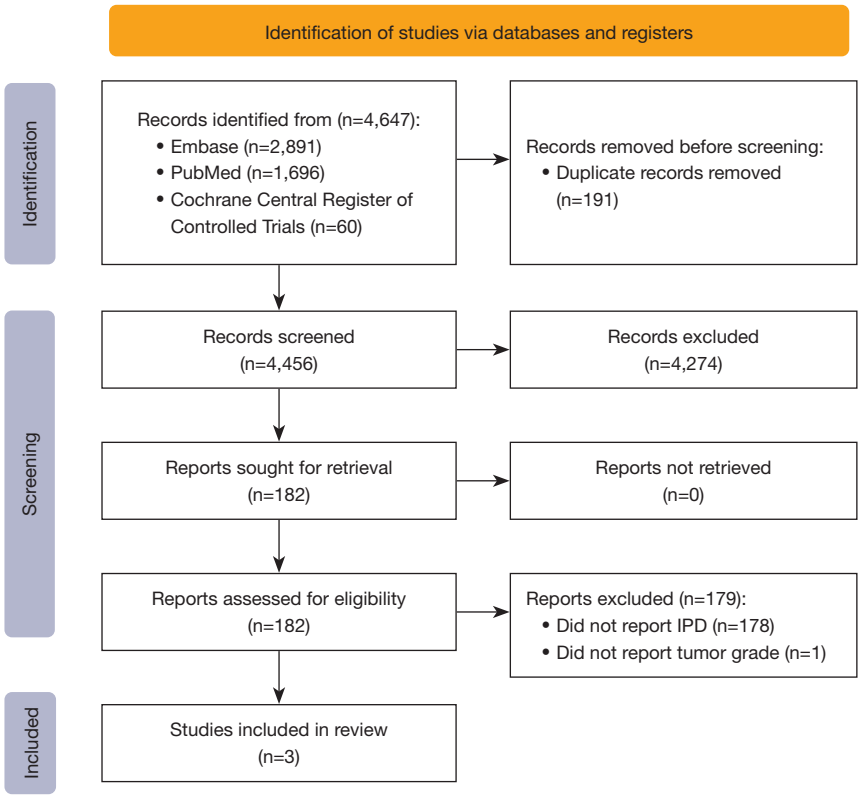

Figure 1 Study selection process. IPD, individual-participant data.

(GTR or STR; partial resection was considered as STR). All analyses were performed in R software {R Core Team [2022]; R: A language and environment for statistical computing; R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org/}.

Results

Of the 4,647 studies screened for inclusion in this study, three were included in the meta-analysis (*Figure 1*) (22-24). The characteristics of the included studies were reported in *Table 1*. Briefly, Kawabata *et al.* (22) and Lundar *et al.* (23) each reported 15 patients with WHO grade II ependymoma who underwent surgery followed by adjuvant RT or observation. On the other hand, Sun *et al.* (24) reported seven patients with WHO grade II ependymoma, all of whom underwent surgery followed by observation.

The characteristics of the study population were summarized in *Table 2*. A total of 37 patients were included in the analysis, of which 51.4% (19 patients) underwent surgery followed by adjuvant RT. The mean (standard deviation) age at the first surgery was 18.9 (16.7) years, and most patients (59.5%, 22 patients) were female. Most tumors were located supratentorially (83.8%, 31 patients), and GTR was achieved in most cases (67.6%, 25 patients). There were no statistically significant differences in terms of patient characteristics between the two treatment arms. During the study follow-up period (mean, 7.4 years; standard deviation, 8.2 years), 15 patients (40.5%) died, and 6 patients (27.3%) had a recurrence.

For the 19 patients who underwent adjuvant RT, details regarding the type and dosage of RT were reported for nine patients (22). Of these nine patients, three underwent adjuvant local RT to the tumor bed (dose range, 50.4 to 54.4 Gy), three underwent adjuvant whole-brain RT (dose range, 50 to 60 Gy), two underwent craniospinal RT (dose range, 30 to 30.4 Gy) with boost to tumor bed (total dose range, 53.8 to 55 Gy), and one patient underwent whole brain RT (dose, 30 Gy) with boost to the tumor bed (total dose, 55 Gy). The fraction sizes for the above treatments were unreported but were presumably delivered with conventional fractionation (~2 Gy per fraction) (22).

Results from the analyses of recurrence and OS were reported in *Table 3* and *Figure 2* respectively. Administration

Table 2 Characteristics of the study population

Variables	Surgery followed by observation (n=18, 48.6%)	Surgery followed by adjuvant RT (n=19, 51.4%)	Total (n=37)	P value
Age at the first surgery (years), mean (SD)	23.1 (19.2)	15.0 (13.3)	18.9 (16.7)	0.40
Female, n (%)	12 (66.7)	10 (52.6)	22 (59.5)	0.50
Tumor location, n (%)				0.66
Supratentorial	16 (88.9)	15 (78.9)	31 (83.8)	
Infratentorial	2 (11.1)	4 (21.1)	6 (16.2)	
Extent of resection, n (%)				0.07
Subtotal resection	3 (16.7)	9 (47.4)	12 (32.4)	
GTR	15 (83.3)	10 (52.6)	25 (67.6)	
Death, n (%)	4 (22.2)	11 (57.9)	15 (40.5)	0.04*
Recurrence, n (%)	2 (15.4)	4 (44.4)	6 (27.3)	0.17
Not reported, n	5	10	15	

*, P<0.05. RT, radiotherapy; SD, standard deviation; GTR, gross total resection.

Table 3 Univariate logistic regression models analyzing the association between the administration of adjuvant RT and recurrence within specific subgroups

Subgroup	Recurrence	
	OR (95% CI)†	P value†
Entire cohort	4.40 (0.64, 40.5)	0.14
Extent of resection		
Subtotal resection	NA	NA
GTR	5.50 (0.64, 60.8)	0.12
Tumor location		
Supratentorial	6.75 (0.70, 91.5)	0.11
Infratentorial	NA	NA
Age at the first surgery		
<18 years old	NA	NA
≥18 years old	3.33 (0.11, 104)	0.44

The effect sizes reported are of patients who received adjuvant RT. †, where the sample size of the subgroup was too small for the analysis to be performed, the values were reported as NA. Logistic regression modeling was used rather than Cox regression modeling as most of the studies included in the evidence synthesis did not report time-to-recurrence. RT, radiotherapy; OR, odds ratio; CI, confidence interval; NA, not applicable; GTR, gross total resection.

of adjuvant RT after GTR was not significantly associated with both recurrence (odds ratio =5.50; 95% confidence interval: 0.64–60.8; P=0.12) (*Table 3*) and OS (P=0.16) (*Figure 2D*). Administration of adjuvant RT was also not significantly associated with both recurrence and OS when the cohort was analyzed as a whole and on subgroup analysis by age at the first surgery and tumor location (*Figure 2A-2C*, *Table 3*).

However, adjuvant RT after STR was associated with significantly longer OS (P=0.03) (*Figure 2D*). Specifically, the median OS of patients who underwent STR followed by adjuvant RT was 6.33 years, as compared to 0.40 years for patients who underwent STR followed by observation (*Figure 2D*).

Discussion

The adjuvant management of WHO grade II ependymoma remains controversial. Many patients fall within the younger age group, with long expected survival. Therefore, optimizing oncological control and survival whilst minimizing treatment-related complications remains paramount. In contrast to other primary gliomas, systemic therapeutics have not been proven effective for ependymomas. The main pillars of management include

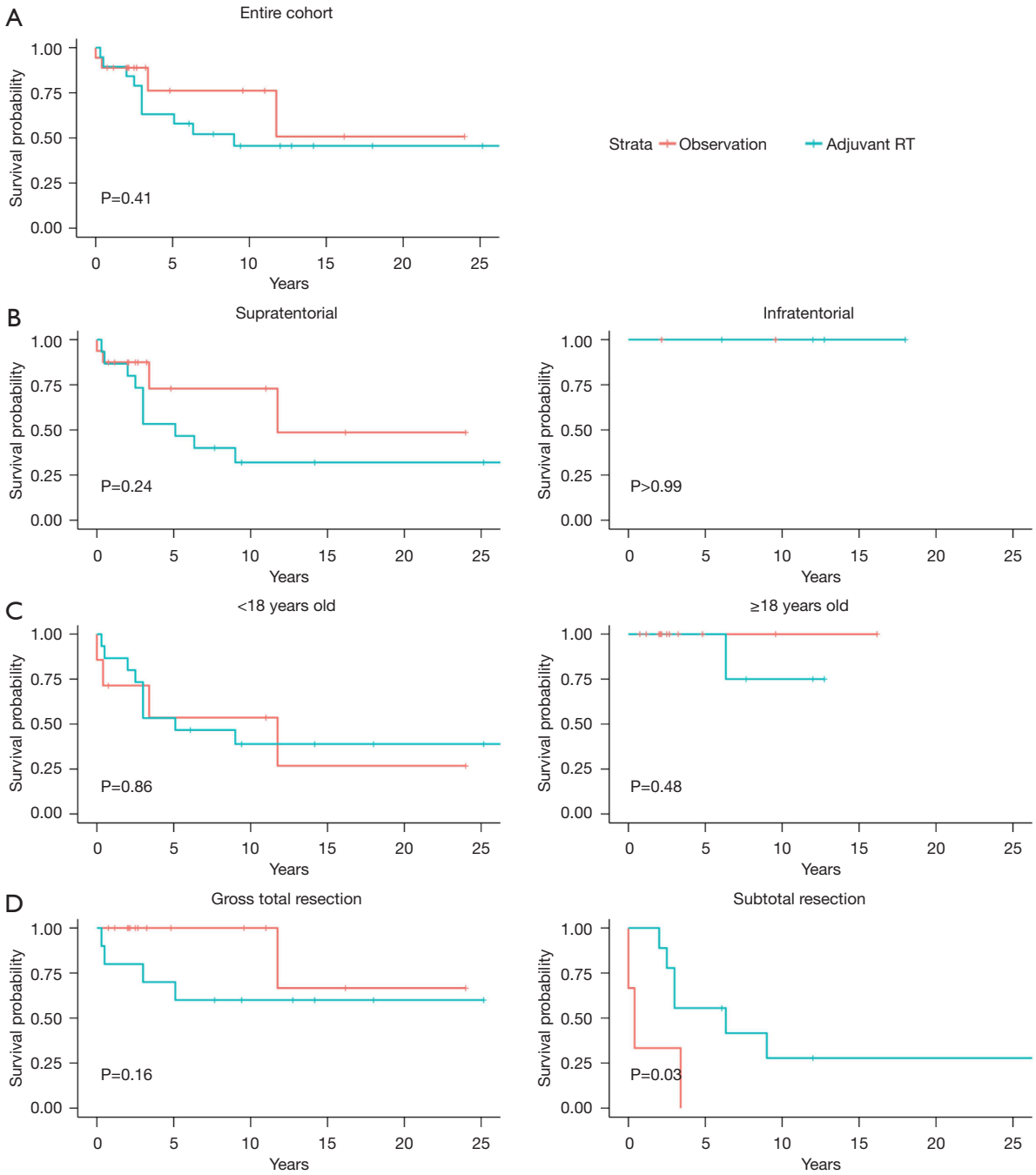

Figure 2 Kaplan-Meier plots illustrating the association between the administration of adjuvant RT and OS in (A) the entire cohort, and subgroups stratified by (B) tumor location, (C) age at the first surgery, and (D) extent of resection. RT, radiotherapy; OS, overall survival.

maximal surgical extirpation and fractionated RT. The controversy lies in the use and timing of postoperative RT. Identifying the group of patients who benefit the most will help to tailor decision-making, which may reduce long-term morbidity in patients.

This study found that the administration of adjuvant RT was not significantly associated with both recurrence and OS after GTR of WHO grade II ependymoma. These findings are in concordance with the conclusions of prior studies that similarly examined the role of adjuvant RT after

GTR of WHO grade II ependymoma (11,19,25-27).

However, in situations of STR with no further surgery possible, our study found that the administration of adjuvant RT significantly prolongs OS. Although based on small numbers, the OS of patients who underwent STR followed by adjuvant RT was approximately 16 times longer than that of patients who underwent STR followed by observation. These findings are also in concordance with the conclusions of prior studies, which similarly found that administration of adjuvant RT after STR of WHO grade II ependymoma significantly prolongs OS (11,26). Based on our findings, the survival benefit of adjuvant RT is limited in patients with WHO grade II ependymoma who have achieved GTR, but should be considered in patients with STR. However, this conclusion comes with the caveat that most of the patients (83.7%) from this cohort had supratentorial ependymomas. Hence, our findings may be most applicable to this group.

Our study has several limitations. First, a low number of studies were incorporated into our meta-analysis due to our decision to only include studies that reported individual participant data (19,25,26,28). Despite the resulting decrease in the number of patients available for our analysis, we chose to include only studies that reported individual participant data to enable us to conduct subgroup analyses based on factors such as age group, location, and extent of resection, which are clinically relevant but may not be possible with studies that did not report individual participant data.

Second, as observational data were analyzed in this study, only associations could be established. Randomized controlled trials (RCTs) are needed for causation to be proved. However, RCTs studying ependymoma may be challenging to conduct due to several reasons. First, the rarity of the condition (1,2) may make patient recruitment challenging. Also, patients with ependymoma generally live multiple years after diagnosis. Hence, RCTs studying patients with ependymoma would necessarily have to span multiple years, which may not be financially and logistically feasible. Therefore, while RCTs are generally the most rigorous method of ascertaining the risks and benefits of adjuvant RT, evidence supporting their use in the context of ependymoma is likely to remain largely from observational studies.

Third, given the relatively small sample size of each of the subgroups, we did not adjust for potential confounders in our analysis, in view of concerns over the risk of model overfitting (29). Nonetheless, we opine that regardless of whether potential confounders were adjusted for in the analysis, the fact that only association and not causation can be proven with the observational data that we analyzed remains unchanged. In other words, adjusting for potential confounders in our analysis will not significantly alter the conclusions that can be drawn from our data, and will hence be unlikely to change management.

Fourth, there are other clinically relevant subgroup analyses that are important but were not performed in this study, such as subgroup analysis by molecular characteristics. These subgroup analyses were not performed as most of the studies included in our analysis did not report such data at the individual-participant level. Future studies evaluating the role of adjuvant RT in the management of patients with ependymoma should attempt to report other clinically relevant subgroup analyses, especially by molecular characteristics (3,5,8-10), as findings from such analyses could potentially change management.

Fifth, several patients received adjuvant whole-brain RT or craniospinal RT, suggesting they may have had disseminated disease, in contrast to the rest of the patients who probably had localized disease. Most of the included studies also did not specify if all patients underwent a thorough workup to rule out metastatic disease. Consequently, our study cohort might exhibit heterogeneity in terms of disease extent, making the interpretation of our findings challenging. Future validation studies should endeavor to conduct subgroup analyses based on disease extent (localized or disseminated) to enhance data interpretability.

Sixth, the method for determining the extent of resection were heterogenous across the included studies. Specifically, Kawabata *et al.* (22) determined extent of resection on postoperative computed tomography (CT) and/or magnetic resonance imaging (MRI), Lundar *et al.* (23) determined extent of resection using the surgeon's report during the pre-MRI era and on surgeon's report as well as MRI findings in the MRI-era, and Sun *et al.* did not specify how the extent of resection was determined (24). This heterogeneity may compromise the interpretability and validity of our findings, as the accuracy of determination of extent of resection is known to differ across the different methods (surgeon's report/MRI/CT).

Last, the subsequent management of the patients included in our analysis was not described in detail. In general, local recurrences are managed with re-resection followed by RT (if no prior RT was given), or craniospinal radiation in the setting of disseminated recurrences.

Therefore, it can be assumed that patients who were observed after the initial diagnosis are likely to have received RT at recurrence. The lack of survival benefit with adjuvant RT in the GTR group suggests that delaying RT may not be detrimental. However, such patients may require additional surgical intervention.

Conclusions

Based on our systematic review of the literature, and meta-analysis, administration of adjuvant RT was not significantly associated with both recurrence and OS after GTR of WHO grade II ependymoma. These findings may be most applicable to patients with supra-tentorial ependymoma. Our findings should be considered as hypothesis-generating due to the small number of patients involved.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://cco.amegroups.com/article/view/10.21037/cco-23-136/rc

Peer Review File: Available at https://cco.amegroups.com/article/view/10.21037/cco-23-136/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://cco.amegroups.com/article/view/10.21037/cco-23-136/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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