Peer Review File

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Reviewer A:

We thank the reviewer for their thoughtful comments and for the opportunity to revise our manuscript. The comments are addressed point-by-point below.

Comment 1: “There are several questions that arise when one chooses only 3 small studies out of over 4600 trials, particularly when the numbers are this small. First, we know that supra and infra-tentorial ependymomas are molecularly different tumors.”

Reply 1: We agree with the reviewer that supratentorial and infratentorial tumors are molecularly distinct tumors. Therefore, we performed subgroup analysis by tumor location (supratentorial/intratentorial) and found that the administration of adjuvant RT was not associated with significantly improved overall survival in both the supratentorial and infratentorial siubgroups (Figure 2B).

Changes in the text: No changes were made.

Comment 2: “The authors mention that they don't know the clinical staging of the patients listed--how many had a thorough workup including spinal MRI with and without contrast and lumbar puncture confirming localized disease vs metastatic.”

Reply 2: We thank the reviewer for the comment. The included studies did not report information on the number of patients who underwent a thorough workup. We have now mentioned this as a limitation in the discussion section.

Changes in the text: We have added the text as advised (see page 8, lines 235 and 236): “Most of the included studies also did not specify if all patients underwent a thorough workup to rule out metastatic disease.”

Comment 3: “What were the radiation doses given and fractionation?”

Reply 3: We thank the reviewer for their comment. The radiation doses and their fractions were reported in the results section: “For the 19 patients who underwent adjuvant RT, details regarding the type and dosage of RT were reported for 9 patients.(22) Of these 9 patients, 3 underwent adjuvant local RT to the tumor bed (dose range 50.4 to 54.4 Gy), 3 underwent adjuvant whole-brain RT (dose range 50 to 60 Gy), 2 underwent craniospinal RT (dose range 30 to 30.4 Gy) with boost to tumor bed (total dose range 53.8 to 55 Gy), and 1 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)" (see page 6, lines 162 to 168)

Changes in the text: No changes were made.

Comment 4: "Was extent of resection based upon surgeons report (unreliable), post-op CT or post-op MRI? We know post-op CT without contrast can miss residual disease."

Reply 4: We thank the reviewer for pointing this out. The included studies utilized different methods to determine the extent of resection. Specifically, Kawabata et al. determined extent of resection on postoperative CT and/or MRI, Lundar et al. 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.

Changes in the text: We have now clarified the inconsistency in methods for determining the extent of resection in the limitations section (see page 9, lines 240 to 247): "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)."

Comment 5: "We know from prior studies (Merchant et al) that young children who had delayed radiation following resection in order to receive chemotherapy had much worse outcomes compared to those who had early post-op radiation."

Reply 5: We thank the reviewer for the comment. In most of the prior studies (including Merchant et al.), patients with WHO grade I and/or III ependymoma were included in the analysis. Hence, the findings from those studies may not be generalizable to our study, which focuses specifically on WHO grade II ependymoma.

Changes in the text: No changes were made.

Comment 6: "How many of the PF ependymomas had 1q gain? We know that is an "at risk" group for recurrence and death."

Reply 6: We agree with the reviewer that 1q gain is an important prognostic marker and hence subgroup analysis by 1q gain status would be relevant. However, subgroup analysis by 1q gain status was not performed as these data were not reported by the

included studies. The absence of subgroup analysis by molecular characteristics was mentioned as a study limitation: “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.” (see page 8, lines 226 to 232).

Changes in the text: No changes were made.

We hope the revised manuscript satisfies the reviewer’s standards for publication.

Reviewer B:

We thank the reviewer for their helpful suggestions and for the opportunity to revise our manuscript. The comments are addressed point-by-point below.

Comment 1: “Systemic review is insufficient for the title of this manuscript. For example, Ruda R et al. Curr Oncol Rep 24(8):985-993 (2022) and Saleh AH et al. Nat Rev Cancer 22(4):208-222 (2022) should be referred.”

Reply 1: We thank the reviewer for the suggestion. The quoted studies are indeed highly relevant, and hence have now been cited in the introduction.

Changes in the text: We have cited the studies as suggested (references 4 and 10).

Comment 2: “Not requotation but WHO classification itself should be referred. Furthermore, WHO classification was updated in 2021. The latest version and the correspondence should be addressed.”

Reply 2: We thank the reviewer for pointing this out. The publications for the 2021 WHO classification of CNS tumors have now been cited.

Changes in the text: We have cited the studies as suggested (references 5 and 6).

We hope the revised manuscript satisfies the reviewer’s standards for publication.