Peer Review File

Article information: https://dx.doi.org/10.21037/tp-23-362

Reviewer A

The author performs a retrospective review of SEER data to exam all-cause mortality of children with brain tumors.

Major:

- As with any analysis of SEER, the data are very heterogeneous, even within tumor pathology, thereby reducing the generalizability.

Reply: Thanks very much for your comment. The limitation has been added in our revised manuscript.

- The authors find that patients who had chemotherapy had increased risk of mortality. This is not surprising as 1) those patients had likely more aggressive tumors to start with and were more likely to die from their tumor and 2) a small number likely died from chemo complications itself.

Reply: Thanks very much for your comment. The related content has been added in our article. Our investigation used the Surveillance, Epidemiology, and End Results (SEER) database to explore the effects of different treatments on the mortality of children with primary brain and CNS epithelial tumors. Furthermore, we categorized CNS tumors according to histology to explore the effects of different treatments on mortality. For primary brain and CNS epithelial tumors, children who received chemotherapy had an increased risk of all-cause mortality compared with children who did not receive chemotherapy; and those who underwent resection had a reduced risk of mortality compared to children who did not receive resection. We also found that other treatment modalities were associated with higher overall all-cause mortality in children with diffuse astrocytoma, ependymal tumor, and malignant glioma, compared with resection alone. For embryonal tumors, resection with radiotherapy or resection with chemoradiation was associated with lower overall all-cause mortality compared with resection alone. Treatment should be comprehensively selected according to histological classification for children with primary brain and CNS epithelial tumors. Resection may be recommended for children with diffuse astrocytoma, ependymal tumors, and malignant glioma, while resection with radiotherapy or chemoradiation may be recommended for children with embryonal tumors.

Changes in the text: We have modified our text as advised (see Page 8, line 260-268; Page 11, line 345-350).

- In the age of molecular subgrouping, it is not reasonable to lump all malignant gliomas into 1 category as they range from DIPG with a median OS of ~12 months and Grade III hemispheric glioma which can have OS of years. Same go for the differences in a PFA ependymoma vs a completely resected supratentorial YAP fusion ependymoma who can be cured with surgery.

Reply: Thanks very much for your suggestion. In the current study, patients with primary brain and CNS tumors were identified using the International Classification of Diseases for Oncology, third edition (ICD-O-3): (C70.0-9, C71.0-9, C72.0-9) or (C30.0 and 9522-9523). We assessed the associations between treatments and overall all-cause mortality according to different histology types. Our findings showed that the treatments should be comprehensively selected according to histological classification for children with primary brain and CNS epithelial tumors. Resection may be recommended for children with diffuse astrocytoma, ependymal tumors, and malignant glioma, while resection with radiotherapy or chemoradiation may be recommended for children with embryonal tumors. Future well-designed studies need to further validate our findings.

Changes in the text: We have modified our text as advised (see Page 5, line 126-132; Page 11, line 345-350).

- The KM curve is also not very helpful given the hetergenity of tumor types and locations.

Reply: The KM curve in our study only displayed the survival of pediatric brain and CNS tumors patients by different treatments.

Changes in the text: None.

- The conclusion that "Resection is recommend for…malignant glioma" is simply not true for DMGs. Additionally, the standard of care for PF ependymomas is post op radiation, not just surgery. Also the standard of care for DMG is radiation. Long story short, the conclusions are simply inaccurate.

Reply: We have revised our conclusion.

Minor

- The paragraph starting at line 100 is a bit random – not really providing useful background data.

Reply: We have revised the content.

Reviewer B

1) First, I suggest the authors to indicate the clinical research design of this study in the title such as a retrospective cohort study based on the SEER.

Reply: Thanks very much for your suggestion. We have revised the title.

2) Second, the abstract needs some revisions. The background did not describe the clinical significance of this research focus and why the SEER data can answer the clinical questions of interest in this study. The methods need to describe the follow up procedures and data collection of treatments and histological subtypes. The results need to first describe the baseline clinical characteristics, histological subtypes, treatments, and overall one-, three-, and five- year OS. Please quantify the findings on the prognosis of histological subtypes and treatments by reporting HR and accurate P values.

Reply: Thanks very much for your suggestion. The related content has been revised in the revised manuscript. Details were as follows:

Background: Evidence on treatment modalities and survival in childhood primary brain and central nervous system (CNS) tumors remains contradictory, with previous studies often lacking sufficient patient cohort sizes to assess the differences in histological subtypes. This cohort study based on a large population investigated the effects of various treatments on the mortality of patients with different histological types of primary brain and CNS epithelial tumors from the Surveillance, Epidemiology, and End Results (SEER) database.

Methods: Data of demography, primary tumor site, histology, tumor grade and treatments from all pediatric patients diagnosed with primary brain and CNS tumors of neuroepithelial tissue between 1975 and 2016 were extracted in this retrospective cohort study. The outcomes were overall, 1-, 5-, and 10-year all-cause mortality. Multivariate Cox proportional hazards models were to explore the associations of treatment with overall, 1-, 5-, and 10-year all-cause mortality risk. Hazard ratios (HRs) and 95% confidence intervals (CIs) were reported. Kaplan-Meier curves were generated for comparing the survival rates of different treatments.

Results: Totally 10,994 children were included, with the mean age at diagnosis of 7.3 years, and the median follow-up time of 5.0 years. Of which, 2,003 (18.2%) were diffuse astrocytoma, 3,188 (29.0%) were embryonal tumors, 3,691 (33.5%) were malignant glioma, and 1188 (10.8%) were ependymal tumors. Then 4,333 (39.41%) children died during the follow-up. The findings on the prognosis of histological subtypes and treatments by reporting HR and accurate P values were showed in the Results section. The abstract section cannot be presented due to word limit.

3) Third, in the introduction of the main text, the authors need to analyze the reasons for the contradictory evidence on the treatment efficacy and prognosis of histological subtypes, describe the strengths of SEER and limitations of prior studies, and explain why the SEER data can answer this research question.

Reply: Thanks very much for your suggestion. The related content has been revised in the revised manuscript. Details were as follows:

In germ cell tumors, radiotherapy alone showed better survival outcomes compared with biopsy and resection, however, there was no difference in survival compared with chemotherapy alone (6). Combining resection with radiotherapy or chemotherapy did not improve survival compared with resection alone (6). Studies have shown that gross total resection was associated with improved survival in pediatric glioblastoma patients (7). Another study demonstrated that gamma knife radiosurgery may be an indispensable tool in pediatric CNS tumor management (8). To date, evidence on treatment modalities and survival in children with CNS tumors remains contradictory, with these studies often lacking sufficient patient cohort sizes to assess the differences in histological subtypes.

In this current investigation based on a large population from the Surveillance, Epidemiology, and End Results (SEER) database, we explored the effects of different treatments on the mortality of children with primary brain and CNS epithelial tumors.

4) Fourth, in the methodology of the main text, please clearly describe the clinical research design of this study and the follow up procedures of the SEER data.

Reply: The study design and the follow up procedures of the SEER data have been added in the methodology of the main text.

5) Finally, please consider to review and cite several related papers: 1. Calimeri T, Marcucci F, Corti A. Overcoming the blood-brain barrier in primary central nervous system lymphoma: a review on new strategies to solve an old problem. Ann Lymphoma 2021;5:20. 2. Resende LL, Alves CAPF. Imaging of brain tumors in children: the basics—a narrative review. Transl Pediatr 2021;10(4):1138-1168. doi: 10.21037/tp-20-285. 3. Shalita C, Hanzlik E, Kaplan S, Thompson EM. Immunotherapy for the treatment of pediatric brain tumors: a narrative review. Transl Pediatr 2022;11(12):2040-2056. doi: 10.21037/tp-22-86.

Reply: Thanks very much for your suggestion. Some articles related to our study papers have been cited in the revised manuscript.