Peer Review File

Article information: Available at http://dx.doi.org/10.21037/apm-20-640.

Article Type: Review Article
Manuscript ID: APM-2019-PCNO-03(APM-20-640)
Title: Prognosis in Glioma in Adults

Reviewer #1

Overall a good job of discussing tumour and patient factors associated with Glioma prognostication. The paper is informative and thorough. It would benefit from at least one table to describing the most significant prognostic features across the different subtypes and the associated HR for example.

Response: Thank you for your comments. The table you suggested has been added as Table 1, but we have decided not to include the HRs or statistical data in this table. This decision was made after careful consideration – we find that there can be variability in HRs and p values across studies, even for factors that are well proven (such as gross total resection). Meta analyses of this data exist and have done a much more thorough job of evaluating the existing evidence. We think that this review should not also try to serve that purpose, and the goal should be to provide an overview of the prognostic factors for the palliative care specialist. We have included citations to all the statements which the reader may explore to learn more and find the appropriate information. We have also added on page 5 and 6 examples of how the HR can be variable.

Please also take into consideration the points below.

Comment 1: The title doesn't sound right – Maybe overview of prognostic factors in adult gliomas?

Reply 1: Thank you for your suggestion, we have changed the title.

Comment 2: Key Points "Clinical features of poor prognosis or decline…" please clarify for all gliomas or subtype.

Reply 2: This has been changed in the key points section to: "Clinical features of poor prognosis or decline **in patients with glioma** can include focal weakness, **new onset or worsening** seizures, mood disturbance, thrombosis, language disturbance, fatigue, cognitive decline and steroid dependence."

Comment 3: Page 2: under "Overview of Gliomas" gliomas are not generally "staged" they are graded.
Reply 3: Wording changed to graded.

Comment 4: I think you need to impress how molecular feature have trumped other prognostic features. For example, 1p19q codeleted tumours do significantly better regardless of grade (II or III) and other patient factors.
Reply 4: We have added several sentences on this in the appropriate paragraphs, and added references (page 7, 11).

Comment 5: Page 7: High grade gliomas in the elderly have a much worse prognosis than stated (16-22 months) and GIII oligo have a much better prognosis than 16-22 months. They should not be discussed together.
Reply 5: We have changed the wording of this paragraph so it does not seem that prognosis applies to all grade III and IV tumors. While you are correct that some grade III tumors have a much better prognosis and that there is variability in treatment across the country, we feel it would be very complicated and even controversial to discuss the nuances of this in this type of article.

Comment 6: Page 7: management of Grade III oligo is at many centres different than GBMs
Reply 6: We have removed this sentence on page 7 to address your concern.

Comment 7: Page 7: Maximal safe resection is a recommendation for all gliomas not just HGG
Reply 7: We have made edits for this on page 7. This was also addressed in the LGG section.

Comment 8: Page 8: TMZ is not used for all GIII and GIV gliomas, PCV in oligos and debatable in some GIII astro. Also concurrent evidence is being challenged
Reply 8: Thank you for noting this, we have made changes to address this (page 9 and 10).

<u>Reviewer #2</u>

Overview: This is a review of the literature on prognostication in gliomas, which represent the majority of CNS tumors and cause significant morbidity and mortality.

Contribution: While there are papers describing prognostication in this population, this has changed significantly in the last decade, and the majority of the current literature targets neurologists and neuro-oncologists, not palliative care providers, and to my knowledge, none of these papers have been published in palliative care journals, making this an important contribution to the current literature.

Strengths: This paper meets the criteria necessary for publication in Annals of Palliative Medicine. As above, it is original and timely, the information is important, topical, and medically relevant, and the conclusions are reasonable and well supported by the data/references.

Weaknesses and suggestions:

Comment 1: While the paper is written clearly, given that the target audience is palliative care providers not neurologists or neuro-oncologists, I recommend including a more basic summary of the different tumor types at the beginning of the article. I also recommend including a figure showing the WHO classification for readers to refer to and a table with the important prognostic features and quality of the data for each of the features. This will be especially important for the molecular features, which will be less familiar to palliative care providers, and will provide the readers with an easy reference table to return to both during and after reading the paper.

Reply 1: Thank you for your kind comments and constructive criticism. We have created Figure 1 that highlights the key molecular features we have highlighted in this paper (which is not meant to be an exhaustive review of the molecular specifics, but an overview of key features with prognostic implications). This also provides an illustrative overview of the WHO classification. Table 1 has been added for the prognostic features; we have decided not to emphasize the quality of the data for purposes of this review. There is wide variability in available data but many analyses and reviews exist that focus more on each specific factor. These provide a more nuanced discussion of the data, and we think it would not be advisable to provide just some of the data without detailed context. We have included examples of the HR variability on page 5 and 6.

Comment 2: I recommend giving an outline of the article at the beginning of the paper (ie in this paper we will discuss prognostication in low grade vs high grade

gliomas, variability in treatment of these tumors, clinical features of poor prognosis, and differences in prognostic understanding between patients and their caregivers). This would make it easier for readers to follow.
Reply 2: Thank you for this advice, we have included this in the abstract.

Comment 3: Consider a brief description of why and how prognostication in gliomas differs from prognostication in other malignancies, which many palliative care providers will be more familiar with. For example, many palliative care providers are used to using the presence of metastatic disease and functional status as tools to prognosticate, but much of the morbidity of gliomas stems from the primary tumor, and assessing functional status may differ in patients with neurological disease.
Reply 3: This has been added to page 4 and 5.

Comment 4: Consider referencing some of the newer literature on survival differences between different racial and ethnical minority groups (presented by Sharon Yu at AAN 2019) and the impact on travel distance to care facility on survival in patients with glioblastoma (presented by Jay-Jiguang Zhu at AAN 2019) if relevant.
Reply 4: Thank you for this advice. Information on race differences has been added on page 7. In regards to Dr Zhu's work, there still remains lack of clarity since other studies have shown no difference in outcomes based on facility : https://pubmed.ncbi.nlm.nih.gov/30671709/ Thus, we hesitate to include this at this point until larger studies or more data is available.