Peer Review File

Article information: https://dx.doi.org/10.21037/cco-23-114

Review Comments

Thank you for the opportunity to review this manuscript. This is an interesting case where non-enhancing T2 hyperintensities noted on pre-treatment MRI in setting of a seizure resolve in the setting of combinatorial therapy for GBM. This case should be reported but it would benefit from a reframing of the findings and discussion. Specific items for consideration.

Minor points:

1- In the introduction, please clarify the treatment in SPARE. It is stated "The SPARE trial (NCT03477110) is a pilot study investigate 54 the feasibility and safety of concurrent TTFields treatment." Please edit to state TTF is administered concurrently with radiation therapy.

Reply: We thank the reviewers for their comment. We have added more clarification to treatment received in the SPARE trial.

Change in Text: "The SPARE trial (NCT03477110) was a pilot study designed to investigate the feasibility and safety of concurrent radiation treatment and TTFields treatment" (line63-64)

2- In the introduction, please explain how TTF is normally administered during adjuvant chemotherapy and the novelty added by SPARE.

Reply: It is revised accordingly

Change in text: "Preclinical studies suggested synergistic effect between TTFields treatment is combined with radiation treatment. The SPARE trial (NCT03477110) was a pilot study designed to investigate the feasibility and safety of concurrent radiation treatment and TTFields treatment" (line 62-65)

3- Please mention EF-32 ongoing study.

Reply: It is revised accordingly:

Change in text: "In addition, the larger EF-32 trial (NCT04471844) currently ongoing is investigating the efficacy of concurrent radiation and TTFields treatment in newly diagnosed GBM." (line 65-67)

4- Case presentation: Please streamline the initial presentation. "The patient is..." is an incorrect statement since the patient unfortunately passed away. It is stated patient was started on Keppra and dexamethasone before it is stated that a tumor was identified.

Reply: Patient was placed on Keppra and steroids due to the seizure. This is done before the identification of tumor. In addition, grammatical and syntactical errors (including improper tense related ones) have been fixed throughout the manuscript.

Change in text: “The patient was a 64-year-old African American male with no significant past medical history presented with dizziness and lightheadedness.” (line 72-73)

5- Avoid use of brand names for medications such as Keppra. Consider whether it is necessary to state whether patient received anticonvulsant or corticosteroid therapy at all.

Reply: It is changed to “Levetiracetam” (line 76)

6- Please revise the section where the histology is outlined. Avoid overly casual terminology such as "pathology showed."

Reply: We thank the reviewers for their comment. Informal terminology has been removed from the sentence and a review of the article for remaining similar instances was done.

Change in text: “The final comprehensive pathology diagnosis wasGBM, IDH wild type, WHO grade 4. MGMT promotor hypermethylation was positive, 15.4%.” (line 85-87)

7- Please do not use present tense such as "hypermethylation is positive." This needs to be corrected throughout the manuscript.

Reply: We thank the reviewers for their comment. We have completed a comprehensive review of the manuscript and corrected grammatical errors.

Change in text: “MGMT promotor hypermethylation was positive, 15.4%.” (line 85-87)

8- Please provide further explanation as to why GC change area was not covered by the radiation treatment field.

Reply: As it is stated in the manuscript, the radiation volume is according to EORTC guidelines, which does not cover FLAIR abnormality.

This is also done to limit radiation induced toxicity. (line 94-97)

9- It is not correct to state GC change remained in remission when patient overall is experiencing serious disease progression. Please revise the section where progression of disease is outlined accordingly. It would be best to state patient had disease progression. It would be acceptable to state T2 FLAIR changes initially attributed to GC pattern remained resolved.

Reply: We thank the reviewers for their comment. We have reworked this statement as we agree the progression of disease from the area of GC change does make the original statement incorrect. We have added further clarification to the statement as the reviewers suggested that the T2 FLAIR signals attributed to GC change remained resolved.

Change in text: “The T2 FLAIR hyperintensity attributed to the GC changes remained resolved on MRI.” (line 114-115)

10- In the section related to progression, please avoid terminology such as "deterioration in KPS." Simply state patient experienced clinical decline that was characterized by left hemiparesis and associated gait difficulty requiring use of a wheelchair. It can then be stated KPS declined to X (state the actual number not just that it was worse).

Reply: We thank the reviewers for their comment. The statement was removed and replaced with more proper phraseology and clear statement of the KPS score at the time.

Change in text: “Unfortunately, 2 months later, the patient experienced significant deterioration, becoming wheelchair bound, developing left hemiparesis with corresponding ataxic gait, slurred speech, and anomic aphasia. His KPS score at this time was 50.” (line 118-121)

11- As above, for a patient who experienced serious clinical deterioration, it is not helpful to state "There is no recurrence of GC." By month 13 patient is devastated with neurological symptoms, TTF is discontinued. Is it really at all clinically relevant that GC changes are not visible on MRI at that point?

Reply: We thank the reviewers for their comment. We agree the phrasing of this statement was not optimal and have changed this to describe the findings on imaging in a more clear way. We also agree that the clinical decline at this point takes precedence over imaging findings and have addressed this issue as well.

Change in text: “Despite this deterioration clinically, there was no recurrence of the GC changes.” (line 124-125)

<u>Major concerns:</u>

1- Discussion should be significantly revised to discuss why GC was abandoned as a diagnostic entity in the first place. An important publication from 2016 (https://pubmed.ncbi.nlm.nih.gov/26493382/) demonstrated GC is NOT a separate tumor entity. From the paper: "Taken together, DNA-based large-scale molecular profiling indicates that GC comprises a genetically and epigenetically heterogeneous group of diffuse gliomas that carry DNA methylation and copy number profiles closely matching the common molecularly defined glioma entities. These data support the removal of GC as a distinct glioma entity in the upcoming revision of the WHO classification."

Reply: We thank the reviewers for their comment. The findings of the paper that contributed to the 2016 reclassification have been included in the manuscript.

Change in text: “Analysis of methylation patterns in GC revealed similar signature seen in multiple pre-defined glioma subgroups (1).” (line 138-140)

2- Another critical paper that must be addressed in the discussion: Broniscer A, Chamdine O, Hwang S, Lin T, Pounds S, Onar-Thomas A, Shurtleff S, Allen S, Gajjar A, Northcott P et al (2016) Gliomatosis cerebri in children shares molecular characteristics with other pediatric gliomas. Acta Neuropathol 131:299–307.

Reply: We thank the reviewers for their comment. The findings of the paper that contributed to the 2016 reclassification have been included in the manuscript.

Change in text: “This finding was corroborated in pediatric GC which corresponded to known glioma methylation profiles as well as both genetic and epigenetic characteristics (Broniscer)” (line 140-141)

3- The above culminated in the following (https://link.springer.com/article/10.1007/s00401-016-1545-1): "Gliomatosis cerebri has also been deleted from the 2016 CNS WHO classification as a distinct entity, rather being considered a growth pattern found in many gliomas, including IDH-mutant astrocytic and oligodendroglial tumors as well as IDH-wildtype glioblastomas [4, 13]. Thus, widespread brain invasion involving three or more cerebral lobes, frequent bilateral growth and regular extension to infratentorial structures is now mentioned as a special pattern of spread within the discussion of several diffuse glioma subtypes."

Reply: We thank the reviewers for their comment. We agree the reclassification of GC was an important change to highlight in this manuscript. In addition to our statements in the introduction we have added multiple sentences to address both the 2016 WHO classification and the papers leading up to it in the discussion.

Change in text: “GC was reclassified as a diffuse pattern of growth within glioma in 2016 due to two key papers identifying a lack of molecular distinction between GC and glioma (Louis).” (lin 137-138)

4- Ultimately, this patient's tumor would be currently classified as glioblastoma, IDH wildtype, MGMT methylated. In the landmark study by Stupp et al, median survival was reported as 14.6 months for RT with concurrent and adjuvant TMZ. In a later paper, "the median overall survival among patients with methylation was 18.2 months." (https://www.nejm.org/doi/full/10.1056/nejmoa043331). In addition, in the clinical trial that led to approval of TTF for new GBM, median overall survival was 20.9 months. The patient presented here had an overall survival of 17 months, which is less than the survival reported with RT and TMZ without TTF in EORTC 26981. It is hard to celebrate this as a success story.

Reply: We agree this case is GBM, IDHwt, G4. However, it has GC, which is associated with very poor outcomes. The trials and data the reviewers quoted excluded patient with multiple focal disease, let along GC. So the results may not directly apply to the current case.

In the introduction: “The prognosis of GC compared to equally graded gliomas is worse(3,4); with a median overall survival (OS) of grade 4 gliomas with GC change being 9 months and 5 year survival rate of 18%(5).” (line 49-52)

5- The authors argue resolution of the T2 FLAIR changes on the initial MRI as proof of response to TTF. How do we know some of this change was not cerebral edema? How do we know some of it was not post-ictal in nature? The discussion should explain why the T2 changes were felt to be certainly representative of non-enhancing tumor.

Reply: We thank the reviewers for their comment. This is already addressed in the manuscript (page 4, paragraph 1): Broad areas T2/FLAIR hyperintense signals were noted throughout the left hemisphere of the brain and along the splenium of the corpus callosum with invasion into the right parietal, temporal, and occipital lobes resulting in gyral thickening and sulcal effacement, consistent with GC. The changes are not consistent with cerebral edema or post-ictal. (line 79-82)

6- Authors should propose a mechanism as to why TTF would lead to response in non-enhancing component of the tumor. It should be noted whether this has been previously reported for other patients with GBM.

Reply: We thank the reviewers for their comment. This case report highlighted the response of non-enhancing component of glioma, which was not well reported in the literature.