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Verona, 25 february 2022

Dear Editor,

We thank the Editor and the Reviewers for their comments, wich contributed substantially to the improvement of the manuscript.

All comments have been taken into full consideration and the appropriate changes made.

REVIEWER 1

Specific Comments to Authors: 1. The factors in this review study have no clear clinical significance and have not been clearly revealed. 2. The inclusion criteria of the article are unreasonable.

Reply to Reviewer 1:

1. We thank the reviewer for the comment.

The review has been conducted standing on the premises that recognised risk factors for extraneural spread of oligodendrogliomas and astrocytomas are tumor grade, previous surgeries, chemo-radiotherapy and ventriculoperitoneal shunt placement. We therefore systematically analysed case reports, case series and articles on oligodendroglial and astrocytic tumours metastasizing outside the CNS, with particular attention to the presence of these risk factors, in order to further determine their impact on metastasization. We also aimed to identify relevant clinical informations that could help transplant professionals to better assess the risk of tumour transmission from donors with brain tumors to recipients. We conclude that the use of imaging techniques targeting primarily bone and the head and

neck nodal stations should be cornerstones of risk assessment in this setting, since these are preferential sites of extraneural spread.

We are confident that this evidence can help transplant community to improve assessement in the particular and fundamental context of organ donation from donors with primary brain tumors.

2. The articles included in this review have been published during a wide timespan, therefore some extracted data are conditioned and limited, also by the changes made during the past decades to the classification of central nervous system tumors. Inclusion criteria were: case reports, case series and literature review reporting data on patients with a history of oligodendroglioma or astrocytoma that subsequently metastasized outside the CNS. Articles with limited data were included if they at least reported the histologic diagnosis of primary and metastatic tumours. We excluded articles reporting metastatic disease not histologically confirmed and those concerning only animal models or cell cultures. Articles reporting extracranial metastases from primary glioblastomas were also excluded.

REVIEWER 2

Specific Comments to Authors: In this article, the authors present some rare brain tumors and the risk of recurrence/metastasis. The subject is of interest. I have some questions/concerns as below

1. If I understand correctly, in this article the authors present the numbers of patients with distance metastasis with these rare brain tumors- who were not organ donors…. So, I am not sure if this article fits the scope of the Transplant journal or should better fit the oncology journal? 2. Are there any data of donor-derived transfer of brain tumors mentioned in this article 3. What was the aim of the study and recommendations from the authors? 4. The range of metastasis ranged from 0-276 months, that is 0-27 years, so it is so vague to make any conclusion if organs from pts with these tumors should be accepted or not.

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Reply to Reviewer 2:

1. As the Reviewer correctly points out, in this systematic review we analysed cases of extraneural spreading of oligodendrogliomas and astrocytomas in patients whith a history of these primary central nervous system tumors. We aimed to extrapolate useful clinical informations that could be used in the transplant practice and investigate how recognised risk factors impact on the profile and timing of extraneural spread.

2. In the Introduction section we reported data from the published literature on diffuse gliomas transmission after solid organ transplantation, with particular reference to data obtained by international transplant registries.

3. Aim of this literature review was to investigate the role of tumour transmission risk factors in donors with oligodendrogliomas and astrocytomas in order to refine the tumour transmission risk assessment and identify clinical strategies for decision making in organ transplantation.

4. The time from the first diagnosis to metastatic spread is indeed extremely variable. In our opinion this variability should be taken into account when assessing the risk/benefit of organ transplant from donors with a previous diagnosis of these tumors, since a long follow-up time do not ensure the absence of metastatic spread in these patients.

RE-REVIEWER

Specific Comments to Authors: Thank you for answering my questions, I have no new comments

Reply to Re-reviewer:

Thanks for your comments.

SCIENCE EDITOR

The authors systematically reviewed the literature on oligodendroglioma and astrocytomas with extraneural metastases to clarify the role of risk factors for tumor transmission, want

to help plan the clinical, imaging, and pathological assessment in this setting of donors, which is an interesting topic. The conclusions are also vague. Furthermore, systematic reviews and meta-analysis manuscripts should follow the PRISMA guidelines. However, the authors did not focus on the role of the recognized risk factors of tumor transmission via organ transplant. Guidelines for Manuscript Type and Related Ethics and Relevant Documents are available at: https://www.wjgnet.com/bpg/GerInfo/287.

Reply to the Science Editor:

Thank you for your recommendations.

The PRISMA flow diagram was already present in the supplementary material submitted (Appendix1). An image of the PRISMA flow diagram has been added to the PPT Figure file.

The systematic review showed that extraneural spreading of primary oligodendrogliomas and lower grade astrocytic tumours can be a late event and the most common affected sites were the skeleton and the cervical lymph nodes, therefore a tailored imaging protocol in donors who died after several years from the first diagnosis could help in the process of risk assessment. Furthermore, seven patients with astrocytic tumours developed metastases without undergoing surgery, chemo-radiotherapy o shunt placement. It is also noticeable how patients with multiple intra-CNS recurrences/metastases developed extraneural metastases after a significantly longer time compared to patients who did not show sings of recurrence. A possible explanation could be found in the lower biological aggressiveness of some tumours, that never acquired a metastatic potential, even after many procedures determining a disruption of the blood brain barrier.

COMPANY EDITOR IN CHIEF

I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal

of Transplantation, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor. In order to respect and protect the author's intellectual property rights and prevent others from misappropriating figures without the author's authorization or abusing figures without indicating the source, we will indicate the author's copyright for figures originally generated by the author, and if the author has used a figure published elsewhere or that is copyrighted, the author needs to be authorized by the previous publisher or the copyright holder and/or indicate the reference source and copyrights. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022. Authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content. Please add a figure of PRISMA.

We thank the Editor for the comments.
PRISMA flow diagram has been previously provided as PDF in the supplementary material and it has been now added as image in the Figure File.
We also added the copyright information under Figure 1 and Figure 2 as required
Tables have been checked to meet the required formatting standards.

Sincerely,

Serena Ammendola