| **Section and Topic** | **Item #** | **Checklist item** | **Location where item is reported** |
| --- | --- | --- | --- |
| **TITLE** | | |  |
| Title | 1 | Identify the report as a literature review. | Donors with gliomas. Systematic review on risk factors of extraneural spreading in astrocytomas and oligodendrogliomas |
| **ABSTRACT** | | |  |
| Abstract | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings.  See the [PRISMA 2020 for Abstracts checklist](http://www.prisma-statement.org/Extensions/Abstracts.aspx) for the complete list. | Background  Patients with a history of primary brain tumours can be eligible for organ donation under extended criteria. The risk assessment of tumour transmission via organ transplant in primary brain tumours is primarily based on the assessment of tumour histotype and grade. Previous surgeries, chemo-/radiotherapy and ventriculo-peritonal shunt placement can lead to a disruption of the blood-brain barrier, concurring to an increase in the transmission risk.  Aim  To investigate the role of tumour transmission risk factors in donors with oligodendrogliomas and astrocytomas.  Methods  We searched PubMed and EMBASE databases for studies reporting extraneural spreading of oligodendrogliomas and astrocytomas and extracted clinical-pathological data on the primary tumour histotype and grade, the elapsed time from the diagnosis to the onset of metastases, sites and number of metastases, prior surgeries, prior radiotherapy and/or chemotherapy, ventriculo-atrial or ventriculo-peritoneal shunt placement, the presence of IDH1/2 mutation and 1p/19q codeletion. Statistical analysis was performed using R software. Statistical correlation between chemotherapy or radiotherapy and the presence of multiple extra-CNS metastases was analysed using Chi-squared and Fischer exact test. The Kaplan-Meier method was used to evaluate the presence of a correlation between the metastasis-free time and i) localization of metastases, ii) the occurrence of intracranial recurrences and iii) the occurrence of multiple metastases.  Results  Data on a total of 160 patients were retrieved. The time from the initial diagnosis to metastatic spread ranged from 0 to 325 months in patients with oligodendrogliomas and 0 to 267 months in those with astrocytomas.  Respectively, 19% and 39% of patients with oligodendroglioma and astrocytoma did not receive any adjuvant therapy. The most frequent metastatic sites were bone, bone marrow and lymph nodes. The lungs and the liver were the most commonly involved visceral sites. There was no significant correlation between the occurrence of multiple metastases and the administration of adjuvant chemo-/radiotherapy. Patients who developed intracranial-recurrences/ metastases had a significantly longer extraneural metastasis-free time compared to those who developed extraneural metastases in the absence of any intra-central nervous system spread.  Conclusions  A long follow-up time does not exclude the presence of extraneural metastases, therefore targeted imaging of bones and cervical lymph nodes may improve safety in the management of these donors. |
| **INTRODUCTION** | | |  |
| Rationale | 3 | Describe the rationale for the review in the context of existing knowledge, i.e., what is already known about your topic. | Organs from donors with a history of a primary brain tumour (PBT) may be considered eligible for transplantation under extended criteria, since these tumours have a low propensity to metastasize outside the central nervous system (CNS). Noteworthy, these patients represent a relevant subgroup of donors that can increase the number of transplants performed, reducing times on the waiting list |
| Objectives | 4 | Provide an explicit statement of the objective(s) or question(s) the review addresses with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | In this study, we performed a systematic review of the literature on oligodendrogliomas and astrocytomas with extra-CNS metastases with the aim to identify clinical or pathological factors that can be helpful to predict the tumour transmission risk and guide decision making in organ transplantation from donors with these tumors. |
| **METHODS** | | |  |
| Eligibility criteria | 5 | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses with study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | Inclusion criteria and data extraction  The full texts of the articles fulfilling the initial screening criteria were retrieved and reviewed (Supplementary material, Appendix 2); disagreement was resolved via consensus. Inclusion criteria were: case reports, case series and literature review reporting 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 (Table 1; Supplementary material, Appendix 2). We included articles mentioning different tumour histotypes only if findings of each case were further detailed. 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. Finally, from the included articles we extracted data on: author and publication year, country, type of paper, sex and age of the patients at metastatic spread, tumour histotype and grade, synchronous or metachronous malignancies, intracranial recurrence, intra-axial spreading, tumour progression, time between the diagnosis and the onset of metastases, sites and number of metastases, tumour progression of the primary neoplasm preceding extracranial extra-CNS spread, prior surgeries, prior radiotherapy and/or chemotherapy, ventriculo-atrial or ventriculo-peritoneal shunt placement, IDH1/2 mutation and 1p/19q codeletion in both the primary and metastatic tumours. |
| Information sources | 6 | Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted. | A literature search without language restrictions was carried out in the electronic databases MEDLINE-PubMed and EMBASE until December 2020. The search terms were: “oligodendroglioma”, “anaplastic oligodendroglioma”, “astrocytoma”, “anaplastic astrocytoma” “oligodendroglial tumours”, “diffuse glioma” “extracranial metastasis” “oligodendroglioma metastatic to”, “astrocytoma metastatic to”, “extraneural metastases” “primary brain tumours”, “metastatic oligodendroglioma”, “metastatic astrocytoma”. Screening of article titles and abstracts was independently performed by three investigators using Rayyan QCRI reference manager web application[20]. |
| Search strategy | 7 | Present the full search strategies for all databases, registers and websites, including any filters and limits used. | See PRISMA FLOW DIAGRAM |
| Selection process | 8 | State the process for selecting studies (i.e., screening, eligibility).  Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process. | Articles with limited data were included if they at least reported the histologic diagnosis of primary and metastatic tumours (Table 1; Supplementary material, Appendix 2). We included articles mentioning different tumour histotypes only if findings of each case were further detailed. 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. |
| Study risk of bias assessment | 11 | Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process. | Screening of article titles and abstracts was independently performed by three investigators using Rayyan QCRI reference manager web application[20]. |
| **RESULTS** | | |  |
| Study selection | 16a | Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram. | The results are summarized in Table 1 and detailed in Appendix 2 of Supplementary material. A total of 2675 articles were identified after duplicates removal. After an initial screening on titles and abstracts, we considered 267 articles as potentially relevant to our study. |
| 16b | Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded. | We excluded 3 articles with unavailable full text and 83 reporting only intracranial or spinal drop metastases, 51 articles were excluded due to language restrictions |
| Study characteristics | 17 | Cite each included study and present its characteristics (e.g., study size, PICOS, follow-up period). | The 130 articles included were case series, case reports and literature review articles reporting data on a total of 90 patients (52 males, 32 females and 6 with undisclosed sex) with extra-CNS metastases from oligodendroglial tumours and 67 patients with extra-CNS metastatic astrocytoma (39 males, 27 females and 1 with undisclosed sex) |
| Risk of bias in studies | 18 | Present assessments of risk of bias for each included study. | It should be noted, indeed, that most of the articles included in this review were published before the 2016 update of the WHO classification of CNS tumours, and do not always include data on 1p19q codeletion and IDH1/2 mutations |
| Results of individual studies | 19 | For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots. | See supplementary material Appendix 2 |
| **DISCUSSION** | | |  |
| Discussion | 23a | Provide a general interpretation of the results in the context of other evidence. | Basing on the present review, extra-CNS metastases of these tumour entities may occur, indipendently from the grade of the primary neoplasm. Indeed, the reported cases of extra-CNS metastases were roughly similar in lower and higher grade oligodendrogliomas.  According to this literature review, while the extraneural spread of PBT appears to be an earlier event in astrocytic tumours, in oligodendrogliomas it can occur after more than 10 years from the primary diagnosis in a non-negligible number of patients. Indeed, the interval between diagnosis and metastatic spread varied widely among patients and many of them underwent multiple treatments that have possibly interfered with the natural history of the tumour[25], therefore the possibility of metastatic spread even after many years should be carefully considered when selecting eligible donors for organ transplantation. |
| 23b | Discuss any limitations of the evidence included in the review. | …the reported cases of extra-CNS metastases were roughly similar in lower and higher grade oligodendrogliomas. This distinction appears to be less sharp taking into account extraneural metastases from astrocytomas, since in many articles the tumour grade is not specified, while terms such “low grade”, “aggressive” or “malignant” are used as substitutes of the grading system. Indeed, it should be noted that the criteria for tumour grading changed substantially over the past decades. As an example, the tumour reported by James and Pagel in 1951[21] as oligodendroglioma, showed areas of necrosis and moderately conspicuous mitotic activity, which are nowadays considered diagnostic criteria of a higher grade oligodendroglioma. These limitations are partly shared by many transplantation registries data, whose reports cover a wide timespan, and, in the past, were often incomplete, not providing data on donors’ tumour histotype[22] or the interval between performed treatments and donation[23] |
| 23c | Discuss any limitations of the review processes used. | The present review has several limitations: firstly we did not include in the literature search articles reporting extracranial metastases from primary glioblastomas, currently classified as grade IV tumours according to the WHO[18]; moreover, the selected literature covers a wide timespan and inevitably, the changes in the classification of tumour entities and in grading systems represent a limitation to every systematic review on this topic. |
| 23d | Discuss implications of the results for practice, policy, and future research. | In conclusion, despite the relatively low propensity to metastasize outside the central nervous system of oligodendrogliomas and astrocytomas, findings in this review confirm the theoretical possibility of tumour transmission when transplanting organs from these donors and that a long interval between tumour diagnosis and donor’s death does not exclude the possibility of metastases. Tumour grade does not seem to be the main feature influencing the metastatic potential, with the caveat that recent diagnostic advances may add useful information in the future. Kidneys and hearts seem to be relatively resistant to metastases, compared with lungs and livers. Finally, we suggest that imaging of the skeleton and cervical lymph nodes could be helpful to identify metastatic disease in donors with a past or present history of these gliomas. |
| **OTHER INFORMATION** | | |  |
| Registration and protocol | 24a | Provide registration information for the review, including register name and registration number, or state that the review was not registered. | Not pertinent |
| 24b | Indicate where the review protocol can be accessed, or state that a protocol was not prepared. | Not pertinent |
| 24c | Describe and explain any amendments to information provided at registration or in the protocol. | Not pertinent |
| Support | 25 | Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review. | Not pertinent |
| Competing interests | 26 | Declare any competing interests of review authors. | No competing interest to declare |
| Availability of data, code, and other materials | 27 | Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review. | A literature search without language restrictions was carried out in the electronic databases MEDLINE-PubMed and EMBASE until December 2020. |