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Risk factors of extraneural spreading in astrocytomas and oligodendrogliomas in donors with gliomas: A systematic review

Ammendola S *et al*. Tumor transmission risk factors in gliomas

Abstract

BACKGROUND

Patients with a history of primary brain tumors (PBTs) can be eligible for organ donation under extended criteria. The risk assessment of tumor transmission *via* organ transplant in PBTs is primarily based on the assessment of tumor histotype and grade. Previous surgeries, chemo-/radiotherapy and ventriculo-peritoneal (VP) 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 tumor 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 tumor 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 VP shunt placement, the presence of isocitrate dehydrogenase 1/2 mutation and 1p/19q codeletion. Statistical analysis was performed using R software. Statistical correlation between chemotherapy or radiotherapy and the presence of multiple extra-central nervous system (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: (1) Localization of metastases; (2) The occurrence of intracranial recurrences; and (3) The occurrence of multiple metastases.

RESULTS

Data on a total of 157 patients were retrieved. The time from the initial diagnosis to metastatic spread ranged from 0 to 325 mo in patients with oligodendrogliomas and 0 to 267 mo 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-CNS spread.

CONCLUSION

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.

Key Words: Metastatic gliomas; Extra-central nervous system metastases; Tumor transmission; Expanded donor; Risk factors; Transplantation

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Core Tip: Recognized risk factors of tumor transmission from donors with a history of primary brain tumors are previous surgery, chemotherapy and radiotherapy. We performed a systematic review of the literature on oligodendroglioma and astrocytomas with extraneural metastases, aiming to clarify the role of tumor transmission risk

factors. We searched PubMed and EMBASE databases for studies reporting extraneural spreading of these gliomas. Performed treatments do not seem to impact on the timing of metastatic spread and a long follow-up time does not exclude extraneural spread. Targeted imaging of bones and cervical lymph nodes may improve safety in the management of these donors.

INTRODUCTION

The transplant community has been struggling with the chronic shortage of donor's organs for transplantation. In order to increase the donor pool, criteria for donation have been expanded[1,2], accepting as donors also individuals with a history of malignancies of low metastatic potential. However, transplantation from these donors carries a risk of cancer transmission[1-4], that should be carefully assessed for each tumour type.

Organs from donors with a history of a primary brain tumor (PBT) may be considered eligible for transplantation under extended criteria, since these tumors 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[5]. According to the 7th edition of the guidelines on quality and safety of organ transplantation, the risk of transmission for patients with a history of PBT is mainly influenced by the tumor histotype and grade[6]. The risk of tumor transmission in donors with a history of CNS tumors is graded as minimal, low to intermediate, high or unacceptable; in detail, donors with World Health Organization (WHO) grade I and II PBTs are considered at minimal risk of tumor transmission, while grade III tumors are now considered at low to intermediate risk in the absence of any recognized risk factors, such as previous surgical resections, ventriculo-peritoneal (VP) or ventriculo-atrial shunt placement and/or chemotherapy/radiotherapy that increase the risk from intermediate to high[6]. These procedures disrupt the blood-brain barrier, increasing the risk of hematogenous and lymphovascular spread of these tumors[7]. Extra-CNS metastases from PBTs do

however occur, with a reported prevalence of up to 4.3%[7] and metastasization mainly occurs in patients with a history of high-grade gliomas and, in particular, of glioblastoma[8-10]. Ventriculo-atrial and VP shunts have also been reported as risk factors for tumor spread[11].

However, the studies on BPT transmission after solid organ transplantation often include limited data on the tumor histological features and the patients' clinical management[9-11,13]. In the United Network for Organ Sharing registry, among 642 patients who received organs from a donor with a PBT, three died due to the transmission of a glioblastoma[8,13]. However, no cases of transmission were reported among 96 recipients in the Australian and New Zealand Organ Donation Registry[14], in 89 and 448 recipients from the Czech Republic[15] and United Kingdom registries[16]. More recently, Lee *et al*[17] reported that none of 87 transplant recipients had tumor transmission from 28 donors with PBTs.

To date, there are no reports of transmission of oligodendroglioma to organ transplant recipients, while donor-to-recipient transmission of grade III/IV astrocytic tumors[6] have been previously reported. Though, the metastatic potential of this tumors in the context of transplantation needs to be clarified and kept up-to-date. Oligodendrogliomas are CNS diffuse gliomas mainly occurring in the adulthood, with a peak incidence in the fourth and fifth decade and a slight male predominance (1.3:1), preferentially arising in the cerebral hemispheres, and mostly in the frontal lobe[18]. According to the WHO, oligodendroglioma is defined by the co-occurrence of isocitrate dehydrogenase 1/2 (IDH1/2) mutation and chromosome 1p/19q whole arm codeletion, and classified into grade II and grade III (anaplastic oligodendrogliomas), based on the presence of histologic features of anaplasia, such as microvascular proliferation and/or brisk mitotic activity[18].

Tumors of astrocytic lineage, contrary to oligodendrogliomas, have a four-tiered grading system, that encompasses a wide spectrum of clinical entities, from grade I tumors, characterized by a benign clinical course, to grade IV tumors, carrying a dismal prognosis[18]. About 5% of all PBTs with extra-CNS metastatic spread are reported to be

oligodendrogliomas, while astrocytomas account for about 10% of extraneural metastatic PBTs[19]. However, data on extraneural metastatic spread mostly come from case reports or small case series, and there is no systematic appraisal of the risk factors or patterns of metastasization.

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 tumor transmission risk and guide decision making in organ transplantation from donors with these tumors.

MATERIALS AND METHODS

Search strategy

This literature review was performed in accordance with the PRISMA. 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].

Inclusion criteria and data extraction

The full texts of the articles fulfilling the initial screening criteria were retrieved and reviewed (Supplementary Table 1); 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 tumors (Table 1; Supplementary Table 1). We

included articles mentioning different tumor 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, tumor histotype and grade, synchronous or metachronous malignancies, intracranial recurrence, intra-axial spreading, tumor progression, time between the diagnosis and the onset of metastases, sites and number of metastases, tumor progression of the primary neoplasm preceding extracranial extra-CNS spread, prior surgeries, prior radiotherapy and/or chemotherapy, ventriculo-atrial or VP shunt placement, IDH1/2 mutation and 1p/19q codeletion in both the primary and metastatic tumors.

Statistical analysis

Statistical analysis was performed using open-source software R 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria) with RStudio 1.4.1106 environment (RStudio Inc, Boston, Massachusetts, United States). The statistical correlation between chemotherapy or radiotherapy and the presence of multiple extra-CNS metastases was analysed using Chi2 and Fischer exact test. Kaplan-Meyer method was used to investigate the correlation between metastasis-free time and metastatic sites, presence/absence of intracranial recurrence and the occurrence of multiple metastases. A probability (*P*) value less than 0.05 was considered statistically significant. No institutional review board approval was needed, as no ethical issue is raised by literature reviews.

RESULTS

The results are summarized in Table 1 and detailed in Supplementary Table 1. 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. 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. A PRISMA flow diagram of the literature screening and article exclusion is shown in Figure 1.

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 tumors and 67 patients with extra-CNS metastatic astrocytoma (39 males, 27 females and 1 with undisclosed sex) (Table 1; Supplementary Table 1). Age at metastatic spread ranged between 1.5 to 74 years (mean 44.7; median 46) in patients with oligodendrogliomas and between 8 mo and 84 years (mean 31.3; median 26) in patients with astrocytoma.

Among patients with metastatic oligodendrogliomas, 11 (12%) progressed from grade II to III in the intracranial relapse or in the metastasis and 1 anaplastic oligodendroglioma recurred as a secondary glioblastoma; two cases diagnosed as oligoastrocytomas at the initial diagnosis were reported as oligodendrogliomas at recurrence. Twenty-one astrocytic tumors also displayed tumor progression and 15 patients received a diagnosis of secondary glioblastoma at the time of recurrence or at microscopic evaluation of the metastasis. Time from the initial diagnosis to metastatic spread of oligodendrogliomas ranged from 0 to 325 mo (mean: 54; median: 36) and from 0 to 276 mo for astrocytic tumors 0 to 276 mo (mean: 31; median: 13) (Table 1). One patient with oligodendroglioma and 10 patients with astrocytic tumors were found with extraneural metastatic disease at the time of the first diagnosis. Two patients with oligodendroglioma and 8 patients with astrocytic tumors did not undergo any surgical resection before metastatic spread; in 7 cases a diagnostic stereotactic biopsy was performed without open craniotomy; the remaining cases received an autoptic diagnosis. Sixty-three (70%) patients with oligodendroglioma and 51 (76%) patients with astrocytoma received radiation therapy, chemotherapy or both before metastases occurred, while 12 patients with oligodendroglioma and 8 with astrocytoma did not receive any adjuvant therapy. Twenty patients with astrocytoma underwent VP shunt

placement, while among patients with oligodendroglioma, only three required VP shunt placement. Forty-three patients with oligodendroglioma (48%) and 37 patients with astrocytomas (55%) had at least one intracranial recurrence and/or intra-CNS metastatic disease, before extra-CNS metastases. Among oligodendrogliomas, metastases were mainly localized at the bone ($n = 48$), bone marrow ($n = 30$) and lymph nodes ($n = 27$), with cervical stations being the most affected ($n = 16$). Metastases to the scalp were present in 8 cases. The most common visceral metastatic sites were the lung ($n = 10$), liver ($n = 8$) and pleural cavity ($n = 5$). Kidneys were always spared (Table 1). The most common extra-CNS metastatic sites of astrocytoma were instead bone ($n = 30$) and lymph nodes ($n = 24$) and in more than half cases the cervical nodal stations were affected ($n = 14$). The scalp was involved in 8 cases and the soft tissues in 11 cases. Visceral metastases were localized to the lungs ($n = 11$), liver ($n = 8$) and to the kidney ($n = 3$) (Table 1).

There was a significantly shorter metastasis-free time in patients with astrocytoma than in those with oligodendrogliomas ($P = 0.016$) and median time from the diagnosis of the primary tumor to metastatic spread was 36 mo [confidence interval (CI): 29-48] in patients with oligodendroglioma and 13 mo in patients with astrocytic tumors (CI: 15-41) (Figure 2). There was no significant correlation between timing of metastatic spread and metastatic sites (bone and lymph nodes *vs* visceral metastases) for both oligodendrogliomas ($P = 0.98$) and astrocytomas ($P = 0.93$).

Considering: (1) Surgical procedures; (2) Radiotherapy/chemotherapy; and (3) VP shunt as risk factors for extracranial metastasization, in the astrocytoma cohort, 7 patients had extra-CNS metastases without any recognized risk factor, 6 patients displayed only one risk factor, 29 of them had 2 risk factors, and only three patients received all the above-mentioned treatments. All patients with metastatic oligodendroglioma had instead at least one risk factor for extracranial metastasization.

Patients with intracranial recurrence or intra-CNS dissemination of oligodendroglioma had a significantly longer free-time interval before extra-CNS metastatic spread (median: 59.8 mo; CI: 36-84) than those who had no local recurrences

(median: 24 mo; CI: 9-37) (P = 0.014) (Figure 3). The same correlation is present when considering patients with astrocytomas: There is indeed a significant correlation between the presence of intracranial metastasization and a longer time of metastasization (P = 0.04) (Figure 3).

DISCUSSION

In this study, we reviewed the literature on oligodendrogliomas and astrocytomas with extra-CNS metastases. Basing on the present review, extra-CNS metastases of these tumor entities may occur, independently from the grade of the primary neoplasm. Indeed, 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 tumor 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 tumor grading changed substantially over the past decades. As an example, the tumor 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' tumor histotype[22] or the interval between performed treatments and donation[23]. Noteworthy, according to the Disease Transmission Advisory Committee, recurrence-free survival can be used as a surrogate for transmission risk and donors with a history of neoplasm diagnosed 5 or more years earlier and with a probability of cure of > 99% are considered at low risk for tumor transmission, while neoplasms with a probability of cure between 90% and 99% are considered at intermediate risk of transmission[24].

According to this literature review, while the extraneural spread of PBT appears to be an earlier event in astrocytic tumors, 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 tumor[25], therefore the possibility of metastatic spread even after many years should be carefully considered when selecting eligible donors for organ transplantation. In the light of these findings, taking into account that diffuse gliomas preferentially metastasize to the bone and cervical lymph nodes, we suggest that protocols for potential donors with a present or past history of oligodendroglioma should include ultrasound imaging of the head and neck and/or computerized tomographic scan of the skeleton. A minority of patients also had metastases in transplantable organs such as lungs, liver and pancreas while metastases to kidney and heart were not reported in oligodendrogliomas, suggesting that these organs are relatively spared from metastatic spread. This is in accordance with two studies on donors with glioblastoma which described a better outcome in recipients of kidneys than in those with lung or liver grafts[9] and worse outcomes in patients with liver metastases compared to those with other extracranial metastatic sites[26].

Of note, patients with intracranial tumor relapse had a significantly longer interval between the initial diagnosis and the metastatic spread. Additionally, we found that patients who had multiple surgeries for intra-CNS relapses or metastases developed extra-CNS disease after a longer time interval than those who had a single surgery. We may speculate that patients with intra-cranial relapses or metastases have tumors with a lower biological aggressiveness, and that acquire "visceral" metastatic potential only in a later stage. 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 tumors according to the WHO[18]; moreover, the selected literature covers a wide timespan and inevitably, the changes in the classification of tumor entities and in grading systems represent a limitation to every systematic review on this topic. 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 tumors, and do not always include data on 1p19q codeletion and IDH1/2 mutations[18].

CONCLUSION

In conclusion, despite the relatively low propensity to metastasize outside the CNS of oligodendrogliomas and astrocytomas, findings in this review confirm the theoretical possibility of tumor transmission when transplanting organs from these donors and that a long interval between tumor diagnosis and donor's death does not exclude the possibility of metastases. Tumor 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.

ARTICLE HIGHLIGHTS

Research background

Under extended criteria, patients with a history of primary brain tumor can be eligible for organ donation. Tumor histotype and tumor grade are considered the main risk factors of tumor transmission and previous surgeries, chemo-/radiotherapy and ventriculo-peritoneal (VP) shunt placement concur to increase the transmission risk.

Research motivation

Most of the literature on the extraneural metastatic spread of diffuse gliomas is based on case reports and case series and there is a lack of systematic appraisal of patterns of metastasization and on factors concurring to increase the risk of extraneural spreading.

Research objectives

We aimed to collect and analyse the existing literature on extraneural spreading of oligodendroglial and astrocytic tumors in order to identify clinical or pathological factors that could help clinicians to assess the risk of tumor transmission from donors with a history of these gliomas and guide decision making in organ transplantation.

Research methods

We performed a systematic review of the literature in accordance with the PRISMA guidelines. A literature search without language restrictions was performed in the electronic databases MEDLINE-PubMed and EMBASE, searching for articles, case reports and case series reporting data on extra-central nervous system metastases of oligodendrogliomas and astrocytomas.

Research results

Elapsed time from the initial diagnosis to metastatic spread ranged from 0 to 325 mo and from 0 to 276 mo for oligodendrogliomas and astrocytic tumors, respectively. The most common metastatic sites were bone and lymph nodes for both tumors, while the most common visceral sites were the lungs and the liver in patients with oligodendrogliomas and lungs, liver and kidneys in patients with astrocytomas. Among patients with astrocytomas, 7 did not undergo surgery, chemo-radiotherapy or VP shunt placement before the onset of metastases.

Research conclusions

A long interval between the tumor diagnosis and the donor's death does not exclude the possibility of extraneural spreading of these tumors. Bone and lymphnodes are the most common metastatic sites, the lungs and the liver are instead the preferential visceral sites of metastatic spread. Follow-up imaging of the skeleton and cervical lymph nodes could be useful to identify metastatic disease in donors with a history of these gliomas.

Research perspectives

The diagnostic advances made recently in tumor classification and targeted follow-up protocols could improve the knowledge on the factors involved in extraneural spreading of gliomas, with repercussions on the tumor transmission risk assessment of potential donors.

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