Short communication

Patients with Primary Brain Tumors as Organ Donors

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Abstract

Organ transplant is now the treatment of choice for many end-stage diseases. The success of solid organ transplantation is accompanied by a severe shortage of available organs for those currently awaiting transplantation. In recent years, there has been an increasing demand for organs, but not a similar increase in the supply leading to a severe shortage of organs for transplant that resulted in increasing waiting times for recipients. This has resulted in expanded donor criteria to include older donors and donors with mild diseases. Malignancy is considered a contra-indication to organ donation, with a few possible exceptions. There is a significant controversy in the transplant literature around the use of organs from donors with primary brain tumors (PBT). While case reports and registry data have certainly documented transmission of PBT with resultant morbidity and even mortality, the loss of quality and quantity of life by those on the waiting list remains a staggering and sobering reality. Ultimately the decision regarding transplantation from such donors lies with the transplanting team that should weigh the risk of donor tumor transmission against the risk of their patient dying on the waiting list.

Key words: organ donors, brain tumors, kidney transplantation

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Introduction

Organ transplant is now the treatment of choice for many end-stage diseases. The success of solid organ transplantation is accompanied by a severe shortage of available organs for those currently awaiting transplantation. In recent years, there has been an increasing demand for organs, but not a similar increase in the supply leading to a severe shortage of organs for transplant that resulted in increasing waiting times for recipients. Therefore, many programs have implemented the aggressive use of extended criteria donors. Consequently, this has resulted in expanded donor criteria to include older donors and

donors with mild diseases. But, recent data reported the discovery of hepatocellular carcinoma in a recipient who received an organ from a serologically positive donor with hepatitis. Furthermore, the use of donors up to 80 years of age will potentially increase the incidence of donor tumor transmission. Malignancy is now considered as a contraindication to solid organ donation, with a few possible exceptions. Malignancy after transplantation can occur in three different ways [1-4]:

- De-novo occurrence;
- Recurrence of malignancy;
- Donor-related malignancy.

Also, there is a potential for development of tumors in recipients due to transmission of oncogenic viruses like human papiloma virus (HPV), human T-lymphotropic virus (HTLV), hepatitis C virus (HCV), hepatitis B virus (HBV), human herpes virus 8 (HHV-8), Epstein-barr virus (EBV) and cytomegalovirus (CMV). The donor malignancy may have been indentified at the time of the organ procurement or may be identified after transplantation [1,2]. Malignant tumors can be transmitted to immunosuppressed patients when organs from donors with neoplastic disease are unknowingly or knowingly transplanted into recipients. But, the actual prevalence of donors with malignant neoplasms and the donor-recipient tumor transmission risk are not well-known. Although, there are some published data on tumor transmission, taking into account the high number of solid organ transplants performed, only a minimum percentage of graft recipients have developed a transmitted tumor disease [1,5]. For example, according to the ONT registry (Spain) the frequency of donors from 1990 until 2006 with an undetected tumors was 5.8 per thousand donors in the ONT registry. Of these donors, only 5 (2.9 per 10.000 donors) transmitted the tumor to the recipients. Only 10 recipients out of the 155 who received a graft from a donor with a tumor developed tumor transmission (6.4%) [6]. Furthermore, according to the Danish registry that studied a 27-year history of Danish transplant registry, 13 malignant tumors were found among 626 donors, of which eight were detected after the organs had been transplanted [7]. But, due to the

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potentially serious consequences, it is mandatory to carefully select all potential donors with the intention of avoiding the transmission of tumor disease. The number of expanded criteria donors (ECD) and especially of older donors has increased due to organ shortages. Actually, there is no age limit for organ donation, but only for organ-specific functional parameters. The rate of tumor occurrence in the donor population increases concomitantly with increasing donor age. Although transplant coordinators and members of transplant teams need guidelines to assist in the management of such complex situations, the treatment of each case will often require an individual approach [1-5].

Some general recommendations to follow in the donation process to prevent transmission of tumors are listed below. During the work-up of obtaining an organ, the complete clinical history of the donor should be recorded, taking into account several basic points:

- Records of any previously diagnosed tumors (or tumors removed without medical documentations of the definitive diagnosis).
- History of menstrual irregularities.
- Intra-cranial tumors or metastases should always be excluded in donors diagnosed with intra-cranial hemorrhage. This is especially important in the cases if no evidence of hypertension or arterio-venous malformation exists.
- If it is possible, the donor's general practitioner and family members should be contacted to provide detailed medical records.
- Standard laboratory investigations sholud be performed in all potential donors with the objective of detecting specific disease that may contra-indicate organ donation. Routine screening of tumor markers is not recommended.
- Abdominal ultrasound and chest-x rays must be carefully investigated, together with the complete clinical history and physical examination. Further imaging methods (e.g. CT-scans) may be necessary for thorough donor evaluation, especially in patients with suspected tumors. In donors with any history of tumor disease, CT-scans of the thorax and abdomen should be carried out to evaluate current disease status and to ensure the highest possible safety for organ recipients.
- During organ procurement, surgeons should examine all intra-thoracic and intra-abdominal organs in order to detect possible hidden tumors or pathological lymphadenopathies. Any suspect lesion must be investigated by a pathologist.
- If no precise histological diagnosis of a suspicious mass can be obtained, the donor should be excluded; although the final decision should be made on the basis of an individual risk-benefit analysis. Transplantation can only be performed in fully-informed recipients [1-5,8].

- According to these observations, the acceptance of organs from donors with tumors differs to a great extent throughout Europe. Countries with organ shortages, long waiting times and significant waiting list mortality are more likely to consider a donor with a malignancy as an acceptable risk than countries with a higher donor rate and shorter waiting times.

A particular problem in the donation process represent primary tumors of the central nervous system (CNS). Therefore, in the text below we will focus on this relatively controversial topic.

Primary tumors of the central nervous system

Approximately 17.500 primary CNS tumors occur annually in the United States, accounting for 1.4% of all tumors and 2.3% of cancer-related deaths [9]. As mentioned above, the use of organs from donors with other malignancy remains generally unacceptable. But, the use of organs from donors with primary tumors of the central nervous system (CNS), where the risk of spread outside the central nervous system, and hence the risk to transplant recipients, is low, remains an exception from this rule. There is a significant controversy in the transplant literature about the use of organs from donors with primary brain tumors. Organs from such donors have been used for transplantation over many years, on the basis that disease transmission was rare. But, according to the literature, there have been some data where transmission of malignancy has occurred from donors with primary malignancy of the central nervous system. The risk of extracranial metastasis of these tumors was recognized first, most commonly with high grade astrocytoma/glioblastoma, medulloblastoma, and ependymoma [10]. According to the Council of Europe guidelines, organs from donors with high-grade brain tumors should not be used because of the perceived high risk of cancer transmission, especially where the integrity of the blood brain barrier is compromised. Therefore, they should no longer be considered safe for transplantation. On the other hand, they stated that donors with low-grade malignant tumors should be used only in very special circumstances. Furthermore, donors with primary CNS tumors have historically been regarded as suitable, but cumulative data suggesting that aggressive intervenetions (craniotomy and ventricular shunting) and/or unfavorable histology (glioblastoma and medulloblastoma) may pose a prohibitive transmission risk has refined our practice over time. Furthermore, case reports of donor brain tumor transmission with transplant subsequently began to appear in the literature and have led to a reassessment of this donor [1-5,8].

In generally, primary tumors of CNS represent 3-4% of the causes of brain death of organ donors. Although CNS tumors rarely develop extra-cranial metastases, these have been described in 0.4-2.3% of cases. These metastases can develop in the lungs, pleura, lymphatic

glands, bone, liver, adrenal glands, kidneys, mediastinum, pancreas, thyroids and peritoneum. The tumors that most often produce extra-cranial metastasis are multiform glioblastoma, meduloblastoma and also ependymoma. Although aggressive interventions and prior derivations are the principal causes of dissemination of CNS tumors, there are cases of spontaneous dissemination to the cranial and cervical lymphatic glands, and even distant metastases [11,12].

According to the literature, the risk factors for transmission of primary CNS tumors are:

- High-grade malignancy tumors;
- The presence of ventriculo-peritoneal or ventriculo-atrial derivations;
- Previous chemotherapy;
- Previous radiotherapy;
- Previous craniotomy;
- Duration of disease may also be important [8,11,12].

According to the literature, the Australian and New Zealand Registry (ANZODR) reported 46/1.781 donors (2.6%) with PBT providing 153 organs. Of these donors, there were eight with a high-grade glioma and five with a medulloblastoma. They reported no cases of donor-derived malignancy at mean follow-up of 40 months [13]. Furthermore, according to the UNOS registry (USA) review from 2002 of 397 donors with a history of primary CNS tumors, from whom 1220 organs were transplanted and after the follow-up of 36-months, no tumor transmission to the recipient was observed. But, UNOS itself warns that some tumors, such as multi-forme glioblastoma (GBM) and medulo-

blastoma, can potentially have a high transmission risk and therefore donors presenting with a history of these tumors should not be used [14]. Furthermore, Israel Penn International Tumor Registry (IPITTR) (USA) states that, when there are no risk factors (listed above) the rate of transmission from donors with primary CNS tumors to organs recipients is 7%. But, if one or more risk factors are present, the rate of transmission to recipients rises to 36-43%. Also, they suggested that organs from donors with low-grade malignant or benign primary CNS tumors can be used for transplantation. Furthermore, donors that have one or more risk factors should be avoided as donor candidates or used only when there is a need for an emergency transplant [15]. On the other hand, the retrospective study of UK registry data has shown that none of the 177 donors with primary intracranial malignancy transmitted the malignnancy to the 448 recipients who received their organs. There were many donors with high-grade tumors, including 23 grade IV gliomas (glioblastoma multiforme) and 9 with medulloblastoma who provided organs for 85 traceable recipients [10]. In contrast to all reports, the IPITTR reported 36 donors with malignant primary brain tumors, including 31 with astrocytoma/GBM and three with medulloblastoma. Fourteen out of 62 recipients (23%) developed presumed donor derived tumor. Ten of the 14 recipients died from disseminated disease [16,17]. Because the denominator in this series remains unknown, it is difficult to interpret these results.

Histological classification of common primary central nervous system tumors is shown in Table 1 and 2.

Table 1. Histological classification of common primary central nervous system tumors

Cell of origin	Tumor type	Grade/tumor subtype
Glial	Oligodendroglioma	Grade 2: Low grade
		Grade 3: Anaplastic
	Astrocytoma	Grade 1: Pilocytic
		Grade 2: Low grade
		Grade 3: Anaplastic
		Grade 4: Glioblastoma variants; gliosarcoma and giant T-cell glioblastoma
	Mixed glioma	Grade 2 or 3 having features of both astrocytoma & oligodendroglioma differentiation
Neuronal	Medulloblastoma Neuroblastoma Esthesioneuroblastoma	

Table 2. Clinical grades of astrocyte gliomas and their histological criteria

Grade	Designation	Histological criteria
1	Pilocytic astrocytoma	Rosenthal fibers, piloid cells; no criteria
2	Diffuse astrocytoma	One criterion, usually nuclear atypia
3	Anaplastic astrocytoma	Two criteria, usually nuclear atypia and mitosis
4	Glioblastoma multiforme	Three or four criteria; the two above plus endothelial proliferation and/or necrosis

Meduloblastoma

Meduloblastoma represents 6% of all CNS gliomas and 44% of gliomas in children. Meduloblastoma metastazises more often in bones, bone marrow and lymphatic glands and less frequently in the lungs, pleura, liver and breast. Tumor transmission from organ donors with this type of tumor has been documented. Therefore, potential donors with medulloblastoma should not be considered for organ donation and should be used only in cases of life-threatening emergency transplants. In these cases, it is recommended that donors who have previously undergone craniotomies and/or peritoneal ventricular derivations are not used [8,15].

Gliomas

The incidence of extra-cranial glioma dissemination is from 0.4 to 2.3%, mainly in the lung, lymphatic glands, bone and liver. Astrocytomas are divided into low-grade tumors such as pilocytic astrocytomas (grade I) and diffuse astrocytomas (grade II); and malignant astrocytomas, namely anaplastic astrocytoma (grade III) and glioblastoma multiforme (grade IV) (Table 2) [18].
Low-grade astrocytomas often appear in young adults. They rarely metastazise, but up to 30% of low-grade astrocytomas may be associated with histological grades of greater malignancy. These tumors have a tendency to relapse and often present a higher grade of malignancy. Therefore, potential donors with low-grade astrocytomas may be considered for organ donation depending on the histological results of the tumor and local invasiveness. At least 80% of malignant gliomas are multiforme glioblastomas. Anaplastic astrocytomas appear more often in adults aged in their 30s and 40s, while GBM is more often present in adults aged in their 50s and 60s. Extracranial metastases of anaplastic astrocytomas and GBM have been reported even in the absence of prior surgery. Also, transmission of these tumors from donors has been reported. Therefore, potential donors with anaplastic astrocytomas and GBM should not be considered for organ donation. They could be used only in cases of life-threatening emergency transplant in which the recipient's risk of dying while on the waiting list is greater than the probability of tumor transmission. In such cases, donors with high risk of tumor transmission (prior surgical intervention) should not be used [8,18,19].

Oligodendrogliomas

These tumors represent 20% of gliomas. According to the histological type there are four types of oligodendrogliomas: low grade (Schmidt grades A and B) oligodendrogliomas and anaplastic (Schmidt grades C and D) oligodendrogliomas. Low grade tumors are the most frequent and typically appear in adults in their 20s and 30s. In most cases they present as spontaneous cerebral

hemorrhages. On the other hand, anaplastic forms of these tumors are very aggressive tumors and extracranial metastases of anaplastic oligodendrogliomas have been documented after surgical interventions. Therefore, potential donors with low grade oligodendroglioma could be considered for organ donation, while anaplastic forms should not be considered. They can be only used in cases of life-threatening emergency transplant in which the recipient's risk of dying while on the waiting list is greater than the probability of tumor transmission. In such cases, donors with high risk of tumor transmission (prior surgical intervention) should not be used [8].

Ependymomas

Ependymomas represent 6% of all CNS glioma. Their metastases are rare and the cases documented correspond to recurrent tumors or those treated with radiotherapy and/or chemotherapy. Therefore, donors with these tumors can be considered for organ donation [8,20].
Furthermore, it is important to note that the brain is also the site of secondary brain tumors, many of which may present as a spontaneous intra-cerebral hemorrhage with no evident primary tumor and at times can be diagnosed as a primary brain tumor without any available histology. Namely, studies have shown that a wrong diagnosis can be disastrous. For example, Buell *et al.* reported 42 organ recipients who received organs from 29 donors who were misdiagnosed to have a primary brain tumor. The most common diagnostic error was intracranial hemorrhage and CNS metastasis misdiagnosed as a primary brain tumor. Following transplantation, the donors were identified with melanoma, renal cell carcinoma, choriocarcinoma, sarcoma and Kaposi's sarcoma, and variable tumors. Therefore, beside a detailed history in such cases, it is important to perform additional imaging methods, frozen sections as well as various laboratory testing [1,21].

Final considerations

- Group I tumors do not contraindicate organ donation.
- Group II CNS tumors can be considered for organ donation when there is an absence of other risk factors.
- Group III tumors should not be considered for organ donation. They can be only used in cases of life-threatening emergency transplant in which the recipient's risk of dying while on the waiting list is greater than the probability of tumor transmission. In such cases, donors with a high risk of tumor transmission (prior surgical intervention) should not be used [8].

According to all of these observations, the available literature remains incomplete. In a perfect world without organ donor shortage, all extended criteria donors would be avoided as they carry an increased risk of graft failure and recipient death. But, in real life the members of

transplant community face the problems of long waiting lists and waiting list mortality. The current knoweldge of donor PBT transmission is incomplete and based on relatively small numbers. Some registry reports, such as UNOS and ANZODR are encouraging in documenting the absence of donor tumor transmission but may under-represent the risk because of incomplete registration. There remains a need for prospective studies which will help us to improve our understanding of real risk of tumor transmission, potential risk factors, and successful therapies for the recipients in the event of tumor transmission. Therefore, the transplant community remains uncertain about the role of PBT donors on the basis of variable practices. Ultimately, the decision regarding transplantation from such donors lies with the transplanting team that should weigh the risk of donor tumor transmission against the risk of their patient dying on the waiting list.

Conflict of interest statement. None declared.

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