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How Safe Is It to Transplant Organs from Deceased Donors with Primary Intracranial Malignancy? An Analysis of UK Registry Data

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Patients dying from primary intracranial malignancy are a potential source of organs for transplantation. However, a perceived risk of tumor transfer to the organ recipient has limited their use. We evaluated the risk of tumor transmission by reviewing the incidence in patients transplanted in the UK. Information from the UK Transplant Registry was combined with that from the national cancer registries of England, Wales and Northern Ireland to identify all organ donors between 1985 and 2001 inclusive with a primary intracranial malignancy and to identify the occurrence of post-transplant malignancy in the recipients of the organs transplanted. Of 11 799 organ donors in the study period, 179 were identified as having had a primary intracranial malignancy, including 33 with high-grade malignancy (24 grade IV gliomas and 9 medulloblastomas). A total of 448 recipients of 495 organs from 177 of these donors were identified. No transmission of donor intracranial malignancy occurred. Organs from patients dying from primary intracranial malignancy, including those with high-grade tumors, should be considered for transplantation and the small risk of tumor transmission should be balanced against the likely mortality for potential recipients who remain on the transplant waiting list.

Key words: Brain tumors, donor malignancy, neoplasms, organ donation, organ transplantation, tissue donors

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Introduction

Transmission of donor-related malignancy by organ transplantation is a well recognized and often fatal complication in immunosuppressed transplant recipients (1–4). As a result, organs from potential donors who have active or recently treated malignant disease are not normally considered suitable for transplantation, even when there is no evidence of metastasis. An important exception to this rule is the use of organs from donors with primary intracranial malignancy, where the risk of spread outside the central nervous system, and hence the risk to transplant recipients, is low. Organs from such donors have been used for transplantation over many years, on the basis that disease transmission was rare. However, there have been case reports of recipients where transmission of malignancy has occurred from donors with primary malignancy of the central nervous system. Since such cases typically involve high-grade malignant tumors in donors who have undergone interventions that compromise the blood brain barrier, a more selective policy for use of organs from donors with primary brain malignancy has emerged. Advice from the Council of Europe in 1997 stated that while the use of organs from donors with low-grade primary malignancy was safe, organs from potential donors with high-grade malignant tumors of the CNS, especially where the integrity of the blood brain barrier is compromised, should no longer be considered safe for transplantation (5). The evidence underpinning this view came from cancer registry data and case reports (6–8), both of which may overestimate the true incidence of disease transmission, and a recent analysis from the United States suggests that the incidence of disease transmission might be significantly lower than previously thought (9).

The shortage of donor organs available for transplantation is such that the risks of disease transmission by organs from a donor with primary CNS malignancy have to be balanced carefully against the risk of a potential recipient remaining on the waiting list for transplantation. At present in the UK, for example, around 1 in 5 patients awaiting lung or liver transplantation dies on the waiting list. Accordingly, a reliable estimate of the true risk of transmission of an intracranial malignancy is necessary to enable a balanced decision to be made regarding the risks to potential recipients.

In order to quantify the risk of transmission of a primary intracranial malignancy from an organ donor, we collated data held on the UK Transplant Registry on transplant recipients and organ donors together with information on new cancers held by the UK national cancer registries.

Materials and Methods

The UK Transplant Registry is maintained by National Health Service (NHS) Blood and Transplant. For the purpose of this study, demographic information on both donor and recipient for organ transplants undertaken between 1985 and 2001 inclusive, together with details of the organs transplanted were reviewed. The key demographic information required for linkage to the cancer registry data bases were the patient name, NHS number (a unique identifier for users of the NHS in the UK), date of birth, gender and post code. In 81% of cases, linkage was achieved on the basis of NHS number and in the remaining 19% by using other demographic information.

There are eight regional cancer registries in England, together with separate registries for Northern Ireland, Wales and Scotland, and all record the occurrence and type of every primary malignancy upon diagnosis (although some registries do not record data on basal cell carcinomas of the skin) and additional data such as patient death rate. For this analysis, information from the eight English and the Welsh and Northern Irish Registries were available for interrogation. Information from the Scottish registry was not obtainable and consequently data were not available on around 10% of UK organ donors or on recipients living in Scotland.

The Cancer Registries coded intracranial malignancy on the basis of available histology and/or other relevant information such as cross-sectional imaging according to the 10th World Health Organization International Classification of Disease (WHO ICD-10). For the purposes of reporting, we have mapped these diagnostic terms to the more commonly used clinical nomenclature.

Cancer registries in the UK are population-based and collect data from histopathology laboratories, radiotherapy, chemotherapy and surgical units and from multidisciplinary site-specific cancer team meetings, all of which submit data routinely in accordance with a central government directive. In addition, the Office of National Statistics submits copies of any death certificate mentioning a registrable neoplasm, and these are further investigated through hospital records, general practitioner notes and any other available data. UK cancer registries have estimated completeness of registration to be 94% for all malignancies excluding nonmelanoma skin cancer (10).

The strategy for data analysis was as follows (Figure 1). The records of all organ donors in the UK held on the UK Transplant Registry were identified and demographic information forwarded to each of the 10 participating cancer registries. The registries then processed the data to identify organ donors in whom a malignancy (current or previous) had been recorded. Using this information, all recipients of organs from donors with a history of malignancy were identified from the UK Transplant Registry data base, and their demographics were then transferred back to the cancer registries to identify the occurrence of recipient cancers up to and including 2006, giving a minimum follow-up period of 5 years for all transplant recipients.

Results

Demographic data from 11,799 deceased organ donors notified to the UK Transplant Registry between 1985 and 2001 were forwarded to the 10 participating UK cancer registries. For 5827 (49%) donors, a valid NHS number was recorded by the UK Transplant Registry allowing direct linkage to the cancer registry data, with the majority of the omissions being in the early part of the study period. A further 107 donors were identified by manually investigating each donor using the NHS Strategic Tracing Service. The majority of the donors where the NHS number was unavailable was from before 1990 and predated the NHSTS records.

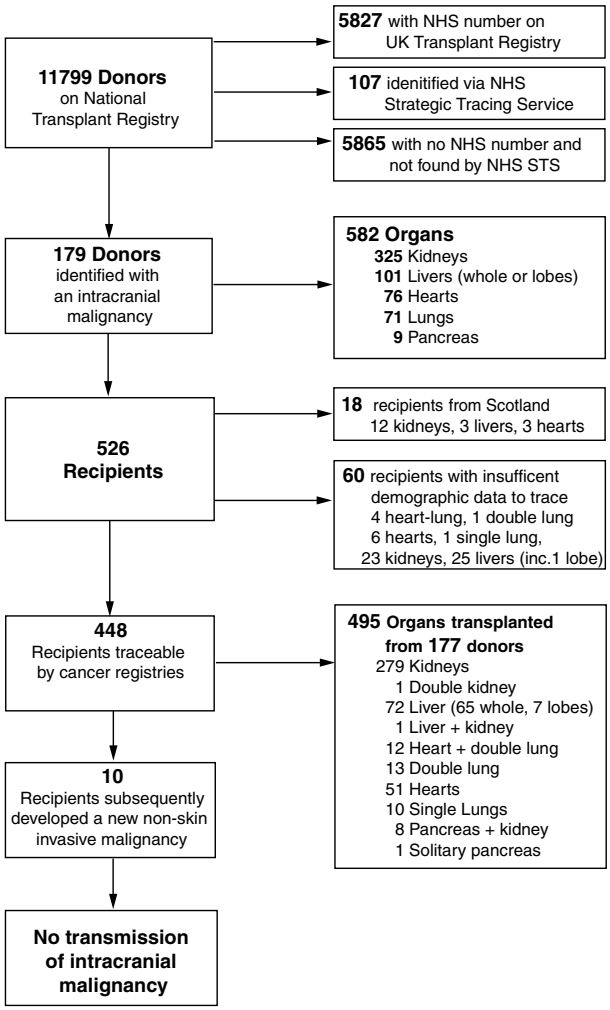

Figure 1: Flow chart for study.

From the resulting 5934 donors with the appropriate information to allow linkage to the cancer registries, 227 donors were identified as having at least one cancer, excluding those with a nonmelanoma skin cancer, benign tumor, *in situ* tumor and those where the histology was graded as 'borderline' for malignancy. Of the 227 donors who had an invasive malignancy, 179 had an intracranial cancer (Figure 1), from whom 582 organs were transplanted into

526 recipients, including 325 kidneys, 76 hearts, 71 lungs, 93 livers, 8 liver lobes and 9 pancreata. Twenty-four recipients received 2 organs (pancreas and kidney, liver and kidney, double lung or double kidney), and 16 received 3 organs (all heart and lung transplants).

Of the 526 recipients, data were available for 448 recipients who received 495 organs from 177 donors with primary intracranial malignancy; data were not available on any of the recipients of organs from two donors. Of the 78 recipients for whom data were not available, 18 (23%) of the recipients lived in Scotland for whom no cancer registry data were available. However, UK Transplant Registry data showed that, of the Scottish recipients, half were still alive with functioning grafts; 4 patients were alive but had lost their graft. Five patients had died, of which the cause of death was unknown in two, and was due to sepsis, rejection or posttransplant lymphoproliferative disease (PTLD) in the remaining three. The remaining 60 patients could not be identified either because there were insufficient demographic details or because they had no NHS number. NHS numbers for military personnel and prison inmates are withheld from cancer registries and numbers are not assigned to overseas residents.

Table 1 shows the nature of the intracranial cancers, and Table 2 the new cancers arising in the recipients following transplantation. The key observation was that there were no recorded cases of transmission of intracranial malignancy to any of the 448 transplant recipients whose data could be analyzed. Only 10 recipients were recorded as developing malignancy following transplantation, excluding those who developed primary skin cancers. As might be expected the most common type of malignancy, which occurred in 4 of the 448 (1%) recipients, was PTLD (Table 2).

Discussion

This retrospective study of UK registry data has shown that none of the 177 donors with primary intracranial malignancy transmitted the malignancy to the 448 recipients who received their organs. There were many donors with high-grade tumors, including 23 grade IV gliomas (glioblastoma multiforme, GBM) and 9 with medulloblastoma who provided organs for 85 traceable recipients. 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 (5). In addition, many donors with primary intracranial malignancy would have undergone interventions such as debulking surgery, radiotherapy and ventriculosystemic shunt placement, all of which breach the blood brain barrier and are potentially associated with systemic dissemination of tumor cells (11). Since the cancer registries did not record complete data on the treatment of intracranial tumors, we were unable to determine the proportion of donors in the data set who underwent such interventions.

The cancer registries classify tumors according to the WHO 10th ICD, and although data were not available on the mode of diagnosis of the tumor (stereotactic biopsy, craniotomy or autopsy) it is likely that in a small proportion of donors the diagnosis was made solely according to the appearance on cross-sectional imaging in the absence of corroborative histology, which carries a risk of both under- and overestimating the grade of intracranial malignancy. When histology was available the registries translated the reports to the appropriate ICD-10 code; the reports were not coded by the reporting pathologist and we have no data on whether the histological diagnosis was made before death or at autopsy.

The total number of potential organ donors in the UK who died from primary intracranial malignancy is uncertain, since following publication of the European Guidelines, many such potential donors would not have been considered suitable for organ donation (12). Equally difficult to quantify are the number of potential recipients who have died on the waiting list for lack of an organ that could have been provided by such a donor. What is clear is that guidelines such as those issued by the Council of Europe should not be taken in isolation, but the risk of disease transmission should be balanced against the risk of recipient death without a transplant, a risk that is ever more acute as the gap between the number of available organs and the number of potential recipients widens, in spite of recent initiatives to increase deceased donation rates (13).

Decision making about organ usage for transplantation is seldom straightforward, and has become less so in recent years (14). As the number of deceased organ donors diminishes, surgeons are forced to consider using organs from potential donors that would previously have been considered unsuitable, hence the renewed interest in donors with a history of intracranial malignancy. The data presented here are reassuring and in agreement with the only other large study, which is from the United Network for Organ Sharing in the United States and reported the outcome of 642 recipients of organs from donors with primary intracranial tumors (9). The series included 175 recipients where the donor tumor was a GBM and the only recorded transmission occurred to three recipients (1.7%) of organs from one donor with a GBM (15). In the donor concerned there was a 2-year interval from diagnosis to death; the only surgical intervention was a stereotactic biopsy; he had completed a course of whole brain irradiation, which was followed, 1 month later, by a fatal intracranial hemorrhage. Metastatic GBM was noted in a lymph node at the time of bilateral lung transplantation (15); it was also transferred to the recipients of the liver and one kidney. This particular case also emphasizes the need for the implanting surgeons to immediately notify the surgeons responsible for

Table 1: Types of intracranial malignancy identified in organ donors according to their international classification of disease (ICD)-10 classification. The table details the cancers as recorded by the registries according to the ICD-10 codes. The more common nomenclature and usage of the ICD-10 terms are given along side. The time between diagnosis of the cancer and death of the donor are detailed, with most tumors occurring within a month of death. Finally, the organs donated from donors with each type of malignancy are listed

ICD-10 morphology code	Classification of tumor by cancer registries according to WHO ICD-10 codes	Usage of code	Total number of		Timing of diagnosis in donor prior to death				Organs used where recipients were traceable					
			Donors	Traceable recipients	≤30 days	31 days to 1 year	1 to 3 years	>3 years	Heart	Lungs	Kidney	Liver/ lobes	Pancreas	Total
Tumors of astrocytes														
9400	Astrocytoma	Code used for astrocytomas, not otherwise specified (grade I, II or III)	43	110	21[1]	13	6	3	18	18	67	19	3	125
9421	Pilocytic astrocytoma	Pilocytic astrocytoma (grade I)	2	6	1	–	1	–	–	–	4	2	–	6
9411	Gemistocytic astrocytoma	Gemistocytic astrocytoma (grade II)	2	5	1	–	1	–	1	2	4	–	–	7
9420	Fibrillary astrocytoma	Fibrillary astrocytoma (grade II)	4	13	–	–	1	3	2	2	8	1	–	13
9381	Gliomatosis cerebri	Gliomatosis cerebri (grade III)	1	3	1	–	–	–	1	–	2	1	–	4
9440	Glioblastoma	Glioblastoma (grade IV)	23	54	18	2	3	–	7	8	37	7	–	59
9441	Giant Cell glioblastoma	Giant cell glioblastoma (grade IV)	1	3	1	–	–	–	–	–	2	1	–	3
Tumors of oligodendrocytes														
9450 & 9451	Oligodendroglioma	Oligodendroglioma (grade II) or anaplastic oligo-dendroglioma (grade III)	8	17	1	2	2	3	1	–	12	4	–	17
Ependymal tumors														
9391	Ependymoma	Ependymoma (grade II)	2	5	2	–	–	–	–	–	4	1	1	6
Nonspecific or mixed glial tumors														

Continued.

Table 1: Continued.

ICD-10 morphology code	Classification of tumor by cancer registries according to WHO ICD-10 codes	Usage of code	Total number of		Timing of diagnosis in donor prior to death				Organs used where recipients were traceable					
			Donors	Traceable recipients	≤30 days	31 days to 1 year	1 to 3 years	>3 years	Heart	Lungs	Kidney	Liver/ lobes	Pancreas	Total
9380	Glioma malignant	General code used for glial tumors, not otherwise specified—may include glioblastomas (grade IV) or astrocytomas (grade I, II or III)	34	74	24	3[2]	2	5	10	2	54	8	1	75
9382	Mixed glioma	Oligoastrocytoma (grade II) or anaplastic oligoastrocy-toma (grade III)	2	6	1	–	–	1	2	2	4	1	–	9
Tumors of meninges														
9530	Meningioma malignant	Meningiomas (grade I, II or III)	5	13	4	–	–	1	1	–	7	5	–	13
Primitive neuroectodermal tumors														
9470	Medulloblastoma	Medulloblastoma (grade IV)	9	21	8	–	–	1	4	4	14	3	1	26
9260	Ewing's sarcoma		1	2	1	–	–	–	–	–	2	–	–	2
9473	Primitive neuroec-todermal tumor		2	7	2	–	–	–	1	2	4	1	1	9
9362	Pineoblastoma	Pineoblastoma (grade IV)	1	1	1	–	–	–	–	–	2	–	–	2
Others														
8000, 8001, 8010, 8140, 9990	Neoplasm malignant	Codes used when no specific morphology identified	35	105	30	3	–	2	15	20	62	19	–	116
9084	Dermoid cyst with malignant transformation	Teratoma with malignant transformation	1	1	1	–	–	–	–	–	1	–	–	1
9161	Haemangioblastoma	Haemangioblastoma (grade I)	1	2	1	–	–	–	–	–	2	–	–	2
Totals			177	448					63	60	292	73	7	495

[1] Previous tumor diagnosed 4342 days earlier.
[2] Previous tumor 3955 days earlier.

Table 2: Nature and occurrence of nonskin malignancy[1] following transplantation in recipients of organs from donors with a history of intracranial malignancy

Recipient cancer		Time (days) to diagnosis of recipient cancer posttransplant	Donor cancer type	Time of donor cancer diagnosis prior to death	Organ transplanted
Cancer type	ICD-10 morphology code				
Non-Hodgkin's lymphoma	9591	124	Glioma malignant	1 day	Liver
Chronic myeloproliferative disease	9960	291	Fibrillary astrocytoma	3.8 years	Liver
Non-Hodgkin's lymphoma	9590	366	Fibrillary astrocytoma	11.1 years	Right lung
Chronic lymphoproliferative disease	9970	390	Medulloblastoma	14.2 years	Left kidney & pancreas
Squamous carcinoma of bronchus	8070	99	Ependymoma	4 days	Left kidney
Malignant neoplasm of bladder neck	8000	277	Glioma malignant	4.1 years	Right kidney
Carcinoma in unspecified endocrine gland or related structures	8010	342	Astrocytoma	63 days	Left kidney
Secondary small cell carcinoma in liver	8041	339	Medulloblastoma	1 days	Both kidneys
Infiltrating ductal carcinoma of breast	8500	406	Astrocytoma	70 days	Right kidney
Malignant neoplasm of pancreatic	8000	423	Glioma malignant	1 days	Left kidney

[1]Excludes basal cell carcinoma, squamous cell carcinoma and malignant melanoma of skin, as well as *in situ* carcinomas and tumors diagnosed in the explanted liver.

implanting other organs from the same donor when they identify any suspicious finding so a decision can be made about whether to proceed or to abandon transplantation.

Other smaller series from transplant registries have also suggested the risk of transmission of donor intracranial cancer is small, although the numbers of high-risk donors reported, such as those with GBM or medulloblastoma, were very small. The Australia and New Zealand registry reported no cases of transmission in 96 recipients of organs from 28 donors with malignant primary brain tumors (4 with GBM and 5 medulloblastoma), including 10 with previous craniotomy of whom 3 had ventriculo-peritoneal shunts, and 3 others with VP shunts without craniotomy (16). Data from Czechoslovakia showed no transmission of 11 high-grade tumors (9 GBM, 2 medulloblastoma) to 27 recipients (17), and a report from Spain also failed to demonstrate a case of transmission of organs from 9 donors with GBM (18).

These data are at odds with those reported by transplant tumor registries such as the Israel Penn International Transplant Tumor Registry (IPITTR), which documented the outcomes of recipients of 34 organs from donors with high-grade gliomas (4 grade III, 30 grade IV) (7,8). There was a 25% incidence of tumor transmission from organ donors with grade III gliomas (1 in 4), 40% (12/30) transmission from donors with GBM. However, registries like the IPITTR suffer from an overreporting bias since they have traditionally been notified regarding the occurrence of a cancer following transplantation but not the cancer-free survival of recipients of organs from donors with intracranial cancer.

Although our data are very reassuring, there remains a small but definite risk of transmitting cancer from donors with primary intracranial malignancy. The occurrence of extraneural metastasis from intracranial tumors is rare, even from high-grade tumors like GBM where vascular invasion is a diagnostic feature (11). This may in part reflect the short survival of patients with GBM. Craniotomy and major resection is a risk factor for extraneural metastasis of brain tumors and, to a lesser extent, so is stereotactic biopsy following which tumor seeding down the needle track has been observed (11,19). Following craniotomy metastasis often manifests with infiltration around the craniotomy site, or in the ipsilateral jugular lymph nodes. Other factors reported to increase the risk of extraneural spread, and donor cancer transmission, include ventriculosystemic shunts, prior radiotherapy or chemotherapy, and an increased time between diagnosis of tumor and death. It is important to note that about half of all intracranial tumors are not primary brain tumors, but represent secondary spread from an extraneural primary and these pose an unacceptably high risk of disease transmission.

The risk of transmission of a malignancy from organ donor to recipient is recognized and feared, but where it occurs it

is just as likely to be from a previously unrecognized donor cancer than a known intracranial cancer (20–23). Transplant statistics usually report separately patient survival following transplantation and waiting list mortality; indeed in the UK no precise data exist for waiting list mortality. What matters to the patient is their likelihood of long-term survival from the time they join the waiting list for a transplant, and this 'intention-to-treat' figure is rarely reported.

In the face of increasing waiting list mortality, it could be argued that the absence of transmission of donor intracranial malignancy in the present UK series reflects an inappropriate degree of clinical conservatism. Certainly, the data we present should be taken in the context of the perceived best practice at the time, which is likely to have selectively declined donors with intracranial shunts and previous craniotomy and or radiotherapy. In addition, there is an inevitable fear of commission, that is, of actively transplanting an organ that might result in a patient dying as a result of transmitted malignancy. In contrast, when the surgeon is guilty of omission, that is, of declining the organs from donors with primary intracranial malignancy, they feel less responsible for a subsequent waiting list death and are less culpable in the eyes of the patient's family. It may be that emphasizing patient survival following listing for transplantation, rather than from the time of transplantation, will result in a change of practice and an increased willingness to use organs from such donors.

When potential donors with intracranial malignancy are referred, it is essential the surgeon should be aware of all the relevant information, including tumor histology and treatment, including radiotherapy and surgery. At the time of organ retrieval a thorough examination of the thoracic and abdominal cavities for metastatic tumor should be undertaken, as well as careful assessment of any craniotomy site and related lymph nodes for evidence of extraneural spread; if found, and confirmed histologically, the organs should probably not be considered for transplantation. Finally, it is important that any patient being considered for transplantation where organs from donors with intracranial malignancy may be used, should be counseled regarding the small but definite risk of transmission, as well as their chance of survival if they choose to remain on the waiting list (14).

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Conflicts of Interest Statement

No author has a conflict of interest to declare in relation to the article and its contents.

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