Advising Potential Recipients on the Use of Organs From Donors With Primary Central Nervous System Tumors

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Deciding to use an organ from a donor with a primary central nervous system (CNS) tumor necessitates offsetting the risk of tumor transmission with the chances of survival if the patient waits for another offer of a transplant. Published data vary in the quoted risk of tumor transmission. We used data obtained by reviewing 246 UK recipients of organs taken from donors with CNS tumors and found no evidence of a difference in overall patient mortality for recipients of a kidney, liver, or cardiothoracic organ, compared with recipients of organs from donors without a CNS tumor. Recent publication of the UK experience of transplanting organs from CNS tumor donors found no transmission in 448 recipients of organs from 177 donors with a primary CNS tumor (Watson et al., *Am J Transplant* 2010; 10: 1437). This 0% transmission rate is associated with an upper 95% confidence interval limit of 1.5%. Using a series of assumptions of risk, we compared the risks of dying as a result of the transmission of a primary brain tumor with the risks of dying if not transplanted. On this basis, the use of kidneys from a donor with a primary CNS tumor provides a further 8 years of life over someone who waited for a donor who did not have a primary CNS tumor, in addition to the life years gained by the transplant itself. The benefits for the recipients of livers and cardiothoracic organs were less, but there was no disadvantage in the impact on life expectancy.

Keywords: Organ donation, Cerebral tumors, Metastasis.

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RECOMMENDATIONS FOR CLINICAL PRACTICE

On the basis of the current analysis, it is recommended that organs donated by deceased individuals with primary central nervous system (CNS) tumors should be used. We suggest the following two caveats:

1. The presence of a cerebrospinal fluid (CSF) shunt does increase the risk of extraneural metastasis. However, this is likely to be less than 1%. Although there are anecdotal reports of extraneural metastasis in patients who have undergone surgery, chemotherapy, or radiotherapy to the tumor, there is no convincing evidence that these forms of treatment will put the recipient at significantly increased risk of tumor transfer, and should not represent an absolute contraindication to transplantation.
2. Histology
   a. If the lesion is a metastasis or a lymphoma (even if a presumed primary CNS lymphoma), the patient should not be used as an organ donor.

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A.N.W. proposed that the issue be researched by SaBTO, chaired and coordinated the Working Group, and wrote the manuscript. R.B., D.C., M.D., and K.G. developed the statistical models and performed the statistical analysis. A.N.W., J.D., G.G., J.N., D.H., I.W., and C.J.E.W. identified the clinically important issues from within their various areas of clinical expertise and developed the appropriate statistical questions. J.N., as part of NHS Blood and Transplant, provided the clinical data from the UK transplant registry and participated in its analysis. All authors reviewed the manuscript in its various iterations.
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b. The overall risk of extraneural spread of all other histological types should be regarded as having an upper 95% confidence interval limit of 1.5%.
c. The estimated risk of extraneural spread from a donor with a CNS tumor with a histological label that would be regarded as representing a contraindication according to previously published guidance (*1*, *2*) is 2.2%, with a upper 95% confidence interval limit of 6.4%. We recommend this figure be used in advising patients of the risks of receiving organs from donors with World Health Organization (WHO) grade 4 tumors (WHO grade 4 tumors and equivalents: glioblastoma, giant cell glioblastoma, gliosarcoma, pineoblastoma, medulloblastoma, CNS primitive neuroectodermal tumor, medulloepithelioma, ependymoblastoma, atypical teratoid/rhabdoid tumor, malignant peripheral nerve sheath tumor [may be WHO grade 2, 3, or 4 depending on features], germinoma, immature teratoma, teratoma with malignant transformation, yolk sac tumor [endodermal sinus tumor], embryonal carcinoma, and choriocarcinoma).
d. On the basis of their biological behavior in other situations, we recommend that WHO grade 3 lesions (WHO grade 3 tumors: anaplastic astrocytoma, anaplastic oligodendroglioma, anaplastic oligoastrocytoma, ependymoma, choroid plexus carcinoma, anaplastic ganglioglioma, pineal parenchymal tumor of intermediate differentiation [may be WHO grade 2 or 3 depending on features], papillary tumor of the pineal region [may be WHO grade 2 or 3 depending on features], malignant peripheral nerve sheath tumor [may be WHO grade 2, 3, or 4 depending on features], anaplastic/malignant meningioma, papillary meningioma, rhabdoid meningioma, hemangiopericytoma [may be WHO grade 2 or 3 depending on features]) be regarded as having an intermediate risk of transfer (with an upper 95% confidence interval limit between the 6.4% for grade 4 lesions and the 1.5% for all primary tumors).

(These recommendations do not deal with a metastatic deposit from a presumed extracranial primary. A retrieval surgeon should always perform a thorough laparotomy and thoracotomy at the time of retrieval, whether or not there is a known malignancy, but it is particularly important to do so in the context of the finding of an intracranial mass. Ideally, the donor will have had previous imaging, including chest radiography, abdominal ultrasound, and possibly also whole body computed tomography scanning, and histological assessment of any lesion found. However, we recognize that this is not always possible and should not act as a brake on proceeding.)

Is Histological Diagnosis Necessary?

A histological diagnosis should be obtained where possible. Generally, the radiological diagnosis of meningeal tumors and tumors of cranial and paraspinal nerves is reliable. In other circumstances, the opinion of a specialist neuroradiologist must be sought and in some circumstance he/she will be confident of the histological type of the tumor. In other circumstances, donation should only proceed when the nature of the tumor is made on histologically.

INTRODUCTION

Despite the considerable shortfall between the demand for and supply of organs for transplantation, it is important to ensure that the risk of transmitting disease with a transplanted organ is minimized. Attention has focused recently on the use of organs from donors with primary cerebral tumors, because these are known to be associated with a low risk of extraneural spread (reported as 0.4%–2.3%) (*3*). Received wisdom has suggested that it is safe to use such donors, if their tumors are known to be low histological grade, but not so for high grade lesions or where there was been a breach of the blood-brain barrier, such as with craniotomy or the insertion of a CSF shunt (*1*, *2*, *4*, *5*). As a result, few such patients become donors: primary CNS tumors represent 3% to 4% of the causes of brain death among organ donors (*2*), but, in one series, less than 0.5% of 13,000 patients dying with a glioma became organ donors (*6*).

Reliable data on the actual risk of transmission after transplantation are sparse and subject to bias due to overreporting to registries. One review reported the transmission of CNS cancers from seven donors (*6*): 11 of 19 recipients developed donor-transmitted cancer, of whom five were reported to have died. Two retrospective reviews reported primary CNS tumor transmission rates of 3% (*7*) and 8% (*8*), respectively. The Israel Penn International Transplant Tumor Registry reported an 18% transmission of such tumors (*9*). However, a Czech series of 42 donors with primary brain tumors reported no transmission (*10*). A small series of cardiothoracic organ recipients found transmission to 1 of 6 recipients (*11*), but a German series showed no transmission with cardiac allografts from 32 donors with primary brain tumors (*12*).

Three donor registries have reported their experiences: United Network for Organ Sharing registry reported no cases of donor-transmitted malignancies out of 397 donors with a history of CNS tumors donating to 1220 recipients (*13*), although a subsequent report identified one of 642 donors with primary brain tumors who had transmitted the tumor to three recipients (*14*). In an Australasian series, none of 151 recipients of 46 donors with primary CNS lesions demonstrated evidence of donor tumor transmission (*14*).

Two of us (C.J.E.W. and D.C., with colleagues) undertook a rigorous review of UK experience in this area (*15*). Information from the UK Transplant Registry was combined with three national cancer registries to identify all organ donors between 1985 and 2001 who had had primary brain tumors and the occurrence of posttransplant spread into the recipients of organs taken from them. Of 11,799 donors, 179 were identified as having primary intracranial malignancy, of whom 33 had high grade histology. Four hundred forty-eight recipients of 495 organs from 177 of these people were identified and reviewed and no case of transmission of donor malignancy was identified. We have relied heavily on this study to develop the practical recommendations reported in this manuscript.

However significant (or not) the risk of transmitting a donor-derived tumor, there is also a risk of a patient with end-stage organ failure dying before a graft is available or becoming too unfit to receive a graft; but no account has been taken of the relative magnitude of each of these risks. As such,

it is difficult to determine whether rejecting organs from such donors represents a logical response. Also, such quantification of risk would be of value in advising a potential recipient of the risk he was taking in accepting a graft from a donor with a primary CNS malignancy. For these reasons, we decided to review further the UK experience of using organs taken from individuals with primary brain tumors with a view to developing practical guidelines.

OUTCOME OF TRANSPLANTATION OF ORGANS FROM DONORS DYING WITH PRIMARY BRAIN TUMORS

To determine the implications of recent UK practice in this area, we analyzed outcome data over a 15-year period after transplantation to determine any association between patient survival (and also graft survival in the case of kidney transplantation) and whether the donor was known, from cancer registry data, to have had a CNS tumor. Transplants involving donors with CNS tumors were identified using data from the study of Watson et al. (*15*). Data on outcomes after first adult recipient deceased donor solid organ transplants were obtained from the UK Transplant Registry. Multiorgan transplants, regrafts, pediatric transplants, heterotopic heart transplants, auxiliary liver transplants, liver transplants for patients with intestinal failure, and transplants involving patients not entitled to NHS treatment were also excluded.

Cox proportional hazards regression modeling was used to determine the strength of evidence against the null hypothesis that donor CNS tumor status does not influence patient and graft survival after transplantation. The factors included in the risk-adjusted models were as follows: donor sex (cardiothoracic and liver), donor age, donor type (lung only and kidney), donor cause of death (kidney), recipient age, sex (cardiothoracic and liver) and body mass index (liver), transplant year, transplant unit (cardiothoracic and liver), indication (liver), primary disease (kidney), human leukocyte antigen mismatch (kidney), recipient ethnicity (kidney), and ischemia time (total: cardiothoracic; cold: liver). Transplants with missing cold ischemia time (heart: 10%; lung: 17%; and liver: 6%) were excluded. An "unknown" category was included in factors to allow for missing values.

This analysis shows no reason to reject the hypothesis that there is no difference in patient survival for recipients of a kidney, liver or cardiothoracic organ, or in renal graft survival, between recipients of transplants from donors with or without a CNS tumor (Table 1). These data would include any effects of tumor transmission. Hence, the criteria that had informed practice over the period of this study had not disadvantaged those patients who had received organs from patients with primary CNS tumors. It may therefore be the case that, during this period, patients may have been disadvantaged by the inappropriate nonuse of donors.

TABLE 1. The risk-adjusted hazard ratio, and the corresponding 95% confidence interval and *P* value, for patients receiving organs from donors with a CNS tumor compared with those receiving organs for donors without such a tumor

Organ transplanted	Hazard ratio	95% Confidence interval	*P*
Kidney (graft survival) (n=139)	0.82	(0.58,1.16)	0.2
Kidney (patient survival) (n=139)	1.06	(0.76,1.47)	0.7
Liver (n=48)	1.33	(0.78,2.27)	0.3
Heart (n=36)	0.71	(0.40,1.24)	0.2
Lung (n=16)	0.72	(0.33,1.56)	0.4
Heart/lung (n=7)	2.04	(0.81,5.14)	0.2

Sample sizes, n, refer to the numbers of donors with CNS tumors.
CNS, central nervous system.

Risk of Acquiring and Dying From a Donor-Derived Primary CNS Tumor

Watson et al. (*15*) identified 448 recipients of 495 organs from 177 donors between 1985 and 2001 who had primary CNS tumors. None developed evidence of transmission of an intracranial malignancy over a minimum follow-up period of 5 years. This 0% transmission rate is associated with an upper 95% confidence interval limit of 1.5%. These data provide greater reassurance than older publications in the literature which we believe were subject to significant reporting bias.

This is despite the fact that significant numbers of these patients (at least 45) had a CNS tumor with a histological label that would be regarded as representing a contraindication according to published guidance. We attempted to quantitate the risk associated with the lack of transmission within a cohort of this size. If one were to assume that a hypothetical 46th patient were to undergo spread, the estimated risk of transmission would be 2.2% with a upper 95% confidence interval limit of 6.4%. Because of all of the individuals in this cohort of 45 had a WHO grade 4 tumor, we recommend this figure be used in advising patients with WHO grade 4 tumors on the risks of receiving such a transplant.

Data on individual tumor types are not available because of the rarity of some lesions. However, on the basis of their biological behavior in other situations, we recommend that WHO grade 3 lesions and ependymomas be regarded as having an intermediate risk of transfer (with an upper 95% confidence interval limit between the 6.4% for grade 4 lesions and the 1.5% for all primary tumors).

If the lesion is a metastasis or a lymphoma (even if believed to be a primary CNS lymphoma), the patient should not be used as a donor because the risk of transmission may be significant. Although it is true that the risks of extraneural spread from a primary CNS lymphoma are low, it can be difficult to exclude the possibility that the lymphoma has spread from an extracranial site.

A histological diagnosis of the CNS tumor should be obtained where possible. Generally, the radiological diagnosis of meningeal tumors and tumors of cranial and paraspinal nerves is reliable. In other circumstances, the opinion of a specialist neuroradiologist must be sought and in some circumstance he/she will be confident of the histological type of the tumor. In other circumstances,

TABLE 2. Simulation of life years gained through using donors with CNS tumors

If there are n transplants resulting from d organ donors with CNS tumors, the number of recipients who do not develop a malignancy is n $(1-p_T)$. This results in number of resulting life years of n $(1-p_T)$ m.

The number of recipients who develop a transmitted malignancy is n p_T, and the life years gained by this group is then n p_T t.

However, it is possible that after the occurrence of a donor-related tumor in a transplanted kidney, the kidney is removed and the patient waits a period of time for a subsequent transplant.

If p_D is the proportion who die after transmission, the number who die is n p_T p_D, and the life years gained by this group is n p_T p_D t. The corresponding number who do not die from the transmitted tumor is n p_T $(1-p_D)$. Their graft is removed, and they wait w_1 years for a transplant, during which time they are at risk of dying. Amongst this group, the number who die waiting for a transplant is n p_T $(1-p_D)$ p_W per year, and so in w_1 years, a total of

$$n\, p_T\, (1-p_D)\, p_W\, w_1$$

are expected to die. If each of those who dies lives for $w_1/2$ yr, the life yrs gained by this group is

$$n\, p_T\, (1-p_D)\, p_W\, w_1^2/2.$$

The remaining number who go on to have a transplant is

$$n\, p_T\, (1-p_D) - n\, p_T\, (1-p_D)\, p_W\, w_1$$
$$= n\, p_T\, (1-p_D)\, \{1-p_W\, w_1\}.$$

Each of these has already survived an average of $w_1/2$ yr waiting for a second transplant and are expected to survive m years after the transplant. The number who go on to transplant will therefore have survived

$$n\, p_T\, (1-p_D)\, \{1-p_W\, w_1\}(m+w_1/2)$$

years from the time of the initial transplant.

The total life years gained by the group who have a transplant after removal for transmission is

$$n\, p_T\, (1-p_D)\, p_W\, w_1^2/2 + n\, p_T\, (1-p_D)\, \{1-p_W\, w_1\}(m+w_1/2)$$

It then follows that the total life years gained through the use of organs from CNS donors is

$$G_1 = n(1--p_T)m + np_Tp_Dt + n\, p_T\, (1-p_D)p_Ww_1^2/2 + n\, p_T\, (1-p_D)\, \{1-p_W\, w_1\}\, (m+w_1/2). \quad (1)$$

Note that the last two terms may be negligible relative to the size of the first.

The number of patients who do not benefit from the availability of donors with a CNS tumor is n. As a result, they have to wait a further w_0 years for a transplant. In this period of time, they are subject to mortality on the waiting list, and the expected number of deaths is n p_W w_0. Each of those who die is expected to survive $w_0/2$ yr and so the life years gained in this group is

$$n\, p_W\, w_0^2/2.$$

The number who receive a transplant in the period of w_0 yr is $n(1-p_W\, w_0)$. If each then survives m yrs, in addition to the average of $w_0/2$ yr waiting for a transplant, their life yrs gained is

$$n(1-p_W\, w_0)(m+w_0/2).$$

The total life years gained by the group of patients who had the potential to receive an organ from a donor with a CNS tumor is therefore

$$G_2 = n\, p_W\, w_0^2/2 + n(1-p_W\, w_0)(m+w_0/2). \quad (2)$$

The difference between Eqs. (1) and (2) is the benefit of using donors with CNS tumors.

CNS, central nervous system.

transplantation should only proceed once an appropriate histological diagnosis has been made, possibly through a postretrieval craniotomy.

To gain sufficient power to undertake this analysis, we have grouped together tumors of different histological types. We cannot exclude the possibility that one or more of these subtypes (especially the rare ones) might behave differently. The presence of a CSF shunt does increase the risk of extraneural metastasis. However, extrapolating from published studies (*16*, *17*), this risk is likely to be less than 1% overall. This should be taken into account in advising the patient about the risks of proceeding with the transplant against the risks of not proceeding.

Although there are anecdotal reports of extraneural metastasis in patients who have undergone surgery, chemotherapy and radiotherapy to the tumor, in our view, there is no convincing evidence that these forms of treatment will put the recipient at significantly increased risk of tumor transfer, and they should not be a contraindication to transplantation.

Comparing the Risks of Death as a Result of Transmission of a Primary Brain Tumor With the Risks of Dying if Not Transplanted

To estimate the potential benefit of using organs from donors with a CNS tumor, a Monte Carlo simulation model was used. In summary, simulated values for the life years gained through the use of organs from a donor with a CNS tumor are compared with simulated values of the life years gained by not using such organs.

Formulae for life years gained are derived in Table 2 and are applicable for any solid organ. The formula for the life years gained after transplantation with an organ from a donor with a CNS tumor is based on survival after transplantation. The formula takes account of the chance of death after transmission of a tumor, and the chance of surviving to a retransplant if the affected organ is removed. The formula for the expected number of life years gained without using donors with CNS tumors assumes that a patient who may have received such an organ has to wait for a subsequent offer, dur-

TABLE 3. Estimates used for calculation of life years gained

Parameter	Kidney	Liver	Heart	Lung
Number of deceased donors with CNS tumors available for organ retrieval (d)	17	14	3	3
Number of transplants resulting from *d* donors (n)	34	14	3	3
Median lifetime after transplantation (m)	22	15	12	6
Time to wait for a transplant if the offer of an organ from a donor with a CNS tumor is declined (interval estimate)				
w_0	2 (0.5, 5)	0.4 (0.1, 1.5)	0.25 (0.1, 0.8)	0.4 (0.1, 1.0)
w_0'	1 (0.3, 3)			
Probability of tumor transmission from donor to recipient (interval estimate) (p_T)	0.01 (0, 0.02)	0.01 (0, 0.02)	0.01 (0, 0.02)	0.01 (0, 0.02)
Survival time (yr) of a recipient to whom a donor tumor is transmitted (interval estimate) (T)	1 (0.5, 3)	0.5 (0.1, 1)	0.5 (0.1, 1)	0.5 (0.1, 1)
Probability of death after transmission of a donor tumor (p_D)	0.3	1.0	1.0	1.0
Time to wait for a transplant after removal of an organ for reason of transmission of a tumor (interval estimate) (w_1)	3 (1.5, 4)	0.4 (0.1, 1.5)	0.25 (0.1, 0.8)	0.4 (0.1, 1.0)
Probability of death in a year while waiting for an organ (interval estimate)				
p_W	0.2 (0.15, 0.25)	0.5 (0.2, 0.8)	0.5 (0.2, 0.8)	0.5 (0.3, 0.7)
p_W'	0.125 (0, 0.2)	0.2 (0, 0.4)		

CNS, central nervous system.

TABLE 4. Additional life years benefit per transplant from a donor with a CNS tumor, showing estimates based on two different assumptions of "time to wait for a transplant if the offer of an organ from a donor with a CNS tumor is declined" (w_0) and "probability of death in a year while waiting for an organ" (p_W) (for values of w_0 and p_W, see Table 3)

Organ transplanted	Additional life years benefit per transplant from a donor with a CNS tumor (based on w_0 and p_W)	95% Confidence interval estimate	Additional life years benefit per transplant from a donor with a CNS tumor (based on w_0' and p_W')	95% Confidence interval estimate
Kidney	8	(3, 17)	2	(0, 7)
Liver	3	(0, 10)	1	(0, 5)
Heart	2	(0, 4)		
Lung	1	(0, 3)		

CNS, central nervous system.

ing which time he may die on the waiting list or become unsuitable for transplantation. Plausible values of the individual parameters in these formulae are given in Table 3. These have been derived from estimates of recent clinical experience (d, n, m, w_0, w_1, p_W), estimates from the literature (p_T) and clinical judgment (t, p_D). For p_W and w_0, alternative values labeled p_W' and w_0' have also been used.

Interval estimates are shown for some of these, where there is uncertainty in their actual values. This uncertainty will in turn lead to variation in estimated life years gained, and the extent of this is estimated using simulation. In summary, values of w_0, w_1, p_W, p_T, and t are simulated from probability distributions that have the same means as in Table 3, and that have a 95% chance of a value in the interval specified for that parameter in Table 3. These individual simulated values lead to an estimate of life years gained. This process is then repeated a large number of times to give the distribution of life years gained, from which the interval that includes 95% of values can be found.

The estimated life years gained from using donors with CNS tumors, over and above the life years gained if the recipient were to wait for an organ from a donor without a CNS tumor is given in Table 4. These are crucially dependent on the assumptions made, including the chances of dying on the waiting list. It is likely that, in practice, the transplanting surgeon may opt to use an organ from a donor with a primary CNS tumor in higher risk recipients, such as older individuals, or people with high comorbidities. This shows that there is a potential for gaining a large number of life years through the use of kidneys from donors with CNS tumors. The benefit from using livers is not as great, but there is the potential for gaining 3 life years per transplant (assuming an annual mortality on the waiting list of 50%) or 2 years (if one assumes an annual mortality of 20%). The larger potential gain from using kidneys from donors with CNS tumors is explained by the waiting time for a subsequent offer of a kidney being longer than that for other organs, if a donor with a CNS tumor is not used. The potential gain from using kidneys is 8 years (assum-

ing an annual waiting list mortality of 20%) and 2 years (assuming an annual mortality of 12.5%). The gain from using cardiothoracic organs is more marginal.

It is estimated that there may be up to 20 potential organ donors with a CNS tumor per year in the United Kingdom. If all major organs from each donor were transplanted, using the assumptions of greater death on the waiting list this would lead to a gain of 320 life years in kidney transplant recipients, 60 in liver recipients, and 40 and 20 in heart and lung recipients, respectively, every year.

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