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DONORS WITH CENTRAL NERVOUS SYSTEM MALIGNANCIES: ARE THEY TRULY SAFE?

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Background. **In an era of organ shortage, the use of expanded or marginal donors has been attempted to increase transplantation rates and diminish waiting list mortality. One strategy is the use of organs from patients with a history of or active central nervous system (CNS) tumor.**

Methods. **Sixty-two recipients were identified as the recipients of organs from donors with a history of or active CNS malignancy. Patient demographics, donor tumor management, incidence of tumor transmission, and patient survival were examined.**

Results. **Of the organs recovered and transplanted from donors with astrocytoma, 14 were associated with at least one risk factor including high-grade tumor (n=4), prior surgery (n=5), radiation therapy (n=4), and systemic chemotherapy (n=4). One tumor transmission was identified at 20 months posttransplant with the patient expiring from metastatic disease. Twenty-six organs were transplanted from glioblastoma patients with 15 demonstrating risk factors including high-grade tumor (n=9) and prior surgery (n=10). Eight transmissions were identified with a range of 2 to 15 months posttransplant, with seven patients dying as the result of metastatic disease. Seven organs were used from donors with a medulloblastoma. Three transmissions were identified at a range of 5 to 7 months, all associated with ventriculoperitoneal shunts. Two medulloblastoma recipients died as the result of metastatic disease, whereas the third is alive with diffuse disease. The rate of donor tumor transmission, in the absence of risk factors, was 7%, whereas in the presence of one or more risk factor this rate dramatically rose to 53% ($P<0.01$).**

Conclusions. **Organs from donors with CNS tumors can be used with a low risk of donor tumor transmission in the absence of the following risk factors: high-grade tumors, ventriculoperitoneal or ventriculoatrial shunts, prior craniotomy, and systemic chemotherapy.**

Transplantation has become the treatment of choice in most patients with end-stage organ disease, with more than 80,000 patients in the United States awaiting a solid-organ transplant in the year 2002. This increase in organ demand has resulted in dramatically increased waiting times for cadaveric organs. Although the demand for organs has grown dramatically during the last decade, the availability of organs has not experienced a comparable increase (*1*, *2*). The resulting increased wait times have led to increased wait-list death rates, prompting many transplant programs to consider the aggressive use of marginal donors as a means for expanding the organ donor pool (*3*). Because the risk of tumor transmission from donor-related central nervous system (CNS) malignancies remains unidentified, the use of these marginal donors remains controversial (*4*–*7*).

Historically, transplant surgeons have been reluctant to accept organs from donors with a history of CNS malignancy, largely because of the absence of substantive or nonconflicting data defining the true risk of tumor transmission. A report released by the Scientific Registry of Transplant Recipients (SRTR) initially reported no instances of donor-transmitted malignancy in its study population. This report contained a subset of 188 organ recipients who received their grafts from organ donors with a history of or active CNS malignancy (*8*). Subsequent to this initial report, Kaufman et al. acknowledged the presence of recipients with donor-transmitted malignancies in the SRTR data, noting that several of the organ recipients had developed malignancies from non-CNS donors, but they failed to identify a single case of donor transmission in the CNS donor population (*9*, *10*). These findings led the SRTR to conclude that there was a negligible risk for tumor transmission from CNS malignancy donors, and that the use of such donors should be liberalized. However, the observations and conclusions from these studies indicating such a blanket strategy of accepting CNS malignancy donors may be potentially dangerous, because data from the Israel Penn International Tumor Registry (IPITTR) and other reports indicate that there is a real occurrence of tumor transmission, and that there may be identifiable risk factors associated with tumor transmission. Moreover, the conclusions from the SRTR study may have been flawed or at least compromised by several factors, including the (1) absence of tumor histology data, (2) failure to analyze risk factors for transmission, (3) underreporting of tumor transmission in recipients, and (4) traditional practice of avoidance of high-risk donors. A similar study involving a series of 28 organs transplanted from donors with CNS malignancies (astrocytomas, glioblastomas, or medulloblastomas), conducted by the Australia and New Zealand Combined Dialysis and Transplant Registry (ANZODR), also reported an absence of donor transmission of malignancy (*11*). These results are in contrast with data reported by several individual centers and the IPITTR, in which donor CNS tumor transmissions were identified and attributed to donor risk factors, including ventriculoperitoneal or ventriculoatrial shunting or high-grade histology of these lesions (*12*–*16*). Conflicting reports such as these have created further controversy and confusion in the transplant community concerning the use of organs from donors with CNS malignancies. This study adds

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clarity to this controversy, by focusing on the impact of tumor histology and donor risk factors on tumor transmission in an attempt to provide a substantive means for evaluating the use of donors with active or previous CNS malignancies.

MATERIALS AND METHODS

A retrospective review of more than 17,000 cases reported to the IPITTR from 1970 to 2002 was performed. All donors with CNS malignancies were evaluated for primary tumor grades and histology, stage of malignancy, extent of surgical excision, radiation therapy, and chemotherapy. In the donor review, potential transmission risk factors were examined including prior therapeutic interventions such as ventriculoperitoneal or ventriculoatrial shunts. Recipient demographics were also examined including age, gender, time from transplant to confirmed tumor transmission, presence of localized or metastatic disease, organ transplanted, immunosuppression used, morbidity, and mortality.

Univariate analysis was performed to determine which risk factors or combinations of risk factors were the strongest predictors of donor cancer transmission. Actuarial survival and time to donor transmission were examined. Statistical evaluations were performed using the Student *t* test or chi-square analysis. All data are presented as mean ± the standard deviation. A P value of less than 0.05 was considered statistically significant.

RESULTS

Sixty-two organs were transplanted from 36 organ donors with malignant CNS potential. Grafted organs included 35 kidneys, 12 hearts, 10 livers, 2 pancreas, and 3 lungs. The histologic distribution of tumors identified in the 36 organ donors included 16 astrocytomas, 15 gliomas or glioblastoma, three medulloblastomas, and two cerebellar tumors. Twenty-four of the 36 donors received some form of cancer therapy before organ donation. These therapies included ventriculoperitoneal or ventriculoatrial shunts (n=12), extensive craniotomy (n=6), radiation therapy (n=4), and chemotherapy (n=2).

Astrocytoma

Of the 25 organs recovered from donors with astrocytomas, 14 were associated with at least one risk factor: high-grade histology (grade III or IV; n=4), prior surgical intervention (n=5), radiation (n=4), or chemotherapy (n=4). A single episode of donor-transmitted malignancy was identified, occurring at 20 months posttransplant (Fig. 1), The sole factor associated with transmission was a high histologic (grade III) lesion in the donor. The recipient developed metastatic disease and died from progressive disease 80 months posttransplantation (Fig. 2).

Glioblastomas

Twenty-six organs were transplanted from donors with gliomas or glioblastomas. Eight organs were recovered from donors with a grade III or IV glioblastoma, whereas the remaining 18 organs were from donors with gliomas. High-grade glioblastoma multiforme lesions were defined as grade IV glioblastomas. Fifteen patients received organs from donors with at least a single risk factor associated with the potential for malignancy transmission. These include prior surgical intervention (n=10) or high-grade malignancies (n=9). Eight transmissions were identified, with all appearing between 2 and 15 months posttransplant (Fig. 1). Three of the eight cases of malignancy transmission were confined to the allograft (two kidney and one liver). Both kidney recipients underwent graft nephrectomy. One recipient was rendered disease-free, whereas the other developed metastatic disease and died from metastatic tumor. The liver recipient died after developing liver failure. The remaining five cases of donor transmission resulted in patients dying between 6 and 26 months posttransplant (Fig. 2).

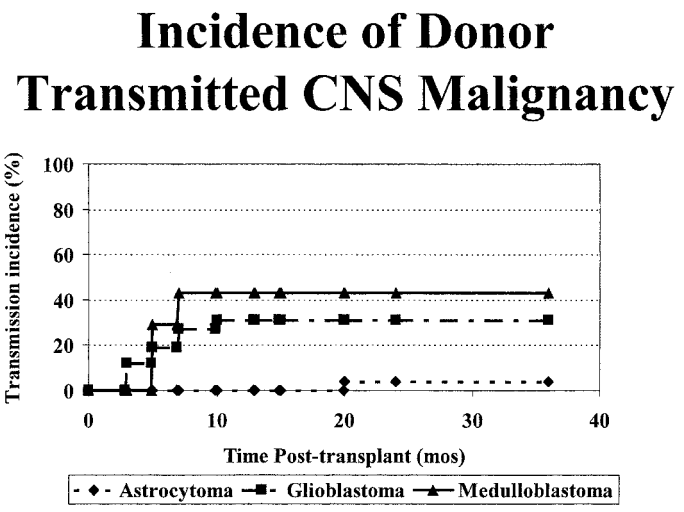

FIGURE 1. Incidence of donor-transmitted central nervous system (CNS) malignancies.

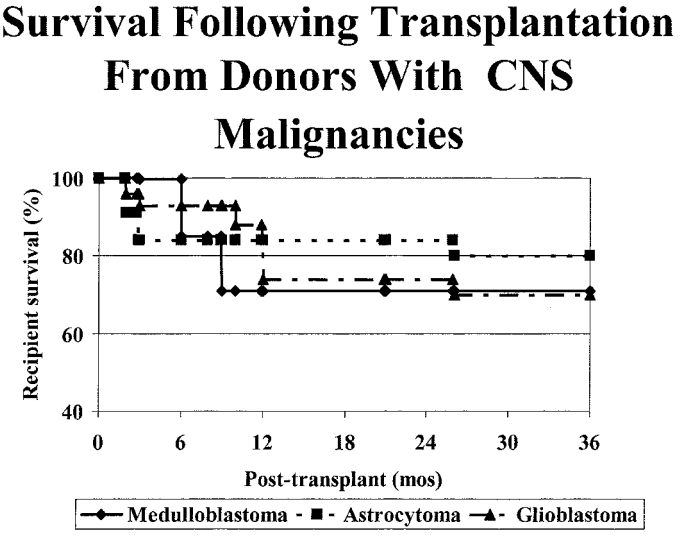

FIGURE 2. Survival after transplantation from a donor with a CNS malignancy.

Medulloblastomas

Seven organs were transplanted from donors with medulloblastomas. Three donors had ventriculoperitoneal shunts, and all of the organ recipients developed malignancies, occurring between 5 and 7 months posttransplant (Fig. 1). Two recipients died of progressive disease at 26 months posttransplant, and the third patient was alive with diffuse metastatic disease at last report (Fig. 2).

Other Central Nervous System Malignancy Donors

The patients in the last group demonstrated miscellaneous tumors including a pineal malignancy, two cerebellar malignancies, and one unspecified primary brain malignancy. Two donor transmissions occurred in this group, both arising from donors with cerebellar malignancies. One of the two recipients died from progressive disease, and the other patient was alive at last follow-up.

Donor Risk Factors Associated with Transmission

Risk factors associated with donor transmission of malignancy were examined in 14 recipients who experienced donor-transmitted malignancies. These risk factors included ventriculoperitoneal shunts (n=5), high-grade tumors (n=6), extensive craniotomies (n=3), and cerebellar lesions (n=2). Thirty-three patients had at least one risk factor present; 14 of those had two risk factors. When a single risk factor was present, the donor malignancy transmission rate was 36%, whereas two risk factors resulted in an equivalent transmission rate of 43%. As an independent factor, a high-grade malignancy was associated with a 43% transmission rate. In the absence of risk factors, the incidence of donor-transmitted malignancies was 7% (Fig. 3).

DISCUSSION

A shortage of donor organs has led transplant programs to consider the increased use of organs from marginal donors (*3*). The use of organs from donors with an active or historic malignancy remains controversial. In 2001, the SRTR reported that organs used from donors with CNS tumors comprised the greatest proportion of all donors with a history of malignancy (*15–17*). A recent report from the SRTR, with a 2-year mean follow-up, failed to identify a single instance of donor-transmitted malignancy in 188 transplant recipients of organs from donors with CNS malignancies (*9*). The report's conclusion, that there is minimal risk of donor-transmitted CNS malignancy, is of concern, because the risk of CNS tumor transmission previously reported by our group and a cluster of case reports is not zero, as their data indicate. A number of potential factors may explain the differences in the SRTS and IPITTR observations, compromised principally by a lack of tumor histology data. The first factor may be linked to the lack of distinction between benign and malignant tumors for most patients in the SRTS series. Only 35 patients demonstrated tumors identified with histologies classified as astrocytomas, gliomas, or medulloblastomas, whereas the histologic grades for all tumors were not known.

A report from the ANZODR also concluded that there were no definitive cases of CNS donor-transmitted malignancies (*11*). In this study, 46 recipients of organs from donors with CNS tumors included 18 benign tumors and 23 malignant lesions (astrocytomas, gliomas, or glioblastomas, and medulloblastomas) (Table 1). When examined, 11 organs originated from donors with a single risk factor or multiple risk factors identified.

In sharp contrast, this current series demonstrates the transmission rate was 36% for high-risk donors and 23% for the overall series. A number of reports have documented that CNS malignancies can be transmitted during organ transplantation (*4–7*). In early experiences, the use of donors with metastatic cancer was not infrequent, with fatal outcomes often observed (*12–15*). Those donor malignancies associated with the highest transmission and mortality rates were melanoma and choriocarcinoma (*13–15*). During the last decade, Penn has reported both the local extension and distant spread of donor-transmitted malignancies in multiple organ recipients (*12–15*). The risk of donor-transmitted malignancy has led to caution in the use of donors with CNS and other tumors. However, reports of these donors being used without tumor transmission remain controversial. The present study characterizes the risk factors associated with donor-transmitted malignancies as a means to provide the transplant community with reasonable guidelines for the use of these marginal donors.

In a retrospective study of patients with primary brain malignancies in the nonimmunosuppressed neurosurgical population, 24 of 282 metastases were identified as spontaneous extracranial metastases (*18*). Most cases with tumor dissemination were attributed to a specific event, namely, surgical disruption of the blood brain barrier by craniotomy or radiation chemotherapy. In addition, the presence of ventriculoatrial or ventriculoperitoneal shunts has been anecdotally reported as a risk factor for metastatic tumor transmission in the neurosurgical literature. There is, however, uncertainty over the impact of new minimally invasive techniques, such as gamma knife technology and stereotactic biopsy. These less invasive procedures may have a minimal impact on the blood-brain barrier integrity, thereby reducing the risk of tumor dissemination.

In contrast with other studies, the current study describes a number of documented cases of donor-transmitted malignancies. Moreover, this experience identified several risk factors associated with tumor transmission. In the absence of identifiable risk factors, a low transmission rate of 7% was noted. However, in the presence of a single risk factor, the incidence of transmission varied from 36% to 43%. In the presence of two risk factors, the transmission rate did not increase, demonstrating that the effect of multiple risk factors was neither additive nor synergistic.

The IPITTR data are in distinct contrast with the SRTR and ANZODR data. One possible explanation for these differences

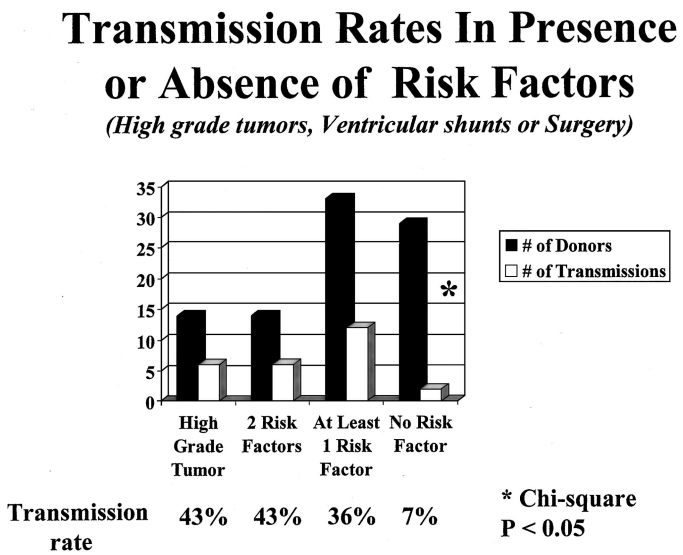

FIGURE 3. Transmission rates in the presence or absence of risk factors.

TABLE 1. Donor malignancy transmission: Registry experiences

	Organs	Benign tumors (%)	Astro/glio/medulo (%)	High-grade tumors (%)	Organs w/risk factor	Transmission rate
SRTR8	188	NR	35 (19%)	NR	NR	0 (0%)
Australian11	46	18 (39%)	23 (50%)	NR	11 (24%)	0 (0%)
IPITTR	62	0 (0%)	58 (94%)	14 (23%)	33 (53%)	14 (23%)

SRTR, Scientific Registry of Transplant Recipients; IPITTR, Israel Penn International Tumor Registry.

may be in the nature of each registry. The SRTR and ANZODR registries identify patients through mandatory reporting, thus underreporting may occur. An example of this underreporting was identified in a preliminary study from the University Renal Research and Education Association, which identified that the SRTR captured approximately half of the cancer cases recorded in patient-linked Surveillance, Epidemiology, and End Results Program data from a single United Network for Organ Sharing region (*19*). In contrast, the IPITTR, a longstanding registry with an international component, is an event-based registry. Event-based registries may result in higher event incidences, and reporting of events may be over-represented compared with the entire population at risk.

Another discrepancy between these three registry experiences is the number of high-risk donors in each group. In the SRTR report (*8*), the proportion of benign tumors, tumor grade, and risk factors (e.g., surgery and shunts) were not reported. In addition, the follow-up interval was short; the mean interval from transplant to tumor dissemination in the IPITTR study was unmet by most patients in the SRTR series. In the ANZODR study, there was a similar lack of reporting of risk factors. All limitations aside, the available data indicate that there is a real, but not clearly defined, risk of tumor transmission from donors with CNS malignancies. The IPITTR study indicates that donors with a higher potential for malignancy transmission can be identified and potentially avoided. The conclusion of the SRTR report is in agreement with this position.

A clearer definition of the risk of CNS tumor transmission provides the basis for a rational decision by which transplant physicians and surgeons in concert with their patients can then decide whether the risk of proceeding with transplantation of an organ from a donor with a CNS tumor is acceptable. In such a decision, the risk of death on the waiting list must be weighed against the risk of tumor transmission. These decisions are easier in extra-renal transplant recipients, including end-stage heart, liver, and lung patients for whom alternative external support systems do not exist and organ shortage is profound. However, in the case of renal and pancreas transplant recipients, these patients have the option to remain on dialysis and insulin therapy. Despite these therapeutic and supportive measures, diabetics and dialysis patients experience significant morbidity and mortality rates on the waiting list. Data from the current series therefore provide the basis for an open discussion so that a decision can be made by the transplant surgeon, physician, and transplant recipient regarding the acceptance of organs from donors with CNS malignancies.

The findings of this study indicate the selective use of donors with CNS tumors, that is, donors with low histologic grade lesions or benign tumors. Donors with one or more risk factors should be avoided or used only in cases in which a life-saving transplant is urgently needed. The IPITTR data indicate that a donor with a low-grade CNS malignancy (astrocytoma, glioblastoma, or medulloblastoma) in the absence of any known risk factor carries a 7% risk of tumor transmission. Given that SRTR and ANZODR data indicate a lower transmission rate, this 7% rate may be an overestimation of the true risk. Thus, the use of such organs may seem reasonable for the patient with a high expected mortality on the wait list for a life-sustaining organ transplant. The series indicates that donors with high-grade malignancies, ventriculoatrial or ventriculoperitoneal shunts, previous surgical intervention, or previous prolonged chemotherapy carry a significant risk of tumor transmission, and their use is discouraged.

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