

Liver Grafts from Donors with Central Nervous System Tumors: A Single-Center Perspective

Randeep Kashyap,¹ Charlotte Ryan,² Rajeev Sharma,¹ Manoj K. Maloo,³ Saman Safadjou,¹ Maureen Graham,¹ David Tretheway,² Ashokkumar Jain,⁴ and Mark Orloff¹

¹Division of Solid Organ Transplantation, Department of Surgery, and ²Department of Pathology, University of Rochester Medical Center, Rochester, NY; ³Department of Surgery, Geisinger Health System, Danville, PA; and ⁴Department of Surgery, Temple University Hospital, Philadelphia, PA

Traditionally, patients who die with a malignancy have been excluded from donation. However, it has become a common practice to accept organs from donors that have low-grade tumors or tumors with low metastatic potential. The aim of this study was to analyze our experience with the use of liver grafts from donors with central nervous system (CNS) tumors. A retrospective review of 1173 liver transplants performed between 1992 and 2006 identified 42 donors diagnosed with a CNS tumor. Thirty-two tumors were malignant, and 10 tumors were benign. Forty-two liver transplant recipients received livers from these donors. All patients were followed until May 2007 with a mean follow-up of 29 ± 17 months. Among 42 donors, there were 28 males and 14 females. The mean donor risk index was 1.78 ± 0.39 . Twenty (47.6%) of the CNS tumors were glioblastoma multiforme (astrocytoma grade IV), 11 (26.2%) were other astrocytomas, and 1 (2.4%) was an anaplastic ependymoma. Twenty (62.5%) neoplasms were grade IV tumors, 8 (25%) were grade II tumors, and 4 (12.5%) were grade III tumors. Over 80% of the patients had at least 1 kind of invasive procedure violating the blood-brain barrier. The rate of recurrence for the entire group was 2.4% (all CNS tumors). There were 7 (7.2%) deaths in all. The most common cause of death was sepsis ($n = 3$, 7.2%). There was no difference in survival between recipients of grafts from donors with CNS tumors and recipients of grafts from donors without CNS tumors (1 year: 82% versus 83.3%, $P =$ not significant; 3 years: 77.4% versus 72%, $P =$ not significant). In conclusion, in our experience, despite violation of the blood-brain barrier and high-grade CNS tumors, recurrence was uncommon. Grafts from these donors are often an overlooked source of high-quality organs from younger donors and can be appropriately used, particularly in patients who, despite low Model for End-Stage Liver Disease scores, carry a high risk of mortality. *Liver Transpl* 15:1204-1208, 2009. © 2009 AASLD.

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According to the United Network for Organ Sharing, at present, there are more than 97,000 patients in need of a donor organ. The severe shortage of organs underscores the need for expanding utilization of organs from marginal donors. Traditionally, patients who die with a malignancy have been excluded from donation. However, it has become a common practice to accept organs from donors that have low-grade tumors or tumors with low metastatic potential. These include premalignant lesions (carcinoma in situ of the cervix), low-grade skin

neoplasms (basal cell carcinoma and some squamous cell carcinomas), and primary brain tumors (PBTs). Much concern has been raised over the last few decades about including the last group in the donor pool because of the small but real risk of transmitting an undetected passenger neoplasm to the recipient. To date, 7 case reports and multiple institutional and registry based reports have been published detailing the rare transmission of a donor tumor to a transplant recipient. Most reported cases have involved a high-grade lesion

Abbreviations: ANZODR, Australia and New Zealand Organ Donation Registry; CNS, central nervous system; HAT, hepatic artery thrombosis; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IPITTR, Israel Penn International Transplant Tumor Registry; MELD, Model for End-Stage Liver Disease; NASH, nonalcoholic steatohepatitis; PBC, primary biliary cirrhosis; PBT, primary brain tumor; PSC, primary sclerosing cholangitis; SD, standard deviation; SRTR, Scientific Registry of Transplant Recipients; VP, ventriculo-peritoneal.

Address reprint requests to Randeep Kashyap, M.D., Division of Transplantation, Department of Surgery, University of Rochester Medical Center, Box SURG, 601 Elmwood Avenue, Rochester, NY 14642. Telephone: 585-275-3560; Fax: 585-271-7929; E-mail: randeep_kashyap@urmc.rochester.edu

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such as a glioblastoma multiforme or medulloblastoma, and none, to our knowledge, have come from a patient with an original diagnosis of a low-grade neoplasm. Every year in the United States, about 200,000 new cases of central nervous system (CNS) cancer are diagnosed, and approximately 13,000 die of this disease, but only 50 to 60 are accepted as organ donors, representing only 1% of the donor pool. Better utilization of these organs can certainly add to the donor pool and improve the organ shortage.

The purpose of this study was to analyze our experience with the use of liver grafts from donors with CNS tumors resulting in transmission of a CNS malignancy.

PATIENTS AND METHODS

A retrospective review of 1173 liver transplants performed between 1992 and 2006 identified 42 donors diagnosed with a CNS tumor. Thirty-two tumors were malignant, and 10 tumors were benign. All records of the 32 donors with a CNS malignancy were obtained from the respective organ procurement organizations and reviewed. The diagnosis was made on the basis of histology (not imaging). Forty-two liver transplant recipients received livers from these donors. All patients were followed until May 2007 with a mean follow-up of 29 ± 17 months.

Statistical Analysis

Means of continuous variables were compared with *t* tests, and correlations were compared with Pearson's test. Categorical variables were compared with the chi-square test. Odds ratios were calculated with logistic regression. Patient survival was calculated with the Kaplan-Meier method. Statistical analysis was performed with SPSS for Windows, version 15.0 (SPSS, Inc., Chicago, IL).

Immunosuppression Protocol

All patients were started on tacrolimus at an initial dose of 0.05 mg/kg twice daily. The dose of tacrolimus was adjusted according to clinical conditions, and target trough levels were maintained around 8 to 10 ng/mL in the first month and then gradually reduced to 6 ng/mL by 12 months. The patients also received methylprednisolone prior to reperfusion of the liver. A total dose of 200 mg per day of methylprednisolone was given over 5 days with 20 mg of prednisone thereafter as maintenance along with 1 g twice daily of mycophenolate mofetil.

RESULTS

Recipient Demographics

Among the 42 recipients, there were 28 males and 14 females. The mean age was 53 ± 9 years, and the mean Model for End-Stage Liver Disease (MELD) score was 25 ± 9 . Four patients (9.5%) were transplanted for hepatocellular carcinoma, 3 of whom were outside the Milan criteria and 1 of whom was within the Milan

TABLE 1. Recipient Characteristics (n = 42)

Demographics (n or mean \pm SD)	
Male	28
Female	14
Age (years)	53 ± 9
MELD score	25 ± 9
HCC outside Milan criteria	3
HCC within Milan criteria	1
Diagnosis [n (%)]	
Hepatitis C	12 (28.6%)
Laennec's cirrhosis	8 (19%)
HAT	4 (9.5%)
HCC	4 (9.5%)
Cryptogenic	3 (7.1%)
Autoimmune	2 (4.8%)
NASH	2 (4.8%)
Hepatitis B	2 (4.8%)
Recurrent HCV	2 (4.8%)
Hemochromatosis	1 (2.4%)
PBC	1 (2.4%)
PSC	1 (2.4%)
Total	42 (100%)

Abbreviations: HAT, hepatic artery thrombosis; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; MELD, Model for End-Stage Liver Disease; NASH, nonalcoholic steatohepatitis; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; SD, standard deviation.

criteria. The most common cause of liver failure in recipients was hepatitis C (n = 12, 28.6%), which was followed by Laennec's cirrhosis (n = 8, 19%). In addition, 4 patients (9.5%) were transplanted for hepatic artery thrombosis, 3 (7.1%) were transplanted for cryptogenic cirrhosis, and 2 patients each (4.8%) were transplanted for autoimmune hepatitis, nonalcoholic steatohepatitis, hepatitis B viral infection-related cirrhosis, and recurrent hepatitis C viral infection. One patient each (2.4%) had hemochromatosis, primary biliary cirrhosis, and primary sclerosing cholangitis (Table 1).

Donor Characteristics

Demographics

Among 42 donors, there were 28 males and 14 females. The mean age was 37 ± 13 years, and the mean donor risk index score was 1.78 ± 0.39 (Table 2).

CNS Tumor Histology

The majority of the CNS tumors were of glial cell origin. Twenty (47.6%) were glioblastoma multiforme (astrocytoma grade IV), 11 (26.2%) were low-grade astrocytomas, and 1 (2.4%) was an anaplastic ependymoma. Included among the astrocytomas were 2 (4.8%) subependymal giant cell astrocytomas and 1 (2.4%) juvenile pilocytic astrocytoma of the cervical spinal cord with metastasis to the brain. The remaining 10 (23.8%) were benign tumors (Table 2).

TABLE 2. Donor Characteristics

Demographics (n or mean \pm SD)	
Male	28
Female	14
Age (years)	37 \pm 13
Donor risk index	1.77 \pm 0.39
Imported organs	38.10%
Tumor histology (frequency)	
Glioblastoma multiforme (astrocytoma grade IV)	20 (47.6%)
Astrocytomas, unspecified subtype	8 (19%)
Subependymal giant cell astrocytoma	2 (4.8%)
Anaplastic ependymoma	1 (2.4%)
Juvenile pilocytic astrocytoma of the cervical spinal cord with metastasis to the brain	1 (2.4%)
Benign	10 (23.8%)
Total	42
Grade of tumor (frequency)	
II	8 (25%)
III	4 (12.5%)
IV	20 (62.5%)
Surgical intervention (frequency)	
Craniotomy	19 (45.2%)
Biopsy	7 (16.7%)
Ventriculostomy	6 (14.3%)
VP shunt	2 (4.8%)
No procedure	8 (19%)
Total	42

Abbreviations: SD, standard deviation; VP, ventriculoperitoneal.

Tumor Grade

Twenty (62.5%) of the neoplasms were grade IV tumors, 8 (25%) were grade II tumors, and 4 (12.5%) were grade III tumors (Table 2).

Surgical Intervention

Over 80% of the patients had at least 1 kind of invasive procedure violating the blood-brain barrier. Nineteen (45.2%) had a craniotomy, 7 (17%) had an intracranial biopsy, 6 (15%) had a ventriculostomy, and 2 (4.8%) had a ventriculoperitoneal shunt. Eight patients (19%) did not have any procedure done (Table 2).

Recurrence

The rate of recurrence for the entire group was 2.8% (all CNS tumor patients were alive). The only patient who developed recurrence was a 54-year-old male with cryptogenic cirrhosis who underwent retransplantation because of primary nonfunction. The donor was a 27-year-old female who reportedly, at the time of offer, had a juvenile pilocytic astrocytoma of the cervical spine with metastasis to brain. She died of intracranial hemorrhaging. None of the other organs from this donor were transplanted. The time to recurrence of the CNS tumor was 150 days. The tumor was evident on a computerized tomography scan (Fig. 1A) at 5 months, which showed numerous, peripherally enhancing mass le-

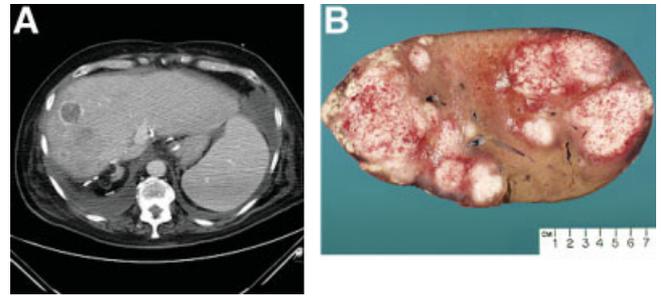


Figure 1. (A) Computerized tomography scan of the patient with recurrence showing characteristic ring enhancement. (B) Gross photograph of the tumor at autopsy.

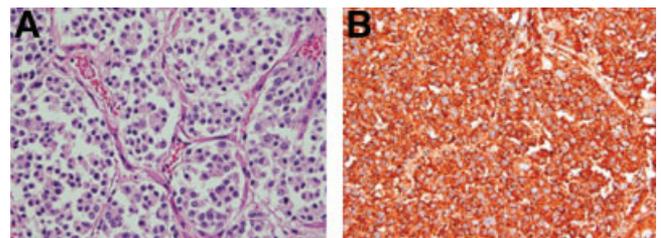


Figure 2. (A) The tumor appeared as nests of discohesive, atypical cells with abundant eosinophilic cytoplasm. Occasional mitoses were identified (hematoxylin and eosin stain, 400 \times magnification). (B) Strongly positive CD57 immunohistochemical stain (red color) supporting a neuronal origin of the tumor (400 \times magnification).

sions throughout the liver, the greatest dimension of the largest being 3.5 cm. No other mass lesions were noted on full body computed tomography scans. Figure 1B presents a gross photograph of the tumor at autopsy. A histopathological examination of 1 of the lesions revealed a poorly differentiated malignant neoplasm of neuroglial origin (Fig. 2A). The tumor cells were strongly positive for S100, protein gene product 9.5, vimentin, and neuronal markers CD56 and CD57 (Fig. 2B) and weakly positive for synaptophysin and neural markers beta tubulin and nestin. Fluorescence in situ hybridization studies performed on both the biopsy and autopsy tissue showed that the tumor cells contained only X chromosomes, confirming the donor origin (Fig. 3). Molecular chimera studies (Fig. 4) also confirmed that the tumor was of donor origin. Upon a review of the donor's original diagnosis by several neuropathologists, it was felt that the tumor would have been better classified as a ganglioglioma, with only the glial component being present in the initial biopsy. The tumor ultimately transformed into a high-grade neoplasm with a final diagnosis at the time of the recipient's autopsy of a metastatic, poorly differentiated neuroglial neoplasm.

Causes of Death

There were 7 (7.2%) deaths in all. The most common cause of death was sepsis (n = 3, 7.2%). One patient (2.4%) had multisystem organ failure, 1 (2.4%) had renal failure, and 1 (2.4%) had cardiac arrest. Care was

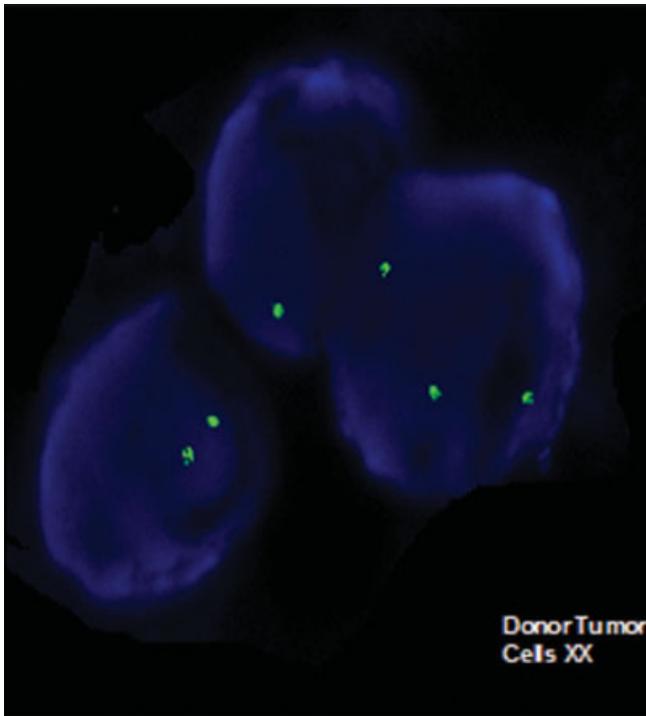


Figure 3. Fluorescent in situ hybridization for X and Y chromosomes on tumor biopsy. Only signals hybridizing to the X centromere (green) were detected.

withdrawn for 1 (2.4%) patient who had metastatic disease. None of the deaths were related to tumor recurrence. The actuarial patient survival was 80% at 5 years. There was no difference in survival between recipients of grafts from donors with CNS tumors and recipients of grafts from donors without CNS tumors (1 year: 82% versus 83.3%, $P =$ not significant; 3 years: 77.4% versus 72%, $P =$ not significant).

DISCUSSION

Donors with CNS tumors are commonly overlooked because of concerns about the transmission of malignancies to immunosuppressed recipients. Transplant surgeons have been reluctant to accept organs from donors with a history of CNS malignancy. There is an absence of substantive data defining the true risk of tumor transmission. A shortage of donor organs has led transplant programs to consider the increased use of organs from marginal donors.^{1,2} In 2001, Smith et al., analyzing the Scientific Registry of Transplant Recipients (SRTR) data, reported that organs used from donors with CNS tumors constituted the greatest proportion of all donors with a history of malignancy.²⁻⁴ 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.⁵ The report's conclusion, that there is minimal risk of donor-transmitted CNS malignancies, has been widely criticized. Several reports have documented transmission of CNS malig-

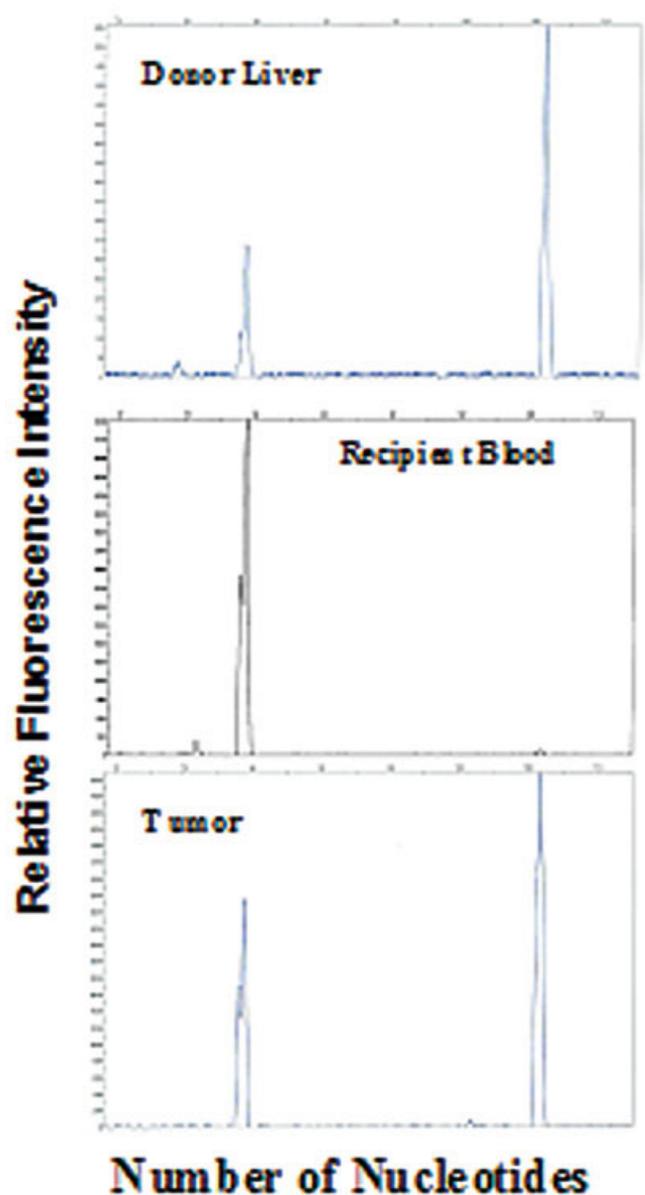


Figure 4. Electropherograms showing results from the analysis of the donor-derived, uninvolved liver, recipient-derived blood, and hepatic neoplasm with the polymorphic marker HUMCD4.

nancies after organ transplantation.⁶⁻⁹ A number of potential factors may explain the differences, such as a lack of tumor histology data and the length of follow-up. This study demonstrates that the recurrence rate based on a common denominator was 2.4% in all CNS tumors, 3.1% in malignant tumors, and 4.2% in malignant/intervention. Moreover, this experience demonstrated that despite surgical manipulation and high-grade CNS tumors, recurrence was uncommon.

The Israel Penn International Transplant Tumor Registry (IPITTR) data showed that in the absence of identifiable risk factors, a transmission rate of 7% was observed. However, in the presence of a single risk factor, the incidence of transmission varied from 36% to 43%.

In the presence of 2 risk factors, the transmission rate did not increase, and this demonstrated that the effect of multiple risk factors was neither additive nor synergistic. The IPITTR data are in distinct contrast to the SRTR and Australia and New Zealand Organ Donation Registry (ANZODR) data. A possible explanation for this difference may lie in the nature of the reporting structure for these registries. The SRTR and ANZODR registries identify patients through mandatory reporting, so underreporting may occur. In contrast, the IPITTR, a longstanding international registry, is an event-based registry. Event-based registries may result in higher event incidences, and reporting of events may be overrepresented in comparison with the entire population at risk because not all cases of CNS tumor-positive donor transplants are reported. Another discrepancy between these 3 registry experiences is the number of high-risk donors in each group. In the SRTR report,¹⁰ the proportion of benign tumors, tumor grade, and risk factors (eg, 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 not met by most patients in the SRTR series.

The findings of our study indicate that despite surgical manipulation and high-grade CNS tumors, recurrence was not common. Thus, the use of such organs may seem reasonable for the patient with high expected mortality on the wait list for a life-sustaining organ transplantation. Buell et al.¹¹ reported 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 the SRTR and ANZODR data indicate a low transmission rate; this 7% rate may be an overestimation of the true risk.

Overall, because of their low metastatic potential, donors with PBTs remain an attractive and underused population of organ donors. In the United States, approximately 12,000 to 13,000 patients die of PBTs each year. However, despite their low rate of extraneural metastases, the United Network for Organ Sharing reports that between 1994 and 2006, only 719 of approximately 160,000 individuals who died of or with the diagnosis of a PBT were used within the donor pool.

In our experience, despite violation of the blood-brain

barrier and high-grade CNS tumors, recurrence was uncommon. Grafts from these donors are often an overlooked source of high-quality organs from younger donors and can be appropriately used, particularly in patients who, despite low MELD scores, carry a high risk of mortality.

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