

Deceased donor liver transplantation from donors with central nervous system malignancy: Experience of the Inonu University

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ABSTRACT

OBJECTIVE: Liver transplantation from deceased donors with a central nervous system (CNS) malignancy has some risk of tumor transmission to the recipient. Though the risk is small, this group of donors is regarded as marginal. The use of marginal grafts may be an acceptable alternative practice in order to expand the donor pool in countries where there is a shortage of donated organs. The aim of this study was to examine and present the outcomes of liver transplantsations performed using donors with a CNS tumor.

METHODS: Between March 2002 and July 2017, 1990 (deceased donor: n=399, 20%; living donor: n=1591, 80%) liver transplantations were performed at the center. Of the 399 deceased donors, 17 (4.2%) had a CNS tumor. The data of donors with a CNS tumor and of recipients who survived for more than 1 month (n=11) were retrospectively reviewed. Demographic data, the grade of the CNS tumor, tumor transmission to recipient data, and survival rates were analyzed.

RESULTS: Only 2 (18%) grafts were provided locally, 6 (54%) were offered to the transplantation center after all of the national centers had declined them, and 3 (37%) were made available to us by the national coordination center for patients with a documented notification of urgency. High-grade (grade III-IV) brain tumors were detected in 7 (64%) donors, while low-grade (grade I-II) tumors were found in 2 patients. The remaining 2 donors were not pathologically graded because the diagnosis was made radiologically. The 1-, 3-, and 5-year overall and tumor-free survival of the patients was estimated at 100%, 70%, and 45%, respectively.

CONCLUSION: A median survival of 40 months (range: 13-62 months) was achieved in recipients of grafts from a donor with a CNS tumor and no donor-related malignant transformation was observed.

Keywords: Central nervous system tumor; deceased; liver transplantation.

In countries where few organ donations are made, including ours, efforts to expand the donor pool continue. Transplantation centers may focus on living donor transplantation programs or may use non-optimal, marginal cadaver grafts. The Inonu

University Liver Transplantation Institute is the most widely used clinic in the country, and applies both of these solutions to perform more than 200 liver transplantations every year (80% from living donors [1-4].



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Cadaveric grafts harvested from donors with central nervous system (CNS) tumors are considered marginal grafts due to the risk of donor tumor cell migration and donor-derived tumor development in the recipient [5]. The World Health Organization classified primary brain tumors from grade I to grade IV based on biological behavior and prognosis. Grade IV tumors are cytologically malignant, usually fatal, and have the greatest risk of transmission from donor to recipient [6].

This study is an analysis of the results of liver transplantation using cadaveric donors with CNS tumors.

MATERIALS AND METHODS

The data of 1990 transplant patients who received a liver between March 2002 and July 2017 at the center from either living ($n=1591$) or cadaveric ($n=399$) donors were retrieved from a prospectively registered data bank. The data were retrospectively screened and 17 patients who received transplant livers from donors with a CNS tumor were identified. Since our objective was to determine whether any transmission of donor tumor cells to the recipients occurred, patients who were followed up for more than 1 month were included in the study. The demographic characteristics of the donors, the diagnostic method used for the CNS tumor, the type and histological stage of the tumor, the harvest and use of any other donor organs, the demographic characteristics of the transplant recipient, the length of survival, and the transmission of tumor cells from donor (if any) were recorded and assessed. Kaplan-Meier analysis was used to estimate survival of the transplant recipients.

RESULTS

The demographic characteristics of the donors with CNS tumors and of the recipients are presented in Tables 1 and 2, respectively. The diagnosis was established with histopathological analysis in 9 (82%), and visualization of a mass in radiological images in 2 (18%) of the donors. The donors had either grade III-IV ($n=7$, 64%; glioblastoma multiforme: $n=4$,

TABLE 1. Demographic data of the donors

Parameters	n (%)
Age, median (years) (distribution range)	34 (3-71)
Gender	
Female	7 (64)
Male	4 (36)
Diagnosis	
Histopathological examination	8 (91)
Resection	8
Biopsy	1
Radiological	2 (9)
Tumor histology	
Glioblastoma multiforme	4 (36)
Medulloblastoma	2 (18)
Lymphoma (large B-cell)	1 (9)
Schwannoma	1 (9)
Neuroepithelial tumor	1 (9)
Cerebral mass (radiological)	
Porencephalic cystic/solid mass	1 (9)
Choroid plexus papilloma	1 (9)
Tumor grade	
Low-grade (I-II)	2 (18)
High-grade (III-IV)	7 (64)
Radiological diagnosis	2 (18)
Transplanted organs	
Liver	4 (36)
Liver+kidneys	4 (36)
Liver+kidneys+cornea	1 (9)
Liver+kidneys+heart+small bowel	1 (9)
Liver+cornea	1 (9)
Risk factors	
Craniotomy	
Yes	9 (82)
No	2 (18)
Ventriculoperitoneal shunt	
Yes	1 (9)
No	5 (45)
Unknown	5 (45)
History of chemotherapy or radiotherapy	
Yes	1 (9)
No	9 (82)
Unknown	1 (9)

medullablastoma: $n=2$, lymphoma: $n=1$) or grade I-II ($n=2$, 18%; schwannoma: $n=1$, neuroepithelial tumor: $n=1$) tumors. The 2 patients whose tumors were diagnosed based on radiological findings did

not have histological grading. The liver, kidneys, heart, and small bowel of the 2 donors who had radiological diagnosis were used. The liver and cornea were transplanted from a donor with chronic renal failure who had been receiving hemodialysis. Only the liver was transplanted from 3 of the 7 patients with a higher histopathological grade, while the liver and kidneys of the other 4 patients in that group were used. The liver was transplanted from 1 patient with a low-grade tumor, while the liver, kidneys, and cornea were transplanted from the other patient with a grade I-II tumor.

The median age of the transplant recipients was 32.9 years (range: 8-57 years) and 6 (54%) were

male. The median Model for End-Stage Liver Disease/Pediatric End-Stage Liver Disease score was 17 (range: 7-30), and 46% were assessed as Child-Pugh classification C. In all, 91% (n=10) of the grafts were a complete liver graft, and 1 was a split graft used for 2 recipients. One of the patients who received the split liver transplantation died within the first month posttransplantation, and was therefore excluded from the study. Long-term mortality was observed in 6 of 11 patients who were followed up for a median 33 months (range: 13-62 months). The cause of death was sepsis in 4 cases and gastrointestinal bleeding in 1. The remaining 5 patients were still living at the time of writing (median follow-up period:

TABLE 2. Demographic data of the recipients

Parameters	Parameters
Age, median (years) (distribution range)	32.9 (8-57)
Gender, n (%)	
Female	5 (46)
Male	6 (54)
Child-Pugh class, n (%)	
A	3 (27)
B	3 (27)
C	5 (46)
MELD/PELD score, median (range)	17 (7-30)
Etiology, n (%)	
Hepatitis B virus	5 (46)
Wilson disease	1 (9)
Decompensated Wilson disease	1 (9)
Alcohol consumption	1 (9)
Echinococcus alveolaris	1 (9)
Primary sclerosing cholangitis	1 (9)
Cholestatic liver disease	1 (9)
UNOS classification, n (%)	
1 (intensive care unit patient)	2 (18)
2 (inpatient)	2 (18)
3 (under medical treatment)	5 (46)
4 (at home; patients with normal liver function)	2 (18)
Graft type, n (%)	
Full-size	10 (91)
Segment 5-6-7-8 (split)	1 (9)
Organ source, n (%)	
National (emergency)	3 (27)
National (not used by other centers)	6 (54)
Local (at our center)	2 (27)
Mortality	
Early (within the first 30 days)	6 (35)
Cause of death (<30 days), n	
Primary non-functional	1
Postoperative bleeding	1
Hepatic artery thrombosis	1
Sepsis	3
Survival, days (months)	
Survived, n (tumor-free survival; median: 43 months; range: 14-60 months)	5 (46)
Died, n (tumor-free; median: 33 months; range: 13-62 months)	6 (54)
Cause of death (>30 days)	
Kaposi sarcoma	1 (9)
Sepsis	3 (27)
Acinetobacter	1 (9)
Influenza A virus	1 (9)
Gastrointestinal bleeding	
Overall survival, months, median	40 (13 - 62)
Disease-free survival, months, median	40 (13 - 62)

MELD: Model for End-Stage Liver Disease; PELD: Pediatric End-Stage Liver Disease; UNOS: United Network for Organ Sharing.

43 months [range: 14-60 months]). The median length of follow-up of all patients was 40 months (range: 13-62 months), and during that time no donor-related malignancy was observed in any patient. The overall and tumor-free 1-, 3-, and 5-year survival rate was 100%, 70%, and 45%, respectively.

DISCUSSION

Among transplant donors, CNS tumor is the most frequently seen type of tumor after skin cancers. Since CNS tumors very rarely spread beyond the brain, there is some willingness to accept organs from these donors for transplant. While some literature data have scientifically proven the transmission of tumor cells from donors with CNS tumors to recipients [7], other reports have indicated only a small risk (or none) of transmission [8-11]. Therefore, the existing guidelines to be followed may be updated in the light of new data [5, 12-14].

In all of these guidelines, absolute contraindications for organ transplantation from donors with primary lymphoma of CNS and secondary intracranial malignancies are emphasized. In addition, whatever the tumor type, it is stressed that preexisting craniotomy, ventriculoperitoneal shunt, or history of chemotherapy/radiotherapy increases the risk of transmission of tumor cells. Based on UK data, the overall risk is 1.5%, and increases to 2.2% in grade IV CNS tumors. It has been accepted that a ventriculoperitoneal shunt increases the risk of extracranial metastases at an estimated rate of less than 1% [13]. In our study, despite the prevalence of unfavorable criteria, such as high-grade CNS tumors (64%) and craniotomy (82%), transmission of donor-related tumor cells was not detected in any transplant recipient. Furthermore, transmission of tumor cells was not detected in a recipient of a liver from a donor with CNS lymphoma, which is generally considered an absolute contraindication [15]. Similarly, other studies with a large database reported no transmission of tumor cells from donors with high-grade CNS tumors to transplant recipients [9-11].

Therefore, in our country, where the procurement of transplant organs is an issue, these donated organs with a very low risk of transmission of tumor cells

should not be discarded. The patients who could benefit from their transplantation should be taken into consideration, and each case should be evaluated individually. Detailed informed consent was obtained from all of our patients to use these organs.

In our study, the transplant of organs of 11 donors with CNS tumors was analyzed. In all, the organs of 9 donors with a histopathological diagnosis (the liver of 4 patients, and the liver and kidneys of 5 patients) and 2 donors with a radiological diagnosis (the liver and corneas of 1 patient with chronic renal failure, and the liver, kidneys, heart, and small bowel of the other patient) were used. Though there is some hesitancy concerning the use of these organs, successful transplantation can be performed. Six (54%) of these organs were made available by the national coordination center to organ transplantation centers but were rejected before being offered to us. Two of these 6 patients exited (at 26 and 62 months), while 4 are still living (range: 14-48 months since transplantation). If we had not used these organs they would have been discarded.

Early phase mortality was observed in 6 of 17 cases (sepsis: n=3, hepatic artery thrombosis: n=1, primary nonfunctional kidney: n=1, bleeding: n=1). Long-term mortality was seen in 6 patients, most frequently related to sepsis (n=4). The other causes of long-term mortality were Kaposi sarcoma (n=1) and gastrointestinal bleeding (n=1). The median follow-up of the patients who died in the long-term was 33 months (range: 13-62 months), and all found to be tumor-free.

In conclusion, including marginal donors with CNS tumors expanded our organ pool by 4.2% (17/399). We achieved a median survival of 40 months (range: 13-62 months) with these grafts, and no transmission of donor-related malignancy was observed in any recipient.

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