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Evaluation and Application of Donors with Primary Central Nervous System Tumors

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ABBREVIATIONS

CNS, Central nervous system

DBD, Donation after brain death

CI, Confidence interval

Background: This study aims to explore the safety of donors with primary central nervous system tumors for kidney and liver transplantations. **Methodology:** Clinical data of 29 donors with primary CNS tumors in January 2007 to December 2017, as well as the follow-up data of 16 liver transplant recipients and 46 kidney transplant recipients, were analyzed. According to the risk factors, the high risk group was classified as Group 1,the low risk factors were classified as Group 2 and the unknown risk group was classified as Group 3. The incidence of donor-transmitted CNS tumors was calculated and compared. **Results:** The duration from the diagnosis of 29 donors to donation was (5.67±6.36) months. None of the liver and kidney transplant recipients who were followed up had tumor metastasis. Although

the mean survival time of Group 1 was lower than that of Group 2 and Group 3, the Kaplan-Meier curve showed no significant difference in survival time. **Conclusion:** No obvious difference was observed between high- and low- and unknown risk CNS tumors in terms of the survival rate of transplants and tumor metastasis rate. High-risk CNS tumor donors can be used with the informed consent of recipients after a full evaluation.

Keywords: primary CNS tumor; liver transplantation; kidney transplantations; tumor metastasis

A serious imbalance occurs between the supply and demand of organs in China. The use of marginal donors and expanded marginal donors has become an important way to increase the transplantations rate and reduce the death rate of transplant recipients. The donors per million people increase yearly. Organ donation after the death of a citizen has become the main source of organ transplantation in China. According to the actual conditions in China, organ donation after the death of a citizen is divided into three categories, as follows: C-I, donation after brain death (DBD); C-II, donation after cardiac death; and C-III, donation after brain death awaiting cardiac death. DBD donors, after brain death, are organs that the donor's family chooses to donate voluntarily after a series of strict brain death judgments.

Primary central nervous system (CNS) tumors are a kind of marginal donation. The status quo of their use in China is that organ donation starts late, only few donors are used, and relevant experience is limited. The process of reasonably evaluating the tumor metastasis

risk of recipients after transplantation surgeries has become an important issue. Among the organ donation cases completed by our center within 10 years from January 2007 to December 2017, donors with primary CNS malignant tumors accounted for 5.3% (29/552). In the present study, through a follow-up analysis of 29 donation cases and 62 recipients (12 recipients lost to follow-up have been excluded), we evaluated the safety of CNS tumor donors for organ donation and the transmission risk of donor-related CNS tumors after liver and kidney transplantations.

Data and Method

Our center completed 552 organ donation cases from January 2007 to December 2017, including 29 cases with primary CNS tumors. A total of 25 livers and 58 kidneys were obtained.Our center performed 3 liver transplantations surgeries and 51 kidney transplantations surgeries. Fifteen livers and 5 kidneys were distributed to other hospitals through China Organ Transplant Response System. The total utilization rate of donor kidneys was 96.6% (56/58). A total of 29 donors with primary CNS tumors, 16 liver transplant recipients (2 recipients lost to follow-up had been excluded), and 46 kidney transplant recipients (10 recipients lost to follow-up had been excluded) were included in our study. We grouped all donors according to the 2016 CNS tumor grades issued by the WHO and the different tumor risk stratifications proposed by Disease Transmission Advisory Committee (DTAC).[1-2] High risk(Group 1) (>10% transmission) includes CNS tumor (any) with ventriculoperitoneal or ventriculoatrial shunt, surgery (other than uncomplicated biopsy), irradiation or extra-CNS metastasis and CNS Tumor WHO grade III or IV.Low risk (Group

2)(0.1–1% transmission) includes Low grade CNS tumor (WHO grade I or II) and Primary CNS mature teratoma.Nnknown risk group (Group 3) includes cases with no pathology.Therefore, these donors included 14 high-risk donors, 5 low-risk donors and 10 unknown risk. The follow-up patient group included the use of high-risk donor groups , low-risk donor groups and unknown risk donor groups.5 liver transplantations and 22 kidney transplantations were conducted on the high risk donor group;4 liver transplantations and 9 kidney transplantations were conducted in low risk group;7 liver transplantations and 15 kidney transplantations were conducted in unknown risk group. The survival rate of recipients and transplants in these two groups was analyzed using Kaplan–Meier survival function.

Compliance with ethical standards

Our study was approved by the Medical Ethics Committee of No. 303 Hospital of People's Liberation Army. Based on the Declaration of Helsinki, written informed consent was obtained from all patients included in the trial.

STATEMENT: NO EXECUTED PRISONERS WERE INCLUDED IN THE DONORS OR PATIENTS PARTICIPATING IN THIS STUDY.

1. The donor data were collected.

The donor data included age, gender, nationality, cause of death, intensive care time, treatment time, hepatic functions (aspartate transaminase, alanine aminotransferase, and γ-glutamyltransferase), serum sodium (Na), renal functions (serum creatinine, urea nitrogen, serum β2-microglobulin, and uric acid) assessed with laboratory parameters, cold ischemia

time, and other risk indexes for donation.

2. The transmission risk of tumor was assessed.

The donation type of donors and the pathological type of tumors were collected.

3. The recipient data and follow-up data were collected.

The recipient data included age, gender, and liver and kidney diseases. The follow-up data included survival time of recipients, survival time of transplants, and morbidity and mortality of local or metastatic diseases.

4. Statistical analysis

SPSS (Version 21.0) and Prism(Version 6.0) statistical software were used to process the data. Enumeration data were represented with frequency and percentage. Enumeration data were represented with frequency and percentage. Measurement data were represented with mean±SD. Kaplan–Meier survival analysis was carried out on follow-up objects.

Results

1. General information of the donors and pathological grading of tumors

Among 29 donors with primary CNS tumors, 22 (75.9%) were from tertiary hospitals and 7 (24.1%) were from secondary hospitals. The donor types were 26 (89.7%) C-I donors, 3(10.3%) C-II donors, and 0 (0.0%) C-III donors, including 15 and 14 male and female donors, respectively. The ages of donors were 23.75±15.39 years old (in the range 4–56 years old), including 12 minor donors aged 9.58±4.32 years (<18 years). The duration from the diagnosis of donors as primary CNS tumors to donation was 5.67±6.36 months (in the range

1.0–29.0 months). Among them, 17 donors had pathology. The pathological grade of central nervous system tumors was 1 case of WHO-I tumor, 4 cases of WHO-II tumor, 2 cases of WHO-III tumor, and 10 cases of WHO-IV tumor.The pathology of the remaining donors was not investigated 8 of them were glioma donors (4 cases of diffuse astrocytoma (WHO-II), 2 cases of Anaplastic astrocytoma (WHO-III), 2 cases of donor glioblastoma (WHO-IV)), 1 case of meningioma donor (WHO-I), 6 cases of Medulloblastoma donor (WHO-IV), 1 case of Glioblastoma subtype (WHO-IV), and 1 case of germ-cell tumor in sellar region (WHO-IV)(Tables 1-2, Fig.1). The results of the last test on hepatic and renal functions before donation showed normal levels. The creatinine was 67.35±57.12 μmol/L, the BUN was 6.28±5.19 mmol/L, the glutamic-pyruvic transaminase was 320.4±1348.4 U/L, and the glutamic-oxalacetic transaminease was 529.9±2276.8 U/L .

2. The treatment of donor tumors.

Before donation, donors with primary CNS tumors received different medical and surgical treatments from the local hospital, mainly including craniotomy, V-P(ventriculoperitoneal)/V-A(ventricle-right atrium) shunt, radiotherapy, chemotherapy, and so on. These therapeutic regimens were considered as risk factors of extracranial metastasis. Such donors are high risk according to WHO classification. Among all donors, The numbers are including 14 high risk, 5 low risk and 10 unknown risk (High risk =2 anaplastic astrocytomas, 2 glioblastomas, 6 medulloblastomas, 1 gliosarcoma subtype, 2 germ cell tumors in sellar region, 1 pineal tumor), (Low risk =4 diffuse astrocytomas, 1 meningioma) ,(Unknown risk =10 “brain tumor” without interventions). (Tables 2).

3. Follow-up data of recipients

The 56 kidney transplant recipients included 38 male recipients and 18 female recipients. The total recipients included 51 kidney transplant recipients in our center (43 with normal follow-up and 8 lost in follow-up). The 43 recipients followed up by our center had no tumor complication. One recipient had transplanted kidney dysfunction, another recipient had transplanted kidney excision, and 5 recipients were distributed to an external unit (three with normal follow-up and two lost in follow-up). All three recipients who were distributed to an external unit were discharged normally. The average follow-up time of kidney transplant recipients was 34.18 months in the high-risk group , 30.78 months in the low-risk group and 21.27 months in the unknown risk group. During follow-up, none of the patients had tumorigenesis after kidney transplantation. In the last follow-up, the creatinine was (135.56±113.43) μmol/L. Five of the recipients had pulmonary infections. Eight recipients had delayed graft function but were discharged normally after treatment. Only one recipient had transplanted kidney dysfunction. One recipient had transplanted kidney excision (Table 3).

Among 18 liver transplant recipients (16 with normal follow-up and 2 lost in follow-up), one recipient had biliary complication but was discharged normally after treatment. The average follow-up time of liver transplant recipients was 19.60 months in the high-risk group ,26.25 months in the low-risk group and 21.42 months in the unknown risk group. Two patients did not show liver function recovery after liver transplantation. One patient died of liver cancer recurrence and liver and kidney failure. Three cases had HCC recurrence

and thus continued with the treatment until the functions of the remaining liver returned to normal. No donor-related tumor metastasis was found in the postoperative follow-up of all liver transplant recipients.

All kidney transplant recipients in Groups 1 and 2 survived by the follow-up date. In the two groups of donors, two recipients had transplanted kidney dysfunction. The Kaplan–Meier curve showed no significant difference between two groups in terms of survival time. Although the mean survival time of liver transplant recipients in Group 1 was lower than Group 2 (19.6±16.13<26.25±21.79 months; 95% CI), the Kaplan–Meier curve showed no significant difference between the two groups (P= 0.63>0.05). Group 1 was lower than Group 3(19.6±16.13<21.43±20.56 months; 95% CI), the Kaplan–Meier curve showed no significant difference between the two groups (P=0.87>0.05). Group 2 was lower than Group 3(26.25± 21.79<21.43±20.56 months; 95% CI), the Kaplan–Meier curve showed no significant difference between the two groups (P=0.73>0.05). (Figs. 2–3).

Discussion

Malignant tumors, such as breast cancer, lung cancer, lymphoma, and renal cell carcinoma, have been reported to metastasize from donors to recipients through transplantation[3]. Organ transplantation with pre-existing cancer cells has also attracted wide attention, and the risk of cancer metastasis has also become a problem that must be considered in organ transplantation. The particularity of CNS anatomy makes the extracranial metastasis rate of CNS tumors extremely low, only 0.4‰–2.3‰[1,3]. The extracranial metastasis rate among minor patients is relatively high. The incidence rate is 0.98% [16],

which makes this kind of donors a current channel to expand donor source. Armanios et al. [4] reported that every year, nearly 17,000 patients in the United States were diagnosed with primary CNS malignant tumors. Among them, approximately 13,000 have died. These patients became an important potential source of organ donation. CNS tumors include intracranial and intraspinal tumors. The incidence rate of such kind of tumors in China is in the range 8.7~12.7 per million people [5]. The safe use of these donors will be a boon for those waiting for transplant. The use of primary CNS tumor donors started early in foreign countries. Hynes et al.[6] analyzed 58,314 recipients using United Network for Organ Sharing (UNOS) data and compared 337 CNS tumor donor recipients with 52,691 non-CNS tumor donor recipients. The Kaplan–Meier curve showed no significant difference between two groups in terms of death time. As high-risk tumor transmission cases often occur from donors to recipients, the overall reported transmission rate ranges from low to high. A study by Buell et al. [7] showed that 62 recipients used high-risk CNS tumor donors, and 14 of them were infected. The transmission rate was up to 22.6%. In the presence of multiple risk factors, such as ventricular shunt, craniotomy, or high-grade tumor, the transmission rate can be up to 46%. Kauffman [8] analyzed UNOS data and found that 642 CNS tumor donors were donated from 2000 to 2005. Only one donor with glioblastoma multiforme was transmitted to three recipients. The recipient transmission rate was 0.012%. Po Zhao[9] reported that one recipient had pineocytoma metastasis at 4 months after combined multiple-organ transplantation. The transplant was carried out with no suspicion of brain tumor in the donor; tumor was detected by donor autopsy with report 7 weeks after transplant. He also summarized that by 2007, a total of 31 CNS tumor metastasis cases were counted in the U.S. UNOS system and

non-UNOS cases. Benkö T et al. [10] reported 27 CNS tumor cases in Germany from 2002 to 2017. The median follow-up time of recipients was 19.9 (0–155) months. No malignant tumor transmission case was reported. The 5-year survival rate of these recipients did not exhibit statistical difference from that of standard donor recipients. Watson [11] reviewed 179 recipients with primary intracranial malignant tumors that were in the British Registry from 1985 to 2001, 33 of whom had high-risk tumors. No malignant tumor transmission was found in 448 recipients who were followed up. Warrens [12] reviewed 246 recipients using organs of CNS tumor donors in Britain and found that the overall mortality of kidney and liver recipients was not different from that of non-CNS tumor donors. A single-center data statistic made by Volkan Ince [13] showed that 17 CNS tumor donors from 2002 to 2017 contained 7 high-risk donors who were discharged safely after surgery. They showed no difference compared with other recipients in terms of the incidence rate of postoperative complications. No donor-sourced occurrence was observed during the postoperative follow-up.

In this paper, by analyzing the data of 29 CNS tumor donors among 552 donation cases in our center, we found several risk factors in donors, such as high-risk CNS tumor and therapeutic interventions (including craniotomy, V-P/V-A shunt, radiotherapy, chemotherapy, and so on). Such donors were often considered an absolute contraindication in other centers abroad [2,7, 14].The causes of death in liver transplant patients were different between the two groups. Although the surgery was successful, the resulting death was due to the failure of postoperative liver function recovery, various complications, and recurrence of primary tumors. However, we did not detect any donor-related tumor cell transmission among all liver and kidney transplant recipients. We observed the distribution of Kaplan–Meier survival

function, analyzed data, and found that two kinds of donors did not have a large gap in transplant survival after liver and kidney transplantations and in survival time of recipients. This finding does not suggest that the survival quality of non-high-risk donors was better than that of high-risk donors. No obvious gap was observed between the two kinds of donors in postoperative follow-up.

We considered that CNS tumors seldom had extra-CNS metastasis. On the one hand, tumor cells can hardly get through due to the existence of blood-brain barrier. On the other hand, the recipients immune system possibly play a certain role in limiting and inhibiting tumor cells. Buell reported that the metastasis of donor tumors may be associated with the following: these tumors are severe malignant tumors; craniotomy and other operations seriously damage the blood brain barrier; and the recipient's immunity is relatively poor. In addition, some of the data in this article were derived in 1970 and are limited by the treatment level of CNS tumors, the maintenance level of donors, and the choice of immunosuppressor at that time. The study by Warrens suggested that the increased risk of extra-CNS metastasis due to the cerebrospinal fluid (CSF) shunt of CNS tumor donors may be less than 1%, and undergoing CSF shunt should not be an absolute contraindication to transplantation. Many large foreign databases had followed up high-risk CNS tumor donors for many years, and no tumor cell transmission from CNS tumor donors to transplant recipients has been observed [6-9,11-13,15](Table 3). In addition, our data also indicated that no difference was found between the use of CNS tumor donors and general donors in liver and kidney transplantations in terms of mortality rate. In China, many patients are in urgent need of transplantation surgeries. The shortage of organs is still an important factor that restricts the development of transplants.

Many patients die because of the absence of a suitable donor. Therefore, we believe a CNS tumor donor can be used as a kind of expanded marginal donor. Donors with high-risk factors must be used appropriately with the informed consent of patients and after a full evaluation of the conditions of the donors and recipients.

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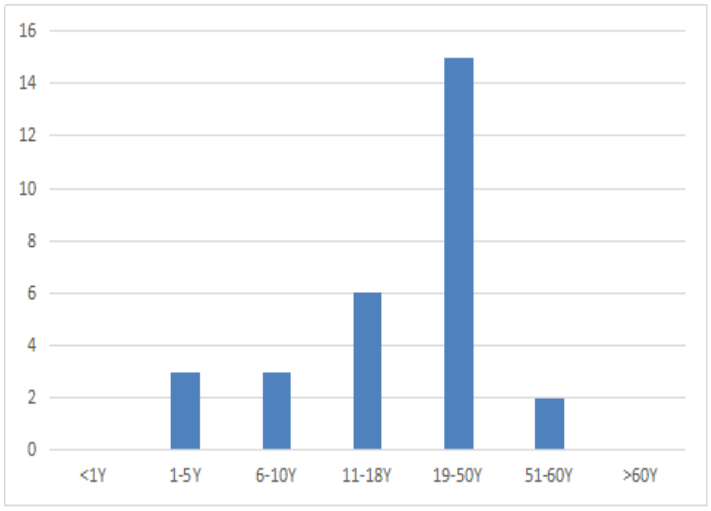
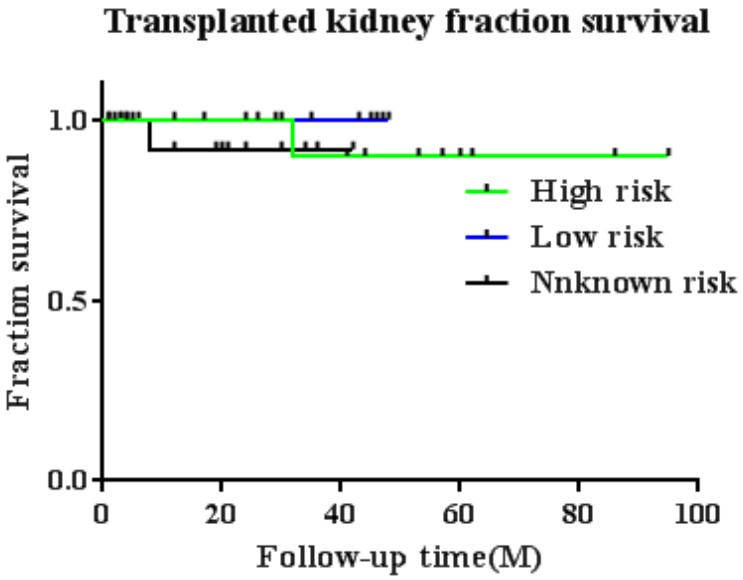
Variables	All		Variables	All	
Age (years)	**n**	**%**	**Hospital level**	**n**	**%**
<1	0/29	0.0%	Tertiary hospital	22/29	75.9%
1-5	3/29	10.3%	Secondary hospital	7/29	24.1%
6-10	3/29	10.3%	**Type of Donors**		
11-17	6/29	20.7%	DCD	3/29	10.3%
18-29	5/29	17.2%	DBD	26/29	89.7%
30-49	10/29	34.5%	**Organ output**		
50-59	2/29	6.9%	Liver	25/29	86.2%
>60	0/29	0.0%	Kidneys	58/58	100%
Gender			**Organ utilization**		
Male	15/29	51.7%	Liver	18/25	72.0%
Female	14/29	48.3%	Kidneys	56/58	96.6%

Variables	**All**						
Tumor pathology	n	WHO grade	Craniotomy	V-A	V-P	Radiotherapy	Chemotherapy
Meningioma	1/17	I	-	-	-	-	-
Diffuse astrocytoma	4/17	II	-	-	-	-	-
Anaplastic astrocytoma	2/17	III	2/10	1/2	-	1/3	-
Glioblastoma	2/17	IV	-	-	-	-	-
Medulloblastoma	6/17	IV	6/10	1/2	1/1	2/3	1/1
Gliosarcoma subtypes	1/17	IV	1/10	-	-	-	-
Germ-cell tumor in sellar region	1/17	IV	1/10	-	-	-	-
No pathology	n	WHO grade	Craniotomy	V-A	V-P	Radiotherapy	Chemotherapy
Sellar area tumor	1/12		-	1/1	-	-	1/1
Pineal tumor	1/12		-	-	1/1	-	-
Brain tumor	10/12		-	-	-	-	-

References(year)	Number of recipients of CNS donors	Average follow-up time（M）	Number of donor tumor spread（%）
Buell JF[7]（2003）	62	-	12（22.6%）
Kauffman[8]（2007）	642	-	3（0.012%）
Watson[11]（2010）	179	≥60	0（0%）
Benkö T[9]（2017）	27	19.9	0（0%）
Warrens[12]（2012）	246	-	0（0%）
Volkan Ince[13]（2017）	17	40.0	0（0%）
Hynes CF[6]（2017）	337	72.0	0（0%）
Desai R[15]（2014）	133	85.2	0（0%）





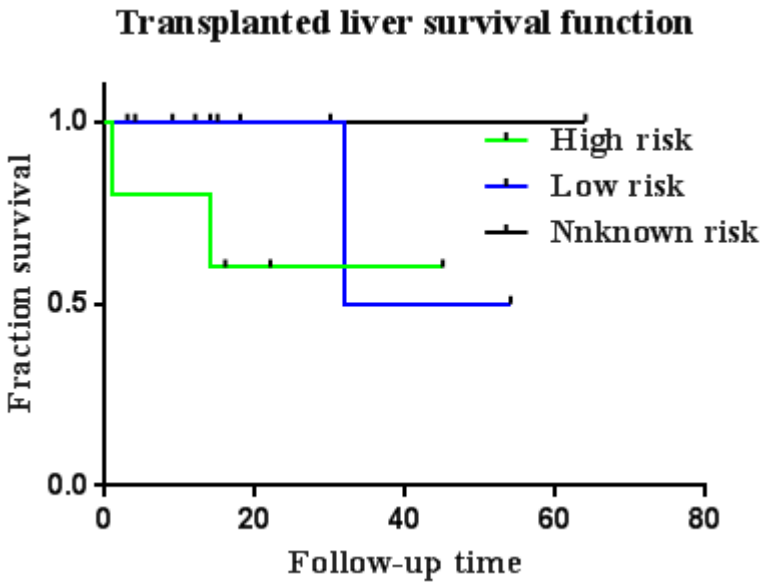


Fig.3 Distribution of fraction survival of liver transplant recipient