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Liver Transplantation From Donors With a History of Malignancy: A Single-Center Experience

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Background. The demand for transplantable organs exceeds donor organ supply. Transplantation of organs from donors with a history of malignancy remains controversial and the transmission of cancer in liver transplant recipients has not been sufficiently examined. **Methods.** From 2002 until 2017, 83 livers from donors with a history of malignancy were transplanted at the University Hospital Essen, Germany. Donor and recipient data, type of malignancy, tumor-free interval at organ procurement, and follow-up data were analyzed. **Results.** Nine different tumor sites (central nervous system [n = 27], genitourinary [n = 24], breast [n = 10], skin [n = 8], colorectal [n = 5], lung [n = 3], hemato-oncological [n = 3], thyroid [n = 2], and larynx [n = 1]) were detected in 83 donors. The majority (58%) of donors had tumor-free intervals of less than 5 years versus 19% of 6 to 10 years versus 23% over 10 years. The risk of tumor transmission from donors was assessed as low in 44 (53%), intermediate in 28 (34%), and high in 11 (13%) cases. During median follow-up of 19.9 (0-155) months, none of the recipients developed donor-transmitted malignancy. **Conclusions.** Liver transplantation with organs from donors with a medical history of malignancy is feasible, and the risk of donor-transmitted malignancy appears to be low in this single-center analysis. A careful selection of donors remains mandatory and can expand the donor pool.

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Liver transplantation is the standard treatment for patients with acute liver failure or end-stage liver disease. Since the 1980s, the number of patients who underwent this procedure has been increasing. The demand for transplantable organs has far exceeded the rate of organ donation, resulting in an increased mortality rate of patients on the waiting list. Because of the severe organ shortage, extended criteria donors, such as donors with steatotic grafts, positive viral serology, or highly elevated liver enzymes, are increasingly used.[1-3] These extended criteria donor organs are known to carry the risk of increased recipient morbidity and mortality due to potentially impaired liver parenchyma resulting in delayed graft function or primary nonfunction.

The persisting organ shortage warrants evaluation of all potential donors, including those with a history of malignancy. Approximately 1.7% of deceased donor organ transplants result from donors with a history of malignancy.[4] Of these donors, 85% had a history of skin, central nervous system (CNS) or genitourinary cancers. The risk of transmission is low; based on a careful donor and recipient selection, 0.05% of recipients develop donor-derived cancer. This risk must be considered against the perspective of the important, life-saving benefits of liver transplantation. Furthermore, these organs do not carry the immediate increased risk of recipient morbidity to the same extent because liver function is usually not impaired.

Nonetheless, it is important to ensure that the risk of transmitting disease with a transplanted organ is kept low. At the beginning of transplantation history, organs from donors with malignancies were routinely used, transmitting cancer with a high frequency and associated mortality. Nowadays, there is a renewed interest in donors with a history of malignancy with reassuring data from 2 large studies.[4,5] In a first report of United Network of Organ Sharing (UNOS) registry data, none of the recipient malignancies were of the same histological type that had been recorded in the donors' history.[6] An analysis of Organ Procurement and Transplantation Network/UNOS data from 2000 to 2005 reported 4 deaths from donor-transmitted malignancy compared to almost 40 000 waitlist deaths.[4] In times of organ shortage, the comparably small risk of disease transmission should be balanced carefully against the high mortality rate of waitlist patients.

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According to the Guide of the European Council for Organ Transplantation in 2016, analyzing data from international and national tumor registries like the Israel Penn International Transplant Tumor Registry, UNOS data, and several European registries, there are recommendations for acceptance of organs from donors with malignancy in their history with unacceptable, high, intermediate, or low risk of tumor transmission.[4] Donors with minimal risk are acceptable for all organs and all recipients. Donors with low to intermediate risk are acceptable, justified by the specific health situation of the recipient or the severity of their clinical condition, based on a risk-benefit analysis. Acceptance of donors with high risk may be discussed in exceptional cases and for some lifesaving transplantation procedures in the absence of any other therapeutic options on a case-by-case basis, after careful and reasonable risk-benefit assessment and informed consent of the recipient. Active malignancy and/or metastatic disease represents an absolute contraindication to transplantation due to an unacceptable risk of tumor transmission.

Because of the lack of conclusive data on donor-transmitted malignancies in liver transplant recipients, our study was performed to assess the occurrence and risk factors of donor malignancy transmission in that population.

MATERIALS AND METHODS

The study was conducted in accordance with the local ethics committee (Ethik-Kommission der Medizinischen Fakultät der Universität Duisburg-Essen) and the Helsinki Declaration of 1975, as revised in 2008, and is based on the retrospective analysis of 1764 deceased donor liver transplantations at the University Hospital in Essen, Germany, between May 2002 and March 2017. Pediatric transplantation, living-related liver transplantation and split transplantation were excluded from the study. A review of the Eurotransplant International Foundation (ET) database identified 83 livers from donors with a known history of malignancy at time of organ allocation matched to recipients undergoing liver transplantation at our department. The decision to accept any of these donors was based on the Guide to the Quality and Safety of Organs for Transplantation.[7] Informed consent regarding the tumor transmission risk was obtained from possible recipients before transplantation.

Collected routine donor data included age, sex, cause of death, body mass index, time of intensive care stay, laboratory parameters assessing liver function (aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, serum sodium [Na]), cold ischemic time, and the ET Donor Risk Index.[8,9]

For evaluation of tumor transmission risk, donor malignancy with histological finding and cancer-free interval were analyzed. In the ET donor forms, the type of cancer was often generically grouped rather than specified as to the precise histological type, and the stage of disease was not always recorded. Tumor transmission risk was defined per the European Council Guide 2016 as unacceptable, high, intermediate, or low.

Recipient demographics were recorded including age, sex, cause of liver disease, preoperative Model for End-Stage Liver Disease (MELD) score, follow-up period, time from transplant to recurrent malignancy, presence of localized or metastatic disease, immunosuppression applied, morbidity, and mortality.

Statistical analysis was performed using GraphPad Prism 4.0 (GraphPad Software Inc., San Diego, CA). Data are presented as median and range. Patient survival was calculated using the Kaplan-Meier method. Comparison of survival between 3 groups was performed with the overall logrank test. A P value less than 0.05 was considered statistically significant.

RESULTS

Donor Data

All 83 patients who underwent liver transplantation using organs from donors with a medical history of malignancy were included in the statistical analysis.

The organ donors had a median age of 57 (2-88) years at organ procurement. Cause of death was cerebrovascular accident in 46 (55%) cases, anoxia in 23 (28%) cases, and trauma in 3 (4%) cases, whereas 11 (13%) donors died of other causes. ET Donor Risk Index in this donor population was 1.706 (1.013-2.927). All accepted donors showed adequate liver function (aspartate aminotransferase, 48 [13-546] U/L; alanine aminotransferase, 32 [5-340] U/L; gamma-glutamyl transferase, 41 [5-611] U/L), whereas Na was slightly elevated (Na, 148 [126-174) mmol/L). Donors spent a median of 3 (1-42) days in the intensive care unit of the donor hospital.

Donor Malignancy Data

A total of 59% of donors with a history of malignancy had cancer at 1 of 3 primary sites: genitourinary, CNS, skin. Overall, 9 different tumor sites were detected. The majority (58%) of donors with a history of malignancy had tumor-free intervals of 5 years or less, whereas 19% had a tumor-free interval of more than 6 years and 23% of more than 10 years (Table 1). Most livers accepted from donors with a history of malignancy had a low cancer transmission risk (n = 44, (53%) versus intermediate n = 28, (34%) vs high n = 11, (13%)). Organs from donors with an unacceptable risk of tumor transmission were not accepted for transplantation.

Recipients Follow-up

The recipients' demographics, underlying disease, and perioperative data are shown in Table 2. Median follow-up was 19.9 (0-155) months. Seven (8%) recipients had to be retransplanted because of primary nonfunction of the liver.

TABLE 1.

Donor malignancy sites

	No. donors	Tumor-free interval, y		
Tumor site	n (%)	<5	5-10	>10
CNS	27 (32.5)	26	1	0
Genitourinary	24 (28.9)	16	4	4
Skin	8 (9.6)	3	4	1
Breast	10 (12)	3	1	6
Colorectal	5 (6)		2	3
Thyroid	2 (2.4)		1	1
Lung	3 (3.6)		1	2
Hematooncological	3 (3.6)		2	1
Larynx	1 (1.2)		1	
Percentage		58%	19%	23%

Nine different cancer sites in 83 donors were detected. Fifty-eight percent of the donors with a history of a cancer had tumor-free intervals of 5 years or less; 19% of the donors, more than 6 years; and 23% of the donors, more than 10 years.

TABLE 2.

Recipient characteristics and underlying liver disease

Recipient age, y	57 (24-71)
Sex: male/female, n (%)	61/22 (73.5%-26.5%)
Time on waiting list, mo	4 (0-74)
BMI, kg/m^2	25.9 (16.5-41.2)
Preoperative laboratory MELD	16 (6-40)
Underlying disease, n (%)	
ALD	28 (34%)
HCV	16 (19%)
HBV	9 (11%)
PSC, PBC	11 (13%)
NASH	9 (11%)
Others	10 (12%)
HCC, n (%)	28 (34%)
Out of Milan, n (%)	19 (68%)

BMI, body mass index; ALD, alcoholic liver disease; HCV, hepatitis C virus; HBV, hepatitis B virus; PSC, primary sclerosing cholangitis; PBC, primary biliary cirrhosis; NASH, nonalcoholic steatohepatitis.

Thirteen (15.7%) patients died within 30 days after liver transplantation due to sepsis (n = 6), primary nonfunction (n = 6), or cardiomyopathy (n = 1).

Recipients With Hepatocellular Carcinoma

Twenty-eight patients had undergone liver transplantation because of hepatocellular carcinoma (HCC). Nineteen of them showed an intrahepatic tumor stadium beyond the Milan criteria. Eleven patients transplanted because of HCC developed a recurrence in the transplanted liver or HCC metastases. Nine of them died in a median follow-up time of 11.8 (4-50.6) months.

Recipients With De Novo Malignancy

During the follow-up period, 8 patients were diagnosed with de novo cancer disease. These tumors were not of the same histological type that had been recorded in the donor's history (Table 3). Patient survival curves are shown in Figure 1.

During the follow-up period of 19.9 (0-155) months, none of the recipients developed donor-derived malignancy.

DISCUSSION

Worldwide, there are an increasing number of waiting list deaths because of the severe donor organ shortage. To expand the donor pool, transplant surgeons are forced to consider donor organs that were previously judged unsuitable. This setting has encouraged the reevaluation of organs from donors with a history of malignancy.

Malignancy after transplantation can occur in 3 different ways: de novo, recurrent, or donor-transmitted malignancy.[10] Tumor growth is often accelerated in immunocompromised patients. In liver and cardiothoracic transplant recipients, de novo cancer-related mortality is significantly elevated compared with a matched general population.[11]

The general role of potential organ donors with a history of malignancy is still undefined. Donor-transmitted malignancy is rare,[12,13] and the definitive risk of tumor transmission remains unknown. The incidence of cancer in donors is approximately 3%, and the risk of transmitting malignancy by transplantation of an organ is roughly 0.01%.[14] Although the risk of tumor transmission is extremely low, it carries a high rate of 38% of overall mortality if transmitted.[15] In liver transplant recipients, the published literature regarding donor-transmitted malignancy primarily includes case reports and does not allow accurate risk estimation. So far, less than 20 cases of donor-transmitted malignancy have been reported with a recipient mortality of over 70%.[16,17]

Therefore, acceptance of organs from donors with a history of malignancy should be discussed further. In an era of severe organ shortage, the risk of tumor transmission needs to be considered against the perspective of the lifesaving benefits afforded by organ transplantation. However, it is mandatory to select all potential donors carefully with the intention of minimizing the risk of transmission of malignancy due to the potentially serious consequences for the individuals affected.

In our study, donor malignancy had originated in 9 different tumor sites with most 75% at only 3 primary sites: CNS, genitourinary system, skin. These days, transplantation of organs from donors with a history of low grade primary CNS malignancy has generally been accepted.[5,18] Early studies by Buell et al[14] showed a CNS tumor transmission rate of 23%. In the presence of risk factors, for example, ventriculoatrial shunting, craniotomy, or high-grade tumors, the transmission rate was 46%. Based on the recent publication of Desai et al,[19] recommendations were formulated to provide guidance on the use of organs from donors with CNS malignancy. In our collective, 27 donors had a tumor in the CNS site, 26 of them with less than 5 years since diagnosis. However, all of them were classified as minimal or low risk.

Previous case series did not report any malignancy transmission from donors with low-grade renal cell carcinoma and low-grade prostate carcinoma.[20,21] A high percentage

TABLE 3.

De novo malignancies in recipients after liver transplantation

Age, y	Liver disease	MELD score	HCC (Y/N)	Donor cancer site	Donor cancer-free period, y	De novo malignancy	Follow-up time, mo	Death (Y/N)
57	HBV	12	Y	Prostate	5	Melanoma	133.2	N
62	ALD	8	Y	Prostate	7	Spinocellular cc	88.1	N
58	HCV	14	Y	Breast	3	Pancreatic head cc	15.8	Y
60	PSC	20	N	Breast	>10	Esophageal cc	85.7	N
55	HCV	12	N	Larynx	7	Spinocellular cc	69.2	N
61	ALD	25	N	Prostate	7	NSCLC	39.6	Y
65	HCV	25	Y	Breast	>10	PTLD	26.1	N
53	ALD	10	N	Skin	2	Esophageal cc	9.4	N

Y, yes; N, no; cc, carcinoma; NSCLC, nonsmall cell lung cancer; PTLD, posttransplant lymphoproliferative disease.

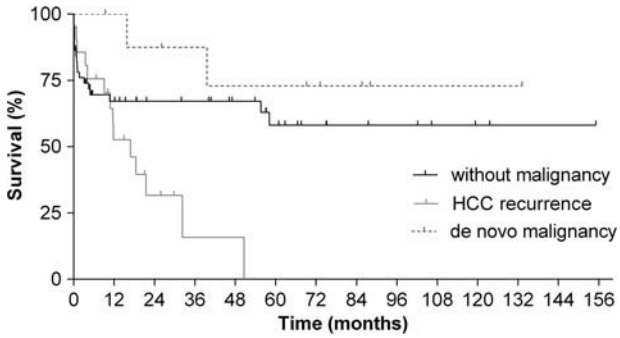

FIGURE 1. Patient survival after liver transplantation with organs from donors with malignancies in the history. Median follow-up time of patients without malignancy was 15.4 (0.1-155.1) months versus patients with HCC recurrence 11.8 (4-50.6) versus patients with de novo malignancies 69.2 (9.4-133.2) ($P = 0.0117$).

of genitourinary tumors develop metastatic disease; however, specifically, liver metastases are seen in about 40% of renal cell carcinomas and in about 25% of prostatic tumors. In our study, 24 donors had a history of genitourinary malignancy, two thirds of them with less than 5 years survival. Donors with very small prostate cancers, Gleason 3 + 3, and unsuspicious follow-up can be accepted for organ donation as minimal transmission risk at any time after diagnosis. Prostate cancer Gleason greater than 6 after curative treatment and cancer-free period of more than 5 years is considered minimal risk as well. Higher stages and higher Gleason grades require an individual risk assessment.[7]

Eight organ donors in our study had a history of skin cancer. Because of very rare metastases, basal cell and squamous cell carcinoma of the skin are considered minimal risk. If precise donor data about staging, therapy, and recurrence-free survival are available, organ donation from donors with treated malignant melanoma might be considered for selected recipients. Kaposi sarcoma, Merkel cell carcinoma, and skin sarcoma in the donor history are considered an unacceptable risk as well as malignant melanoma diagnosed during donor procurement due to the very aggressive behavior of these tumors.[7]

For clinical decision-making, time interval between diagnosis, treatment, and organ donation as well as tumor grading need to be considered on a case-by-case basis. In our study population, time interval between diagnosis of malignancy and organ donation varied widely. Among the total of 83 donors with a history of malignancy, 23% had a cancer-free interval of more than 10 years at the time of organ procurement. Risk of malignancy transmission from these donors would be relatively modest; however, a long cancer-free interval should not forestall an extensive search for an active site of malignancy at organ procurement.

Careful risk/benefit assessment by each individual transplant surgeon remains crucial. Nalesnik et al[22] proposed 6 risk categories for donor tumor transmission although high level evidence is not yet available. Donors with a history of malignancy with potential late metastases, for example, breast cancer, colon carcinoma, leukemia, lymphoma, or melanoma, are always to be placed in a high-risk category. These organs are only to be considered for transplant in recipients at urgent risk without transplantation, based on clinical judgment and with informed consent after detailed reviewing of the pathological reports. Donors with active malignancies, other than CNS or certain skin cancers, remain totally unacceptable for transplantation.

In our study, none of the recipients developed donor-transmitted malignancy. Despite our excellent results, the question remains if our median follow-up of 19.9 months is sufficient to identify donor-derived malignancy. In previous studies, time to diagnosis of donor-derived malignancy ranged from 0 to more than 35 months posttransplantation. Within a mean follow-up of 45 months, none of the recipients of organs from donors with primary CNS malignancies developed a donor-derived tumor.[6] Therefore, we believe most of our patients had an adequate follow-up period. Nevertheless, we will continue follow-up of our study population for malignancy after transplantation. In 13 patients, oncological follow-up could not be achieved because they died of other causes within 30 days of transplant.

There are some limitations to our study. First, this is a single-center study, which carries the risk of bias for treatment. All recipients were carefully selected to undergo liver transplantation using donors with a medical history of malignancy. At the time of organ allocation, the recipients were listed with a true MELD score of 16 (6-40), reflecting a relatively stable disease. Nevertheless, the patients were in immediate need of a liver transplantation for various reasons not well reflected in the MELD-based allocation system, for example, HCC not meeting Milan criteria at the time of diagnosis, recurrent episodes of severe hepatic encephalopathy, or recurrent hydropic decompensation. Three patients were listed with a MELD score of 40 but were not timely offered any regular criteria donor organs.

In conclusion, liver transplantation with organs from donors with a medical history of malignancy is feasible and the risk of donor-transmitted malignancy appears to be small in this single-center analysis. The careful selection of donors remains mandatory and can expand the donor pool.

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