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TRANSPLANT TUMOR REGISTRY: DONOR RELATED MALIGNANCIES

H. MYRON KAUFFMAN,[1,4] MAUREEN A. MCBRIDE,[1] WIDA S. CHERIKH,[1] PAMELA C. SPAIN,[1] WILLIAM H. MARKS,[2] AND ALLAN M. ROZA[3]

Background. **Transmission of donor malignancies has been intermittently reported since the early days of clinical transplantation. The incidence of United States donor related malignancies has not previously been documented.**

Methods. **All donor related malignancies reported to the Organ Procurement and Transplantation Network/United Network for Organ Sharing from 4/1/94–7/1/01 in a cohort of 34,933 cadaveric donors and 108,062 recipients were investigated by contacting the transplant centers to verify that the reported tumors were of donor origin. Time and mode of discovery, as well as graft and patient outcome, were determined. The status of other recipients from the donor was investigated.**

Results. **A total of 21 donor related malignancies from 14 cadaveric and 3 living donors were reported. Fifteen tumors were donor *transmitted* and 6 were donor *derived*. *Transmitted* tumors are malignancies that existed in the donor at the time of transplantation. *Derived* tumors are de novo tumors that develop in transplanted donor hematogenous or lymphoid cells after transplantation. The cadaveric donor related tumor rate is 0.04% (14 of 34,993). The donor related tumor rate among transplanted cadaveric organs is 0.017% (18 of 108,062). Among patients developing donor related malignancies, the overall mortality rate was 38%, with that of *transmitted* tumors being 46% and *derived* tumors being 33%. The cadaveric donor related tumor mortality rate is 0.007% (8 of 108,062).**

Conclusions. **The United States incidence of donor related tumors is extremely small. The donor related tumor death rate is also extremely small, particularly when compared with waiting-list mortality.**

INTRODUCTION

The first reports of cancer in transplant patients involved transmission of donor cancers to the recipients (*1–3*). An early summary of 47 patients who received kidney transplants from donors with known active malignancy indicated that 17 recipients developed a malignancy of donor origin (*4*). Although immunologic rejection of the cancer, after discontinuation of immunosuppression was documented in 2 of these 17 patients, six other patient deaths were directly caused by the transplanted cancer (*4*).

[1] Research Department, United Network for Organ Sharing, Richmond, VA.

[2] Organ Transplant Program, Swedish Medical Center, Seattle, WA.

[3] Department of Surgery, Medical College of Wisconsin, Milwaukee, WI.

[4] Address correspondence to: H. Myron Kauffman, UNOS, 1100 Boulders Parkway, Suite 500, Box 13770, Richmond, VA 23225. E-mail: kauffmhm@unos.org.

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The Denver Transplant Tumor Registry, first started by Israel Penn in 1968 (*5*), ultimately became the Cincinnati Transplant Tumor Registry (CTTR). This voluntary registry was managed by Penn until his untimely death in 1999 and had both a United States and an international component. Following the first summary publication (*4*), the CTTR continued to collect cases of tumors of donor origin and published periodic updates of their data (*6*, *7*). The last publication in 1997 detailed 117 cases of cancer transmission (*8*). The CTTR data were quite beneficial in making surgeons aware of this ongoing problem, but because the registry had no patient denominator, the true frequency of cancer transmission from all cadaveric donors could not be calculated.

From 1994 through 1998, the United Network for Organ Sharing (UNOS) collected limited posttransplant malignancy data that consisted of whether the patient developed skin cancer, posttransplant lymphoproliferative disorder (PTLD), or other cancer (specify). On January 1, 1999, UNOS began collecting detailed data on all recipients of solid organ transplants who developed posttransplant malignancies, including donor related tumors, recurrence of preexisting malignancies, de novo solid tumors including skin, and PTLD. This report details all donor related malignancies reported to the Organ Procurement and Transplantation Network (OPTN) database from 4/1/94–7/1/01.

Donors with a past history of, or dying from, primary central nervous system malignancies were not analyzed or reported separately in this study as they were the focus of a previous publication (*9*).

MATERIALS AND METHODS

UNOS policy requires that all solid organ transplants be reported to the OPTN. Baseline demographic data are collected on all patients at the time they are listed on the cadaveric waiting list. Further data are reported at the time of transplantation and at the time of initial discharge from the hospital after the transplant procedure. Donor data are submitted by the Organ Procurement Organizations, and donor and recipient histocompatibility data are submitted by the respective histocompatibility laboratories. In addition, data are reported at the time of graft failure, at death, or at six months after transplantation for abdominal organs and annually for all organs.

Detailed data on donor related cancer have been collected since 1/1/99. However, because only limited data on cancer occurrence were collected between 4/1/94 and 1/1/99, the individual transplant centers were contacted for more detailed information on cases reported during this period. In addition, transplant centers were contacted regarding all donor related tumors reported after 1/1/99 to verify that the tumors were of donor origin. In selected cases, pathology reports were received from the transplant centers. When a donor was identified as the source of a recipient malignancy, all other recipients of organs from that donor were investigated for tumor development.

The time period of 4/1/94–7/1/01 was used for follow-up collection of reported cases of tumors of donor origin. Because there is a

varying period of time between the date of the transplant and the discovery of the posttransplant malignancy, we used the last transplant date of 10/24/00 for patients with a reported donor related malignancy to calculate both patient denominators and deaths on the waiting list. Thus, the period of time used to determine the total number of donors, the total number of transplants by organ, and deaths on the waiting list was 4/1/94–10/24/00.

RESULTS

In this report, we have made the distinction between donor *transmitted* and donor *derived* tumors because the difference has both practical and medical-legal implications (*10*). Donor *transmitted* tumors are those that existed in the donor at the time of transplantation. In contrast, donor *derived* tumors are, in fact, de novo tumors that develop in transplanted donor cells. Theoretically, at least, donor *transmitted* tumors are preventable by meticulous donor evaluation. However, they are more frequently encountered than donor *derived* malignancies. Recorded examples include a donor *derived* acute promyelocytic leukemia (*11*), donor *derived* PTLD (*12*), and a graft pancreatic adenocarcinoma discovered 3.5 years posttransplantation (*13*). These cases are shown in Table 1 and will be detailed below.

During the study period, a total of 21 donor related tumors were recorded, of which 15 were donor *transmitted* and 6 were donor *derived* (Table 1). Three cases were from living donors—2 related and 1 unrelated to the recipient—and the remaining 18 cases were from 14 cadaveric donors. Multiple tumors were transmitted from 2 of the cadaveric donors—organ transplants from 1 donor resulted in tumors in 4 recipients—and organs from another donor resulted in tumors in 2 recipients. The time from transplantation to tumor diagnosis varied from 3 months to 40 months (mean 14.2 months) posttransplantation(Table 1). The mean time from transplantation in 8 liver recipients (10.8 months) was less than that of the 10 kidney patients (15.2 months).

Donor Transmitted Tumors

Malignancies were *transmitted* from donors to five liver, eight kidney, and two heart recipients. Two of the five liver recipients of *transmitted* tumors died as a result their tumors, while three are alive following resection of the tumor-bearing graft and retransplantation. One of the two liver recipients who died received a donor *transmitted* melanoma (*14*). Three other recipients from that donor, two kidney recipients and one heart recipient, also developed transmitted melanoma and died as a result of their tumors as well (Table 1). The second liver recipient who died from his transplanted tumor had a poorly differentiated malignancy that was probably of neuroendocrine origin. One of two kidney recipients from that same donor also developed a donor related "small cell" malignancy but is currently surviving following nephrectomy, cessation of immunosuppression, and return to hemodialysis. Of the three surviving liver recipients, one patient with donor *transmitted* metastatic adenocarcinoma successfully had his tumor-bearing graft removed and was immediately retransplanted, as has previously been reported (*15*). The other two liver recipients with donor *transmitted* tumors underwent graft hepatectomy and were retransplanted for probable metastatic pancreatic carcinoma and undifferentiated squamous cell carcinoma, respectively (Table 1).

Six cadaveric donor and two living donor *transmitted* tumors occurred in kidney transplant recipients (Table 1). Two cadaveric kidney recipients of donor *transmitted* tumors died from malignant melanoma, which was also *transmitted* to both the heart and liver recipients (*14*). Three of the four

TABLE 1. Donor related malignancies reported between 4/1/1994 and 7/1/2001

Tumor type Organ	Donor type	Time Post-TX	Histology	Outcome	Reference
Transmitted					
Liver	CD	12 mo	Neuroendocrine	Dead	
Liver	CD	12 mo	Metastatic Pancreas	Alive—Retransplant	
Liver	CD	6 mo	Adenocarcinoma	Alive—Retransplant	15
Liver	CD	15 mo	Melanoma	Dead	14
Liver	CD	10 mo	Undiff. squamous	Alive—Retransplant	
Kidney	CD	15 mo	Melanoma	Dead	14
Kidney	CD	17 mo	Melanoma	Dead	14
Kidney	CD	14 mo	Lung	Alive—Nx—Dialysis	
Kidney	CD	13 mo	Small cell	Alive—Nx—Dialysis	
Kidney	CD	3 mo	Oncocytoma	Alive—Nx—Dialysis	
Kidney	CD	37 mo	Papillary	Alive—Nx—Dialysis	
Kidney	LR	32 mo	Lung	Alive—Nx—Dialysis	16
Kidney	LUR	6 mo	Breast	Alive—Nx—Dialysis	
Heart	CD	10 mo	Melanoma	Dead	14
Heart	CD	10 mo	Prostate	Dead	17
Derived					
Liver	CD	24 mo	Leukemia	Dead	11
Liver	CD	3 mo	PTLD	Alive	12
Liver	CD	5 mo	PTLD	Alive	12
Kidney	CD	10 mo	PTLD	Alive—Nx—Dialysis	
Kidney	LR	5 mo	PTLD	Alive	
Pancreas	CD	40 mo	Adenocarcinoma	Dead	13

TX, transplantation; CD, cadaveric donor; LR, living related donor; LUR, living unrelated donor; Nx, nephrectomy; PTLD, posttransplant lymphoproliferative disorder.

survivors of cadaveric kidney *transmitted* tumors underwent graft nephrectomy, all ceased immunosuppression, and returned to hemodialysis. One of these survivors had a widely disseminated lung cancer of donor origin discovered approximately 1 year posttransplantation. After transplant nephrectomy, he has remained on hemodialysis for over 2 years. Of note, the recipient of the other kidney from this donor is alive and well without evidence of tumor. The second surviving cadaveric kidney recipient had his tumor described as a "small cell" malignancy, and his kidney came from the same donor who transmitted a fatal neuroendocrine tumor to the liver recipient. The third and fourth surviving cadaveric kidney recipients of donor *transmitted* tumors had a renal oncocytoma and a papillary tumor of unknown primary origin, respectively.

There were two living kidney donor *transmitted* tumors (Table 1). In the first case, the donor was found to have a carcinoma of the lung at 10 months follow-up. At 32 months posttransplantation, an ultrasound of the transplanted kidney showed a mass that was found to be a donor *transmitted* small cell lung carcinoma. The recipient underwent graft nephrectomy, cessation of immunosuppression, return to hemodialysis, and was alive at last follow-up (*16*). The second living donor *transmitted* tumor occurred following a wife to husband transplant (W. H. Marks, personal communication). Six months posttransplant, the recipient was found to have both osteolytic bone and central nervous system metastases due to ductal breast adenocarcinoma. Immunosuppression was stopped, chemotherapy instituted, and the graft left in situ. The patient rejected both the graft and the tumor and is tumor free after 4 years and has been listed for a cadaveric kidney transplant.

Both heart recipients who developed donor *transmitted* tumors died as a result of the tumors. In the first patient, the heart transplant operation was near completion when prostatic adenocarcinoma was discovered in pelvic lymph nodes of the donor (*17*). Metastatic prostate cancer was discovered in the recipient at 10 months posttransplantation, and in spite of reduction in immunosuppression plus chemotherapy, the patient died 36 months after transplantation. The other heart recipient died from a *transmitted* malignant melanoma that was also fatal to the liver and both kidney recipients as described previously (*14*).

Donor Derived Tumors

Donor *derived* malignancies occurred in three liver, two kidney, and one pancreas recipient (Table 1). One of the three liver recipients with donor *derived* tumors died as a result of the malignancy while two patients with donor *derived* PTLD survived. The patient who died was diagnosed with donor *derived* acute promyelocytic leukemia that occurred 2 years after the liver transplant. It is believed that donor hematogenous cells survived in a state of microchimerism before undergoing malignant transformation (*11*). The two surviving liver recipients of donor *derived* tumors developed Epstein-Barr virus associated B-cell lymphoma of donor origin in hepatic hilar lymphoid tissue (*12*). Both cases had regression of the lymphomatous tumors following reduction of immunosuppression and antiviral therapy, and both patients were surviving at the time of this report (*12*).

One cadaveric kidney recipient is surviving following nephrectomy due to donor *derived* PTLD. The second kidney recipient with a donor *derived* tumor received a living related graft and developed PTLD that responded to reduction in immunosuppression and rituximab therapy.

The report of an adenocarcinoma of donor origin developing in a pancreatic allograft 3.5 years posttransplantation suggests that this tumor was a donor *derived* and not a donor *transmitted* tumor (*13*). This assumption was made because of the age of the donor (55 years), the long duration of time before the tumor was manifest, and no evidence of the tumor at either the time of transplantation or on an ultrasound examination of the pancreas at 2.5 years posttransplantation (*13*).

Transmission Rates

During the time of this study, UNOS recorded 34,933 cadaveric donors and 108,062 cadaveric organ transplants. The 108,062 cadaveric recipients were followed for a mean period of 30 months.

During this same time, donor-related tumors were reported in recipients of organs from 14 cadaveric donors, resulting in a reported cadaveric donor related tumor rate of 0.04% (Table 2). Similarly, *transmitted* tumors were reported from 9 cadaveric donors, resulting in a cadaveric donor tumor *transmission* rate of 0.025%, or 1 tumor *transmission* for every 3,881 cadaveric donors. Eighteen of 108,062 transplanted cadaveric organs had a donor related tumor, resulting in a rate of 0.017% or 1 donor related tumor for every 6,003 transplanted cadaveric organs. Similarly, 13 of the 108,062 cadaveric organs carried *transmitted* tumors for a transmission rate of 0.01% or 1 *transmitted* tumor for each 8,312 transplanted organs.

Overall, 8 of the 21 patients with donor related malignancies died, resulting in a mortality rate of 38%. These 8 deaths, in a cohort of 108,062 recipients, represent an overall donor related tumor death rate of 0.007% or 1 donor related tumor death for every 13,508 recipients. Six of the 13 patients (46%) who had cadaveric donor *transmitted* tumors died from the malignancy while 7 survived (Table 1). The 6 deaths occurring from donor *transmitted* tumors in 108,062 recipients represent a death rate of 0.006% or 1 death for every 18,010 cadaveric transplants. Two of the 6 patients (33.3%) with donor *derived* malignancies died from their tumors, while all 4 patients with donor *derived* PTLD were surviving at the time of this report (Table 1). In relation to the time of tumor discovery, deaths occurred as early as 1 day (leukemia) to as late as 26 months (prostate carcinoma) following diagnosis. In comparison with the death rates from donor related malignancies, there were 14,300 kidney, 8,012 liver, and 4,815 heart deaths on the waiting list during this study period (4/1/94–10/24/00).

DISCUSSION

The number of donor related malignancies in this report (*21*) is small compared with the 117 cases reported by the CTTR from 1968 through 1997 (*8*). However, a substantial number of the cases in the CTTR were reported many years before the time that UNOS began collecting information about malignancies in transplant recipients. In fact, in his 1991 report, Penn had already reported 64 cases of donor related malignancies (*7*). Additionally, the CTTR collected cases both from the United States and international trans-

plant programs. Because the CTTR could not calculate tumor incidence because it lacked the patient denominator, it is not possible to compare the UNOS reported tumor incidence with the CTTR tumor incidence. The relatively small number of cases in this report may also be due to an increased surgeon awareness from the early warnings of Penn (*7*, *8*), or to underreporting to UNOS by transplant centers.

Quantification of the amount of underreporting to the OPTN/UNOS database is a difficult task and a major concern. Between 1988 and 2000, 221,077 solid organ transplants were reported from 867 different transplant programs. Data from the 1997 Center Specific Report (*18*) indicated a greater than 91% 3-year patient follow-up. If we assume that patients lost to follow-up in this study are twice as great as indicated in the Center Specific Report, or 20%, the calculated number of donor related tumors would increase from 21 to 25, and the incidence rates of donor related tumors would still remain very low. It is difficult to calculate the overall mortality in the CTTR reports of donor transmitted tumors. In the last comprehensive CTTR report, there was a 67% mortality rate in the 66 patients who developed disseminated disease, but the survival rate of patients with more localized malignancies is not clear (*8*). It therefore becomes difficult to compare our 38% overall mortality for patients who developed donor related tumors with the historical data from the CTTR. It is clear from this cohort of 108,062 recipients that donor related tumors are uncommon, and death from donor related malignancy is rare.

Survival in our series, for both donor *transmitted* and donor *derived* tumors, seemed dependent upon relatively early diagnosis followed by aggressive management. In most instances, the presence of a tumor was discovered by ultrasound, or other imaging techniques, and the diagnosis confirmed by biopsy. Survival following donor *transmitted* tumors in liver recipients depended upon resection of the tumor-bearing graft and retransplantation. In kidney recipients, survival was accomplished by cessation of immunosuppression, and in some instances, chemotherapy. Three of four kidney recipients surviving donor *transmitted* tumors underwent graft nephrectomy while one rejected kidney was left in situ (*26*). The merits of graft excision for donor related kidney tumors probably should be determined on an individualized basis. To our knowledge, none of these kidney recipients has been retransplanted, but several have been returned to the waiting list. In the cases of donor *derived* tumors, reduction of immunosuppression for patients with PTLD, as earlier advocated by Starzl et al. (*19*), was the first line of treatment. In two instances, it was supplemented by antiviral drugs (*12*), and in one case by anti-B cell monoclonal antibody treatment (*20*).

Although the use of donors with active malignancies is clearly contraindicated, there has been a reluctance to use donors with a past history of cancer. UNOS previously published a report on 257 donors with a past history of cancer that resulted in 650 organ transplants and indicated that there were no instances of donor tumor transmission after a mean follow-up time of 45 months (*21*). An recent update of that data now includes 488 donors with a past history of cancer that resulted in 1,276 organ transplants and shows that although the recipients developed a total of 54 posttransplant malignancies, none of these malignancies were donor related. Nevertheless, because melanoma, choriocarcinoma, lymphoma, and carcinoma of the lung, breast, kidney, and colon pose a high transmission risk, we recommend avoiding donors who have a past history of any of these cancers. Additional UNOS data have shown that among 1,220 transplants from 397 cadaveric donors with either a past history of central nervous system tumors or dying from a central nervous system tumor, no instances of donor tumor transmission were reported (*9*). However, great caution should be used with donors with glioblastoma multiforme (*22*) or medulloblastoma (*23*) because of case reports of transmission of these tumors with organ transplants. Patients with malignant brain tumors who have undergone ventriculoperitoneal or ventriculoatrial shunts should also be avoided (*24*).

The fact that there were two living donor *transmitted* tumors in this series, in spite of careful donor evaluations, indicates that the risk of donor tumor *transmission* will unlikely be reduced to zero. However, certain precautions should minimize the risk. It should be mandatory that *B*-HCG levels are obtained on any female who dies from a nontraumatic intracerebral hemorrhage and is being considered as an organ donor to avoid metastatic choriocarcinoma (*25*).

At the beginning of the cadaveric organ retrieval process, surgeons should carefully examine all accessible intrathoracic and intra-abdominal organs as well as lymph node tissue for evidence of a neoplasm (*8*). If any suspicious masses are found, they should be biopsied and a prompt frozen section examination performed. Ideally, every cadaveric donor should have a complete autopsy performed, but in many cases this is impractical (Table 2).

TABLE 2. Donor related tumors reported to UNOS and transmission rates cadaveric transplants performed between 4/01/94 and 7/01/01

	Cadaveric donors (n = 34,933)		Cadaveric Organ transplants (n=108,062)	
	Number	Rate (%)	Number	Rate (%)
Donor-related tumors	14	0.04	18	0.017
Donor-transmitted tumors	9	0.025	13[a]	0.012

[a] One donor transmitted four tumors and another donor transmitted two tumors. UNOS, United Network for Organ Sharing.

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RISK FACTORS FOR FRACTURES IN KIDNEY TRANSPLANTATION

EILEEN A. O'SHAUGHNESSY,[1,2] DAVID C. DAHL,[1] CHARLES L. SMITH,[1] AND BERTRAM L. KASISKE[1]

Background. **Risk factors for fracture after kidney transplantation need to be identified to target patients most likely to benefit from preventive measures.**

Methods. **Medical records were reviewed for 1572 kidney transplants done at a single center between February, l963 and May, 2000 with 6.5±5.4 years of follow-up.**

Results. **One or more fractures occurred in 300 (19.1%), with multiple fractures in 101 (6.4%). After excluding fractures of the foot or ankle (n=130 transplants, 8.3%), avascular necrosis (n=86, 5.5%), and vertebral fractures (n=28, 1.8%), there were one or more fractures in 196 (12.5%), with a cumulative incidence of 12.0%, 18.5%, and 23.0% at 5, 10, and 15 years, respectively. In multivariate Cox proportional hazards analysis, age had no effect on fractures in men. Compared with men and younger women, women 46–60 and >60 years old were, respectively, 2.11 (95% confidence interval 1.43–3.12, $P=0.0002$) and 3.47 (2.16–5.60, $P<0.0001$) times more likely to have fractures. Kidney failure from type 1 and 2 diabetes increased the risk by 2.08 (1.47–2.95, $P<0.0001$) and 1.92 (1.15–3.20, $P=0.0131$), respectively. A history of fracture pretransplant increased the risk by 2.15 (1.49–3.09, $P<0.0001$). Each year of pretransplant kidney failure increased the risk by 1.09 (1.05–1.14, $P<0.0001$). Obesity (body mass index >30 kg/m^2) was associated with 55% (17–76%, $P=0.0110$) less risk. Different immunosuppressive medications, acute rejections, and multiple other factors were not independently associated with fractures.**

Conclusions. **The population of transplant patients at high risk for fracture can be identified using age/gender, pretransplant fracture history, diabetes, obesity, and years of pretransplant kidney failure.**

INTRODUCTION

Fractures are common after kidney transplantation, and there are a number of potential reasons for this. These include pretransplant uremia, acidosis, and hyperparathyroidism. Corticosteroids (*1*), persistent hyperparathyroidism (*2*), length of hospitalization (*3*), immunosuppression (*4*), and sometimes continued renal insufficiency (*5*) may also contribute to bone disease after kidney transplantation. Retrospective studies with variable length of follow-up after kidney transplantation have reported a fracture incidence of 8–26% (*6–9*). However, most of these studies have included relatively few patients (range=100–432 patients); few studies

[1] Department of Medicine, Hennepin County Medical Center, Minneapolis, MN
[2] Address correspondence to: Eileen A. O'Shaughnessy, Department of Medicine, Hennepin County Medical Center, 701 Park Avenue South, Minneapolis, MN 55415. E-mail: oshau001@umn.edu.
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