EDITORIALES

Transmision of cancer from organ donors

I. Penn, M. D.
University of Cincinnati Medical Center. Department of Surgery. 231 Bethesda Ave. Cincinnati, OH 45267–0558

Experiments have shown that cancers can be successfully transplanted into inbred, immunodeficient or immunosuppressed animals [11, 12]. The experience in the last group has been inadvertently duplicated in man when organs from donors with neoplasms were transplanted [1, 3, 4, 5, 7-18].

Clinical material

Since the first reports appeared in the 1960´s [8, 11, 15] the Cincinnati Transplant Tumor Registry (CTTR) has collected data on such cases [1, 12-15, 17]. Up till January 1995 the CTTR has data on 248 patients who received organs from donors with neoplasms, excluding those who had been treated for a major malignancy 10 years or more before donation. In the past we excluded donors with primary brain tumors, as these seldom metastasize outside the central nervous system, but as several cases of such spread have been reported to the CTTR, we will include donors with primary cerebral tumors in this report [15].

Donor data

Cadaver Donors

Two-hundred and nineteen organs were harvested from 153 cadaver donors of which 100 were single organ and 53 were multiple-organ donors from whom 119 organs were used for transplantation. Of the 53 multiple-organ donors 43 each provided 2 organs, 7 each provided 3, and 3 each provided 4 organs.

In the pioneering years of transplantation many donors had widely disseminated neoplasms. In more recent cases cancer was discovered after harvesting of organs when an autopsy was performed on the donor; or when recipients developed cancers, which were shown, in retrospect, to have arisen in the donors (multiple recipients developing the same type of cancer, such as malignant melanoma); or by HLA testing of the tumor, the allograft and the recipient; or when there were sex differences between donor and recipient, for example, male donor and female recipient; or by DNA fingerprinting of the tumor. Some donors had a history of treatment of cancer in the past but had no malignancy either at harvesting or autopsy examination.

The cause of brain death was misdiagnosed [1, 15] in at least 23 donors (involving organs transplanted into 44 recipients). The diagnosis was either primary brain tumor or cerebral hemorrhage although one donor was diagnosed as having multiple brain abscesses. The misdiagnosis was made in 6 donors with choriocarcinoma, 5 with bronchial carcinoma, 4 with malignant melanoma, 3 with renal cell carcinoma, and 5 with miscellaneous cancers.

Overall the 153 donors had a total of 157 different types of tumor. The most common were primary brain neoplasms (45), carcinomas of the kidney (31), lung (30), malignant melanoma (10), choriocarcinoma (6), hepatobiliary (5), and breast cancers (4).

With the exception of 8 primary renal tumors which were discovered at the time of harvesting all allografts obtained from cadaver donors appeared grossly normal and free of malignancy.

Living Related Donors

The 26 living related donors had been treated for cancer within 10 years before nephrectomy, or were found to have neoplasia at the time of donation, or developed evidence of it within 18 months after the procedure. They had a total of 28 malignancies of which the most common were carcinomas of the kidney 7, colon (4), and breast (3). One donor had had 3 tumors.

Living Unrelated Donors

The three donors had a total of four neoplasms [12, 14]. One donor had had a carcinoma of the cervix treated

Correspondencia: Dr. Israel Penn.
Cincinnati Veterans Affairs Medical Center.
3200 Vine St.
Cincinnati, OH 45220.

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approximately six years before death and had chronic myeloid leukemia, which was in remission, at the time of death. The other two donors provided «free» kidneys which were removed in the treatment of colon carcinoma and renal carcinoma respectively.

Cancer in recipients

Allograft recipients included 227 renal, 10 hepatic, 7 cardiac, 2 pancreatic, 1 cardiopulmonary and 1 pulmonary, so that 248 patients were at risk for the transmission of cancer. Overall 103 patients (42 %) received organs that transmitted or had contained malignancies (in eight instances a small tumor of the renal allograft was removed immediately before transplantation) (see below) (table I)[13-15, 17]. After transplantation the neoplasms were discovered from days (when several renal and 1 hepatic allograft were removed for varying reasons) through various periods up to 63 months later. It is possible that a few late occurring malignancies may have been primary tumors of the allograft that arose de novo after transplantation instead of having been transmitted with the donor organ at the time of transplantation. In the case of the recipients who did not show evidence of cancer we presume that the allografts were free of tumor or that transmitted malignant cells failed to survive after transplantation. In the recipients who developed neoplasms these usually were histologically identical to those in the original donors.

Table I. Transmission of cancer with donor organs

Type of Donor	# of Organs	Cancer in Allograft	Local Spread	Distant Metastases
Cadaver	219	33*	5	57
Living related	26	6*	–	1
Living unrelated	3	–	1	–
Total	248	39*	6	58

* In 8 instances a small carcinoma was removed from a renal allograft immediately prior to transplantation.

Malignancies Confined to the Allograft

The 39 patients included 35 kidney (29 cadaveric and 6 living related donor) allograft recipients, 3 liver recipients and one combined heart-lung recipient. The types of cancers in the allografts are listed in table II.

Renal carcinomas

Of the 26 patients with primary carcinomas in the kidney allograft 14 were recognized at the time of harvesting and 12 were not. In the 14 kidneys in the first group (8 cadaveric and 6 living related) a small primary renal carcinoma or an oncocytoma (in one instance) was found at harvesting. In 8 instances the lesion was widely excised and the kidney then transplanted. On another five occasions initial frozen section examinations were not diagnostic but several days later permanent sections showed carcinomas, and the recipients underwent transplant nephrectomies 2-10 days after transplantation. An equivocal initial diagnosis («pleomorphic adenoma») was also made regarding a small mass in the fourteenth allograft. It was reexplored 3 months later because the lesion had increased in size. A partial nephrectomy was performed to widely excise a carcinoma. In all 14 patients there has been no recurrence of malignancy in follow-ups ranging from 1-210 (average 79 months). Of the 12 kidneys (all cadaveric) where no apparent tumor in the allograft was apparent at harvesting transplant nephrectomy was performed in 10 cases from 3 days to 14.5 months (average 3 months) posttransplantation. This was necessitated by rejection, bleeding, thrombosis, or in the case of one donor, involving two of the recipients, the discovery at donor autopsy, of a brain metastasis from a renal cell carcinoma. In each case the tumor was an unexpected finding on pathologic examination of the removed allograft. An eleventh recipient was noted on routine posttransplant ultrasonography to have a small hypoechogenic area[5]. This slowly increased in size and necessitated transplant nephrectomy more than two years later, when a renal cell carcinoma was discovered. The companion kidney from the same donor showed no problems until 46 months posttransplantation when ultrasound examination showed a mass at the upper pole. The significance of this was misinterpreted. However, 63 months after transplantation this had grown to 6 cm in size. Transplant nephrectomy showed a renal cell carcinoma. Follow-up ultrasound studies of both tumors suggested a growth rate of 0.5 cm/year, making it highly probable that they were present in the allografts at the time of

Table II. Malignancies confined to the allograft

	Number	%
Carcinoma of kidney	26*	67
Choriocarcinoma	4	10
Carcinoma of breast	2	5
Carcinoma of bronchus	2	5
Brain neoplasm	2	5
Lymphoma	1	3
Kaposi's sarcoma	1	3
Carcinoma of thyroid	1	3

*Includes 6 recipients of kidneys from living related donors.

transplantation. Of the 12 kidneys no recurrences occurred in follow-ups ranging from days to 199 (average 50) months.

Other tumor

Two donors with choriocarcinoma each provided two organs. A combined heart/lung allograft recipient died of rejection a month after transplantation. Autopsy revealed tumor in one lung. A liver recipient from the same donor manifested tumor in the left lobe of the allograft after transplantation. The tumor appeared to be regressing spontaneously 3.5 months after transplantation. Soon after transplantation a kidney recipient was found to have elevated human chorionic gonadotropic (HCG) levels and a 2 cm lesion in the allograft on CT scan. Allograft nephrectomy was performed 12 days posttransplantation and the patient was treated with interferon and chemotherapy. She remains disease-free 75 months after nephrectomy. Soon after transplantation a liver recipient was found to have elevated HCG levels and a lesion in the allograft on CT scan. The patient was treated with methotrexate with no improvement, and died of pulmonary complications almost one month after diagnosis. Autopsy of choriocarcinoma in the allograft.

Two donors with breast cancer provided kidneys to two recipients. Tumor was discovered in one allograft at autopsy done 2 weeks after transplantation (death was not related to the malignancy). The second recipient underwent allograft nephrectomy five days after transplantation because of infection. Metastases were discovered in the specimen. The patient remained tumor free thereafter (length of follow-up not stated).

Two donors with bronchial carcinoma provided kidneys to two recipients. One died of sepsis 3.5 months after transplantation. Autopsy showed oat cell carcinoma involving the allograft ureter. The second recipient died of sepsis and a pulmonary embolus 7.5 months after transplantation. Metastatic bronchial adenocarcinoma was found in the allograft.

A donor who died of glioblastoma multiforme 6 months after craniotomy and radiation therapy provided kidneys to two recipients. Both developed symptoms 17 and 18 months respectively after transplantation leading to ultrasound studies which showed a mass in each allograft. Both recipients underwent allograft nephrectomies and discontinuation of immunosuppressive therapy and remain well 15 months later.

Nine months after receiving a liver allograft from a donor who died of an intracranial hemorrhage and, who was later suspected to have had Kaposi´s sarcoma, the recipient developed bloody ascites and ultrasound showed multiple lesions in the graft. Biopsy findings were consistent with Kaposi's sarcoma[8]. The patient was treated with reduction of immunosuppression and chemotherapy but died of infection. Autopsy showed the allograft to be densely infiltrated with Kaposi's sarcoma.

Two days after transplantation routine ultrasound examination showed a 2 cm mass in a cadaver renal allograft obtained from a donor who died of a head injury. This grew to 5 cm in the ninth month posttransplantation when transplant nephrectomy was performed and immunosuppression discontinued. The mass was a monoclonal B cell lymphoma of donor origin proven by HLA typing of the tumor cells. The recipient was well two years later.

A cadaver donor had cancer of the thyroid gland with no gross metastases below the diaphragm[11]. Examination of the nontransplanted kidney showed microscopic metastases. The allograft was therefore removed seven days after transplantation and was also found to contain microscopic metastases. The cancer did not become established in the recipient.

Local Spread From the Allograft

Six patients who received kidney transplants not only developed cancer in them but, also, invasion of tissues adjacent to them. Five donors were cadavers and one a living unrelated donor. Two cadaver donors had been treated for primary brain tumors (one by ventriculoatrial shunt and the other by craniotomy), another two had lung cancers and the fifth donor had malignant melanoma. A recipient of a kidney from a donor with cerebellar medulloblastoma was found to have tumor in the kidney by 10 ultrasound and arteriography 5 months posttransplantation[7]. Transplant nephrectomy and discontinuation of immunosuppression were insufficient to control residual tumor. This was eradicated with chemotherapy. The recipient was well one year later. The other brain tumor was a glioblastoma multiforme. Eighteen months posttransplantation masses were found in the allograft. Allograft nephrectomy, discontinuation of immunosuppression, and local radiation therapy were used to control the residual tumor. The patient was well 44 months later.

One recipient of a kidney from a donor with lung cancer died of infection 17 months posttransplantation. At autopsy tumor was found in the allograft and in adjacent tissues. Another recipient of a kidney, from a donor with lung cancer, developed a large mass 5.5 months posttransplantation. This involved the allograft renal vein and ureter and fatty tissue and vessels in the recipient´s iliac fossa. Allograft nephrectomy, discontinuation of immunosuppression and chemotherapy resulted in disappearance of the mass. The patient was well 15.5 months after treatment.

An allograft obtained from a cadaver donor was removed because of chronic rejection 44 months after transplantation. It was found to contain malignant melanoma, which was discovered to be of donor origin as the second recipient of a kidney from the same donor died of widespread metastases of this tumor.

One individual received a «free» kidney removed from an unrelated living donor who had undergone nephrectomy to treat a renal carcinoma [12–15]. The organ was intentionally transplanted into the recipient, who was dying of uremia, during the pioneering era of transplantation when very few cadaver donors were available. The kidney rejected at 12 weeks and despite a second transplant the patient died of renal failure 3 weeks later. At autopsy, despite rejection of the first allograft, the cancer was viable and actively invading adjacent structures.

Widespread Metastases

Fifty-eight patients had widespread metastases. The types of tumors in the donors are shown in table III. Fifty-seven patients received allografts from cadaver donors and one from a living related donor. In the last case the donor (the patient´s father) presented with an anaplastic carcinoma at the nephrectomy site several months after transplantation. The recipient developed an identical malignancy in the allograft and died of widespread metastases ten months after transplantation [12–15]. Overall 40 recipients died of cancer. However, 16 renal allograft patients had complete remissions following treatment [13, 15-18]. In 10 of them regression following reduction of the tumor burden by nephrectomy and cessation of immunosuppressive therapy. Presumably their depressed immune systems were able to recover and to reject the malignancies. In 5 other patients these measures were supplemented by chemotherapy (2 patients), immunotherapy 2 patients (interferon in one and interleukin-2 in the second), radiotherapy (1 patient). The final patient´s tumor regressed following reduction of immunosuppression, chemotherapy and radiotherapy. In addition to these 16 recipients, two other patients are currently alive with tumor after undergoing transplant nephrectomy and discontinuation of immunosuppressive therapy.

Although removal of the allograft and discontinuation of immunosuppression has been successful in 16 patients it is disappointing that the neoplasms in 15 other recipients failed to regress and caused a fatal outcome despite discontinuation of immunosuppression (15 patients), graft nephrectomy (13 patients), cytotoxic therapy (4 patients), immunotherapy (3 patients) and local radiotherapy (2 patients). Presumably the immune systems of these patients were unable to cope with widespread and extensive metastases which caused the fatal outcomes.

Table III. Tumors causing distant metastases

	Number of pts	%
Malignant melanoma	16	28
Carcinoma kidney	11	19
Carcinoma bronchus	10	17
Choriocarcinoma	9	16
Brain tumors	5	9
Unknown primary carcinoma	2	3
Carcinoma of pyriform sinus	1	1.7
Hepatoma	1	1.7
Carcinoma of breast	1	1.7
Carcinoma of colon	1	1.7
Kaposi's sarcoma	1	1.7

While allograft removal and discontinuation of immunosuppression is an option in kidney transplant recipients who can be returned to dialysis it cannot be utilized to any extent in recipients of nonrenal organs [13-15]. Of 21 nonrenal allograft recipients 10 died of metastatic tumor, and another patient died of other causes but was found to have tumor in the allograft at autopsy; 7 are alive free of tumor (follow-up 1-57, average 14 months), 1 patient is alive with cancer, and 1 died of other causes 22 months after transplantation but had no evidence of malignancy. When autopsy examination of a cadaver donor showed widespread metastases surgeons removed a hepatic allograft 7 days after transplantation and replaced it with another obtained from a donor without cancer. Histologic examination of the first allograft showed no evidence of transmitted malignancy and the recipient remains well 46 months later.

Of concern is the spread of cancer from multiple organ donors [8]. Of 119 recipients of organs from 53 donors 59 developed transmitted malignancies (19 in the allograft, 4 with local spread and 36 with distant metastases). These tumors were transmitted from 30 of the 53 multiorgan donors. The most common cancers in this group of donors were carcinoma of the kidney (19 recipients in 12 of whom the allograft only was involved), malignant melanoma (13 recipients), choriocarcinoma (12 recipients), carcinoma of the lung (6 recipients), and primary brain tumors (5 recipients).

Special Subgroups of Transmitted Maliqnancies

Several donor malignancies deserve special mention of which two were particularly dangerous: malignant melanoma and choriocarcinoma.

Malignant Melanoma

Eleven donors provided organs to 20 recipients of whom only 3 did not develop tumors. One patient

evidenced melanoma in the allograft with local spread of the neoplasm and 16 developed distant metastases. Eleven of the latter patients died of their cancers, four survived after transplant nephrectomy and discontinuation of immunosuppression, and one is currently receiving treatment of residual tumor.

Choriocarcinomas

Six donors provided organs to 14 recipients, only one of whom did not develop a transplanted carcinoma. In four the tumor was confined to the allograft but 9 others had distant metastases of whom six died of the cancers. The other three had complete remissions following treatment.

Primary Brain Tumor

Forty-five donors provided organs to 54 recipients. The types of brain tumors were glioma/glioblastoma (16), medulloblastoma (9), astrocytoma (7), histologic type unspecified (7) and miscellaneous (6). Unsuspected extracranial spread had occurred from the neoplasms of 5 donors, 3 with glioblastoma multiforme, 1 with medulloblastoma and 1 with an unspecified brain tumor. In 4 donors factors that may have contributed to such spread were craniotomy (2 donors), ventriculoatrial shunt (1 donor) and ventriculostomy (1 donor). Nine of 54 recipients (17 %) developed evidence of transmitted cancer. In two it was confined to the allograft, two others manifested local spread beyond the allograft, and five had distant metastases which caused the deaths of 4 patients. The fifth is alive and well 62 months after transplantation having had a transplant nephrectomy and discontinuation of immunosuppressive therapy. Multiple subcutaneous metastases and a mass in the allograft slowly regressed thereafter.

Renal Carcinomas

This was one of the biggest groups of tumors. Of 53 patients who received transplants from 38 donors with renal carcinomas 26 had tumors confined to the allograft (described above), one also had invasion of adjacent tissues (described above) and 11 had distant metastases (10 renal recipients and 1 pulmonary recipient). Fifteen patients have remained free of cancer including 13 recipients of the contralateral healthy kidney, 1 cardiac and 1 hepatic allograft recipient.

Prevention of tumor transplantation

The risk of accidental transmission of cancers from donors to recipients must be examined in perspective. Most cases were reported in the pioneering era of transplantation, when the dangers were not appreciated. Currently, more than 300,000 solid organ transplants have been performed, but only a minute fraction of recipients have developed transplanted malignancies. At present, with careful selection of donors, inadvertent transplantation of neoplasms should be a rare event.

Each donor must be carefully screened for possible tumors [1, 3, 10-15]. Careful attention must be paid to the patient´s history, such as past treatment of a neoplasm, or a history of menstrual irregularities following a pregnancy or abortion. However, a detailed history of past illnesses is often not available to physicians caring for a suddenly stricken individual and previous hospital records may not be available in the few precious hours, often late at night, that are available to organ procurement teams dealing with hemodynamically unstable donors. Great care must be exercised to rule out a metastasis as the cause of intracranial bleeding when a donor has no evidence of hypertension, an intracranial aneurysm, or an arteriovenous malformation [13–15]. Caution is needed when evaluating a female donor of child bearing age, who has a history of menstrual irregularities, as a metastatic choriocarcinoma may be the underlying cause. Measurement of betahuman chorionic gonadotropin (beta-HCG) levels is a major safeguard and, perhaps, is advisable in all female donors in this age group. However, facilities for such testing may not be available in community hospitals or the test may not be performed at night time. A blood sample should be taken to the institution where the organ procurement team works and should be measured as rapidly as possible.

With several exceptions donors who have cancers should not be used: low grade skin tumors such as basal cell carcinomas and many squamous cell carcinomas; carcinoma in situ of organs such as the uterine cervix; or primary brain tumors which rarely spread outside the central nervous system [13-15]. However, one must be certain that brain malignancies originated there because, in some instances, autopsy examinations performed after organ retrieval have shown that the apparent brain neoplasms were actually metastases from occult primary tumors [1-13-15]. We should also avoid the use of donors with brain tumors that have been treated with ventriculoperitoneal or ventriculoatrial shunts, extensive craniotomies, radiotherapy, or chemotherapy, as these may open pathways for malignant dissemination [6,13-l5]. If a potential donor has not received any such treatments, the danger of spontaneous spread of tumors outside the CNS is extremely small. Up to 1985 282 cases of extracranial spread had been reported in the world literature, of which only 24 had occurred spontaneously [6]. To put this figure in perspective, nearly 12,000 people in the

U.S. alone die *every year* of primary brain tumors [14]. In our experience in Cincinnati nearly 2 % of local donors used over the last 22 years died of primary brain malignancies. The cases of extracranial spread reported to the CTTR [2, 7, 10, 13-15] do emphasize the need for caution in using such donors. However, the CTTR data tend to exaggerate the risk of transmission of cancer from intracranial tumors as many recipients, who remained well, despite having received organs from donors with primary brain neoplasms, were not reported to the CTTR, as for many years it was considered safe to use organs from donors with primary brain tumors. For instance, the current manual of the United Network for Organ Sharing (UNOS) lists patients dying of primary brain tumors as suitable donors.

A difficult decision arises when a donor has a history of cancer treatment in the remote past [14, 15]. Most surgeons would accept a five-year and, certainly a ten-year, disease-free interval as evidence of «cure». However, it is well recognized that late metastases do occur from carcinomas of the breast or colon or from malignant melanomas. It is possible that these may be present as micrometastases at the time of organ retrieval and a diseased organ could be transplanted. The transplant surgeon must evaluate each donor on an individual basis and weigh the small risk of transplanting malignancy with organs from such a donor (none have been reported to date) against discarding many potentially usable organs in view of the profound shortage of cadaver organs in most countries.

During organ retrieval surgeons should carefully examine all accessible intrathoracic and intra-abdominal organs for evidence of malignancies. This has occasionally yielded positive findings, particularly with primary renal carcinomas [13-15], so that a particular organ or that particular donor was not used [3]. Unfortunately, micrometastases cannot be detected and even macroscopic deposits may be missed if located deep inside a large organ such as the liver or kidney. Some authors recommend the use of intraoperative ultrasound to try to locate hidden macrometastases [3]. However, this equipment is not available at most community hospitals. Perhaps, in the future, routine ultrasound examinations may be possible if organs are taken to a transplant center that has the necessary equipment. However, this test will fail to detect small metastases and micrometastases.

If a suspicious nodule is found while retrieving a kidney, it should be biopsied and a prompt frozen section examination obtained. If a primary renal carcinoma is diagnosed, it may be widely excised and the kidney transplanted, as was done successfully in several patients (see above) [13-15]. All such recipients must be carefully followed for long periods for signs of recurrence. However, the kidney should not be transplanted if the tumor is large or excision gives inadequate margins.

Theoretically every cadaver donor should have an autopsy examination performed as soon as possible and certainly before any organs are transplanted [3]. However, in practice permission for autopsy examination is seldom given and if it is performed it is usually done after the organs have been transplanted. Furthermore, as the pathologist has to fix the brain in preservative for a week or more, the results of an autopsy are usually not available for several weeks. To complicate matters further, even when an autopsy is performed at the donor hospital, the results may not be made available to the various recipient transplant surgeons. Therefore, an added duty for the procurement team is to check with the donor hospital concerning any possibly dangerous autopsy findings [13-15].

When a kidney has been transplanted from a cadaver donor in whom a later autopsy shows a previously unsuspected, but widespread malignancy, the surgeon should promptly remove the allograft because there is at least a 42 % risk that it contains malignant cells [13-15]. However, the patient may refuse to have the allograft removed, in which case he/she must be carefully evaluated at frequent intervals. In addition to clinical examination, computerized axial tomography or magnetic resonance imaging may be performed and beta-HCG levels measured in cases where the donor had choriocarcinoma. If a transplanted cancer becomes apparent at a later date, the allograft should be removed, immunosuppressive therapy discontinued, and the patient placed on regular dialysis [13-15]. This may permit the immune system to recover and reject residual malignant cells [13-18]. If necessary, any residual neoplasm can be treated with radiotherapy, chemotherapy, or immunotherapy using agents such as alpha-interferon or interleukin-2. If the cancer regresses completely further renal transplantation should be delayed until the patient has been free of neoplasia for at least one year [12, 14].

The situation is more complicated when a hepatic or cardiac allograft is involved by cancer [13-15]. One could excise the graft and replace it with a healthy one. However this may result in removal of a perfectly healthy organ as mentioned above and the operation has the risk of significant mortality and morbidity. On the other hand, despite retransplantation, there is a risk that residual cancer cells that have escaped from the first allograft may grow under the heavy immunosuppression necessary to sustain the second graft. This danger applies particularly to choriocarcinoma where tumor cells may rapidly become blood-borne from a transplanted organ [4]. Possible alternatives are: to reduce immunosuppressive therapy (risk of rejection); to resect portion of a liver allograft

if the tumor is suitably located; to reduce immunosuppressive therapy and treat the patient with chemotherapy if the malignancy is likely to respond to such treatment (danger of overimmunosuppression); or, in a cardiac recipient, to remove the allograft, stop immunosuppression, place the patient on an artificial heart device, and retransplant him/her at a later date [13-15].

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