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Donor derived malignancy following transplantation: a review

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Abstract Organ and tissue transplant is now the treatment of choice for many end stage diseases. In the recent years, there has been an increasing demand for organs but not a similar increase in the supply leading to a severe shortage of organs for transplant resulted in increasing wait times for recipients. This has resulted in expanded donor criteria to include older donors and donors with mild disease. In spite of implementation of more stringent criteria for donor selection, there continues to be some risk of donor derived malignancy. Malignancy after transplantation can occur in three different ways: (a) de-novo occurrence, (b) recurrence of malignancy, and (c) donor-related malignancy. Donor related malignancy can be either due to direct transmission of tumor or due to tumor arising in cells of donor origin. We will review donor related malignancies following solid organ transplantation and hematopoeitic progenitor cell transplantation. Further, we will briefly review the methods for detection and management of these donor related malignancies.

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Abbreviations

AML	Acute myeloid leukemia
B-HCG	B-human choroinic gonadotrophin
CIS	Carcinoma in situ
CML	Chronic myeloid leukemia
CMV	Cytomegalovirus
CNS	Central nervous system
CTTR	Cincinnati Transplant Tumor Registry
EBV	Epstein Barr Virus
FISH	Fluorescent in situ hybridization
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HHV-8	Human herpes virus 8
HPCT	Hematopoeitic progenitor cell transplantation
HPV	Human papilloma virus
HTLV	Human T-lymphotropic virus
IPTTR	Israel Penn Transplant Tumor Registry
MDS	Myelodysplastic syndrome
NHL	Non-Hodgkin's lymphoma
OPTN	Organ Procurement and Transplantation Network
PTLD	Post-transplant lymphoproliferative disorder

RFLP	Restriction fragment length polymorphism
SNP	Single nucleotide polymorphism
STR	Repetitive sequence of 2–7 nucleotides long
UNOS	United Network of Organ Sharing
VNTR	Repetitive sequence of 9–45 nucleotides long
WHO	World Health Organization

Introduction

Organ transplant as the treatment of choice for end stage disease has evolved since the pioneering work started in the 1960s. During this time, organs from donors with disseminated malignancies were utilized. This resulted in a summary publication of an unacceptable increase in malignancy in transplant recipients (Penn 1975). In fact, the first reports of cancer in recipients involved transmission of donor malignancy (Martin et al 1965; Wilson et al. 1968; Matter et al. 1970). These experiences lead to transplant physicians shying away from utilizing organs from donors with a past history of malignancy. However, with increasing demand for organs but not a similar increase in the supply, a severe shortage of organs for transplant resulted in increasing wait times for recipients (Kauffman et al. 1997). As per the Organ Procurement and Transplantation Network (OPTN)/United Network for Organ Sharing (UNOS), in September 2006, there are more than 90,000 recipients on the waitlist for solid organs. This has resulted in expanded donor criteria to include older donors and donors with mild disease (Palacios 1999; Alexander and Vaughn 1991; Kauffman et al. 1997). In spite of implementation of more stringent criteria for donor selection, there continues to be some risk of donor-derived malignancy. The recent scandal concerning body snatching and the use of under tested tissue for transplantation has once again brought attention to the issue of transmission of malignancy by transplantation (Childress 2006).

Malignancy after transplantation can occur in three different ways: (a) de-novo occurrence, (b) recurrence of malignancy, and (c) donor-related malignancy. Additionally, there is a potential for development of tumors in transplant recipients due to transmission of oncogenic viruses like human papilloma virus (HPV), human T-lymphotropic virus (HTLV), hepatitis C virus (HCV), hepatitis B virus (HBV), human herpes virus 8 (HHV-8), Epstein-barr virus (EBV), cytomegalovirus (CMV), however, this issue will not be addressed in this review.

Donor-related malignancy can be further classified into two broad categories:

Tumor transmission

This category includes development of tumors in recipients due to transmission of tumors that existed in the donor at the time of transplantation. The donor malignancy may have been identified at the time of the organ procurement or may be identified after transplantation. The majority of tumor transmissions have been reported in solid organ transplants with only few case reports of transmission by hematopoeitic progenitor cell transplantation (HPCT: includes both bone marrow transplantation and peripheral stem cell transplantation). The major mechanism postulated for this is altered immune surveillance along with HLA matching which is reinforced by the fact that decreasing immunosuppression may result in treatment of the malignancy.

Donor-derived malignancy

This includes de-novo development of malignancy in the donor cells with no preexisting malignancy in the donor. This category may also include post-transplant lymphoproliferative disorders (PTLD) which are well-recognized and potentially fatal complications after transplantation. The majority of cases are associated with EBV driven malignant transformation of the B cells (80%) secondary to the effect of immunosuppression on EBV. However, malignant transformation of T cells (15%) and other viruses like HTLV are also reported. Most of the PTLD after HPCT are donor cell derived while the majority of PTLD following solid organs are recipient derived (Taylor et al. 2005; Loren and Tsai 2005). In this review, we will only be discussing donor-derived tumors that are not PTLD.

Several mechanisms have been postulated for malignant transformation of the donor-derived cells and include; viral or oncogene transfection from the host into the donor cells, which is favored by the

altered immune surveillance; chronic antigenic stimulation of the donor cells in the recipient; altered host microenvironment (includes alterations secondary to residual radiotherapy and chemotherapy) predisposing to malignancy; or premature aging of the donor cells as a consequence of the replicative effort to repopulate the recipients marrow in HPCT (Sala-Torra et al. 2006; Reichard et al. 2006; Bodo et al. 1999; Cooley et al. 2000).

The discussion of donor-related malignancy in this review is divided into

(a) donor-related malignancy in solid organ and tissue transplants
(b) donor-related malignancy in HPCT
(c) a brief discussion on the methods for detection and
(d) management of donor-related malignancy

Solid organ transplants

Transmission of tumor

Transmission of malignancy in an immunosuppressed recipient usually occurs when the tumor is undetected before or during the organ donation or it may be misdiagnosed. Dr Israel Penn started collecting worldwide data on such cases as a part of the (Denver) Cincinnati Transplant Tumor Registry (CTTR) from 1968 onwards (Penn et al. 1971) which is now renamed the Israel Penn Transplant Tumor Registry (IPTTR) (Witherow et al. 2003). This lead to the first publication in 1975 (Wilson and Penn 1975) followed by updates in 1991 (Penn 1991), 1997 (Penn 1997), and 2004 (Buell et al. 2004). Analysis of these data and similar reports lead to the development of an International consensus document for organ donor screening to prevent transmission of neoplastic disease (Select Committee of Experts on the Organisational Aspects of Cooperation in Organ Transplantation 1997) (which is discussed later). This document, as well as all subsequent guidelines, emphasizes the need for a complete medical history of the donor, along with a thorough physical examination, including intra-abdominal and intra-thoracic inspection. Additional imaging studies when inspection of the body cavities is not possible and appropriate screening laboratory tests like prostate specific antigen, ß-human choroinic gonadotrophin (ß-HCG) should be performed. Also recommended is the use of frozen sections for suspicious nodules. Thus transmission of a preexisting tumor is currently an unlikely cause of post transplantation malignancy, however, it should always be considered as one of the differentials. This topic is discussed in two major categories of transmission, those of central nervous system (CNS) tumors (Tables 1, 2) and those of non-CNS tumors (Table 3).

Non-CNS tumor-transmission

The CTTR data from 1968 to 1997 found that cancer was transmitted in 43% of transplant recipients who received their graft from a donor with malignancy (Penn 1997). In this study, 154 cadaveric donors with cancer provided organs to 237 recipients. Malignancy was transferred from 70 donors to 103 recipients, with kidney being the transplanted organ in 71 recipients. Renal cell carcinoma (57%) followed by melanoma (10%) and choriocarcinoma (9%) were the most common cancers transmitted. However, of the recipients at risk of renal cell carcinoma, transmission occurred in 63% (43/68), while choriocarcinoma transmission occurred in 93% (13/14) of the recipients and melanoma transmission occurred in 77% (23/30) recipients. Other solid tumors demonstrating high risk of transmission are lung (41%), breast (29%), prostate (29%) and colon (19%). An updated publication in 2004, reported transmission of malignancy in 124 of the 296 (42%) cases of high-risk transplants performed using donors with known or incidentally discovered malignancy (Table 1) (Buell et al. 2004).

Another report from IPTTR found a similar overall cancer transmission rate of 45% (10 of 22) in cardiothoracic transplant recipients from donors with malignancy (Buell et al. 2001). Of the 22 transplant recipients (17 hearts, three lungs and two heart-lungs), six donors had CNS tumors and 16 had non-CNS tumors. Only one donor with medulloblastoma (one of six, 17%) transmitted the cancer while nine of 16 donors (56%) with non-CNS tumors transmitted the tumor. Of the non-CNS tumors five were renal cell carcinoma and three were choriocarcinoma and two were melanoma. The most aggressive of these was melanoma with tumor transmission in both cases (two of two, 100%) followed by choriocarcinoma

Table 1 Summary of publications analyzing transmission of tumor in recipients receiving solid organs from donors (living and cadavers) with known *non-CNS* malignancies (both low- and high-grade)

Publication	Total number of recipients	Number of recipients with tumor transmission	Number of tumor transmission[a]	Comments
Buell et al. (2004)	296	124	42	Voluntary reporting
Buell et al. (2001)	21	9	43	CT-Tx[Ψ], voluntary reporting
Kauffman et al. (2000, 2002a)	1,276	0	0	Low-grade malignancy and non-melanoma skin cancer
Birkeland and Storm (2002)	37	1	3	17/37 organs from individuals with CIS[b]
Serralta et al. (2003)	6	0	0	Liver transplant recipients

[a] Rate cannot be estimated since this reflects tumor transmission in selected population only

[b] CIS = carcinoma in situ

[Ψ] CT-Tx = cardio-thoracic transplant

Table 2 Summary of major studies analyzing the rate of tumor transmission and rate of transmitted tumors (non-CNS) in solid organ transplant recipients

Publication	Recipients			Donors		
	Number with tumor Tx	Total number	Transmitted tumor rate[a]	Number that transmitted tumor	Total number	Tumor transmission rate (%)[b]
Kauffman et al. (2002a)	13	108,062	0.01%	9	34,933	0.006
Birkeland and Storm (2002)	1	NA[c]	NA[c]	1	626	0.2
Serralta et al. (2003)	0	582	0%	0	582	0

[a] Transmitted tumor rate = Number of recipients with tumor transmission/Total number of recipients

[b] Tumor transmission rate = Number of donors that transmitted the tumor/Total number of donors

[c] NA = not available

Table 3 Summary of publications analyzing transmission of tumor in recipients receiving solid organs from donors with known CNS malignancies

Publication	Total number of recipients	Number of recipients with tumor transmission	Number of tumor transmission[a]
Colquhoun et al. (1994)	84	2	2
Jonas et al. (1996)	46	1	2
Chui et al. (1999)	151	0	0
Pokorna and Vitko (2001)	89	0	0
Kauffman et al. (2002b)	1,220	0	0
Buell et al. (2003)	62	14	23
Hornik et al (2004)	32	0	0

[a] Rate cannot be estimated since this reflects tumor transmission in selected population only

(two of three, 67%) and renal cell carcinoma (two of five, 40%, both with vascular invasion). However, since these data were based on voluntary reporting and the population base was not known, this does not represent the true risk or incidence of tumor transmission. In contrast, Kauffman et al., based on the

UNOS data, found no tumor transmission in 650 transplanted organs from 257 donors with past history of skin or solid tumor malignancy (Kauffman et al. 2000). An update on the same data found no tumor transmission in 1,276 organs from 488 donors with a history of skin or solid tumor malignancy during a 57-month period from April 1,1994 to December 31, 1998 (Kauffman et al. 2002a; Feng et al. (2002). However, most of these were individuals who had non-melanoma skin cancers or other low-grade malignancy (Table 1).

A further report from UNOS analyzed donor related malignancies in the United States from 1994 to 2001 (Kauffman et al. 2002a). During this time there were 34,933 cadaveric donors and 108,062 transplant recipients. There were a total of 21 reported donor related malignancies in transplant recipients from 14 cadaveric and three living donors. Of these, 15 were due to tumor transmission while six were donor-derived. Of the 15 instances of tumor transmission, 13 (five liver, six kidney, two heart transplants) were from cadaveric donors while two (kidney transplants) were from living donors. One donor with melanoma transmitted the tumor to all four recipients (Stephens et al. 2000), while another transmitted the malignancy to two recipients. One living donor was found to have a lung carcinoma ten months after kidney transplant (Bodvarsson et al. 2001), while another was found to have metastatic breast carcinoma six months post-transplant. Nine cadaveric donors transmitted the malignancy in 13 of the 108,062 cadaveric organ recipients resulting in a transmitted tumor rate of 0.01% and a tumor transmission rate of 0.025% (9/34,933 total cadaveric donors). Six of these 13 patients died due to the transmitted malignancy representing a death rate of 0.006% in the total recipient population (Table 2).

A single center from Denmark reported on the risk of tumor transmission in solid organ transplants from 1969 to 1996 (Birkeland and Storm 2002). Of the 626 donors (491 cadaveric, 135 living), there were ten with carcinoma in situ (CIS) or dysplasia cervix uteri (nine cadaveric, one living) and 13 with malignant tumors (seven living and six cadaveric). Malignancy was detected in 5/7 living donors after transplant (0.5–21 years post-transplant). One living donor had carcinoma of the rectum while the other had carcinoma of the breast, both of which were diagnosed at least 8 years before the transplant and none of the recipients developed malignancy. This resulted in 17 recipients receiving a transplant from a donor with CIS/dysplasia, of whom two developed cancer post-transplant, however, they were not considered to be related to the donor. Twenty recipients received a transplant from a donor with malignancy of which three developed a cancer post-transplant and only one with melanoma was considered to be transmitted from the donor (Table 1). This gives a risk of tumor transmission of 0.2% (one in 626) and the risk of having a donor with an undetected malignancy of 1.3% (eight in 626 or one in 78).

In a retrospective review from Spain, there were 682 liver procurements from cadaveric donors and 582 liver transplants from January, 1996 to December, 2001. A malignant genitourinary tumor was detected in six donors after liver transplantation (four renal cell carcinoma, one prostate carcinoma and one with prostate carcinoma and glioblastoma). During a mean follow up of 50.8 ± 19.8 months, there was no evidence of any tumor transmission (Serralta et al. 2003) (Table 2).

Besides these retrospective studies there have been many case reports of tumor transmission (melanoma, sarcoma, renal cell carcinoma, etc) (Stephens et al. 2000; Milton et al. 2006; Neipp et al. 2006; Cankovic et al. 2006; Detry et al. 2005; Morris-Stiff et al. 2004; Gerstenkorn and Thomusch 2003; Lipshutz et al. 2003; Loren et al. 2003; Kakar et al. 2002; Barrou et al. 2001; Winter et al. 2001; Conlon and Smith 1995; Oesterwitz and Lucius 1991; Barnes and Fox 1976), some of which may have been included in the reviews described.

Considering all the studies described above, the most frequently reported transmission of non-CNS tumor has been renal cell carcinoma followed by melanoma and choriocarcinoma. However, melanoma and choriocarcinoma are more aggressive than renal cell carcinoma. There are few case reports about transmission of other tumors like adenocarcinoma and sarcoma, both of which appear to be highly aggressive. In one case of liver transplantation for hepatitis B cirrhosis, histological examination of a lung mass found on autopsy showed metastatic adenocarcinoma. Despite urgent re-transplantation within 7 days, the recipient developed metastatic pulmonary adenocarcinoma diagnosed 11 months after transplantation and died soon thereafter (Lipshutz et al. 2003).

Early reports of tumor transmission and the understanding of how the malignancy metastasize lead to the recommendations by Dr. Penn that cancers with late appearance of metastasis like breast, lung, colon should be avoided (Penn 1991). He also recommended that except for tumors that are known to have late metastasis, individuals with a 10-year disease free interval after treatment for the primary cancer can be used as organ donors. Based on these recommendations, the experts in the International Consensus Document from Europe recommend that donors diagnosed with cancer should not be used except those with low-grade skin tumors like basal cell carcinoma, carcinoma in situ of the uterine cervix (Select Committee of Experts on the Organisational Aspects of Cooperation in Organ Transplantation 1997). However, since there was no consensus on the disease free survival period, they recommended that those donors should also be not considered for organ donations (Select Committee of Experts on the Organisational Aspects of Cooperation in Organ Transplantation 1997).

Based on a consensus conference (Kasiske et al. 2001), the 2003 third annual ASTS state-of-the-art winter symposium, categorized the risk posed by various tumors based on the type and stage of the malignancy into low, moderate and high. They also suggested recommendations for appropriate waiting periods between diagnosis, definitive cancer treatment and organ transplantation (Feng et al. 2003).

A recent abstract reports on successful transplantation of kidneys from deceased donors with past history of cancer and were disease free for at least two years. In a three year follow up of 23 recipients from 16 donors (n; 5 = breast, 3 = prostate, 3 = cervical and one each lung, Hodgkin's lymphoma, thyroid, colon and laryngeal cancer), there was no evidence of tumor transmission (Kumar et al. 2006). However, no details on the stage or the type of the malignancy were reported.

Donor renal cell carcinoma apparent at transplant

Penn reported data on 15 cadaver donors with a small renal cell carcinoma (<2 cm) in one kidney and a normal contra lateral kidney. All the normal kidneys and seven affected kidneys after tumor excision were transplanted and with a mean follow-up of 55 months (range 0.5–153 months), only one patient died from a renal cell carcinoma and DNA fingerprints indicated that the tumor was not of donor origin (Penn 1995). In a report from France, a cadaver donor with renal cell adenoma in one kidney, donated another kidney and heart. The kidney recipient was tumor free, while the heart recipient died seven months after transplantation due to metastasis from renal cell carcinoma (Barrou et al. 2001). The tumor at the time of discovery was called an adenoma based on the World Health Organization (WHO) criteria of 1981, however would be classified as a malignancy based on the new WHO criteria. The published guidelines do not address this issue either.

Molecular techniques and gene expression analysis have lead to a better understanding of cellular and biological mechanisms responsible for metastasis and they continue to evolve. One thing that is evident is that not all malignancies behave similarly and have unique genetic signature that may be able to predict their progression. In the current scenario of huge disparity between organ supply and demand, a team approach to evaluation of potential organ donors with malignancy will be very prudent. The team should include a pathologist who has an understanding of the cancer and its behavior including the possibility of late metastasis, the transplant team who evaluate the urgency of the situation and the recipient who can make an informed decision. Implementation of a new stringent protocol in Italy (Fiorentino et al. 2003) based on a team approach and understanding of the cancer demonstrates how patient safety can be maximized while optimizing the use of marginal donors. In this protocol for cancer-related risks, the donors are stratified into three groups by a pathologist

(a) *standard risk*: absence of any evident risk factor for transmission of cancer, including donors with basal cell skin carcinoma, non-metastatic squamous cell skin carcinoma, in situ carcinoma of the uterine cervix or larynx and papillary non-invasive carcinoma of the urinary bladder.
(b) *non-standard risk*: potentially low risk of transmission and can provide life-saving organs only in cases of certified clinical emergency and pending informed consent.
(c) *unacceptable risk*: (absolute contraindication) includes any history of breast cancer, melanoma, leukemia, lymphoma, small cell lung cancer and any other tumors (past or present)

that are judged by the pathologist to have a high potential of metastasis.

This protocol does not directly address the issue of cancer free survival; it is probably left to the judgment of the pathologist in conjunction with the clinical team and the recipient.

Primary brain tumors

Since the extra-neural spread of primary brain tumors is rare (0.4% to 2.3%) (Pasquier et al. 1980; Campbell et al. 1984), many physicians will accept organs from such donors. However, the rarity of the spread noted maybe explained by the fact that these patients have a shorter survival since the rapid tumor expansion without complications is limited by the skull. Better treatment modalities leads to better survival and thus the probability of metastasis. Many factors including the biological nature of the dura mater, blood brain barrier and, lack of lymphatics have been proposed to be the reasons for this low rate of metastasis (Detry et al. 2000). The risk factors for extra neural spread have been determined and include, cell type and tumor grade, history of neurosurgical processes like craniotomy, ventriculo-systemic or peritoneal shunt, history of tumor radiation and duration of the disease (Healey and Davis 1998; Hoffman and Duffner 1985; Fecteau et al. 1998). However, the absence of risk factors does not exclude the possibility of extra neural spread. It has been reported that less then 3% of the CNS tumors have extra neural spread, but 10% of these do so in the absence of any risk factors (Detry et al. 2000; Wallace et al. 1996).

There are no prospective studies to define the risk of transfer of CNS tumors in organ recipients; however retrospective studies have tried to estimate this risk.

The CTTR report in 1997 (Penn 1997) included 46 donors with CNS tumors to 55 recipients of whom 10 (18%) developed a donor-transmitted malignancy. Besides this there were seven reported cases of transmission of primary CNS tumors by 1997 (Lefrancois et al. 1987; Morse et al. 1990; Val-Bernal et al. 1993; Ruiz et al. 1993; Konigsrainer et al. 1993; Colquhoun et al. 1994; Jonas et al. 1996; Bosmans et al. 1997). These resulted in procurement of 18 transplantable organs (two kidneys, three hearts, two lungs and one kidney/pancreas). Tumor was transmitted from each donor in a total 11 of the 18 transplanted organs. Two other authors also conducted a retrospective review to estimate the risk of tumor transmission. Colquhoun et al. (1994) reviewed the Los Angeles regional organ procurement statistics from 1986 to 1992. They noted that besides the case of transmission of a glioblastoma from one donor to two kidney transplant recipients, there were no other cases of tumor transmission in 34 donors with primary CNS tumors providing 84 organs, thus estimating the risk of tumor transmission of 3% (1/34) and the rate of transmitted tumor of 2% (2/84, Table 3). In 46 recipients of organs from 13 donors with primary brain tumor, Jonas et al. (1996) found only a single case of transmission of glioblastoma to a liver transplant recipient. Interestingly there was no tumor transmission in the heart from the same donor. This results in the estimated risk of tumor transmission of 8% (1/13) and the rate of transmitted tumor to be 2% (1/46, Table 3).

Based on these reports, in 1997 the Council of Europe published the International Consensus Document for Standardization of Organ Donor Screening to Prevent transmission of Neoplastic Diseases (Select Committee of Experts on the Organisational Aspects of Cooperation in Organ Transplantation 1997). The experts recommended that organs from donors with high-grade malignant CNS tumors should not be used for transplant while the donors with low-grade malignant tumor should be used only in very special circumstances. However, the CTTR data as well as the case reports do not reflect the real incidence of tumor transmission as they were biased data.

From 1989 to 1996, the Australian and New Zealand Organ Donation Registry presented its experience with 46 cadaveric donors with CNS tumor that provided organs to 151 recipients (Chui et al. 1999), 60.9% (28/46) of them had malignant neoplasms and 25% (7/28) with other risk factors for tumor spread. Among the 153 recipients of organs from these donors, follow-up was complete for 151 patients for an average 40 months and no case of tumor transmission was reported (Table 3).

In a report from the Czech Republic from 1986 to 1998, 42 (2.1%) cadaveric donors with primary CNS tumors provided 91 organs to 89 recipients with no evidence of tumor transmission in a follow up period ranging form 24.2 months to 14.5 years (Pokorna and

Vitko 2001). Meninigioma was the most common tumor (n = 13, 31%), followed by glioblastoma multiforme in nine (21%) with 29% of the donors having undergone some neurosurgical procedure (Table 3).

UNOS reported on 397 of the 42,340 cadaveric donors with a history of CNS tumors from January, 1992 to December, 1999 (Kauffman et al. 2002b). The organs retrieved from these donors were transplanted to 1220 separate recipients and followed for a mean of 36 months. A total of 39 recipients developed post-transplant malignancy, 62% (n = 24) skin cancers, 20% (n = 8) PTLD and 18% (n = 7) de novo solid tumors, however, there were no graft-transmitted tumors (Table 3).

Buell et al. (2003) published an update on the 1997 CTTR data on the transmission of primary CNS in 2003. In their analysis from 1970 to 2002 there were 62 organs transplanted from 36 donors with primary brain malignancy (16 astrocytomas, 15 gliomas, three medulloblastomas, two cerebellar tumors) with an overall tumor transmission rate of 23% (14 cases, Table 3). They also examined the impact of other reported risk factors on the risk of tumor transmission and found that when no risk factor were identifiable, the transmission rate was 7%, whereas a single or more risk factors increased the rate from 36% to 43%, demonstrating no additive or synergistic effect of the presence of multiple risk factors. Univariate analysis suggested that a high-grade malignancy was an independent risk factor that represented the strongest predictor of donor-related tumor transmission. However, once again this data may not represent the true incidence, since this analysis was based on a highly biased data consisting of voluntary reporting of cases of tumor transmission.

There were two additional case reports of transmission of glioblastoma from two donors to three recipients (Frank et al. 1998; Armanios et al. (2004). In one case there was transmission of glioblastoma from the donor to the liver recipient (Frank et al. 1998). However, there was no tumor transmission to both kidney recipients. In another case, the tumor was transmitted to two recipients (lung and liver) but not transmitted to kidney and heart recipients (Armanios et al. 2004). However, liver recipient from a donor with glioblastoma and prostate cancer demonstrated no evidence of tumor after 44 months of follow up (Serralta et al. 2003).

Hornik et al. (2004) reviewed 32 cardiac allograft recipients that had received organs from donors with primary CNS tumor from 1989 to 2003 and found no incidence to donor-transmitted malignancy with a mean follow up of 80.6 months.

Collignon et al. (2004) have reviewed the types of gliomas and the biological and cellular pathways involved in the spread of the gliomas. Glioma metastasis may correlate with hyperactivity of certain signaling pathways like Ras, Akt and mTOR downstream of growth factor receptors. Rapamycin and/or its analogs block mTOR and thus theoretically can be used to prevent tumor transmission in organ recipients.

Although, primary CNS tumors may have a relatively lower risk of transmission, the brain is also the site of secondary brain tumors, many of which may present as a spontaneous intra-cerebral hemorrhage with no evident primary tumor and at times can be diagnosed as a primary brain tumor without any available histology. A wrong diagnosis can be disastrous, as evidenced by a report of 42 organ recipients who received organs from 29 donors who were misdiagnosed to have a primary brain tumor (Buell et al. 2005). In this study the most common diagnostic error was intracranial hemorrhage (62%) followed by CNS metastasis misdiagnosed as a primary tumor (21%) and anoxia at 17%. Following transplantation, the donors were identified with melanoma (23%), renal cell carcinoma (19%), choriocarcinoma (12%), sarcoma (10%), Kaposi's sarcoma (7%), and variable tumors (22%). The overall tumor transmission rate was 74% (31/42) with 64% of them experiencing a metastatic disease. Overall survival was 32% (10/31) at five years with a better survival amongst recipients where the transplanted organ was explanted. Thus besides a detailed history in such cases, it is important to have additional imaging studies, frozen sections as well as laboratory tests like B-HCG levels to identify choriocarcinoma are strongly indicated.

With the data available after the first formal guidelines in 1997, many centers have adopted different guidelines with regards to primary brain tumors. The Guidelines on Renal Transplantation published by European Association of Urology consider that donors affected by low-grade primary brain tumors (WHO grades 1 and 2) to be suitable for kidney donation, while those affected by high-grade

tumors (grades 3 and 4) are suitable for kidney donation only when deemed clinically urgent. However, donors with any grade of tumor with ventriculoperitoneal shunting are not acceptable (Kalble et al. 2005). Similar guidelines from Italy consider donors with low-grade tumors (grade 1 and 2) as standard risk, i.e., no evidence of risk factors for tumor transmission, while a select group of high-grade tumors (anaplastic astrocytoma, anaplastic oligodendroglioma, anaplastic oligoastrocytoma, anaplastic ependymoma, choroid plexus carcinoma, and gliomatosis cerebri) are considered as non-standard risk, i.e., donation of life-saving organs is justified by certified clinical urgency, pending informed consent of the recipient (Fiorentino et al. 2003). Donors with any other high-grade primary tumors are considered an unacceptable risk. In addition ventriculo-systemic deviation with any grade of tumor is considered unacceptable.

Summarizing, it can be safe to say that the literature on the risk of tumor transmission from donors with primary CNS tumors is conflicting and incomplete and more systematic prospective studies are required.

Because of this incomplete literature, there are variable guidelines adopted by different centers around the world, but in conclusion, when in doubt or in cases with questionable diagnosis, the transplant physician in consultation with a recipient that needs the life-saving organ should make a decision on a case by case basis and guided by the newer published criteria.

Corneal transplants

Since cornea is an avascular organ, the criteria for donors eligible for corneal donation are less stringent. Two retrospective reviews looking at a total of more than 500 corneal transplants, including donors with malignancy, found no transmission of malignancy (Wagoner et al. 1981; Salame et al. 2001). Thus the current Eye Bank of America Standards considers such donors to be safe for corneal donation (Medical Standards 1999). However, a single case report of transmission of a poorly differentiated adenocarcinoma 19 months after corneal transplant was reported (McGeorge et al. 2002). The donor in this case had metastatic adenocarcinoma with bilateral choroidal masses consistent with choroidal metastases. The donor origin of the tumor was confirmed by molecular typing. Another recipient of a cornea from the same donor however, showed no evidence of malignancy. Based on this single report the authors conclude that the current guidelines for corneal donors should not be changed, however, great caution must be exercised in individuals with evidence of ocular metastases. It should be noted that there has been no evidence of tumor transmission by corneal transplantation from donors with primary choroidal melanoma (Harrison et al. 1995).

Bone grafts and tumor transmission

Allograft bone is the most frequently chosen bone substitute next to autograft and accounts for about one-third of bone grafts performed in the United States (Boyce et al. 1999). Different types of allografts include fresh, frozen or freeze-dried forms, cortical or cancellous (Giannoudis et al. 2005). Frozen and freeze-dried allograft are more osteoconductive but are considered to have weak osteoinductive capabilities compared to fresh allograft. However, fresh allografts are rarely used because of the risk of transmission of infections. Frozen and freeze-dried are considered safe and it is believed that there are no viable cells in them although some cells may survive in the frozen grafts. For example, recent publications have demonstrated the presence of donor derived living cells in a culture medium from frozen bone grafts (Heyligers and Klein-Nulend 2005; Weyts et al. 2003). Although, there are no reports of tumor transmission using bone grafts, a study that evaluated osteoarthritic femoral heads removed during hip arthroplasty and potentially useable as bone grafts, showed 8% evidence of diseases not previously known including malignancy (Palmer et al. 1999). Thus considering the fact that there can be viable cells even after freezing the bones and previously undiagnosed malignancy, there is a potential of tumor transmission by bone grafts.

Donor derived tumor

To our knowledge there are only five reports of donor derived malignancy following solid organ transplantation (Bodo et al. 1999; Morath et al. 2005; Flemming et al. 2003; Barozzi et al. 2003; Roza et al. 2001). Although PTLD in solid organ

transplants are mostly of recipient origin, donor origin PTLD have been described (Taylor et al. 2005; Kauffman et al. 2002a; Peri et al. 2006).

Bodo et al. (1999) reported the development of a fatal acute promyelocytic leukemia of donor origin in a recipient of a liver transplant two years after liver transplantation. The leukemic clone bore the genetic and phenotypic markers of the donor. The donor was a previously healthy 16-year-old boy who died of a head injury.

Kaposi's sarcoma (KS) is a slow-growing endothelial tumor caused by HHV-8, and is 400–500 times more common in transplant recipients as compared to the general population (Mendez and Paya 2000). It is generally believed that HHV-8 reactivation in the recipient or the direct transmission of HHV-8 from the donor is responsible for this high incidence of KS in transplant recipients. However, Barozzi et al. (2003) reported that donor derived HHV-8 infected cells and not the free virus gave rise to post transplant KS in five of the eight renal transplant recipients. Similarly, Morath et al. (2005) reported a donor to recipient transmission of small cell carcinoma cells with a renal transplant and no macroscopic or microscopic evidence of malignancy in the resected renal allograft. Flemming et al. (2003) reported two cases of hepatitis B virus associated de novo hepatocellular carcinoma of donor origin in liver transplant recipients. While, Roza et al. (2001) reported development of adenocarcinoma of donor origin in pancreatic allograft 3.5 years after transplantation. Although the donor was a 55-year-old male who died of an intra-cerebral bleed, there was no evidence of tumor in the pancreas at procurement or by an ultrasound examination 2.5 years after transplantation and thus the authors speculate this to be a donor-derived tumor and not a donor-transmitted malignancy. In summary donor-derived malignancy post-solid organ transplantation is an extremely rare event.

Hematopoeitic progenitor cell transplants

Tumor transmission

Although, secondary cancer is a well-established long-term complication of HPCT (Curtis et al. 1997; Deeg and Socie 1998), it is rarely donor derived. Of the donor-derived malignancies, tumor transmission from the donor is extremely rare and to the best of our knowledge there are only six reports involving a total of 11 HPCT recipients (Sala-Torra et al. 2006; Berg et al. 2001; Heyll et al. 1994; Baron et al. 2003; Mielcarek et al. 1999; Niederwieser et al. 1990). It is not possible to estimate the frequency of this transmission since 5/6 reports are isolated case reports. In a large retrospective multi-center review of more then 10,000 transplantations performed between 1974 and 2004, the authors reported six cases of transmission of malignant clones following HPCT (Sala-Torra et al. 2006). Malignant clones were first identified in four recipients and in two donors and the tumor transmission was confirmed by molecular methods. Interestingly in all the six cases the malignant clones were of lymphoid origin and included CLL in three cases and one case each of marginal zone lymphoma, mantle cell lymphoma and ALL. The time interval from transplantation to detection of the malignant clones was relatively short in 5/6 cases (28–294 days) and 10 years in the remaining case. The mean age of the donors was 52.5 years (range 36–70 years). In a case from Seattle, a 50-year-old donor for her HLA-identical sister with refractory non-Hodgkin's lymphoma (NHL), was retrospectively diagnosed to have myelodysplastic syndrome (MDS) with a deletion of the long arm of chromosome 20 [del(20q)] (Mielcarek et al. 1999). The recipients' peripheral blood demonstrated clonal cells with the same del(20q) as early as 18 days post-transplant and were present even after 1 year. The recipients bone marrow examination demonstrated myeloid and erythroid dysplasia. Besides these cases, there have been reported transmissions of chronic myeloid leukemia (CML) (Baron et al. 2003), acute myeloid leukemia (AML) (Niederwieser et al. 1990) and sarcoidosis (Heyll et al. 1994), wherein the donor malignant clone could be identified in the recipient in less then four months. However, Berg et al. (2001) reported a case of transmission of T-cell lymphoma from one sister to another HLA matched sister, wherein the donor malignancy was clinically evident only after 3 years of transplantation.

Thus in summary, tumor transmission by HPCT is extremely rare and when it occurs, the malignant clone is usually evident very early in the recipient.

Donor derived tumor

In the realm of HPCT, most cases of PTLD are of donor origin as opposed to those in solid organ transplantation PTLD and are associated with altered immune surveillance and the presence of EBV (Taylor et al. 2005; Loren and Tsai 2005; Ades et al. 2002. Most cases of PTLD after HPCT are diagnosed within the first 5–6 months after transplantation and the estimates vary based on the definition of PTLD. In a large series involving 18,104 patients who underwent HPCT at 235 centers worldwide, PTLD developed in 78 cases (Curtis et al. 1999). For this review, however, we will only focus on donor-derived malignancies other than PTLD.

Donor derived leukemia following HPCT is a rare event and estimates have ranged from anecdotal to a single study estimating it to be as high as 5% (Boyd et al. 1982). In this study based on the cytogenetic analysis of relapses in 54 sex-mismatched HPCT, the authors suggested that donor-derived malignancy accounts for approximately 5% of the relapses.

However, in a recent multi-center retrospective review of more then 10,000 transplantations performed between 1974 and 2004, the authors found only six cases of donor derived malignancy based on multiple molecular methods of detection (Sala-Torra et al. 2006). The significance of the method of detection is discussed below. In this study, all the donor-derived malignancies were of myeloid origin (five cases of MDS and one case of AML). The median age was 36.5 years (range 4–48 years) and the time from transplantation to the detection of new malignant clone was more than one year (median 4 years; range 1.25–26 years). Except for this large study most of the other reports are single case reports that have been reviewed recently by various authors (Sala-Torra et al. 2006; Reichard et al. 2006; Cooley et al. 2000; Hertenstein et al. 2005). Considering all the reported cases, since the first reported case in 1971 (Fialkow et al. 1971), there are approximately 30–45 cases of donor-derived malignancy following HPCT (Reichard et al. 2006; Cooley et al. 2000; Smith et al. 1985; Witherspoon et al. 1985; Thomas et al. 1972; Newburger et al. 1981; Marmont et al. 1984; Goh and Klemperer 1977; Elfenbein et al. 1978; Palka et al. 1986, 1991; Zaccaria et al. 1987; Schmitz et al. 1987; Feig et al. 1988; Browne et al. 1991; McCann and Lawler 1993; McCann et al. 1992; Cullis et al. 1992; Katz et al. 1993; Mouratidou et al. 1993; Cransac et al. 1993; Lowsky et al. 1996; Deeg et al. 1984; Gossett et al. 1979; Au et al. 2002; Gopcsa et al. 2002; Brunstein et al. 2002; Komeno et al. 2003; Au et al. 2003; Bielorai et al. 2003; Haltrich et al. 2003). Unlike the multi-center review in all these cases there are as many myeloid donor derived malignancies as those of lymphoid origin. However, the constant theme in most of these cases is the longer time interval between transplantation and the detection of a new malignant clone as compared to those where there is transfer of neoplastic cells. The mechanisms leading to this are not understood and treatment modalities are not yet established. Despite its rarity cases of donor cell derived malignancies are considered of great interest, as they may provide insights into mechanisms of tumorogenesis. Various mechanisms have been postulated and include; viral or oncogene transfection from the host into the donor cells, which is favored by the altered immune surveillance; chronic antigenic stimulation of the donor cells in the recipient; altered host microenvironment (includes alterations secondary to residual radiotherapy and chemotherapy) predisposing to malignancy; or premature aging of the donor cells as a consequence of the replicative effort to repopulate the recipients marrow in HPCT (Sala-Torra et al. 2006; Reichard et al. 2006; Bodo et al. 1999; Cooley et al. 2000). However, it seems that there can be no single mechanism but a multifactorial mechanism for the origin of donor-derived malignancy. This was evident by the fact that most of the cases of donor-derived malignancies occur in HLA matched siblings and genetic factors are presumed to play an important role in the development of leukemia. Furthermore, in many of these cases, the recipients had also received total body ionization as a part of conditioning regimen. Also the longer interval between transplantation and development of the new malignant clones reflect the role of chronic antigenic stimulation and premature aging.

In one case a 47-year-old woman with CML received HLA-matched HPCT from her 50-year-old brother (Au et al. 2002). The brother who was a non-smoker died 15 months after donation due to squamous cell bronchogenic carcinoma. The recipient 4 years after transplant was found to have a relapse with AML which was shown to be of donor origin cytogenetically and molecularly.

In another case, an Ashkenazi Jewish patient with relapsed ALL had received HPCT from his HLA-matched sister, 2 years later developed an isolated relapse that was treated with local radiation and after another two years developed MDS/AML which was cytogenetically confirmed to be of donor origin (Bielorai et al. 2003). The sister who was fine at the time of donation developed a B-cell lymphoma thirteen years later and was found to be heterozygous for the Ashkenazi mutation of Bloom's syndrome. Homozygous mutation results in genomic instability and predisposes the patients to a wide variety of malignancies. Both these cases illustrate that there is no single mechanism for the development of donor derived malignancy and it is most likely a multi-factorial mechanism.

The detection of donor-derived malignancy leads to the issue of donor screening and counseling. Various guidelines for donor screening for HPCT have been published and reviewed by Neiderwieser et al. (2004). With increasing age of the donor and the increased frequency, there is a concern of increased transmission of tumor. Although the screening tests for infectious disease are well described, work up for malignancies is not standardized and there is no age-related donor screening. Some centers use bone marrow aspiration for screening of the related donors to exclude hematological malignancy (Niederwieser et al. 2004). However, in the authors' institution where bone marrow screening has been conducted since 1987, no donor was identified to have a malignant disease that would not be detected by routine screening. Considering that there are so few cases of donor-derived tumors in HPCT, Sala-Torra et al. (2006) proposed that concrete advice is not possible, however, a thorough physical and laboratory examination of the donor is recommended.

Diagnosis of donor origin of the tumor

Once a donor-transmitted malignancy is suspected, a confirmation is essential since treatment in this case may involve explanting the organ with emergency re-transplant. In fact UNOS allows this option when it can be proved that the organ transplanted came from a donor with active malignancy. In the early days, diagnosis of donor origin was made by histological comparison of the recipient and the donor tumor. In the 1970s with the introduction of traditional cytogenetics (Caspersson et al. 1970, 1972) in a sex mismatch transplant the donor origin was inferred by traditional karyotyping, which is reviewed in the book chapter (Perry 2005). Chromosomal abnormalities when present in the tumor were used to compare the recipient and the donor tumors. The major limitation of this method is that the analysis can be performed on viable tissue specimens that contain proliferating cells, thus rendering it of no use in comparison of paraffin embedded tissue. Thus, this method has been used for detection of donor origin of tumor in bone marrow transplants (Fialkow et al. 1971; Newburger et al. 1981; Goh and Klemperer 1977; Elfenbein et al. 1978; Zaccaria et al. 1987; Schmitz et al. 1987; Cullis et al. 1992; Bielorai et al. 2003; Thomas et al. 1972).

This limitation can be overcome by using fluorescent in situ hybridization (FISH) or other molecular methods. Amongst the other molecular methods, FISH is unique in that it utilizes direct microscopic visualization of the probe specific intranuclear signals, which allows a spatial resolution with regards to the location of the probe at cellular level. Thus one can identify which cell expresses the unique probe (Perry 2005). This property has been utilized to identify the donor origin of tumor cells in sex mismatched transplant recipients, utilizing the presence of two X versus one Y chromosome in the donor or the recipients cells (Reichard et al. 2006; Hertenstein et al. 2005; Goh and Klemperer 1977; Thomas et al. 1972; Baehner et al. 2000). The advantages of FISH include its applicability to a variety of specimen types, including fresh frozen tissue, cytologic preparations, and formalin-fixed paraffin-embedded tissue. Further, unlike traditional cytogenetics, it does not need mitotic nuclei and metaphase chromosomes. However, FISH also has its limitations including sensitivity, nuclear truncation artifacts, and partial hybridization failures. Further, leukemic clones may loose sex chromosomes and thus its utility as a stand alone method has been questioned. This has been emphasized by a report from Spinelli et al. (2000), where conventional cytogenetics, FISH, and PCR amplification for a Y-chromosome specific region suggested a donor origin of a secondary leukemia after BMT, however extensive molecular analysis determined that the leukemia was of host origin.

Other molecular methods are nucleic acid based methods. The basic principle in all these methods is

to screen the donor and the pre-transplant recipient sample for genetic markers where the donor and the recipient differ; called informative markers. Subsequently, these informative markers are used to analyze the tumor cells to determine their origin. Following digestion with restriction endonucleases, polymorphisms in individual DNA sequences result in DNA fragments of differing lengths known as restriction fragment length polymorphisms (RFLPs). RFLPs are inherited as co-dominant Mendelian traits and produce specific patterns (Botstein et al. 1980; Blazar et al. 1985) that can be detected by Southern blotting or automated electrophoresis. Comparison of these unique patterns from the tumor DNA with the recipient and donor DNA has been used for detection of the origin of the tumor (Reichard et al. 2006; Witherspoon et al. (1985; Feig et al. 1988; Katz et al. 1993). Although, RFLPs are sensitive, they are very time consuming, labor intensive and need a relatively larger amount of DNA as compared to other molecular methods described below.

The method considered as the gold-standard for identification of donor or recipient origin is PCR based amplification of highly polymorphic regions in the DNA. These polymorphic regions may be biallelic single nucleotide polymorphisms (SNPs) or consist of tandem repetitive blocks of DNA. When the repetitive sequence is 9–45 nucleotides long it is termed VNTR, while repetitive sequences 2–7 nucleotides long are termed STR or microsatellite markers. Jeffreys et al. (1985) first identified VNTRs as the hypervariable microsatellite regions in the human DNA. Edwards et al. (1991) first described the use of STRs as linkage markers. VNTRs were identified by a probe-based method, while STRs are identified by PCR based methods. A single STR locus such as D1S80 can offer a high discrimination rate of 60–90% between donor and recipient (Elmaagacli et al. 2001). Thus the use of several STR loci allows discrimination in almost all cases (>99%). Commercially available kits simplify this process and amplify around 13 loci (GenePrint Powerflex, Promega Corporation, AMPFLSTR Profiler Plus and COfiler, PE Applied Biosystems). Various groups have used these methods based on DNA polymorphism to identify the donor origin of the tumor. For solid tumors this involves careful microdisection or immunohistochemistry to separate the tumor cells from the normal surrounding cells followed by DNA extraction from the cells. For donor origin of hematological or lymphoid malignancy, flow cytometric separation of the tumor cells followed by DNA extraction has been used successfully. Other methods that have been used include the immunoglobulin gene rearrangement to identify the specific clonal signature of the tumor cells. In summary, because of the implications of the diagnosis of donor origin of the tumor, a sensitive method using multiple STRs or SNPs should be used.

Management of donor-derived malignancy

In the 1960s, the early days of transplantation, transmission of tumor could be the result of using donors with active malignancy. However, in the recent cases, tumors are discovered after harvesting of organs, when a tumor is detected in some other part of the body; or when the donor develops a tumor subsequent to donation.

Solid organ transplants

In patients with donor transmitted malignancy and kidney transplant, the majority of cases were managed by cessation of immunosuppression and transplant nephrectomy with subsequent return of the patient to regular dialysis (Penn 1997; Buell et al. 2004; Feng et al. 2003; Buell et al. 2005; Kauffman et al. 2001).

In a study of 42 recipients who received organs (kidney allograft, 84%) from 29 donors with misdiagnosed primary brain deaths; there was tumor transmission in 31 cases. Explantation was performed in 17 cases and 10/17 cases were alive after 5 years as compared to 0/14 where no explantation was performed (Buell et al. 2005). Similarly in a retrospective review, there was transmission of tumor in eight renal allografts, six of which underwent the above regimen and were alive at a two-year follow-up (Kauffman et al. 2002a). In some patients, cessation of immunosuppression leads to rejection of the tumor by the recovering immune system of the receipient (Kauffman et al. 2002a; Morath et al. 2005). However, a majority of the patients also need specific antineoplastic treatment in the form of chemotherapy and/or radiotherapy (Kauffman et al. 2002a; Bodvarsson et al. 2001).

Explantation was not immediately possible in life sustaining organs like heart, lung and liver, although

a ventricular assist device is now an alternate option for heart transplant. Three out of eight liver transplants and both the heart transplants where no explantation was possible, died due to metastatic cancer. In yet another study, two recipients of lung transplants from a donor with sarcoma received emergency explantation followed by re-transplantation. The recipients were shown to be tumor free after three and 36-month follow-up. Similarly, in another heart transplant recipient, melanoma was diagnosed after transplantation. An emergency re-transplantation was performed on day 17 and the patient was disease free after 22-months follow up (Loren et al. 2003). Again, in a case of re-transplantation of a liver allograft recipient with localized adenocarcinoma from the donor, the recipient was doing well at the one year follow up (Donovan et al. 1997). In contrast, despite emergency re-transplantation in a liver recipient from a donor found to have metastatic adenocarcinoma in the lung, the recipient died within 7 days due to metastatic adenocarcinoma (Lipshutz et al. 2003).

In cases of donors with renal cell carcinoma without capsular invasion, there is no tumor transmission, while in the case of vascular invasion of the tumor in the donor, tumor transmission appears to be early (Buell et al. 2001; Sack et al. 1997). Thus in six of the 582 liver transplants recipients that had received their organ from donors with a low-grade genitourinary malignancy, the authors chose not to perform transplantectomy and, in all the cases were without evidence of tumor after an average follow-up of 51 ± 20 months (Serralta et al. 2003).

There are no consensus guidelines for patient management. However, in most instances, when the donor is subsequently shown to have a metastatic tumor, immunosuppression should be reduced/ceased, the renal and/or pancreatic transplant should be removed and the patient returned to regular dialysis. However, for life-sustaining organs, early replacement of the heart, lung or the liver transplant should be planned. While waiting for re-transplant, immunosuppression should be tapered and specific anti-neoplastic therapy begun. For heart transplant recipients, ventricular assist devices may offer yet another option. After explantation, specific cancer marker levels (if available) should be frequently monitored.

Hematopoeitic stem cell transplant

There are approximately 50 reported cases of donor-related malignancy (both tumor transmission and donor-derived) following HPCT (Sala-Torra et al. 2006; Reichard et al. 2006; Cooley et al. 2000; Berg et al. 2001; Heyll et al. 1994; Baron et al. 2003; Mielcarek et al. 1999; Niederwieser et al. 1990; Boyd et al. 1982; Hertenstein et al. 2005; Fialkow et al. 1971; Smith et al. 1985; Witherspoon et al. 1985; Marmont et al. 1984) and thus it is not possible to derive any consensus management strategies for these cases. Unlike solid organ transplantation, in these cases, explantation is not possible. Management has been specific anti-neoplastic therapy and/or HPCT. In a multi-institutional review of >10,000 cases of HPCT, there were a total of 12 donor related malignancy (six donor derived and six donor transmission), 1/6 recipient with a donor transmitted malignancy received chemotherapy and 5/6 recipients with donor derived malignancy received HPCT (Sala-Torra et al. 2006). In four (Berg et al. 2001; Baron et al. 2003; Mielcarek et al. 1999; Niederwieser et al. 1990) other reports of transmission of tumor, the recipient received specific chemotherapy, while in a case of transmission of sarcoidosis via HPCT, the recipient was treated with high-dose methylprednisone (Heyll et al. 1994). In other cases with donor-derived malignancy, chemotherapy and/or HPCT have been the management.

Prevention of Donor-Related Malignancy

The incidence of donor-related malignancy is a rare event, however with increasing demand and an inadequate supply of organs, more centers are now using peripheral donors and older donors. As the chance of malignancy increases with age, one would expect that use of such donors can lead to an increased incidence of donor-related malignancy. Such malignancies are associated with a high rate of mortality and thus one way to decrease the incidence is to implement more stringent donor screening guidelines. A number of different associations have published guidelines for donor-screening as discussed above. The common themes in most of them can be summarized as follows:

(a) Extensive history including that of past treatment for malignancy, menstrual or irregularities

following pregnancy or abortion, mole removal, risk taking behavior like smoking.

(b) A thorough physical examination looking for scars, abnormal pigmentation, enlarged lymph nodes. Intra-cranial bleeds in a donor with no explanation for them (e.g., hypertension, intra-cranial aneurysm) need to carefully evaluated to rule out metastasis.

(c) Laboratory investigations to test for markers for malignancy like B-HCG, PSA, etc.

(d) Radiological examination including chest X-Ray, abdominal ultrasound, CT scans.

(e) Inspection and palpation of the thoracic and abdominal organs for nodules, removal of Gerota's fascia from both kidneys should be done during organ procurement.

(f) Multiple biopsies and frozen sections and/or pathological examination when required.

(g) A limited or a complete autopsy if possible.

Conclusions

Donor-derived malignancies are extremely rare events and can be classified as malignancies due to transmission of tumor and those that arise in cells of donor origin. The initial cases of donor-transmitted malignancies were clearly due to the use of donors with active malignancy. However, Dr. Penn's work resulted in better guidelines for donor eligibility and now donors with any malignancy except low-grade skin and brain cancers are ineligible to be organ donors. There is no consensus on the disease free interval before which individuals with certain malignancies can be eligible to be organ donors. Currently, most cases of donor-transmitted malignancies are because either, the tumor was detected after the organs have been harvested (as in heart/lung) when a detailed examination reveals a tumor on autopsy or on frozen sections or, the donor developed a malignancy after the organ donation. Such malignancies are more common in the solid organ transplants as compared to HPCT. Malignancies occurring in donor cells without evidence of any malignancy in the donor are more common in HPCT as compared to solid organ transplants and are due to a multitude of factors. As the management of the post-transplant malignancy that is donor-derived may be different, it is very critical to diagnose them correctly. Diagnosis should be based on more sensitive DNA based techniques that can detect the tumor signature to diagnose if it is of donor origin. There are no consensus management guidelines for such cases. Prevention of such cases by employing more stringent guidelines that will balance with the constant shortage of organs is being implemented. However, when faced with a critical situation, when lack of a transplant may be fatal, the physician may choose to go ahead with a marginal organ after an informed consent from the patient.

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