



# Organ transplantation from donors (cadaveric or living) with a history of malignancy: Review of the literature



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## ABSTRACT

The evolution of organ transplantation has resulted in extended lifespan as well as better life quality of patients with end-stage diseases, which in turn causes an increased demand for organs. The persistent organ shortage requires a careful reconsideration of potential donors (living or cadaveric) that have current or historical malignancies. Donors with low-grade skin tumors, carcinomas in situ of the uterine cervix, and primary central nervous system (CNS) tumors can be considered as potential donors for recipients dying on wait list longing for organ transplantation. Recently, transplant centers have turned to other types of malignancies including low grade renal cell carcinoma, prostate, ureteral, endometrial and breast cancer, and favorable outcomes have been shown in such innovations. When considering donors with a history of malignancy, general biologic behavior of the tumor type, histology and stage at the time of diagnosis, and the length of disease-free interval should be considered (*Transplantation* 2002;74(12):1657–1663). With the review of literatures, we illustrate the organ utilization from donors with malignancies all around the world since earlier times and give some suggestions for decision making under the circumstance of whether to choose those marginal donors or not on the basis of reviewed literatures.

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## 1. Introduction

The persistent shortage of organ supplies is a major obstacle to carry out organ transplantation for the large number of people waiting on the list. Both the size of the candidate waiting list and the number of deaths on the waiting list are progressively increasing [1]. The disparity between organ demand and organ supply has never been moderated. In order to decrease the mortality on the waiting list, transplant centers make every effort to increase the number of donors. Thus, utilization of extended criteria donors (ECD) has been suggested [2]. In the early 2000s, the concept of extended criteria kidney donor was defined to older individuals with hypertension, diabetes, or renal dysfunction, who were expected to produce allografts at greater risk of graft loss than standard donors, albeit sufficiently adequate for transplantation [3]. While the definition of extended criteria liver donor was characterized by individuals with advanced age, steatotic livers, donation after cardiac death (DCD), livers with seropositivity for hepatitis B virus (HBV) and hepatitis C virus (HCV). Besides, occult malignancies become a part of extended criteria donor factors [4]. Using organs from donors with malignancy is not uncommon, and it has plays an important role in expanding the donor pool. Though

this may carry risk of malignancy transmission, the risk of tumor transmission or donor related death is extremely small when compared with the benefits of organ transplantation.

## 2. Review of the literature

Buell et al. [5] reviewed all cases reported to the Israel Penn International Transplant Tumor Registry (IPITTR) that demonstrated a potential for donor-transmitted malignancy from the year 1965 to 2003. 296 cases of high-risk transplants performed using donors with known or incidentally discovered malignancies were reviewed. From the overall series, 124 cases (42%) were identified with confirmed donor transmission. Among them, CNS tumor, malignant melanoma, choriocarcinoma, renal cell carcinoma (RCC), lung cancer, colon cancer, and breast cancer were discovered with donor malignancy transmission. The transmission rate ranges from 23% to 93%. This study showed a relatively higher rate of tumor transmission, given that the donors might have high grade malignancies or misdiagnosed CNS tumors, which carry a much higher transmission risk.

Later, an analysis of Organ Procurement and Transplantation Network/United Network for Organ Sharing (OPTN/UNOS) data on 39,455 deceased donors from 2000 to 2005 showed 1069 donors had a past history of malignancy, resulting in 2508 transplants. The most common type of previous cancer in the donor was nonmelanoma skin cancer (n = 776) followed by central nervous system malignancies (n = 642) and carcinoma of the uterine cervix (n = 336). Four recipients died from donor transmitted malignancy. However, these

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four deaths from donor transmitted malignancies should be weighed against the 39,519 deaths on the waiting list during the same period of time. Donors with a past history of cancer may be particularly appropriate for urgent or high risk recipients such as Status 1 hearts or livers. Although the 2508 organ transplants from donors with a past history of cancer constitute only 2.2% of the 113,167 deceased donor organs transplanted from 2000 through 2005, they resulted in successful transplants and improved length and quality of life for many patients [6].

Another report from Italy found a similar overall cancer transmission rate of 0.2% (14 of 231) in transplant recipients from donors with malignancy [7], while the Spanish National Transplant Organization Registry reported transmission of malignancy in 10 of the 100 (10%) cases of transplants performed using donors with known malignancy. The transmission rates were supposed to be 6 per 10,000 related to the global recipients [8]. The Disease Transmission Advisory Committee (DTAC) reviewed donor-transmitted malignancy in 2009. There were a total of 15 reported donor transmitted malignancies in transplant recipients from 55 donors. Six of these 15 patients died due to the transmitted malignancy representing a death rate of 40% in the tumor transmitted population [9]. An updated publication of the United Kingdom Transplant Registry from 2001 to 2010 reported that of 30,765 transplants from 14,986 donors, 15 recipients developed donor-transmitted cancer, and 3 (20%) recipients with DTC died as a direct consequence of cancer [10].

Recently, Fiaschetti et al. [11] evaluated the experience of the Centre-Sud Transplant Organization (OCST) area using cadaveric donor with neoplastic diseases from 2003 to 2010. 28 evaluated donors (8.2%) were suitable for transplantation according to the histological types and grades. 45 organs were retrieved (22 livers, 19 kidneys, 3 hearts, and 1 pancreas) and transplanted into 44 recipients. No donor-transmitted tumor was detected among the recipients (Table 1).

Though the transmission rate varies in different areas and different tumor types or even with the organs transplanted, the experience of using donors with a history of malignancy seems to be favorable for expanding the organ donor pool, and the donor related tumor death rate is extremely small, particularly when compared with waiting-list mortality. We will review the literatures regarding several types of donor malignancies, hopefully to give some suggestions in decision making under the difficult circumstance of whether to choose the marginal donors or not afterwards.

### 3. Risk category assignment to specific tumors

Since the early days of transplantation, the risk of transmission of malignancy from donor to recipient has been recognized. In 2011, the subcommittee to examine donor-related malignancy transmission (Malignancy Subcommittee) of the DTAC of OPTN /UNOS suggested risk categorizations for specific tumor types (Table 2). Suggested approach to donor utilization is given for each category, recognizing

**Table 1**  
Summary of publications analyzing transmission of tumor in recipients receiving solid organs from donors with known malignancies.

Publication	Total number of recipients	Number of recipients with tumor transmission	Transmitted tumor rate (%)
Buell et al. (2004)	296 <sup>a</sup>	124	41.9
Kuaffman et al. (2007)	2508	4	0.2
Zucchini et al. (2008)	231	14	0.2
Garrido et al. (2008)	100	10	10
Ison et al. (2009)	55	15	28
Rajeev et al. (2012)	NA <sup>b</sup>	15	NA
Fiaschetti et al. (2012)	44	0	0

<sup>a</sup> These data were based on voluntary reporting and there may be a tendency for centers to report interesting, unusual, or challenging cases.

<sup>b</sup> NA = not available.

the primacy of individual clinical judgment and often emergent clinical circumstances [9]. According to the third edition (May 2011) of United Kingdom guidelines for living donor kidney transplantation [12], recommendations regarding donor malignancy can be summarized in Table 3.

### 4. Melanoma

Though rare, malignant melanoma is one of the most commonly reported donor-derived malignancies and has a high transmission rate and mortality when unwittingly transmitted to a recipient [5,13]. Buell et al. [5] reviewed the data from IPITTR and identified that two donor tumor histologies with the highest certainty of transfer were choriocarcinoma and melanoma. The malignant melanoma was demonstrated with a 74% tumor-transmission rate and a resulting 58% mortality. Earlier in the 1990s, Penn [13] recorded 11 donors with a history of melanoma who provided organs for 20 recipients. Melanoma transmission occurred in 16 recipients (75%), of whom 11 (68%) died from metastatic disease. The transmission rate is extremely high and the caused death rate also cannot be ignored.

Stephens et al. [14] reported in 2000 of a transfer of malignant melanoma from a single donor to four solid organ transplant recipients (kidney, liver, heart). All the four recipients died from metastatic melanoma. The donor was said to have died of cerebral hemorrhage and had no history or physical signs of melanoma. Similarly, Morris-Stiff et al. [15] reported three graft recipients (two kidney and hepatic) who developed metastatic melanoma from a cadaveric multi-organ donor who died from a subarachnoid hemorrhage. Two of the recipients presented with symptomatic metastatic lesions and the third patient, despite being carefully monitored, developed evidence of metastatic cutaneous melanoma. Two of the patients died as a direct result of their melanomas. Both donors in these two reports died of intracranial hemorrhage, and neither was identified with a history of melanoma. These two studies demonstrate the potential of melanoma to metastasize into any organ of the body and the fatal results caused by its metastasis. This may also suggest that donors who die from intracranial hemorrhage must be used with caution in case of the undetected metastatic melanoma due to its special biological behavior. As with another case, transmitted malignant melanoma was reported following a renal transplantation from a multi-organ donor [16]. The donor was a 48-year-old male who died from a subdural hemorrhage and at the time of organ collection there was no clinical evidence of melanoma. One of the renal transplant recipients underwent nephrectomy with cessation of immunosuppression after the lung transplant recipient presented melanoma of donor-origin, and a 3 mm melanoma deposit was shown in the resected kidney.

A history of melanoma is an absolute contraindication for a patient to be eligible for organ donation because of the possibility of late and ultra-late recurrence in melanoma [6,17], and late recurrence has been reported even in patients who have had melanomas less than 1 mm in thickness [18] and this possibility should be considered during clinical evaluation [19]. The current recommendation for treating donor-related melanoma in renal transplant recipients includes cessation of immunosuppression, allograft rejection and nephrectomy. As for non-renal transplant recipients, reduction of immunosuppression and an immediate retransplantation may be the best strategy [20]. With all the literatures reviewed above, we can conclude that donors with a history of melanoma should not be used as a source to expand the donor pool.

### 5. Choriocarcinoma

Reports on choriocarcinoma transmission are rare, but the high death rate related to transmitted choriocarcinoma though organ transplant has been highlighted. Earlier from the IPITTR data, 14 recipients were

**Table 2**  
Suggested risk categorizations for specific malignancy types from DTAC.

Risk category	Malignancies
Minimal risk (<0.1% transmission)	Basal cell carcinoma, skin Squamous cell carcinoma, skin without metastases Carcinoma in situ, skin (nonmelanoma) In situ cervical carcinoma In situ vocal cord carcinoma Superficial (noninvasive) papillary carcinoma of bladder (TONOMO by TNM stage) (nonrenal transplant only) Solitary papillary thyroid carcinoma, ≤0.5 cm
Low risk (0.1–1% transmission)	Minimally invasive follicular carcinoma, thyroid, ≤1.0 cm (Resected) solitary renal cell carcinoma, ≤1.0 cm, well differentiated (Fuhrman 1–2) (Resected) solitary renal cell carcinoma, >1.0 cm ≤ 2.5 cm, well differentiated (Fuhrman 1–2) Low grade CNS tumor (WHO grade I or II) Primary CNS mature teratoma Solitary papillary thyroid carcinoma, 0.5–2.0 cm Minimally invasive follicular carcinoma, thyroid, 1.0–2.0 cm History of treated non-CNS malignancy (≥5 years prior) with >99% probability of cure
Intermediate risk (1–10% transmission)	Breast carcinoma (stage 0 i.e. carcinoma in situ) Colon carcinoma (stage 0 i.e. carcinoma in situ) (Resected) solitary renal cell carcinoma T1b (4–7 cm) well differentiated (Fuhrman 1–2) stage I History of treated non-CNS malignancy (≥5 years prior) with probability of cure between 90–99%
High risk (>10% transmission)	Malignant melanoma Breast carcinoma > stage 0 (active) Colon carcinoma > stage 0 (active) Choriocarcinoma CNS tumor (any) with ventriculoperitoneal or ventriculoatrial shunt, surgery (other than uncomplicated biopsy), irradiation or extra-CNS metastasis CNS Tumor WHO grade III or IV Leukemia or lymphoma History of melanoma, leukemia or lymphoma, small cell lung/neuroendocrine carcinoma Any other history of treated non-CNS malignancy either (a) insufficient follow-up to predict behavior, (b) considered incurable or (c) with probability of cure <90% Metastatic carcinoma Sarcoma Lung cancer (stages I–IV) Renal cell carcinoma >7 cm or stage II–IV Small cell/neuroendocrine carcinoma, any site of origin Active cancer not listed elsewhere

reported to have received organs from donors with choriocarcinoma. 13 of these recipients developed metastatic choriocarcinoma, with a transmission rate of 93% and a resulting 64% mortality rate [21]. Choriocarcinoma is considered as a high aggressive cancer and is unanimously rejected in organ donors.

Lately, Bruan-Parvez et al. [22] reported an accidental transmission of placental choriocarcinoma from a multi-organ donor to 4 different recipients (combined pancreas-kidney, kidney, liver, heart). The donor was a 26-year-old woman who died from a massive cerebral hemorrhage

at 7 months of pregnancy, and no abnormality was found in the macroscopic examination of the donated organs. Choriocarcinoma of the donor was detected 1 month after transplantation to the four recipients. The authors confirmed high transmission of choriocarcinoma and bad prognosis in liver transplantation.

So it is risky to use donors with choriocarcinoma, and special attention should be paid to women donors at childbearing age. Besides, given that donors who died of cerebral hemorrhage may carry the risk of metastatic choriocarcinoma, careful examination of choriocarcinoma should also be taken in such donors.

**Table 3**  
Previous cancer and fitness for living donation.

Recommendation	Type of cancer
Absolute contraindication	Melanoma Testicular cancer Renal cell carcinoma* Choriocarcinoma Hematological malignancy Lung carcinoma Breast cancer Monoclonal gammopathy
Possible donation	Treated cancer with high probability of cure after 5–10 years (favorable classification and staging) e.g. colon cancer (Dukes A >5 years ago), non-melanoma skin cancer, carcinoma-in-situ of the cervix or vulva

\* In some centers, donation may be considered where there is a small (<4 cm) subcapsular renal cell carcinoma with complete bench excision at the time of donor surgery and no distant spread. ([http://www.bts.org.uk/MBR/Clinical/Guidelines/Current/Member/Clinical/Current\\_Guidelines.aspx?hkey=a1eb37c5-3824-4836-b0b2-ad118479e53c](http://www.bts.org.uk/MBR/Clinical/Guidelines/Current/Member/Clinical/Current_Guidelines.aspx?hkey=a1eb37c5-3824-4836-b0b2-ad118479e53c)).

**6. CNS tumors**

CNS tumors have been classified into four histologic grades by the World Health Organization (WHO) [23,24]. Each year in the United States, approximately 17,000 patients are diagnosed with malignant primary brain tumors, and more than 13,000 succumb to these diseases [25], and the summaries of tumor registry reports by Penn and Buell [26,27] concluded that, in light of the unmet patient need, organs from donors with central nervous system malignancies should not categorically be rejected, but should be offered to recipients with limited short-term life expectancy. Though commonly used in many transplant centers, whether it is safe or not still remains controversial as the real risk of tumor transmission remains unknown [28].

According to UNOS data from 1992 to 2005, 1039 donors had either a past cancer history of CNS tumors or the cause of death recorded as CNS tumor [1,6], and only one of the donor with an active glioblastoma multiforme was confirmed to have transmitted fatal tumors to three separate recipients (kidney, liver, lung) [29]. On the contrary, Buell et al. reported a much higher risk of utilization of such

donors by reviewing the cases reported to the IPITTR from 1970 to 2002. 62 organs were transplanted from 36 donors with CNS malignancy, resulting in 14 (23%) donor transmitted CNS malignancies [28]. The significant difference between the data of UNOS and that of IPITTR causes controversy. The high calculated risk of CNS cancer transmission in the IPITTR is thought to be caused by the underestimation of the denominator of the ratio [30]. Because the IPITTR is a passive forum for voluntary reporting, there may be a tendency for centers to report interesting, unusual, or challenging cases and as such, the true denominator is not known. However, the UNOS registry may suffer from underreporting [27].

In a retrospective review from 1992 to 2006, 42 donors diagnosed with a CNS tumor were identified in liver transplantation. Twenty (47.6%) of the CNS tumors were glioblastoma multiforme (astrocytoma grade IV), 11 (26.2%) were other astrocytomas, and 1 (2.4%) was an anaplastic ependymoma. Twenty (62.5%) neoplasms were grade IV tumors, 8 (25%) were grade II tumors and 4 (12.5%) were grade III tumors. Over 80% of the patients had at least 1 kind of invasive procedure violating the blood–brain barrier, but the result shows no difference in survival between recipients of grafts from donors with CNS tumors and recipients of grafts from donors without CNS tumors. The authors conclude that grafts from such donors can be appropriately used, particularly in patients who carry a high risk of mortality [31].

Similarly, a recent study reviewed 246 UK recipients of organs taken from donors with CNS tumors and found no evidence of a difference in overall patient mortality for recipients of a kidney, liver, or cardiothoracic organ, compared with recipients of organs from donors without a CNS tumor [32], and on the basis of a series of assumptions, the authors even found the use of kidneys from a donor with a primary CNS tumor could provide a further 8 years of life over the ones waiting for a donor without CNS tumor, in addition to the life years gained by the transplant itself.

Recently, the Malignancy Subcommittee of the DTAC committee of OPTN/UNOS [19] suggested that low grade CNS tumors (WHO grades I or II) and some high grade tumors such as glioblastoma multiforme may have relatively low transmission rates, and suggested that such organs may be usable for recipients at significant risk without transplant. In contrast, higher grade CNS tumors (WHO grades III–IV), or any CNS tumor, regardless of grade, with ventriculoperitoneal or ventriculoatrial shunt, prior surgery (excluding uncomplicated biopsy), chemotherapy, radiotherapy or extra-CNS metastasis was provisionally placed into the high risk category, and use of organs from these donors was discouraged except in rare and extreme circumstances. However, the increased incidence of donor transmitted malignancy due to the misdiagnosed brain death has to be taken into consideration, especially in donors who died from intracranial hemorrhage [5]. So it is significant to confirm the etiology of brain death to reduce the probability of transferred malignancy. Anyway, transmission from donors with CNS tumors is quite rare and those donors in absence of the risk factors can contribute to expanding the donor pool.

## 7. Renal cell cancer

Donors with renal cancer were not thought to be eligible for organ transplantation at earlier time because of the high metastasis [5]. However, with the burden of increased population on the waiting list, innovative strategies considering donors with small renal cell cancer (RCC) have recently emerged.

The largest series of 43 cases are presented in 2008 from Princess Alexandra Hospital by Nicol et al. [33]. 43 kidneys were transplanted from 41 donors with small (<3 cm) RCC into patients who were elderly or had significant comorbidities between 1996 and 2007. Among the 41 donors, 3 were deceased donors and 38 were donors who underwent radical nephrectomy for a presumed RCC. Successful results were shown in the report with kidneys transplanted after excision of the RCC and confirmation of no distant metastasis.

Only one case showed tumor recurrence 9 years after transplantation in the follow-up (mean 32 months). Furthermore, the study of Brook et al. [34] has also showed favorable results on the utilization of tumorectomized kidneys from patients with small, localized, incidentally detected RCC. Both the patient and graft survival of such type of renal transplant are comparable to that of conventional live unrelated transplants, and display a significant survival advantage for those who would otherwise not receive a transplant. Also it is recommended that detection of a small renal lesion during assessment of potential live donor should not necessarily prevent transplantation proceeding [35].

Except for kidneys, livers from donor with RCC may also be used for transplantation. As it was reported by Serralta et al. in 2003, 4 cadaveric donors with early-stage (T1–T2) renal cell carcinoma were detected after implantation of the livers [36], but no evidence of tumor transmission was observed in all the recipients after an average follow-up of 51 months. Another study in 2009 also reported the utilization of donor with genitourinary malignancy [37]. 2 donors affected by low-grade RCC were classified as “standard risk” and transplanted livers to recipients pending informed consent, with no death consequent to a neoplastic disease. Both studies showed great results of liver use from donors with genitourinary cancer.

Review of cases of cardiothoracic transplant recipients of an organ from a donor with renal malignancy showed that renal cell carcinomas without capsular invasion did not result in tumor transmission. However, in the case of vascular invasion of the tumor in the donor, tumor transmission appears to be early [36]. Buell and colleagues [38] reported on 5 recipients of cardiothoracic organs from the same registry who received organs from donors with a renal-cell carcinoma. Two tumors that presented initially with vascular invasion led to metastatic spread in the recipients, whereas 3 tumors were small and contained within the renal capsule and did not develop metastases after a follow-up of 30–70 months. Moreover, 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 [39].

It seems that those incidentally discovered, small RCC with low histological grade (Furhman grades I and II) have a relatively low potential for aggressive clinical behavior, and it has become the general consensus [40]. However, a full discussion with the patient and family are essential before transplantation about the risk of receiving such organs, which may include tumor recurrence or metastases and so on. Besides, kidneys from patients with small renal tumors who have elected to undergo radical nephrectomy might provide a valuable resource for many patients with end-stage renal failure, but the utility of these organs should not influence the decision of the donor with a renal tumor about their surgery [33]. With the review of the literature, we believe that kidneys (or livers) from donors with small, incidental RCC as well as RCC heart donors without capsular invasion can be safely used and will become a novel source for transplantation, and thus, expand the constrained donor pool.

## 8. Prostate cancer

Prostate cancer is the most prevalent malignancy in males over 60 years old, and the use of elderly donors may consequently carry the risk of presented prostate cancer. However, donors with prostate cancer now do not seem that contraindicated as it was before. The acceptance of organs from donors with prostate cancer was first introduced in the Emilia-Romagna Region of Italy in 2001 [41]. Before then, all candidate donors with prostate cancer were excluded, as the risk of neoplastic transmission among recipients who received organs from donors carrying prostate cancer was pretty high (29%) [42]. The revised Italian National guidelines in 2005 recommend an acceptance of potential candidates with prostate cancer to extend the donor pool

and introduce the function of a second opinion expert [43]. All donors with localized and Gleason score  $\leq 6$  prostate cancer are defined as the “standard risk” category in the new guidelines [44].

However, just from present literatures, it is still difficult to guarantee the absolutely safety of widespread utilization of donors with prostate cancer. As it is commented by the European guide for safety and quality assurance for transplantation “There is no written consensus regarding the procedure for donors with prostate carcinoma. The procedure should be individualized assessing the characteristics of the donor and the condition of the recipient.” [45]. Still, donors with prostate cancer may be a new source in the endeavor to decrease the disparity between the available organs and recipients on the waiting list.

## 9. Ureteral cancer

Mitsuhata [46] reported 3 cases of successful renal transplantation from live-related donors with lower ureteral cancer. The tumors were excised and the margins of the remaining ureters were free of cancer by frozen section detection. These ureteral cancers were at low-grade in histology. All recipients survived without cancer recurrence for 62–109 months. In a subsequent study [47], the authors reviewed all 8 kidney transplants using living donors with ureteral cancers, and there was only one recurrence of ureteral cancer in the transplanted kidney 15 months after operation.

Both reports may suggest that organs from donor with low-grade lower ureteral cancer can be used for transplantation with informed consent in the condition of severe shortage of donor organs.

## 10. Endometrial cancer (EC)

EC is the most common malignancy of the female genital tract, and is typically seen in post-menopausal women [12]. Patients with EC are always diagnosed at early stages and have a good prognosis with a 5-year overall survival rate greater than 85% [48]. To our knowledge, reports about organ transplants from donors with EC are quite limited, and no transmission of cancer has ever been recorded through transplantation from such donors. As recorded in the OPTN/UNOS [6], 65 deceased donor transplants were from donors with a history of uterine EC from 2000 to 2005, and three of them had a cancer-free interval less than 5 years. Though no detail is acquired about the stage or histological type of the cancer, there was no transmitted cancer occurred from donors with EC. While according to the review from Kälble et al., donors with a past history of endometrial cancer are placed into the intermediate risk category (10–25%) along with patients with colon, breast and prostate cancers [49]. Still, more studies are needed to estimate the risk of recurrence of using such donors in organ transplantation.

## 11. Breast cancer

Breast cancer is the second highest cancer-related cause of mortality in the United States, second only to lung cancer. Donors with a past history of breast cancer are placed into the high risk category and are suggested be avoided despite curative resections due to the potential late metastases, but patients with a history of stage T1a or T1b breast cancer in remission for 10 or more years may be taken into consideration [20].

An early review from the IPITTR noted a donor tumor transmission rate of 29%. Tumor transmission was only noted in cases involving invasive breast cancer, and was not associated with in situ carcinomas, such as ductal carcinoma in-situ (DCIS), and lobular carcinoma in-situ (LCIS). As with melanoma, breast cancer is notorious for late and aggressive recurrences. For this reason, the use of donors with a history of breast cancer should be limited to those with non-invasive forms, such as DCIS and LCIS, or those with early-stage invasive lesions who have completed an extended disease-free interval [5]. According to the

OPTN/UNOS data from 2000 to 2005, 126 deceased donor transplants were from donors with a history of breast cancer, and 21 (16.7%) of them had a cancer-free interval less than 5 years [6].

Currently, there is no existing guideline to show the duration of recurrence-free survival time for breast cancers before it is safe for them to undergo transplantation. Usually, a transplant team would evaluate such patients in great detail to rule out any clinical or radiological signs or symptoms of recurrence before transplantation. Also, most centers would wait from 2 to 5 years for recurrence-free interval before subjecting a patient to transplantation. Penn et al. [50] retrospectively examined 1297 cases of pre-existing malignancies in renal transplant patients. A recurrence rate of 21% was found in patients who were successfully treated before renal transplant and he suggested that a waiting period of 5 years was desirable for breast cancer.

## 12. Lung cancer

Published risk factors based on OPTN data provided a foundation for assigning lung cancer to the high risk category. Of the report received by the OPTN, seven donors with a history of lung cancer donated their organs between 2005 and 2007. Lung cancer transmission occurred in three recipients, of whom two died from metastatic disease [9]. This result collaborated with the data from IPITTR by which lung cancer was identified as high risk (41%) for donor transmission.

As recorded in the OPTN/UNOS [6], a cancer-free interval of only 0–5 years was reported for 30% of the lung cancers, but the total number was only 10 tumors.

Recently, a large series of 30,765 transplants from 14,986 donors were presented by Rajeev and colleagues. 18 recipients developed donor transmitted cancer, and 5 were lung cancer [10]. According to the author, donor transmitted lung cancer is rare but frequently results in graft loss and death which showed the importance to highlight the rarity of transmission and also the possible outcome when such transmission does occur.

## 13. Hematologic malignancies

Transmission of hematologic malignancies in solid organ transplants is rare, and has been reported in the literature only a handful of times. However, based on the data from DTAC and OPTN/UNOS, donors with a past history of leukemia or lymphoma have relatively high tumor transmission rates [9], and the consequences of transmission of hematologic malignancies can be devastating to the organ recipient, and present a particular challenge to those patients receiving life-saving organs such as liver, heart or lung, due to the necessity of retaining the transplanted diseased organ.

A total of 154 events have been reported through the Patient Safety System between 2005 and 2007. There were 65 reports (42%) of unexpected malignancy related events made to the OPTN. According to the study, 4 recipients were confirmed to have donor-transmitted lymphoma and two of them died as the result of lymphoma transmission [9]. In addition to lymphoma, acute promyelocytic leukemia has been transferred by the transplantation of a cadaveric liver allograft [51], metastatic glioblastoma multiforme has been transferred in kidney and liver transplants [52,53], and acute myeloid leukemia has been transmitted by the transplantation of donor bone marrow [54].

In 2008, Harbell et al. reported a case of anaplastic T-cell lymphoma transmitted to four recipients of solid organ transplants from a DCD donor suspected of having bacterial meningitis [55]. The transplanted kidneys and pancreas were excised from the respective recipients, and the kidney and pancreas recipients responded well to chemotherapy. The liver recipient underwent three cycles of chemotherapy, but later died due to complications of severe tumor burden. It is concluded that lymphoma can masquerade as other

causes of death, and may be missed in potential donors, and in cases of lymphoma transmission, excision of the graft may be the only chance at long-term survival.

#### 14. Other intra-abdominal cancers: hepatocellular, pancreatic and colorectal cancer

The utilization and report of donors with a history of hepatocellular, pancreatic or colorectal cancer are low due to various reasons, but we still noticed that there were some anecdotal reports.

The UNOS transplant data 1997–2002 illustrated that in 27,846 isolated liver transplantations, there were 10 cases of donor related malignancy [56]. Later, a series of 69 cases of transmission of donor malignancy were reported by IPITTR and no transmission was identified in organ recipients from donors with hepatobiliary malignancies [42]. It should be pointed out that some benign tumors have the potential to undergo malignant transformation, and this should be kept in mind when such tumors are encountered. For example, some hepatocellular adenoma subtypes (particularly beta-catenin-expressing [55]) have a significant risk of hepatocellular carcinoma, which has the potential to lead to nonoptimal triage of donor organs.

In 2001, Roza et al. reported the first known combined kidney-pancreas recipient who developed adenocarcinoma in the transplanted pancreas [57]. Later, Gerstenkorn and colleagues reported a case of a pancreatic adenocarcinoma of donor origin presented as lymphangitis carcinomatosa of the lung in a renal transplant recipient 9 months after transplantation, which is likely to have contributed to the death of the patient 15 months after transplantation [58]. In 2009, DTAC summarized the data from OPTN/UNOS between 2005 and 2007 and 65 cases of unexpected malignancy related events were reported. There was only one pancreatic adenocarcinoma transmission [9].

Despite the limited information about the transplantation of donors with a history of pancreatic or hepatocellular cancer, uncertainties exist in the utilization of these donors, and the risk categories of these malignancies were not assigned by the DTAC Malignancy Subcommittee [19]. In the absence of good quality evidence, preoperative screening should be personalized and based upon the individual's risk, clinical history, and preference.

Colorectal cancer represents the second most common cancer in women and third most common in men. Donors with a past history of colon carcinoma are placed into the high risk category for donor tumor transmission by the DTAC [9]. The Israel Penn International Transplant Tumor Registry covering a period between 1965 and 2003 reports two cases of donor-transmitted colon cancer [5]. In 2004, the OPTN/UNOS analyzed 108,062 recipients from 34,933 donors for a period of 51 months and reported 15 cases of donor-transmitted cancer, including only one case of transmitted colon cancer [59]. Similarly, the United Kingdom Transplant Registry reported 30,765 transplants from 14,986 donors in 2012 and also found only case of transmitted colon cancer [10]. Interestingly, not every diagnosed malignant tumor in the donor is necessarily transmitted to the recipient; the UNOS registry (2005–2007) [9] reporting one donor with proven colon cancer without transmission to the recipient. Feng et al. concluded that potential donors with a history of colon carcinoma in situ (stage 0) could provide organs without any disease-free waiting period, but donors with a history of stage 1 (T1–T2) colon cancer would require a variable disease-free interval, or may never be able to serve as donors, depending upon differences in tumor recurrence and survival rates based on gender and race [60].

#### 14. Discussion

The success of solid organ transplantation is accompanied by a severe shortage of available organs for those currently awaiting transplantation. In recent years, many programs have implemented

the aggressive use of extended criteria donors, being of either malignancy or viral infections. However, donor-transmitted malignancy has been increasingly reported as a complication of organ transplantation.

Compared with the benefits of organ transplantation, the risks for tumor and disease transmission are small; however, donors with a past history of aggressive tumors, such as breast cancer, melanoma, and choriocarcinoma may possess the potential of unpredictable recurrence. The use of donors with extended disease-free intervals after curative breast or uterus surgery must be made after a detailed review of the pathology reports, and even then, should be done with informed consent of the recipient. However, patients with a history of CNS tumor without active disease are not segregated into risk categories in organ donation, and tumor donors with prostate cancer, low-grade lower ureteral cancer, EC, and T1a or T1b breast cancer in remission for 10 or more years may also contribute to expanding the donor pool. Besides, the use of organs from donors with in situ cancers can be considered with minimal hesitation and informed consent [5].

Still, using organs from donors with malignancy may carry the chance of tumor transmission. Once a donor-transmitted malignancy is suspected, in situ hybridization for sex chromosomes, HLA typing, DNA polymorphism or microsatellite analysis can be used to differentiate donor from recipient origin of tumors [19]. If one recipient develops cancer from a multi-organ donor, it is essential to make other recipients informed of the risk of tumor transmission and take measures before it is too late. Immunosuppression should be ceased or minimized when donor tumor transmission occurs [6]. Renal or pancreatic recipients may have cessation of immunosuppression and grafts removal together with adjuvant therapy. For liver recipients, if transferred cancer is limited to the organ, partial hepatectomy or retransplantation can be life-saving. However, as for cardiac and lung recipients, immunosuppression should be lowered and antineoplastic therapy should begin, while retransplantation is considered [42,48].

In conclusion, a careful individualized risk–benefit assessment for using organs from donors with malignancy should be made and presented to the recipients before transplantation, and a fully informed consent is mandatory in any circumstance where risk is considered to exceed standard expectations [42]. More precise evaluation for the risks of tumor transmission from donors with malignancy will be obtained through the global updated data in the future. With careful selection and analysis, donors with malignancies will hopefully act an important role in easing the organ shortage and diminishing the mortality on the wait-list.

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