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Donor-Transmitted Malignancies in Organ Transplantation: Assessment of Clinical Risk

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The continuing organ shortage requires evaluation of all potential donors, including those with malignant disease. In the United States, no organized approach to assessment of risk of donor tumor transmission exists, and organs from such donors are often discarded. The *ad hoc* Disease Transmission Advisory Committee (DTAC) of the Organ Procurement and Transplantation Network/United Network for Organ Sharing (OPTN/UNOS) formed an *ad hoc* Malignancy Subcommittee to advise on this subject. The Subcommittee reviewed the largely anecdotal literature and held discussions to generate a framework to approach risk evaluation in this circumstance. Six levels of risk developed by consensus. Suggested approach to donor utilization is given for each category, recognizing the primacy of individual clinical judgment and often emergent clinical circumstances. Categories are populated with specific tumors based on available data, including active or historical cancer. Benign tumors are considered in relation to risk of malignant transformation. Specific attention is paid to potential use of kidneys harboring small solitary renal cell carcinomas, and to patients with central nervous system tumors. This resource document is tailored to clinical practice in the United States and should aid clinical decision making in the difficult circumstance of an organ donor with potential or proven neoplasia.

Key words: Complications, disease transmission, malignancy, organ donation

Abbreviations: CNS, central nervous system; DTAC, Disease Transmission Advisory Committee; HRSA, Health Resources and Services Administration; IPITTR, Israel Penn International Transplant Tumor Registry; MeSH, medical subject headings; OPTN, Organ Procurement and Transplantation Network; RCC, renal cell carcinoma; SEER, surveillance epidemiology and end results; UNOS, United Network for Organ Sharing; WHO, World Health Organization.

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Introduction

Organ transplantation successfully extends the lives of thousands annually but is not without risks, one complication being the unintended transmission of donor malignancy. In the United States, the Organ Procurement and Transplantation Network/United Network for Organ Sharing (OPTN/UNOS) established an *ad hoc* Disease Transmission Advisory Committee (DTAC) to monitor potential transmissions and advise policy to maximize organ allocation while minimizing untoward side effects. In 2008 the DTAC formed an *ad hoc* subcommittee to examine donor-related malignancy transmission and to provide a framework from which to address this issue. This report summarizes the resulting discussions, deliberations and research conducted by the DTAC Malignancy Subcommittee.

Material and Methods

Subcommittee structure

The subcommittee included six transplant surgeons, two medical oncologists, one representative each from nephrology, pathology and infectious diseases, and four *ex officio* representatives from HRSA and six UNOS staff.

The DTAC Vice-Chairman served as Subcommittee Chair (see Acknowledgments for details of membership).

Communication was via teleconferences and e-mail discussion supplemented by literature review and document distribution. Categorization systems that evolved from this process underwent multiple iterations.

Data sources and evaluation

PubMed search of English language literature was performed using searches for 'donor-transmitted malignancy', 'donor malignancy transplantation', or MeSH searches combining 'tissue donors' or 'organ transplantation' with 'neoplasms' or names of individual tumors. Within resource constraints, the review was considered representative but not absolutely comprehensive.

Reports were evaluated according to the National Cancer Institute Criteria for Levels of Evidence for Adult and Pediatric Cancer Treatment Studies. All reports were categorized as level 3 and comprised case series, or individual cases. OPTN Registry data were also used to inform decision making.

In some cases, no data were available regarding transmission of individual tumor types. To frame discussion, data concerning tumor behavior in nontransplant hosts were invoked as Supporting Information. Disease-free survival figures, where available, were preferred in contrast to overall survival figures to inform decision making. The Cancer registry sources of these data are indicated to distinguish them from OPTN-derived data.

Role of the sponsor

Facilities for teleconference discussions were provided by the OPTN. Beyond providing a forum for this process, the OPTN did not design the direction of discussions, collect, manage, analyze or interpret any data. No funds were provided for this study.

Results

The approach consisted of (a) defining an overall framework for categorizing relative tumor transmission risks, (b) populating categories with individual tumors according to available data and (c) focusing on issues derived from the OPTN Patient Safety system and reviewed by DTAC (1) or recent scientific literature.

Risk categories for donor tumor transmission

The risk categorization framework for donor tumor transmission is shown in Table 1. This specifies ordinally ranked risk categories, provides definitions and offers a clinical perspective. At present, no high level evidence is available to establish true transmission frequency estimates, and these figures are meant to provide a basis from which to suggest different levels of concern for transmission risk. For example, use of low transmission risk organs might take into consideration risk of death on the waiting list versus risk from organ use, whereas intermediate risk organs would be considered in life-saving transplants with patients with an immediate risk of death otherwise. Since no categorization system can accommodate unique patient circumstances, the subcommittee was unanimous in agreeing that informed clinical judgment, along with the approval of the recipient, remains the final arbiter. The unknown risk category includes donors with specific tumors for which there is no information regarding the potential for transmission. It is recommended that organs be considered for transplant only in recipients at urgent risk without transplant (similar to low risk category or higher) based on clinical judgment and with informed consent. Individual cases may have differing levels of uncertainty, and unique circumstances need to be carefully weighed.

Risk category assignment to specific tumors

The DTAC Malignancy Subcommittee assigned risk categories to a number of tumors summarized in Tables 2–3 and Supporting Tables S1 and S4.

Table 2 categorizes tumors into specific risk categories. Table 3 is a list of benign tumors with malignant potential or other factors relevant to transplantation, and Supporting Table S4 lists benign tumors without these features. Benign tumors by definition would be placed into the 'no significant risk' category. If absence of malignant transformation cannot be assured, then these donors are placed into the unknown risk category. The Tables are not intended to be comprehensive.

Solitary well-differentiated (Fuhrman nuclear grade I-II) renal cell carcinoma (RCC) 1 cm or less in diameter and resected prior to transplant was placed into the minimal risk category based on literature reports (Supporting Table S2) and information from the Israel Penn International Transplant Tumor Registry (IPITTR) (2). These data demonstrated no recurrences when such carcinomas up to 3.5 cm in diameter were resected prior to transplant (E. S. Woodle MD, personal communication). Behavior of resected tumors in the nontransplant setting (3) is consistent with these reports. Solitary resected well-differentiated RCC greater than 1.0 and up to 2.5 cm in diameter were placed into the low risk category because these were felt to be theoretically more likely to be transmitted despite preimplantation resection. Higher grade or stage resected RCC are placed into the intermediate or high risk categories.

Some small and solitary thyroid carcinomas diagnosed at or near time of donation are also placed within the minimal risk category based on data derived from a recent study of 366 nontransplant patients with papillary and 134 with follicular carcinoma (4). Neither papillary carcinomas 0.5 cm or less, nor solitary minimally invasive follicular carcinomas under 2.0 cm showed extrathyroidal growth or lymph node metastases. Since the diagnosis of minimally invasive follicular carcinoma requires strict adherence to histopathologic criteria, a conservative approach of limiting the upper size to 1.0 cm was taken. Papillary or minimally invasive follicular tumors up to 2.0 cm in size were placed into the low risk category (Table 2).

CNS tumors have been classified into four histologic grades by the World Health Organization (WHO) (Supporting Table S1) (5,6). Published risk factors based

Table 1: Risk categories for donor tumor transmission

Risk category		Definition		
		Nominal	Frequency estimate (f)[1]	Recommended clinical use[2]
0	No significant risk	No active malignant tumor or history of tumor found during evaluation	0%	Standard
1	Minimal	The literature suggests minimal risk of tumor transmission	$0\% < f \leq 0.1\%$	Clinical judgment with informed consent[3]
2	Low	The literature suggests low grade risk of tumor transmission	$0.1\% < f \leq 1\%$	Use in recipients at significant risk without transplant. Informed consent required[3]
3	Intermediate	The literature suggests significant risk of tumor transmission	$1\% < f \leq 10\%$	Use of these donors is generally not recommended. On occasion, a lifesaving transplant may be acceptable in circumstances where recipient expected survival without transplantation is short (e.g. a few days or less). Informed consent required[3]
4	High	The literature suggests high risk of tumor transmission	>10%	Use of these donors is discouraged except in rare and extreme circumstances. Informed consent required[3]
U	Unknown risk	Evaluation for risk factors is incomplete or no literature exists to assess risk	N/A	Use should be based on clinical judgment with informed consent[3]

[1]Transmission events/organ transplants from donor with specific tumor.
[2]Recommended clinical use does not incorporate expected tumor behavior or available antitumor therapies in cases of transmission. However, these factors should be considered during the clinical decision-making process and may modify these recommendations in individual cases (e.g. indolent tumor behavior or effective antitumor therapy).
[3]Required as per OPTN policy 4.2.

on IPITTR data (7) provided a foundation for assigning low grade CNS tumors (WHO grades I or II) to the low risk category, and higher grade CNS tumors (WHO grades III–IV) to the high risk category. This approach may represent an oversimplification, since aggregated case reports suggest that some high grade tumors such as glioblastoma multiforme may have relatively low transmission rates (Supporting Table S3).

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 on the basis of data from the transplant (7) and nontransplant (8) populations and the collective opinions of subcommittee members.

The most recent update (9) of published OPTN registry data (9–11) documented 2508 organ transplants derived from 1069 donors with a past history of cancer. Transmission occurred in one example involving a donor with a history of melanoma. Based on these data along with other expert opinion (12), it was felt reasonable to provide limited interim guidance. Donors with a past history of aggressive tumors with potential late metastases, such as breast or colon carcinoma, melanoma, leukemia or lymphoma, are placed into the high risk category (9). Exceptions may be made for patients with a history of stage T1a or T1b (13) breast carcinoma or T1 (13) colon carcinoma in remission for 10 or more years (12). In general, recurrence-free survival or 'cure' is recommended as a surrogate marker for transmission risk, given the absence of specific transmission data in most cases. Therefore those donors with a history of treated cancer 5 or more years earlier and with a probability of cure of >99% are considered at low risk for tumor transmission, and those with a probability of cure between 90% and 99% are considered intermediate risk. Donors with a history of incurable cancer, insufficient follow-up, or cure probability <90% are considered at high risk for tumor transmission. Oncologic consultation is recommended when possible to individualize assessment of historical malignancy. OPTN registry data document no tumor transmission from 642 donors with a history of CNS malignancy (9), including 175 organs from patients with glioblastoma multiforme. On this basis, patients with a history of CNS tumor without active disease are not segregated into risk categories in a manner similar to patients with active CNS tumors.

Table 2: Suggested risk categorizations for specific tumor types[1]

Risk category	Tumors
No significant risk	Benign tumors in which malignancy is excluded (see Table 3 and Supporting Table S4)
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 (T0N0M0 by TNM stage) (nonrenal transplant only)[5]
	Solitary papillary thyroid carcinoma, ≤0.5 cm
	Minimally invasive follicular carcinoma, thyroid, ≤ 1.0 cm
	(Resected) solitary renal cell carcinoma, ≤1.0 cm, well differentiated (Fuhrman 1–2)[4]
Low risk (0.1–1% transmission)	(Resected) solitary renal cell carcinoma, >1.0 cm ≤2.5 cm, well differentiated (Fuhrman 1–2)[4]
	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 [4,6]
	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)[2]
	Colon carcinoma >stage 0 (active)[2]
	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 (see Supporting Table S3)[7]
	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)[6]
	Renal cell carcinoma >7 cm or stage II–IV[6]
	Small cell/neuroendocrine carcinoma, any site of origin
	Active cancer not listed elsewhere[3]

[1]Based on level 3 evidence (nonconsecutive cases) unless otherwise specified.
[2]Based on survival data in nontransplant patients.
[3]Based on collective committee opinion only.
[4]Assumes complete resection of tumor prior to transplant.
[5]Does not apply to renal transplant, as lesions may be multicentric.
[6]American Joint Commission on Cancer 7th ed. (13)
[7]Risk assessment by WHO grade alone may be an oversimplification; evidence suggests that some grade IV tumors such as uncomplicated glioblastoma may more appropriately be considered intermediate risk tumors, whereas others such as medulloblastoma are high risk (see text and Supporting Table S3).

Discussion

The continuing organ shortage and use of extended criteria donors emphasize that vigilance is needed to minimize the risk of donor disease transmission, including malignancy (14).

Although there has been extensive publication and discussion about infectious disease transmissions, the literature related to donor-derived malignancy transmission is limited to anecdotal reports, registry series and retrospective studies. Interpretation of data regarding cancer in this setting is further complicated by the fact that reports to transplant cancer registries may overestimate transmission, whereas underreporting, at least historically, may be more likely in the general OPTN database. Previous efforts by the Spanish National Transplant Organization (15) and Italian National Transplant Centre (16) have been published.

In our approach, generic risk categories were first created. Opinions varied on including quantitative frequency

Table 3: Benign tumors with potential associated malignancies or other factors relevant to organ donation

Organ/Site	Tumor	Potential associated malignancy	Comments
Soft tissue, vessels, nerves, blood vessels	Paraganglioma	Malignant paraganglioma	Variable malignant change, estimated up to 50% in abdominal tumors. Histology not an absolute indicator of benign versus malignant
Thyroid and parathyroid	Follicular adenoma	Follicular carcinoma	May be difficult to exclude follicular carcinoma
Salivary gland	Pleomorphic adenoma	Adenocarcinoma	
Heart and pericardium*	Atrial myxoma		Literature suggests that donor hearts containing myxoma either not be used or used only under special circumstances
	Mesothelioma of AV node	Malignant mesothelioma	
Liver and Biliary	Hepatocellular adenoma	Hepatocellular carcinoma	Subtypes have variable risk of transformation into hepatocellular carcinoma
	Von Meyenburg complex (VMC) (biliary hamartoma)	Cholangiocarcinoma	Multiple VMC may rarely occur with cholangiocarcinoma.
Gastrointestinal tract	Adenoma	Adenocarcinoma	
Kidney and urinary tract	Adrenal heterotopias	None	May be confused with renal carcinoma when it occurs on renal capsule
	Angiomyolipoma	May rarely coexist with other renal cell neoplasms (reported in native and allograft kidneys)	
	Bladder paraganglioma	Malignant paraganglioma	Malignant variants estimate <7%. Histology not an absolute indicator of benign versus malignant
	Oncocytoma	May rarely contain or coexist with renal cell carcinoma	Oncocytoma should be resected prior to implantation, RCC, esp. chromophobic type, should be excluded
Adrenal	Pheochromo cytoma	Malignant pheochromo cytoma	Malignancy estimated at 4–22% Case report of capsular invasion, 2 year posttransplant disease-free follow-up (27)

*Benign cardiac tumors may themselves be a cause for heart transplantation.

estimates as part of the definition, since little or no data exist upon which to base transmission frequency estimates. We concluded that a 'quantitative estimate' would provide landmarks upon which future studies could be interpreted, beyond subjective and descriptive terminology. A log scale was considered more appropriate than a linear scale in this regard. In other words, donor tumors with 11–100% estimated transmission frequency are all considered high risk situations.

Benign tumors were included for two reasons first, many bear uncommon names which may not be readily recognizable. Second, some benign tumors do have malignant potential which should be recognized.

The decision was made not to address therapy effect since the categorization is designed to evaluate transmission risk and not patient outcome. However, from a practical perspective, the physician should incorporate expected tumor behavior and available therapies into the decision-making process. Similarly, the categorization of most minimal or low risk tumors in Table 2 presumes discovery at or near time of donation. The actual situation may not be this simple, and other variables such as time interval between tumor diagnosis or treatment and donation, or tumor grade or histology, may be important contributors to clinical decision making in specific instances. Our approach is based on estimated risk of transmission per total number of transplanted organs, and this general estimate can also be influenced in individual cases by specific patterns of tumor behavior as well as allograft type.

Dire clinical circumstances may preclude waiting for final test results or historical medical records. Subcommittee members repeatedly stressed that decisions were best left to the transplant physician with informed consent from the patient and/or family. The best information available at the time should be provided to the patient/family member(s) and risks discussed and documented prior to transplantation.

Despite data limitations, some trends do emerge. For example, the literature is virtually unanimous in suggesting that kidneys with small, solitary, well-differentiated RCC may be usable for transplantation provided the lesion itself is completely resected. Outcomes are variable when resection is not performed (17,18). Care must be taken, as small tumors may be multifocal (19). A search for extrarenal

tumors should be conducted, since approximately 7% of small tumors may demonstrate metastases (3). Transplant surgeons might choose not to use such kidneys based on clinical judgment (e.g. a small renal tumor in the setting of unexplained cerebral hemorrhage). Notification of the organ procurement organization is recommended so the organs can be offered to other transplant centers. Given observed variability in current practice, a consensus conference addressing this topic within the context of donor malignancy seems appropriate. Importantly, the approach of resecting small RCC in donor organs does not extend to urothelial (transitional cell) carcinomas (20).

In contrast, we currently consider all melanoma patients as high malignancy transmission risk donors, regardless of stage or active versus historical disease. One possible exception may be *in situ* melanoma, where metastatic risk is low. However, late recurrence has been reported in patients who have had melanomas less than 1 mm in thickness (21) and this possibility should be considered during clinical evaluation.

In the case of CNS tumors, the committee assigned low and high grade risk on the basis of WHO tumor grades (5,6) and published risk factors (7). Collected data (Supporting Table S3) lend some support to this approach. However, compilation of the published literature suffers from reporting bias and may overestimate the risk of transmission in some cases. In contrast, recent reports have suggested a low risk of disease resulting from use of organs from donors with CNS tumors (22,23). Given the quality of current data, we opted for a conservative approach but realize that actual risk may not strictly correlate with WHO grade and emphasize that risk assessment should be interpreted in light of best available and constantly updated data. In particular, present data (Supporting Table S3) suggest that some grade IV tumors such as glioblastoma multiforme may more appropriately be placed into the intermediate risk category, whereas others such as medulloblastoma may represent true high transmission risk neoplasms. This important problem needs to be addressed in a comprehensive manner. Evaluation of the donor with potential CNS tumor and problematic aspects of diagnosis have been recently summarized (24).

The use of elderly donors raises concern regarding increased risk of malignancies such as prostate carcinoma. This is further complicated by the fact that frozen section of donor prostate has low sensitivity and is inefficient at evaluating both Gleason grade and extraprostatic extension due to technical artifacts (25). Yin et al. (26) examined 340 prostates from donors with no known prostate disease. Adenocarcinoma was found in 23% of donors age 50–59, 35–45% in those 70–81. However no data show a corresponding increase in donor-transmitted adenocarcinomas. Five examples of donor prostate carcinoma, found after organ donation and presumably restricted to prostate, have been reported to the DTAC. Within the 45 day follow-up required by current policy, no tumor transmission has been seen. Additional OPTN follow-up information finds no reported malignancies in these nine recipients of the five donors with a median follow-up of 725 days.

Another commonly identified occurrence is discovery of an 'incidental' tumor (most commonly of donor kidney), later during the transplant procedure. This can be minimized by ensuring that perinephric fat is cleaned and inspected before leaving the recovering operating room. Prompt pathologic assessment of suspicious lesions may prevent transmission of unsuspected tumors. Donor autopsy might be considered in elderly or other higher risk patients, as this may provide the first indication of donor malignancy.

The DTAC recommends that all tumors (except PTLD) occurring within 1 year post-transplant be reported to the Patient Safety System as potential donor-transmitted tumors in addition to reporting by means of standard forms. Tumors arising after this time should be reported to the OPTN using standard post-transplant malignancy forms only unless circumstances suggest donor transmission. Tumors reported using routine post-transplant malignancy forms will be screened at the OPTN against outcomes of other recipients from the same donor, but not on the same emergent basis as cases reported directly to DTAC. An effort should be made to differentiate donor from recipient origin of tumors, since some tumors within allograft organs may be of recipient origin. Analysis may employ *in situ* hybridization for sex chromosomes, HLA typing, DNA polymorphism or microsatellite analysis. Reference laboratory information is available from the DTAC upon request.

Prospective data collection such as that performed by the OPTN will eventually improve evidence-based decisions and will provide data to support or supersede our initial risk estimates. Extant data such as modeling of survival using predictive nomograms may provide some interim guidance. Potential donors with 5 or 10 year predicted disease-free survival exceeding 90% with significant disease-free follow-up may be reasonable candidates for organ donation. Predictive nomograms for ductal carcinoma *in situ*, gastrointestinal stromal cell tumor, renal, prostate and colorectal carcinoma are available from Memorial Sloan–Kettering Cancer Center at http://www.mskcc.org/mskcc/html/5794.cfm. Five-year survival figures for various cancers can be obtained at the National Cancer Institute Surveillance Epidemiology and End Results (SEER) website at http://seer.cancer.gov/. Data in both cases are derived from registries and should be applied accordingly.

We have attempted to balance recommendations with current clinical knowledge and concepts, while providing a framework that is easily updated to accommodate new

data. Individual recommendations may in retrospect prove to be too conservative or aggressive, underscoring the need to focus on patient welfare in individual cases. Little is known concerning patient preferences for organ transplantation from donors at risk for transmitting malignancies under different clinical scenarios, and this appears to be an important area for future investigation. However, in the final analysis, the combination of thoughtful clinical judgment and a solid doctor-patient relationship provide the strongest tools for charting a reasonable course in this difficult clinical situation.

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Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation.*

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Supporting Information

Additional information may be found in the online version of this article

Table S1: Suggested donor CNS tumor transmission risk categorization as based on World Health Organization tumor grades

Table S2: Reports of transplantation using donor kidneys with resected renal cell carcinoma

Table S3: Reported transmission events involving donor CNS tumors

Table S4: Benign tumors with no significant malignant potential or complicating factors relevant to transplantation

References

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