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Donor Cancer Transmission in Kidney Transplantation: A Systematic Review

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Transplantation of any biological material from a donor to a host will carry some inherent risk of disease transmission. Our aims were to summarize the totality of the published evidence about donor cancer transmission among kidney transplant recipients and to determine the cancer-specific survival of these patients. We systematically reviewed all case reports, case series and registry studies that described the outcomes of kidney transplant recipients with donor cancer transmission published to December 2012. A total of 69 studies with 104 donor-transmitted cancer cases were identified. The most common transmitted cancer types were renal cancer (n = 20, 19%), followed by melanoma (n = 18, 17%), lymphoma (n = 15, 14%) and lung cancer (n = 9, 9%). Patients with melanoma and lung cancers had the worst prognosis, with less than 50% of recipients surviving after 24 months from transplantation. Recipients with transmitted renal cancers had the best outcomes, with over 70% of recipients surviving for at least 24 months after transplantation. Overall, the risk of donor transmission of cancer appears low, but there is a high likelihood of reporting bias. Our findings support the current recommendations for rejecting organs from donors with a history of melanoma and lung cancer, but suggest that the use of donor kidneys with a history of small, incidental renal cell cancer may be reasonable.

Keywords: Cancer transmission, donor cancer, kidney transplantation

Abbreviations: CNS, central nervous system; CNT, National Transplant Centre; DTAC, Disease Transmission Advisory Committee; EBV, Epstein–Barr virus; GBM, glioblastoma multiforme; IPITTR, Israel Penn International Transplant Tumor Registry; NHL, Non-Hodgkins lymphoma; ONT, National Transplant Organisation; OPTN, Organ Procurement and Transplantation Network; PTLD, posttransplant lymphoproliferative disorder; RCC, renal cell carcinoma; UNOS, United Network for Organ Sharing; WHO, World Health Organisation

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Introduction

Transplantation is the treatment of choice for most patients with end-stage kidney disease because it incurs both survival and quality of life benefits. However, transplantation of any biological material from a donor to a host will unavoidably carry some risk of disease transmission, such as infection and malignancy (1–4). Although the incidence of cancer transmission is low (approximately two cases per 10 000 organ transplant recipients) (1), if it occurs, significant morbidity and mortality are likely. Over the recent years, there have been increasing reports of fatal donor cancer transmission worldwide (5), such as the transmission of glioblastoma multiforme (GBM) (6) from donors with a history of cerebral tumors and transmission of melanoma from donors with localized disease as long as 32 years prior to lung transplantation (7). Transplant clinicians are therefore reluctant to accept organs from donors with a cancer history, except for those with low-grade tumors such as small, localized renal cell carcinomas (RCCs) or those with treated localized solid organ and skin cancers (8–12).

Despite concerted efforts by the transplant community to incorporate evidence of donor transmission risk into policy and guidelines for organ screening and acceptance such as the World Health Organisation (WHO) (13), the Italian National Transplant Centre (CNT) (14) and the European Union–funded Projects on Vigilance and Surveillance of Substances of Human Origin (15) and European Framework for the Evaluation of Organ Transplants (16), the current recommendations for rejecting or accepting a donor organ with a history of malignancy are based predominantly on single case reports in different transplant settings (17). In addition, published guidelines for the screening of donor organs and tissues in transplantation have been inconsistent, particularly among donors with borderline transmission risk (17). In this study, we aimed to systematically review the totality of published evidence on the confirmed

cases of donor cancer transmission among kidney transplant recipients and to determine the cancer-specific survival of recipients with donor-transmitted cancers.

Methods

We conducted a systematic review based on standard methods and reporting in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (18,19).

Inclusion and exclusion criteria

Studies were included if the following criteria were met: probable, possible and proven cases of donor cancer transmission according to the United Network for Organ Sharing/Organ Procurement and Transplantation Network (UNOS/OPTN) and the Disease Transmission Advisory Committee (20), kidney transplant recipients from live or deceased donors and if the outcomes of the affected recipients were described. Any study types that contain data pertinent to the donor cancer events were included. Editorials, reviews and discussion articles were not eligible. Disagreement about study inclusion was resolved by consensus between two of the authors (D.X. and G.W.).

Search strategies

We performed a comprehensive literature search of MEDLINE (1948 to November 2012), Embase (1980 to November 2012), the Cochrane Central Register of Controlled Trials (CENTRAL) (1991 to November 2012) and ClinicalTrials.gov (1997 to November 2012) to identify studies that documented the outcomes of donor-transmitted cancer after kidney transplantation using key search terms: ''Kidney transplantation/,'' ''malignan$,'' ''cancer$,'' ''tumo?r,'' and ''transmission$'' (Appendix S1).

The search was limited to human studies but without any language restriction. Conference proceedings and abstracts were evaluated. Reference lists comprising all relevant articles were also searched, including that of the NOTIFY Library (21). When more than one publication of a trial or a cohort study existed, articles with complete information required for the analysis and review were included. Further information was requested from the corresponding authors when necessary.

Data extraction

Two authors (D.X. and G.W.) independently assessed all titles and abstracts for eligible studies. Data extraction was carried out using standardized data extraction forms. Relevant information, such as donor age and gender, live or deceased donor status, prior cancer history, the number of organs affected by cancer per donor, recipient age and gender, time from transplant to cancer diagnosis, metastases, treatment, follow-up time, recipient outcome, relapses and time from transplant to death, was extracted from individual patients of each included study for analysis.

The primary outcome of the review was the cancer-specific survival of recipients with donor-transmitted cancers. Secondary outcomes included the frequency of metastases, time to cancer diagnosis following transplantation, treatment modality, time from cancer diagnoses to cancer death and the duration of disease remission after treatment.

Quality assessment

The methodological quality of all included studies was assessed independently by two authors according to the standard checklists of quality assessment for case reports and series (22). The checklist for methodological rigor included the following: comprehensive description of the characteristics of the recipients and donors, the diagnostic and therapeutic methods, information about cancer stage and the time to cancer diagnoses, explicitness and detailed description of the recipients' cancer and overall survival. A follow-up time of at least 6 months or until recipient deaths were defined *a priori* as adequate follow-up time for cancer recurrences. Any discrepancies between the two reviewers were resolved by discussion.

Data synthesis and statistical analyses

The frequency and the rates of site-specific donor cancer transmission were calculated for all included studies. The primary outcome was recipient survival rates. Other outcomes included recurrence rates after treatment, frequency of disease metastases and the treatment modalities for donor-transmitted cancers. We analyzed the included studies for factors that may predict the prognoses of those with donor-transmitted cancers, such as donor age, gender and donor types. Other sources of variability such as health status of the recipient prior to transplant, skill level of the surgeon and whether autopsies performed on donors prior to transplantation were explored and analyzed descriptively.

The proportion of individuals alive was calculated using the Kaplan–Meier method. Time to event analyses were conducted to examine the overall and site-specific cancer survival among those who were diagnosed with donor-transmitted cancer. All analyses were performed using SAS® 9.2, SAS Institute, Inc. (Cary, NC).

Results

Literature search

Of the 739 articles identified electronically, 12 were duplicates and 588 articles were ineligible after title and abstract review (Figure 1). The remaining 151 articles were retrieved and reviewed in full text form, with 66 case series and reports and three registry studies found to be eligible and included in the final analyses. We contacted authors of four included studies for additional information and did not receive any of the required information.

Study characteristics

A total of 41 case reports (n = 41 cases of donor-transmitted cancers), 25 case series (n = 49 cases of transmitted cancers) and three registry studies (n = 14 cases of transmitted cancers) with 104 kidney transplant recipients were included (Appendix S2). Each case of donor-transmitted cancer corresponded to a single kidney transplant recipient. The number of transmitted cancer cases varied by the region of origin: Australasia (n = 10), Europe (n = 66), North America (n = 38) and South America (n = 3).

Quality appraisal of included studies

The quality appraisal of included studies is shown in Appendix S3. The quality of reporting was adequate, with 80% or more studies giving clear descriptions in six domains, and over 70% of included studies providing adequate information in nine out of the 10 domains. The

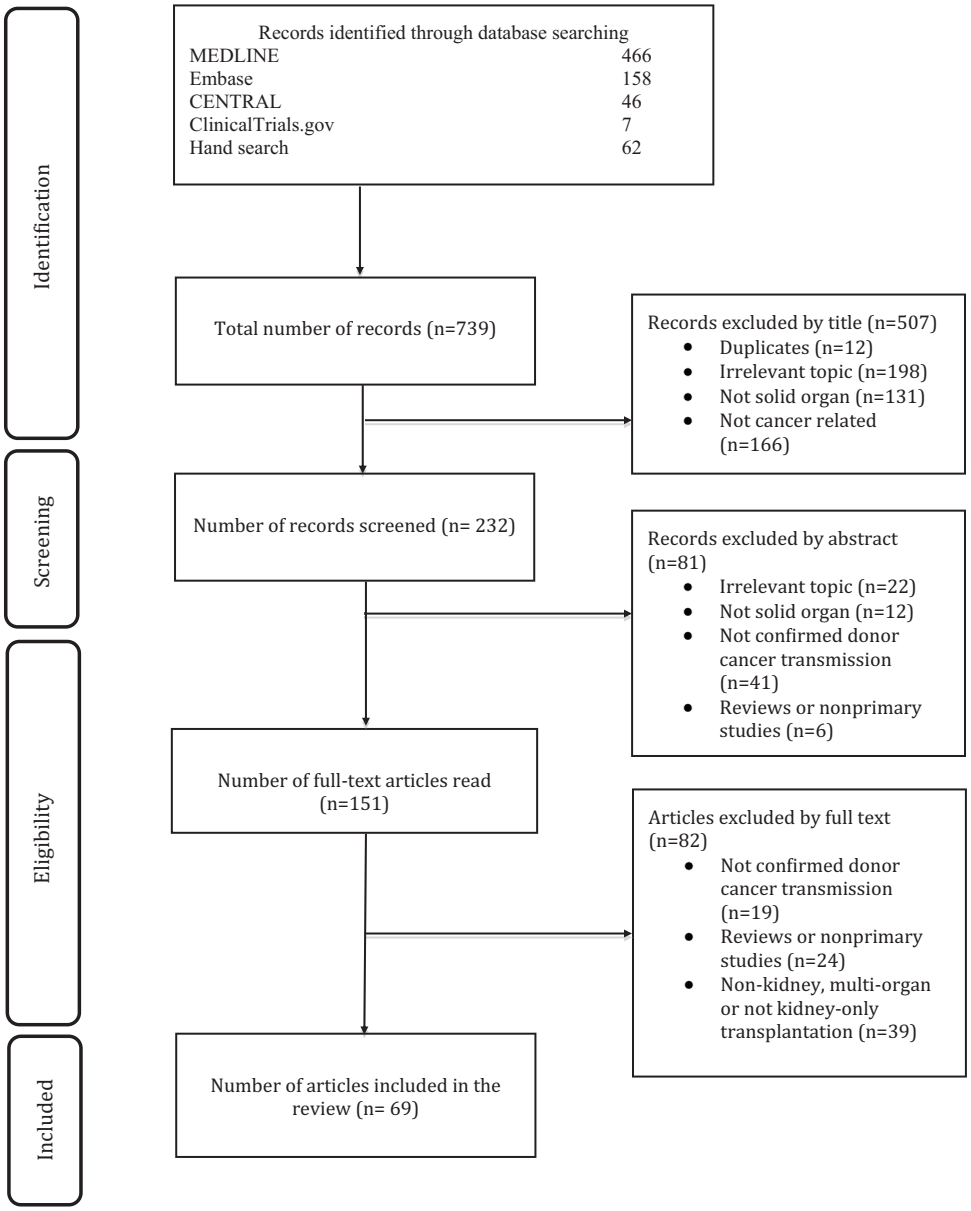

Figure 1: Search flow diagram.

majority of studies provided detailed follow-up information of all recipients and the time to cancer diagnoses from transplantation; as well as clear descriptions of the diagnostic and therapeutic methods used for recipients with donor-transmitted cancers.

Characteristics of donors with donor-transmitted cancer

The characteristics of donors who have transmitted cancer through donation are shown in Table 1. A total of 91 donors (living = 16, deceased = 75) transmitted malignancy through donation. The mean ages of these donors varied by cancer types, ranging from 33 years (SD ±4.2) among donors who transmitted choriocarcinoma, to 54 years (SD ±15.1) among those who transmitted lung cancer. Over 50% of cases were derived from male donors, with the exception of those who transmitted choriocarcinomas. Otherwise, all donor-transmitted cases of choriocarcinomas (n = 5) were from female donors. The majority (n = 75, 82%) of donor-transmitted cancers were from deceased donors, with the remaining cases of donor-transmitted renal cancers (n = 8, 42%) and sarcomas (n = 4, 57%) originating from living kidney donors. With the exception of GBM, whereby all of these cancers were known to the surgeons prior to the transplant surgery, transplant surgeons were not aware of the presence of donor

Table 1: Characteristics of donors by cancer type (n = 91)

	Cancer type							
	Renal cancer	Melanoma	Lymphoma	Lung cancer	Sarcoma	Glioblastoma multiforme	Choriocarcinoma	Other
Number of donors (n, %)	19 (21)	16 (18)	11 (12)	8 (9)	6 (7)	5 (5)	5 (5)	21 (23)
Mean age (years, SD)	53 (9.9)	54 (12.6)	33 (24.6)	54 (15.1)	53 (4.7)	41 (5.1)	33 (4.2)	48 (15.4)
Male (n, %)	11 (58)	2 (13)	5 (45)	5 (63)	4 (67)	5 (100)	0 (0)	8 (38)
Deceased donors (n, %)	11 (58)	18 (100)	10 (91)	7 (88)	2 (33)	5 (100)	5 (100)	17 (85)
Number of donors with cancers known prior to transplantation (n, %)	1 (5)	2 (18)	0	2 (25)	0	5 (100)	0	5 (25)

cancers at the time of the transplanted surgery among other cancer types.

Characteristics of recipients with donor-transmitted cancers

The mean ages of recipients at the time of diagnoses varied by cancer type, ranging from 30 years (SD ±11.4) and 40 years (SD ±14.6) among those diagnosed with choriocarcinoma and renal cancers, to over 40 years among those with lung cancer, sarcoma, melanoma and lymphoma. The duration from transplantation to cancer diagnoses varied by cancer sites, ranging from an average of 1.4 months (median: 1.0, interquartile range [IQR]: 0.2–3.0, ranging from 1 day to 3 months) for choriocarcioma to 40.2 months (median: 10.5, IQR: 3.0–40.0, ranging from 0.3 months to 18.8 years) for renal cancer.

Frequency of malignancy transmission

Of the 104 confirmed cases of transmitted cancers, 20 (19%) were renal cancers, followed by melanomas (n = 18, 17%), lymphomas (n = 15, 14%), lung cancers (n = 9, 9%), sarcomas (n = 7, 7%), GBM (n = 6, 6%), choriocarcinomas (n = 5, 5%) and other cancer types (n = 24, 23%). Appendix S4 shows the frequency of other cancer types.

Outcomes of recipients with donor-transmitted cancers

Recipients with donor-transmitted melanoma and lung cancers incurred the worst overall survival. Of the 18 patients diagnosed with melanomas, 13 (72%) had advanced stage disease (with disease metastasis) at the time of diagnoses, and only five (28%) patients survived after a mean follow-up time of 30 months from transplantation. The average time from transplantation to death for those diagnosed with transmitted donor melanomas was 14.1 months (median: 12.5, IQR: 10.1–17.8). Of the nine recipients with donor-transmitted lung cancer, only three (33%) patients survived after 20 months from transplantation and the average time from transplantation to death for those who died was 29.0 months (median: 25.0, IQR: 18.0–37.0). Among those diagnosed with lymphoma (n = 15), only one (7%) patient presented with metastatic disease at the time of diagnoses, and later died from lymphoma within 30 days of diagnosis. For recipients with transmitted renal cancers, three (15%) patients presented with metastatic disease at time of diagnosis and all three patients died from advanced stage renal cancer within 15 months of diagnoses with an average time from transplantation to death of 7.6 months (median: 9.0, IQR: 6.4–9.5).

The cancer-free survival of recipients after transplantation for the three most common donor-transmitted cancers after adjustment for age and gender is shown in Figure 2. The median time to cancer diagnoses among those with donor-transmitted renal cancer was 10.5 months, but varied between 3 and over 45 months. In contrast, all cases of melanomas and lung cancers were diagnosed within 3 years of transplantation. The median time to cancer diagnoses for lung and melanoma was 13.0 (IQR: 11.0–17.0) months, and 10.5 (IQR: 8.0–16.5) months, respectively.

Figure 3 shows the probability of cancer-specific survival among recipients with donor-transmitted cancers. Although there were no statistically significant differences across the three cohorts with the different types of donor-transmitted cancers (log-rank test, p = 0.17), over 70% of

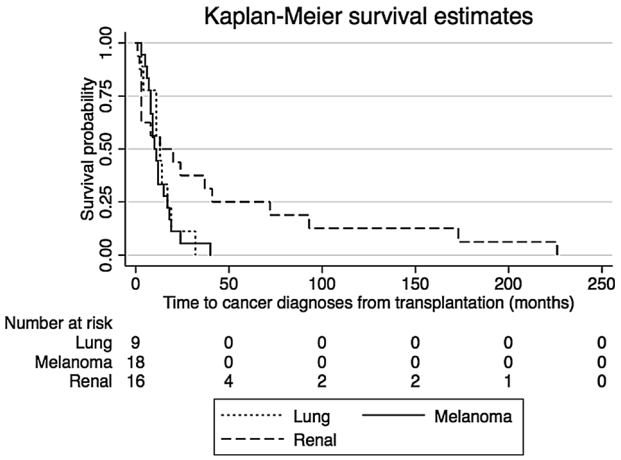

Figure 2: Cancer-free survival from transplantation by cancer types.

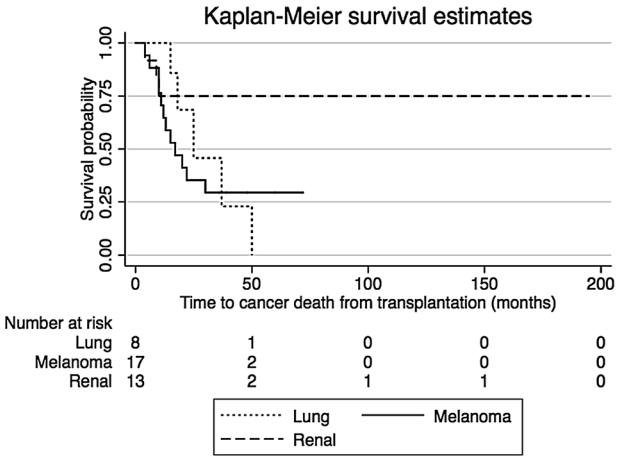

Figure 3: Survival probability of recipients with donor transmitted cancer.

transplant recipients with donor-transmitted renal cancer survived after 2 years from transplantation. In contrast, the 5-year survival for recipients with donor-transmitted melanoma is less than 30%.

Management of recipients with donor-transmitted cancers

The various types of treatment options for patients with donor-transmitted cancers are shown in Table 2. Immunosuppression withdrawal and graft nephrectomy were the two most common forms of therapeutic and surgical interventions. Subtotal nephrectomy was performed in two cases (23,24), where one of these cases proceeded to total nephrectomy after 3 months. Over 80% of recipients with donor-transmitted choriocarcinoma, lymphoma, sarcoma and GBM withdrew immunosuppression after cancer diagnoses were made. A total of 70 (67%) patients with transmitted cancer had graft nephrectomy after immunosuppression withdrawal. Of these, 19 (27%) patients returned to dialysis, 18 (26%) died within a mean of 17.7 months (SD $\pm$21.5) and eight (11%) recipients with failed graft received another transplant within an average of 18.1 months (SD $\pm$13.8). Other treatment modalities included chemotherapy for metastatic melanomas (n = 1, 6%), lymphomas (n = 6, 40%), choriocarcinomas (n = 4, 80%) renal cancers (n = 1, 5%) and lung cancers (n = 2, 22%). For recipients with localized lung and renal cancers, radiotherapy was the primary treatment of choice. Immunotherapy was infrequently used for the treatment of transmitted lung, renal, melanomas and choriocarcinomas.

Discussion

Although the overall risk of donor cancer transmission is small, kidney transplant recipients with donor-transmitted melanoma, sarcoma and lung cancers have the worst prognosis with advanced stage metastatic disease at the time of diagnoses. The overall survival for patients with metastatic lung cancer and melanoma is less than 50% 2 years after initial diagnoses. In comparison, the prognoses for recipients with renal cancer are favorable, with a 5-year survival rate of over 70%. Treatment options for patients with donor-transmitted cancers are also limited. Immunosuppression withdrawal appears to be the treatment of choice in most cases, but often at the expense of graft dysfunction and failure with return to dialysis.

Given the continual shortage of donor organs, coupled with the growing number of patients requiring renal replacement therapy, the number of patients waiting and dying on the kidney transplant waiting list is continuously rising. There is increasing pressure among transplant units worldwide to increase the overall donor pool, including the use of extended criteria donors, donors of extreme ages, donors with prolonged intensive care admission and donors who may potentially transmit disease to their recipients (25,26). However, the use of these marginal donors is often associated with a greater risk of undiagnosed disease such as cancers and infections (27).

The observed findings with reference to the outcomes of patients with transmitted melanomas and lung cancers were not unexpected. Melanoma is an immune-driven malignancy. Melanoma cells can remain dormant for a long period of time, but may reactivate as late recurrence, metastatic disease or newly developed *de novo* melanomas under the influence of immunosuppression (28). The outcomes of recipients with transmitted lung cancers were also poor and a similar immunological mechanism may be implicated, where transplantation of the organ harboring dormant metastases allowed subsequent tumor growth in the immunosuppressed host (29,30).

On the contrary, our findings suggested that the outcomes of those with transmitted donor renal cancers are generally reasonable. The majority of these tumors are small, localized and not apparent at the time of the transplanted surgery. There was also substantial variability in the duration from transplantation to cancer development, suggesting that many of these tumors may perhaps be less susceptible to the influence of immunosuppression or may have a longer sojourn time from preclinical phase to clinical manifestation compared to other solid organ cancers.

Similar findings were observed by a recent initiative, the NOTIFY project, commissioned by the WHO and in collaboration with the Italian CNT. Their recommendations were derived from the Council of Europe Guide to Safety and Quality Assurance for the transplantation of organs, tissues and cells (31), an internally conducted literature review and expert opinions. Their findings suggested that donors with a history of malignant melanomas, lung

Table 2: Clinical characteristics and outcomes of recipients (n = 104)

	Number of recipients with donor-transmitted cancers (n = 104)							
Recipient outcomes	Renal cancer (n = 20)	Melanoma (n = 18)	Lymphoma (n = 15)	Lung cancer (n = 9)	Sarcoma (n = 7)	Glioblastoma multiforme (n = 6)	Choriocarcinoma (n = 5)	Other cancers (n = 24)
Mean age at transplantation (years, SD)	40 (14.6)	48 (13.8)	46 (15.0)	41 (11.7)	47 (11.8)	38 (14.2)	30 (11.4)	43 (13.9)
Male (n, %)	11 (58)	8 (44)	6 (43)	4 (44)	1 (14)	3 (50)	1 (25)	15 (63)
Time from transplantation to cancer diagnosis (months) (median, IQR)	10.5 (3.0–40.0)	10.5 (8.0–16.5)	4.0 (0.8–7.0)	13.0 (11.0–17.0)	19.0 (14.3–20.0)	10.0 (10.0–17.0)	1.0 (0.2–3.0)	8.0 (5.5–18.5)
Recipients with metastatic cancer at the time of diagnoses (n, %)	3 (15)	13 (72)	1 (7)	7 (78)	5 (71)	1 (17)	2 (40)	17 (71)
Follow-up time (months) (median, IQR)	26.0 (10.5–36.8)	26.0 (12.5–41.3)	15.0 (6.0–24.0)	19.0 (15.0–28.0)	18.0 (n/a)	32.0 (16.0–33.0)	9.5 (6.2–15.0)	12.0 (7.5–28.5)
Withdrawal of immunosuppression (n, %)	12 (60)	13 (72)	13 (87)	7 (78)	6 (86)	5 (83)	5 (100)	21 (88)
Graft nephrectomy (n, %)	13 (65)	11 (61)	13 (87)	7 (78)	0	4 (67)	4 (80)	18 (75)
Chemotherapy (n, %)	1 (5)	1 (6)	6 (40)	2 (22)	0	0	4 (80)	8 (33)
Radiotherapy (n, %)	1 (5)	0	2 (13)	2 (22)	0	1 (17)	0	1 (4)
Immunotherapy (n, %)	2 (10)	6 (33)	0	1 (11)	0	0	1 (20)	2 (8)

IQR, interquartile range; n/a, insufficient data.

cancers, sarcomas and grade IV central nervous system (CNS) neoplasms are considered unacceptable for donation. Given the somewhat positive outcomes of certain donor cancer types and the scarcity of available donors to meet the continuous demand for organs, several exceptions have been made for donors with a cancer history and are considered acceptable for transplantation. These include donors with a history of grade I–II neoplasms of the CNS or grade III in the absence of ventriculo-peritoneal or ventriculo-atrial shunts, previous craniotomy, and previous radiotherapy or chemotherapy and donors with low-grade, small and localized RCC (32). In general, donors with RCC diagnosed at the time of organ recovery could be considered as suitable donors if the tumor is less than 4 cm, Fuhrman grade I or II and the margins of resection are tumor free (31).

Our study has several strengths. To our knowledge, this is the first systematic review of all published data regarding donor cancer transmission in kidney transplantation. Using a rigorous and systematic approach to critical appraisal and data analyses, we were able to generate meaningful prognostic information regarding the outcomes of recipients who have developed donor-transmitted cancers after kidney transplantation and therefore provide valuable evidence for transplant healthcare providers and recipients when considering the benefits and risks involved with using organs from donors with a history of cancer.

There are some limitations to this systematic review. First, we may have underestimated the total number of donor-transmitted malignancies as comprehensive and detailed individual level patient data among those with donor-transmitted cancers were not available from all published registry data. The lack of consistent reporting from these included studies may have precluded accurate assessment of all potential confounders, risk evaluation, diagnostic and treatment effectiveness of each reported case of transmitted malignancy. There was substantial variability in the overall follow-up times between the times of transplantation, times of cancer diagnoses and cancer death across individual studies. As such, direct comparison of cancer-specific mortality rates between cancer types was not feasible. There is likely to be selective underreporting of published donor-transmitted cancer deaths whereas those reporting recipient survival may be more prevalent in the gray literature. In addition, we were unable to provide prognostic information about the morphological and histological stages of all included renal cancers in the review. Although we had included some early case reports, we did not observe major differences in the number, the prognoses and the types of cancers observed between the different eras of transplantation. Also, the reporting of metastatic renal cancers did not seem to correlate with the year of publication, where one case was published in the 1970s and the two cases were from the 1990s (23,33,34).

There is ongoing controversy regarding whether lymphoma should be defined as donor-*derived* cancers (i.e. *de novo* tumors developing in transplanted donor cells), or donor-*transmitted* cancers (i.e. cancers that existed in the donor at the time of transplantation) (35). While posttransplant lymphoproliferative disorders could potentially arise from the recipient or donor lymphocytes, the majority of lymphomas originate from reactivation of previously acquired Epstein–Barr virus (EBV) infection, and of the recipient lymphoid cells after solid organ transplantation (36). The 15 reported cases of post–kidney transplant lymphomas included in our review were proven to be of donor origin. In addition, three out of these 15 cases occurred in EBV-naïve recipients (37–39). In general, tumors arising after extended posttransplant intervals are often regarded as donor derived, suggesting that tumor development proceeded in the posttransplant period. However, there is currently no time limit to differentiate these cases from those where small tumors may have been present and transmitted at transplantation (9). In this study, we had included tumors that may arise any time after transplantation as long as they satisfied our inclusion criteria.

Future research and clinical implications

Our review has focused on donor cancer transmission in kidney transplantation only, which is the most common type of solid organ transplant. It would be informative to conduct future prognostic reviews that describe the outcomes of potential transmitted donor malignancy in other solid organ transplant types, such as liver, lung and cardiac transplants. Future research should also consider comprehensive assessment of individual patient data from all available national and international donors and transplant registries. A donor selection policy screening for possible cancer transmission should be in place for living and deceased donor transplantation, and transplant clinicians should also consult the Notify Library (21), an open access database, to obtain comprehensive information regarding donor cancer transmission events. For living donation, comprehensive cancer screening among live donors is now in place, particularly for common cancer types such as breast, colorectal, prostate and cervical cancers (40). However, routine cancer screening among deceased donors is not always feasible, as it is neither a practical nor an efficient use of resource to perform autopsies on all potential donors. Transplant clinicians should be aware of the potential donor's medical history and, if in doubt, should exclude organs from donors with any history of high-risk cancers.

Finally, a system of mandatory reporting for suspected and confirmed cases of donor cancer transmission events is obligatory for monitoring and governance and should be instigated in transplanting centers worldwide. One example of policy implementation in recent years is the Directive 2010/53/EU of the European Parliament and the Council of 7 July 2010 (41), which set out a judicial framework on quality and safety standards for organ transplantation, stating that Member States shall ensure that there is a reporting system to allow relevant information to be reported and transmitted if a serious adverse event should occur following organ transplantation.

Conclusion

Renal cancer, melanoma, lymphoma and lung cancer are the most commonly transmitted donor cancers among kidney transplant recipients. Recipients with transmitted melanoma and lung cancer incurred the worst overall survival, with less than 50% of recipients surviving after 24 months from transplantation. Recipients who developed donor transmitted renal cancer had the best longer-term cancer survival outcomes. Our findings support the current recommendations for rejecting organs from donors with a history of melanoma and lung cancer, but may consider the use of donor kidneys with a history of small and incidental RCC.

Authors' contributions

D.X. participated in research design, the writing of the article, the performance of the research and data analysis. J.C.C. participated in research design and the writing of the article. J.R.C. participated in research design and the performance of the research. B.D.-G. participated in research design. A.T. participated in research design and writing of the article. G.W. participated in research design, the writing of the article, the performance of the research and data analysis.

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 Supporting Information may be found in the online version of this article.

Appendix S1. Search strategies.

Appendix S2. Characteristics of included studies (n = 69).

Appendix S3. Quality appraisal of included studies.

Appendix S4. Frequency of other reported cancer types.