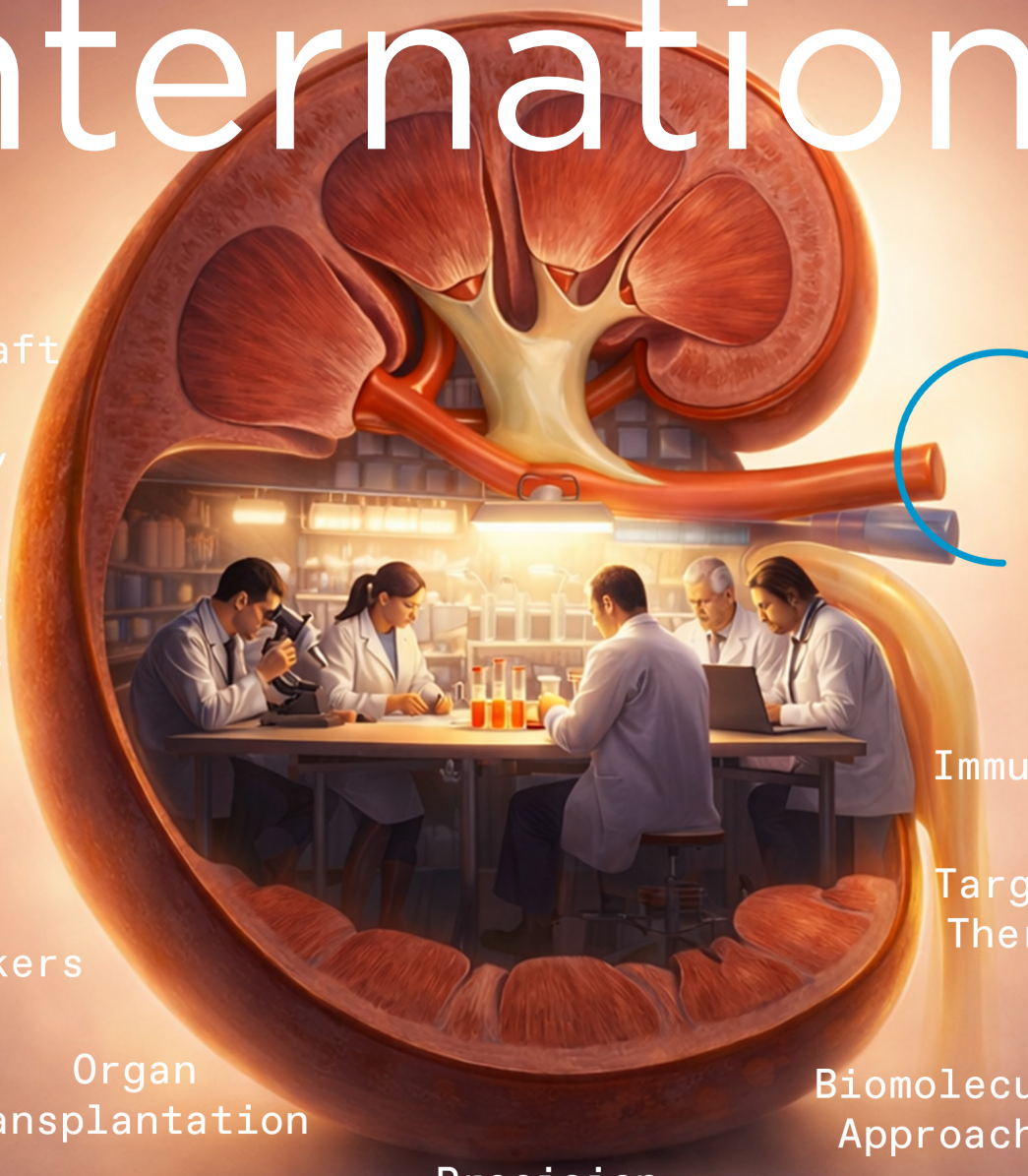
ESOT

Special Issue

Transplant International



Allograft

Oncology

Checkpoint Inhibitors

New Clinical

Biomarkers

Organ Transplantation

Precision

Biomolecular Approaches

Targeted Therapy

Immunotherapy

Oncology and Solid Organ Transplantation: New Biological and Clinical Insights

Transplant International

frontiers | Publishing Partnerships

Transplant International

Oncology and Solid Organ Transplantation: New Biological and Clinical Insights

Special Issue Editors

Gianluigi Zaza — Sapienza University of Rome, Italy
Annemarie Weissenbacher — Innsbruck Medical University, Austria
Alessandro Vitale — University Hospital of Padua, Italy
Lorna Marson — University of Edinburgh, United Kingdom
Pål-Dag Line — University of Oslo, Norway
David Cucchiari — Hospital Clinic of Barcelona, Spain
Andreas Kronbichler — Innsbruck Medical University, Austria

ISSN 1432-2277
ISBN 978-2-8325-8007-3
DOI 10.3389/978-2-8325-8007-3

Generative AI statement
Any alternative text (Alt text) provided alongside figures in the articles in this ebook has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

Transplant International

Table of contents

Original Research

Review

Mini Review

Review

Consensus Report

ESOT®
Leading the way
in transplantation

Are You a Member?

Join us to help shape and nurture the future of ESOT!

Learn more about membership benefits, access, discounts, including reduced publishing fees in Transplant International

ESOT Membership

ESOT®
Leading the way
in transplantation

2026 CALENDAR OF EVENTS

Join us for a dynamic lineup of educational **hands-on workshops** and **in-person events**, dedicated to advancing transplantation through shared knowledge and collaboration.

For the full scope of events, visit:

www.esot.org/events

ESOT®
Leading the way
in transplantation

Transplanting Health:

OVERCOMING METABOLIC BARRIERS

in Modern Medicine

1-3 December, 2026 • Barcelona, Spain

Abstract application submissions are now open!
Deadline to submit: **29 June 2026**

Submit today!

ESOT | Transplant International

SPECIAL ISSUE EDITORIAL
published: 24 March 2026
doi: 10.3389/ti.2026.16528

Oncology and Solid Organ Transplantation: New Biological and Clinical Insights

Gianluigi Zaza[1], Annemarie Weissenbacher[2], Alessandro Vitale[3], Lorna Marson[4], Pål-Dag Line[5,6], David Cucchiari[7] and Andreas Kronbichler[8,9]*

[1]Department of Translational and Precision Medicine, Division of Nephrology, Policlinico Umberto I Hospital, Sapienza University of Rome, Rome, Italy, [2]Department of Visceral, Transplant and Thoracic Surgery, OrganLife Organ Regeneration Center of Excellence, and Daniel Swarovski Research Laboratory, Medical University of Innsbruck, Innsbruck, Austria, [3]Department of Surgical Oncological and Gastroenterological Sciences, Padova University, Padova, Italy, [4]Edinburgh Transplant Centre, Royal Infirmary of Edinburgh, Edinburgh, United Kingdom, [5]Department of Transplantation, Oslo University Hospital, Oslo, Norway, [6]Institute of Clinical Medicine, University of Oslo, Oslo, Norway, [7]Department of Nephrology and Kidney Transplantation, Hospital Clínic of Barcelona, Barcelona, Spain, [8]Department of Internal Medicine IV, Nephrology and Hypertension, Medical University Innsbruck, Innsbruck, Austria, [9]Department of Health, Medicine and Caring Sciences, Linköping University, Linköping, Sweden

Keywords: kidney transplantation (KT), liver transplantation (LT), lung transplantation (LTx), oncology, solid organ transplant (SOT)

Editorial on the Special Issue

Oncology and Solid Organ Transplantation: New Biological and Clinical Insights

Solid organ transplantation represents a major challenge in modern medicine, as malignancy is one of the leading comorbidities affecting both patient and graft survival. Cancer risk in this large and heterogeneous population is affected by multiple donor- and recipient-related factors and, most importantly, by long-term immunosuppression [1]. Indeed, immunosuppressive therapies impair immune surveillance, predisposing to oncogenic viral infections and may directly influence tumor behavior [2]. In addition, although rare, donor-transmitted cancer remains a serious concern, requiring stringent assessment protocols and continuously updated guidelines [3].

Significant advances have been made in expanding the donor pool, particularly in liver transplantation, where indications have extended beyond hepatocellular carcinoma to include selected primary and metastatic liver tumors within the evolving field of transplant oncology. At the same time, precision medicine and next-generation sequencing technologies have led to the identification of new diagnostic and therapeutic targets. Immune checkpoint inhibitors are a standard of care for many cancer types, although their use in transplant patients is still challenging.

Therefore, this Special Issue addresses these topics through several rigorous original articles, mainly based on large clinical experiences, and comprehensive reviews. Each contribution addresses a distinct yet interrelated aspect of solid organ transplantation and oncology, collectively providing an in-depth overview of the field's current achievements and outlining its future transformative perspectives. Briefly, below are reported, in summary, the main evidence and results of the paper included in the special issue titled: *"Oncology and solid organ transplantation: new biological and clinical insights."*

- In a large 20-year single-center experience with right lateral sector grafts (RLSG) in adult living donor liver transplantation (a 661-case series from the University of Tokyo Hospital), Hayakawa et al. clearly demonstrated the value of this approach in expanding donor options with low donor complication rates and no donor mortality. Recipients experienced higher rates of vascular and

OPEN ACCESS

***Correspondence**
Gianluigi Zaza,
gianluigi.zaza@uniroma1.it

Received: *05 March 2026*
Accepted: *13 March 2026*
Published: *24 March 2026*

Citation:
Zaza G, Weissenbacher A, Vitale A, Marson L, Line P-D, Cucchiari D and Kronbichler A (2026) Oncology and Solid Organ Transplantation: New Biological and Clinical Insights. Transpl. Int. 39:16528. doi: 10.3389/ti.2026.16528

biliary complications than those with other graft types; however, 5-year survival was comparable. RLSG increased the donor pool by 5% and represented the only viable option for certain patients. Despite the higher complication rates, it remains a feasible and life-saving alternative when standard grafts are not suitable.

- Pommerolle et al. conducted a multicenter, retrospective, case-control study to evaluate the impact of screening in patients with renal cell carcinoma after kidney transplantation. The patients followed up in centers performing annual screening had smaller cancers, a lower relapse and cancer-related mortality rates, highlighting the importance of implementing annual screening to improve patient prognosis.
- Benoni et al., in a nationwide, population-based study analyzed data from a Swedish national registry to compare 98 organ transplant recipients with colorectal cancer (CRC) to 474 non-transplanted patients and identified differences in cancer characteristics and treatment-related factors that affected patients' survival. They found that transplant patients with stage I–III CRC were less likely to undergo abdominal surgery than non-transplant patients. Among patients treated with surgery, transplant patients with CRC were less likely to receive adjuvant chemotherapy, and transplant patients with rectal cancer had a higher rate of relapse than non-transplant patients. The 5-year cancer-specific and overall survival rates were lower in transplant patients (56% and 35%, respectively) than in controls (68% and 57%, respectively). The authors suggested that multidisciplinary evaluation involving transplant specialists should be applied in the management of CRC for all organ transplant recipients to ensure an optimal therapeutic strategy for this patient population.
- Stenman et al. studied post-transplant cancer incidence and survival in 664 heart transplant recipients at Sahlgrenska University Hospital. Over a median follow-up of 7.7 years, 19% of patients developed malignancies. The overall cancer risk was 6.2-fold higher than the general population, and 2.9-fold higher when excluding non-melanoma skin cancer (NMSC). The most common cancers were NMSC, non-Hodgkin lymphoma, and lung cancer. The risk factors included age, smoking, hypertension, cytomegalovirus (CMV) status, ischemic time, and azathioprine. A history of prior cancer did not affect post-transplant survival.
- The same research group also highlighted the main factors associated with an increased risk of cancer after lung transplantation. The key determinants were older donor and recipient age, type of immunosuppression, and whether the transplant was single or bilateral. The authors also noted that the improvement in 5-year survival after lung transplantation, from 46% in 1990 to 57% in 2015, should be considered, as longer post-transplant survival may contribute to a higher cumulative risk of cancer Stenman et al.
- Re Sartò et al. investigated the epidemiology of cancer after kidney transplantation, its risk factors, and its impact on management and survival in a retrospective single-center study. An Italian cohort of 930 kidney transplant recipients (KTR) followed up for 7 years was analyzed. During the follow-up, 19% of patients developed cancer, most commonly NMSC (55%). The identified risk factors included older age at the time of transplantation, higher body mass index (BMI) 1 month after transplantation, vasculitis, autosomal dominant polycystic kidney disease (ADPKD), and anti-thymocyte globulin (ATG) induction. ATG was associated with earlier cancer onset, while modification of immunosuppression after cancer diagnosis, particularly conversion to mTOR inhibitors, was linked to improved survival.
- Similarly, Srisuwarn et al. analyzed a Thai single-center cohort of 2,024 kidney transplant recipients and reported that 6.2% developed 133 post-transplant malignancies (over 16,495 person-years at risk). Urothelial cancers and non-Hodgkin lymphoma showed the highest excess risk, with urothelial cancer particularly increased among women. Consistent with the Italian cohort, skin cancers were also among the most frequent malignancies.
- Given the high risk of skin cancers among solid organ transplant recipients and the lack of standardized triage guidelines to assist dermatology clinics in scheduling new patients pre- or post-transplant, Hirotsu et al. developed triage recommendations based on expert panel consensus for dermatologic management of this high-risk population. The proposed algorithm offers practical, risk-stratified guidance to support prevention and prompt diagnosis to reduce the skin cancer burden and progression of high-risk skin cancers in solid organ transplant recipients, together with a reduction of overall healthcare costs.
- Rare malignancies pose a significant challenge in transplantation. Lefevre et al. reported a metastatic donor-derived BKV-induced Bellini duct carcinoma in a kidney transplant recipient, successfully managed without chemotherapy or immunotherapy. Withdrawal of immunosuppression enabled spontaneous tumor rejection through alloimmune and antitumor responses.

Collectively, these studies highlight the importance of pre- and post-transplant cancer surveillance together with the tailoring of maintenance immunosuppressive therapy to address the high cancer risk in this patient population and optimize long-term graft and patient outcomes.

- Vanlerberghe et al. examined *de novo* malignancy (DNM) risk post-liver transplant in a retrospective analysis of 174 patients transplanted for alcoholic liver disease (ALD). Nineteen patients (10.9%) developed DNM between 12 and 60 months post-transplant. Independent risk factors included higher tacrolimus drug exposure, together with other factors (such as older age, greater smoking history, and active smoking at transplant). Minimizing tacrolimus exposure in the first year and promoting smoking cessation before transplantation may reduce the risk of DNM.
- Moreover, as reported by Zakrocka et al., paraneoplastic glomerular diseases, complex renal manifestations associated with malignancy, are currently understudied in transplant recipients but deserve careful evaluation and consideration to ensure long-term preservation of graft function. Ongoing advances in clinical and molecular nephrology are expected

to enhance our understanding of the underlying mechanisms and support the development of more effective diagnostic and therapeutic strategies for these conditions.

- Another important topic that has been analyzed in this special issue by Barbir et al. is the use of immune checkpoint inhibitors (ICIs) in KTRs, currently challenged by the risk of allograft rejection and loss. However, analyzing the available literature, the authors concluded that this risk can be reduced by optimizing maintenance immunosuppressive therapy and potentially by close follow-up to enable early intervention. Extra-renal immune-related adverse events are less common, though data on recurrent glomerulonephritis in the allograft are limited. Risk stratification using protocol biopsies, non-invasive biomarkers, or PD-L1 staining could help guide therapy, but further validation is needed. A patient-centered, multidisciplinary approach and unified transplant-oncology protocols are essential, and future studies should compare immunosuppressive strategies to optimize both cancer control and allograft survival.
- This was in line with Bolufer et al. who emphasized that cancer management in KTRs requires a multidisciplinary approach. The use of ICIs demands careful risk-benefit assessment, maintaining at least two immunosuppressants, adjusting corticosteroid dose, and switching from calcineurin inhibitors to mTOR inhibitors. However, further prospective studies are needed to refine these strategies.
- Finally, Turra et al. critically analyzed the current knowledge on the use of donors with known malignancy histories (focusing on cancer types, stages, and patient survival outcomes) to improve strategies for safe and effective organ transplantation from these donors. Individualized and multidisciplinary clinical judgment is essential when using organs from donors with cancer, with recipients being fully informed of risks, including the consequences of not proceeding with transplantation, before giving consent.

In conclusion, this Special Issue, involving clinicians and researchers worldwide, offers a comprehensive overview of this important topic in transplant medicine, providing new clinical evidence, guidelines, and translational research insights. It highlights the importance of innovative multidisciplinary management strategies to improve both allograft and patient outcomes.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

CONFLICT OF INTEREST

The authors(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

GENERATIVE AI STATEMENT

The author(s) declared that generative AI was not used in the creation of this manuscript.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

REFERENCES

1. Huo Z, Li C, Xu X, Ge F, Wang R, Wen Y, et al. Cancer Risks in Solid Organ Transplant Recipients: Results from a Comprehensive Analysis of 72 Cohort Studies. *Oncoimmunology* (2020) 9(1):1848068. doi:10.1080/2162402X.2020.1848068
2. Seyed-Khorami SM, Azadi A, Habibian A, Hosseini M, Fan X, Soleimanjahi H, et al. Oncogenic Viruses in Organ Transplantation: Implications of Virus-Host Interactions for Cancer Development. *Viruses* (2025) 17(10):1299. doi:10.3390/v17101299
3. Turra V, Manzi J, Rombach S, Zaragoza S, Ferreira R, Guerra G, et al. Donors with Previous Malignancy: When Is It Safe to Proceed with Organ Transplantation? *Transpl Int* (2025) 38:13716. doi:10.3389/ti.2025.13716

ESOT | Transplant International

ORIGINAL RESEARCH
published: 19 February 2024
doi: 10.3389/ti.2024.12055

Tacrolimus Drug Exposure Level and Smoking Are Modifiable Risk Factors for Early *De Novo* Malignancy After Liver Transplantation for Alcohol-Related Liver Disease

Benedict T. K. Vanlerberghe[1,2,3,4*†], *Hannah van Malenstein*[1,2†], *Mauricio Sainz-Barriga*[5,6†], *Ina Jochmans*[5,6†], *David Cassiman*[1,2†], *Diethard Monbaliu*[5,6†], *Schalk van der Merwe*[1,2†], *Jacques Pirenne*[5,6], *Frederik Nevens*[1,2†] *and Jef Verbeek*[1,2†]

[1]*Department of Gastroenterology and Hepatology, University Hospitals Leuven, Leuven, Belgium,* [2]*Laboratory of Hepatology, Department of Chronic Diseases and Metabolism (CHROMETA), KU Leuven, Leuven, Belgium,* [3]*Department of Internal Medicine, Division of Gastroenterology and Hepatology, Maastricht University Medical Centre, Maastricht, Netherlands,* [4]*School of Nutrition and Translational Research in Metabolism (NUTRIM), University Maastricht, Maastricht, Netherlands,* [5]*Transplantation Research Group, Department of Microbiology, and Transplantation, Laboratory of Abdominal Transplantation, KU Leuven, University of Leuven, Leuven, Belgium,* [6]*Department of Abdominal Transplant Surgery, University Hospitals Leuven, Leuven, Belgium*

OPEN ACCESS

***Correspondence**
Benedict T. K. Vanlerberghe,
jef.verbeek@uzleuven.be

†ORCID:
Benedict T. K. Vanlerberghe
orcid.org/0000-0002-4665-2042
Hannah van Malenstein
orcid.org/0000-0003-0673-0939
Mauricio Sainz-Barriga
orcid.org/0000-0002-9981-4340
Ina Jochmans
orcid.org/0000-0003-4592-2810
David Cassiman
orcid.org/0000-0002-6154-0970
Diethard Monbaliu
orcid.org/0000-0002-0506-1609
Schalk van der Merwe
orcid.org/0000-0002-9891-2686
Frederik Nevens
orcid.org/0000-0003-2905-5112
Jef Verbeek
orcid.org/0000-0002-1549-8003

Received: *15 September 2023*
Accepted: *07 February 2024*
Published: *19 February 2024*

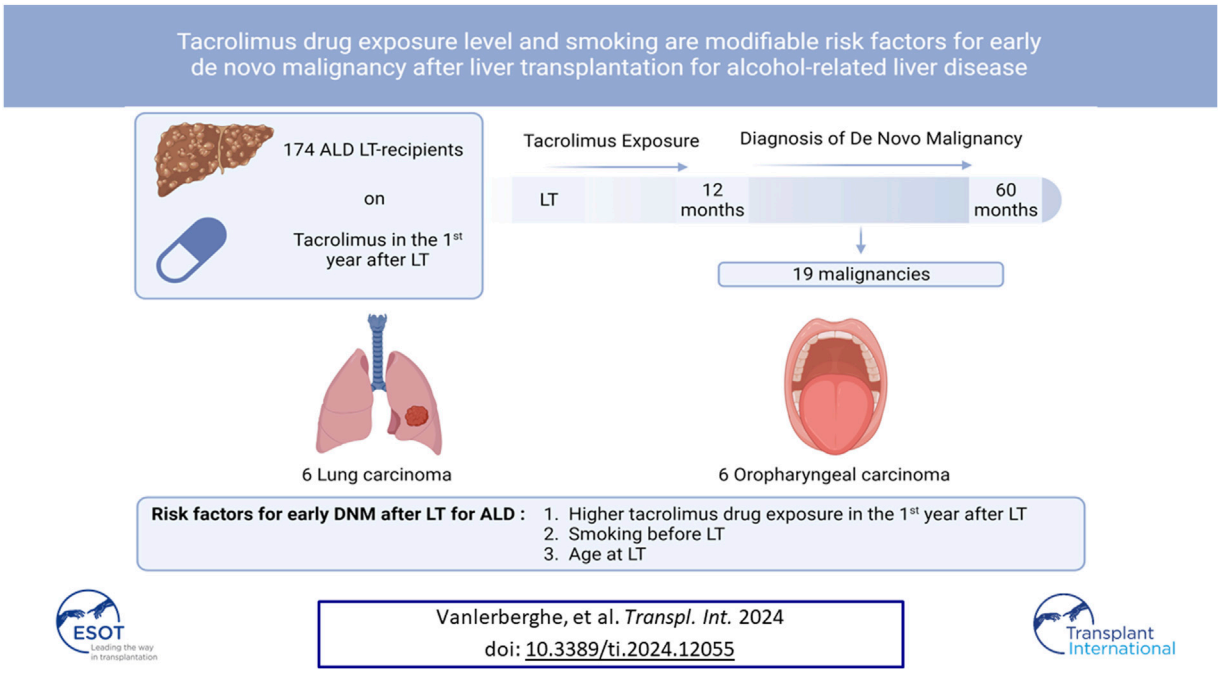
Citation:
Vanlerberghe BTK, van Malenstein H, Sainz-Barriga M, Jochmans I, Cassiman D, Monbaliu D, van der Merwe S, Pirenne J, Nevens F and Verbeek J (2024) Tacrolimus Drug Exposure Level and Smoking Are Modifiable Risk Factors for Early De Novo Malignancy After Liver Transplantation for Alcohol-Related Liver Disease. Transpl Int 37:12055. doi: 10.3389/ti.2024.12055

De novo malignancy (DNM) is the primary cause of mortality after liver transplantation (LT) for alcohol-related liver disease (ALD). However, data on risk factors for DNM development after LT are limited, specifically in patients with ALD. Therefore, we retrospectively analyzed all patients transplanted for ALD at our center before October 2016. Patients with a post-LT follow-up of <12 months, DNM within 12 months after LT, patients not on tacrolimus in the 1st year post-LT, and unknown smoking habits were excluded. Tacrolimus drug exposure level (TDEL) was calculated by area under the curve of trough levels in the 1st year post-LT. 174 patients received tacrolimus of which 19 (10.9%) patients developed a DNM between 12 and 60 months post-LT. Multivariate cox regression analysis identified TDEL [HR: 1.710 (1.211–2.414); $p = 0.002$], age [1.158 (1.076–1.246); $p < 0.001$], number of pack years pre-LT [HR: 1.021 (1.004–1.038); $p = 0.014$] and active smoking at LT [HR: 3.056 (1.072–8.715); $p = 0.037$] as independent risk factors for DNM. Tacrolimus dose minimization in the 1st year after LT and smoking cessation before LT might lower DNM risk in patients transplanted for ALD.

Keywords: alcohol-related liver disease, *de novo* malignancy, calcineurin inhibitor, tacrolimus drug exposure level, liver transplantation

INTRODUCTION

Alcohol-related liver disease (ALD) is the primary indication for liver transplantation (LT) in Europe and the United States [1]. *De novo* malignancies (DNM) are the leading cause of mortality in patients transplanted for ALD [2–4], a population with an increased risk of DNM compared to patients who received a LT for other indications [5]. This might be attributed to the oncogenic effects of long-term alcohol consumption [6, 7] and the high prevalence of tobacco use in patients with ALD [8]. Another risk factor for DNM is the immunosuppressive therapy patients receive after LT [9, 10]. Calcineurin inhibitors (CNIs) are the most frequently used agents for long-term immunosuppression and



GRAPHICAL ABSTRACT

tacrolimus is currently the most frequently used CNI [1]. Tacrolimus reduces the risk of allograft rejection after LT by inhibiting calcineurin, which leads to decreased cytokine transcription, particularly interleukin-2 (IL-2), and reduces T-cell proliferation [11]. Tacrolimus and its immunosuppressive properties are also associated with the development of DNM due to diminished immunosurveillance [12]. However, studies analyzing the risk of tacrolimus exposure and trough levels on DNM development after LTx are scarce [13–15]. These few studies did not specifically analyze ALD LT recipients [13, 14] and did not examine the effect of lifetime tobacco consumption and alcohol relapse after LT, factors that might have a strong contributive effect on malignancy formation. Furthermore, these studies assessed the lifetime DNM risk after LT based on 1st year of tacrolimus drug exposure. However, the 1st year exposure might only reflect the DNM risk within a shorter time after LT. Therefore, in this study we assessed the risk factors for DNM in the 1st 5-year period after LT for ALD, with specific emphasis on tacrolimus drug level in the 1st year post-LT and other modifiable risk factors such as smoking and alcohol use.

PATIENTS AND METHODS

Patient Characteristics

We analyzed the Liver Transplantation Cohort from the University Hospitals KU Leuven for adult patients (age ≥ 18 years) transplanted for ALD between 1990 and October 2016. Diagnosis of ALD was made based on the patient's history of excessive and habitual alcohol consumption, clinical and laboratory findings, histology of the explanted liver, and exclusion of other causes of liver disease (viral hepatitis, autoimmune hepatitis, hereditary hemochromatosis, Wilson's disease, primary biliary cholangitis, and primary sclerosing cholangitis), and based on the consensus of the multidisciplinary medical team. Patients with less than 12 months follow-up post-LT, a DNM in the 1st year post-LT or patients who did not receive tacrolimus during the 1st 12 months after LT were excluded from the analysis. Patients with unknown smoking habits (no information available on smoking history, i.e., pack years smoked before LT) were also excluded from the analysis. We retrospectively collected data on general patient characteristics, type and timing of DNM, excluding non-melanoma skin cancer and recurrence of hepatocellular carcinoma as events. DNM were reported as events if they occurred between 12 and 60 months of follow-up. Positive smoking history (defined as ≥ 1 pack year pre-LT), absolute number of pack years (PY) smoked before LT and active smoking at LT were extracted from patient's medical files. Active smoking was defined as smokers who still had an active smoking habit when admitted to the hospital for the LT procedure. Alcohol relapse was defined as relapse with any alcohol use.

In the work-up before LT, each patient is systematically screened for malignancies. Patients receive a gastroscopy, colonoscopy, chest x-ray, liver MRI and/or CT abdomen, abdominal ultrasound, and an assessment by an ear-nose-throat specialist and dermatologist. Female LT candidates also receive a mammography and a gynecological ultrasound. After LT for ALD, patients do not receive additional systematic

screening for DNM aside from the Belgian government's population screening for colon and breast cancer.

Immunosuppressive Regimen

After LT, the standard immunosuppressive protocol consists of tacrolimus, an antimetabolite, and corticosteroids. After 3 months, corticosteroids are discontinued. If possible, antimetabolite is discontinued after 12 months. The used antimetabolites are mycophenolate, and azathioprine in the minority of patients. Deviations from the protocol are only performed on clinical indication. Tacrolimus trough levels are analyzed daily during hospital admission directly following LT. After hospital discharge, trough levels are determined twice a week during the first month, every 2 weeks during the first 3 months, three monthly from 3 months to 1 year post-LT and per 3–6 months thereafter. On clinical indication, tacrolimus trough levels are analyzed more frequently.

Statistical Analysis

Normality was checked by the Shapiro-Wilk test. Qualitative variables were compared using the χ^2 test. Normally distributed values are presented as means with 95% confidence intervals (95% CI) or standard deviation (SD) and were compared using an independent t-test. Non-normally distributed values are presented as medians with interquartile range (IQR) and were compared using the Mann-Whitney U and Kruskal-Wallis tests.

Hazard ratios (HR) for the risk of DNM between twelve and 60 months after LT were evaluated by Cox proportional hazards regression. Patients were considered at risk from twelve to 60 months post-LT or until reaching the study endpoints (diagnosis of DNM or death). Patients lost to follow-up were censored at time of loss from data analysis. A proportional hazard model was performed with categorical, continuous, and time-dependent covariates to identify risk factors. Additional covariates were selected by expert opinion and based on literature [13, 14]. The proportional hazard assumption was tested for each covariate by correlation testing of Schoenfeld residuals and rank time; only covariates without significant correlation were included (see **Supplementary Table S1**). Multivariate analysis was performed by backward elimination with a selection criterion of 0.100. Statistical analysis was performed by SPSS v.28 (SPSS Inc., Chicago, IL, United States). Statistical significance was defined as $p \leq 0.05$.

Total tacrolimus drug exposure level (TDEL) was based on the area under the curve of tacrolimus trough levels in μg/L [analyzed in R by PKCNA package (linear)] and corrected by the trapezoidal rule as previously described by Vivarelli et al. [16].

RESULTS

Patient Characteristics

Within the study period, 317 patients were transplanted for ALD at our center, of which 174 were included in the analysis. Patients who had a follow-up of 12 months or less (n = 23; 22 died within the 1st year post-LT and one patient was lost to follow-up at 11 months post-LT), patients who were diagnosed with a DNM within 12 months after LT (n = 11) and patients who did not receive tacrolimus in the 1st year after LT (n = 46) were excluded. 56 patients were excluded because there was insufficient information available on their smoking habits. Seven patients were excluded because of missing data on tacrolimus trough levels in the 1st year post-LT. All included patients were transplanted after December 1998.

During the 1st year after LT, 117 (67.2%) patients received *Prograf* and 57 (32.8%) *Advagraf*. 144 (82.8%) patients received mycophenolate and 20 (11.5%) patients received azathioprine as an antimetabolite. The median age at LT was 59.5 years (IQR: 54.0–65.0) (**Table 1**). Median follow-up was 91 months (IQR: 65.0–143.0).

Of the total group, 112 (64.4%) patients had a positive smoking history, of which 44 (25.3% of the total group) actively smoked at the time of transplantation (**Table 1**). 60 patients (34.5%) had a relapse of any alcohol use after LT. 47 patients (78.3% of the relapsers) relapsed within 5 years after LT, with a median time until relapse of 15.0 months (IQR: 4.0–32.0).

De Novo Malignancy

19 (10.9%) patients were diagnosed with a DNM between 12 and 60 months after LT. Characteristics of patients diagnosed with a DNM compared to those who did not can be found in **Table 1**. Median time until diagnosis of DNM was 46 months (IQR: 18.0–56.0). 17 patients developed a solid organ malignancy with oropharyngeal (n = 6) and lung carcinoma (n = 6) being the most prevalent (**Table 2**). One patient developed a simultaneous lung and oropharyngeal carcinoma at 54 months post-LT. Of the 17 solid organ DNMs, 5 (29.4%) patients had metastatic disease, 9 (52.9%) had only local disease and in 3 (17.6%) patients staging at the time of diagnosis was not reported. Four of the six patients diagnosed with lung carcinoma died from the malignancy during follow-up. The other two only had local disease at diagnosis and were alive after 1 and 23 months of follow-up. Two out of six patients diagnosed with an oropharyngeal carcinoma died because of the carcinoma, yet all diagnoses were made in a non-metastatic stage. All patients diagnosed with a lung or oropharyngeal malignancy had a smoking history. Two patients have developed hematological malignancies (1.1%) being a post-transplant lymphoproliferative disease and a plasmacytoma. One patient developed a soft tissue tumor (Kaposi sarcoma).

Patients diagnosed with a DNM between 12 and 60 months after LT had a higher mortality than those not diagnosed with a DNM [HR: 2.981 (95% CI: 1.573–5.652); $p < 0.001$)] (see **Figure 1**). Of patients diagnosed with a DNM, 13 (68.4%) died during follow-up, of which 10 died due to DNM. The overall 60 months survival was 81.0% (n = 141), and was significantly higher in the group without DNM (83.9%) compared to the group with a DNM (57.9%) (p = 0.006), corresponding with a shorter median follow-up in the DNM group than in the non-DNM group [69.0 months (IQR: 53.0–89.0) vs. 95.0 (IQR: 70.0–145.0); p = 0.020].

TABLE 1 | General characteristics of patients at liver transplantation diagnosed with a *de novo* malignancy compared to those not diagnosed with a *de novo* malignancy.

	Overall (*n* = 174)	DNM (*n* = 19)	No DNM (*n* = 155)	*p*-value
Male sex (%)	133 (76.4)	17 (89.5)	116 (74.8)	0.156
Median age in years (IQR)	59.5 (54.0–65.0)	66.0 (58.0–68.0)	59.0 (54.0–64.0)	0.145
HCC on explant (%)	70 (40.2)	10 (52.6)	60 (38.7)	0.243
Combined transplant (%)	14 (8.0)	2 (10.5)	12 (7.7)	0.674
Median Child-Pugh Score at LT (IQR)	10.0 (8.0–11.0)	9.0 (7.0–11.0)	10.0 (8.0–11.0)	0.976
Median MELD-Na at LT (IQR)	18.0 (11.0–24.0)	18.0 (9.0–22.0)	18.0 (11.8–24.0)	0.805
Smoking history (%)	112 (64.4)	18 (94.7)	94 (60.6)	**0.003***
Active smoking (%)	44 (25.3)	8 (42.1)	36 (23.2)	0.074
Median pack years of patients with a smoking history (IQR)	30.0 (20.0–43.8)	42.5 (35.0–50.3)	30.0 (20.0–40.0)	**0.004***
MFM (%)	144 (82.8)	14 (73.7)	130 (83.9)	0.267
Azathioprine (%)	20 (11.5)	4 (21.1)	16 (10.3)	0.166
No antimetabolite (%)	10 (5.7)	1 (5.3)	9 (5.8)	0.923
mTOR inhibitor ǂ (%)	10 (5.7)	0 (0)	10 (6.5)	0.254
Basiliximab at LTx (%)	15 (8.6)	1 (5.3)	14 (9.0)	0.581
Alcohol relapse after LT (%)	60 (34.5)	6 (31.6)	54 (34.8)	0.778
Median Donor age in years (IQR)	57.0 (44.0–64.0)	57.0 (38.0–66.0)	57.0 (45.0–64.0)	0.810
Cold ischemia time (hours: minutes)	7:36 (5:29–9:08)	7:17 (5:00–9:07)	7:45 (5:30–9:11)	0.470

LT, liver transplantation; DNM, de novo *malignancy; IQR, interquartile range; HCC, hepatocellular carcinoma; MFM, mycophenolate mofetil; mTOR, mammalian target of rapamycin inhibitor; ǂ: number of patients who received an mTOR inhibitor combined witch CNI for at least 1 month in the 1st year after LTx, * = statically significant.*
Bold values denote statistical significance.

TABLE 2 | Types of *de novo* malignancies diagnosed after liver transplantation.

Type of DNM	Time diagnosis (months after LTx)	Stage at diagnosis	CNI	Pack years before LTx	Follow-up after DNM (months)	Cause of death
Lung carcinoma (spinocellular)	16	T4N3M1	Tacrolimus	60	20	Lung carcinoma
Lung carcinoma (spinocellular)	21	T3N0M1	Tacrolimus	51	90	Lung carcinoma
Lung carcinoma (adenocarcinoma)	25	TN*n/a*M1	Tacrolimus	35	13	Lung carcinoma
Lung carcinoma (undifferentiated)	45	*n/a*	Tacrolimus	45	1	Lung carcinoma
Lung carcinoma* (spinocellular)	54	T2N0M0	Tacrolimus	60	23	
Lung carcinoma (spinocellular)	57	T1N0M0	Tacrolimus	50	1	
Oropharyngeal carcinoma	13	T1N1M0	Tacrolimus	50	11	Oropharyngeal carcinoma
Oropharyngeal carcinoma	17	T1N0M0	Tacrolimus	40	52	Oropharyngeal carcinoma
Oropharyngeal carcinoma	18	T2N0M0	Tacrolimus	35	125	
Oropharyngeal carcinoma	25	T1N0M0	Tacrolimus	30	63	Pneumonia
Oropharyngeal carcinoma*	54	T1N1M0	Tacrolimus	60	23	
Oropharyngeal carcinoma	58	*n/a*	Tacrolimus	40	31	
Colorectal carcinoma	47	TN*n/a*M1	Tacrolimus	30	6	Colorectal carcinoma
PTLD	56	IVa	Tacrolimus	12	8	PTLD
TCC (Bladder)	46	TxG1	Tacrolimus	45	59	COPD
TCC (Bladder)	57	TN*n/a*M1	Tacrolimus	36	1	TCC (Bladder)
Esophagus carcinoma	49	*n/a*	Tacrolimus	60	28	
Ovarian carcinoma	60	FIGO II	Tacrolimus	50	27	
Plasmacytoma	13		Tacrolimus	0	218	Alcoholic cirrhosis
Sarcoma Kaposi	48	High Grade	Tacrolimus	40	5	Sarcoma

DNM, de novo *malignancy; LTx, liver transplantation; CNI, calcineurin inhibitor; n/a, not available; PTLD, post-transplant lymphoproliferative disorder; COPD, chronic obstructive pulmonary disease; TCC, transitional cell carcinoma; * DNM diagnosed in the same patient.*

Risk Factors for Developing DNM

Tacrolimus Drug Exposure Level

The mean tacrolimus drug exposure level in the 1st year post-LT was 7.41 μg/L (SD. 1.60) and was higher in patients who developed a DNM within 5 years after LT (8.14 μg/L; SD. 1.56) compared to patients who did not (7.31 μg/L; SD. 1.59) ($p = 0.016$). Univariate cox regression analysis identified TDEL as a risk factor for DNM between 12 and 60 months after LTx [HR: 1.357 (95% CI: 1.027–1.790); $p = 0.031$].

When analyzing the ROC of TDEL plotted against DNM prevalence, a TDEL of 6.94 μg/L had the highest discriminative value. 15 out of 98 patients (15.3%) with a TDEL above 6.94 μg/L

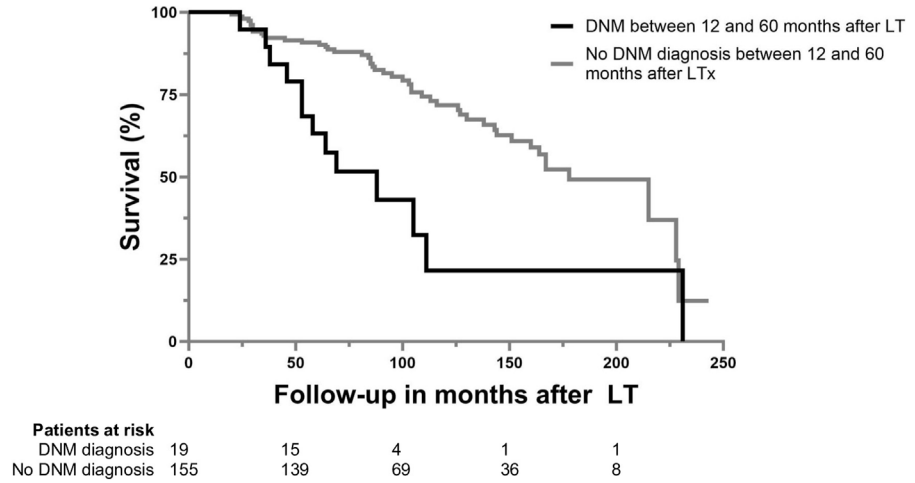


FIGURE 1 | Patient survival after LTx for ALD based on the diagnosis of *de novo* malignancy between 12 and 60 months after LT.

developed a DNM compared to 4 out 76 patients (5.3%) with a TDEL lower than 6.94 μg/L. Also when implementing TDEL as a categorical value using the cut-off of 6.94 μg/L, TDEL remained a significant risk factor for DNM [HR: 3.009 (95% CI: 1.000–9.067); $p = 0.050$].

Other Risk Factors for DNM

18 (94.7%) patients with a DNM had a positive smoking history (≥1 pack year pre-LT) compared to 94 (60.6%) of patients who did not develop a DNM ($p = 0.003$). Patients who smoked and were diagnosed with a DNM had a higher tobacco consumption at LT than those without a DNM diagnosis [median pack years: 42.5 (IQR: 35.0–50.3) vs. 30.0 (IQR: 20.0–40.0); $p = 0.004$].

Univariate cox regression analysis identified age at LT [HR: 1.115 (95% CI: 1.039–1.197), $p = 0.002$], smoking history [HR: 11.136 (95% CI: 1.486–83.451); $p = 0.019$] and number of pack years pre-LT [HR: 1.024 (95% CI: 1.010–1.038); $p = 0.001$] as risk factors for developing DNM in the 1st 5 years after LT. In multivariate analysis, only pack years and not smoking history (defined as ≥ 1 pack year pre-LT) was included to avoid multicollinearity (**Table 3**).

Multivariate analysis identified age at LT [HR: 1.158 (95% CI: 1.076–1.246); $p < 0.001$], number of pack years pre-LT [HR: 1.021 (95% CI: 1.004–1.038); $p = 0.014$], active smoking at LT [HR 3.056 (95% CI: 1.072–8.715); $p = 0.037$] and TDEL in the 1st year after LT [HR: 1.710 (95% CI: 1.211–2.414); $p = 0.002$] as independent risk factors for developing DNM in the 1st 5 years after LT (**Table 3**). The use of mycophenolate mofetil compared to azathioprine, sex, and any alcohol relapse within 5 years after LT were not associated with a higher risk on DNM after LT.

Rate of Liver Graft Rejection

21 (12.1%) patients of the total group developed an acute cellular rejection (ACR) within the first 30 days after LT. Patients with a graft rejection in the first month had a higher TDEL in the first year after LT [mean TDEL: 8.10 μg/L (SD. 1.69) vs. 7.31 μg/L (SD. 1.57); $p = 0.034$]. This resulted in a trend towards a higher number of DNM in the ACR-group [$n = 4$ (19.0%)] vs. the non-ACR-group [$n = 15$ (9.8%)], but this did not reach statistical significance ($p = 0.203$).

DISCUSSION

Identifying modifiable risk factors for DNM in patients transplanted for ALD is crucial to optimize their outcome. In our study, we found that in patients transplanted for ALD, tacrolimus drug exposure level (TDEL) in the 1st year after LT, number of pack years before LT, active smoking at LT and older age at LT are independent risk factors for the development of early DNM within 12 and 60 months after LT. Hereby, we provide the first evidence on the impact of TDEL in the 1st year after LT for ALD on the occurrence of early DNM, taking into account a detailed analysis on smoking habits.

The development of malignancies after LT is a complex interaction between an individual's risk on DNM based on genetic predisposition, exposure to carcinogenic viruses, previous and current behavior such as smoking and alcohol use, and immunosuppressive therapy [12]. The observed association of TDEL and DNM is in line with the findings of Carenco et al. [14] and Rodriguez-Perálvarez et al. [13], although these two studies were conducted in LT patients transplanted not merely for ALD, and used DNM at any time point after LT as outcome parameter. Taken together, these observations underline the potential of optimizing tacrolimus drug exposure in clinical care. Prospective studies should focus on identifying protocols aiming for the minimally acceptable tacrolimus through level in order to lower the DNM risk, without increasing allograft rejection. This might be achieved by the use of induction therapy and/or the concurrent use of other immunosuppressive agents such as mammalian target of rapamycin (mTOR) inhibitors. However, there is conflicting evidence on the impact of mTOR inhibitors on DNM and if

TABLE 3 | Univariate and multivariate cox proportional hazard regression for risk on *de novo* malignancy between 12 and 60 months after liver transplantation (174 patients) in patients under tacrolimus in first-year after liver transplantation.

	Univariate	Sig.	Multivariate	Sig.
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age at LT (mean-centered)	1.115 (1.039–1.197)	**0.002***	1.158 (1.076–1.246)	**<0.001***
Male sex	2.971 (0.686–12.871)	0.145		
Alcohol relapse (T)	0.681 (0.197–2.356)	0.544		
Smoking history	11.136 (1.486–83.451)	**0.019*‡**		
Pack years pre-LT	1.024 (1.010–1.038)	**0.001***	1.021 (1.004–1.038)	**0.014***
Active smoking at LT	2.356 (0.947–5.860)	0.065	3.056 (1.072–8.715)	**0.037***
TDEL	1.357 (1.028–1.790)	**0.031***	1.710 (1.211–2.414)	**0.002***
MFM vs. Azathioprine	0.494 (0.163–1.502)	0.214		

*HR, hazard ratio; CI, confidence interval; LT, liver transplantation; TDEL, tacrolimus drug exposure level; MFM, mycophenolate mofetil; * = statically significant, ‡ = not included in multivariate analysis, T = time-dependent variable.*
Bold values denote statistical significance.

their underlying effect is associated with their antiproliferative properties or their tacrolimus-saving effect [17]. The development of pharmacometric tools to accurately predict TDEL based on daily tacrolimus dosage, patient characteristics and concomitant medication could be another approach, which we are currently studying in our center [18, 19]. In our study, we observed a higher TDEL in the 1st year after LT in patients that experienced an acute cellular rejection, but could not associate low TDEL with an increased risk for rejection.

Identifying tacrolimus trough level cut-offs that are associated with an increased risk for DNM, yet not with an increased risk on rejection, would be helpful in the follow-up and care of our LT patients. Within our cohort the cut-off over which DNM risk was disproportionately increased was 6.94 μg/L. However given the retrospective nature of our study this cut-off should not be extrapolated to other cohorts. Prospective studies are needed to further establish cut-offs that are usable in clinical care.

Patients with a positive smoking history (≥1 pack year pre-LT) had a substantially higher risk of developing DNM. Accordingly, all patients with lung or oropharyngeal carcinoma, the most frequent DNMs, had a positive smoking history. There seemed to be a dose-related effect since for every pack year smoked before LT there was an increase in DNM risk (HR: 1.021). Furthermore, patients who actively smoked at LT had an increased risk of DNM independent from the number of pack years they smoked before LT or TDEL. Together, these data stress the importance of smoking cessation in the pretransplant period and support the implementation of smoking cessation programs [20]. Since alcohol is a carcinogen [21], we expected that alcohol relapse could lead to a higher incidence of DNM. However, we did not find a higher risk for DNM after any alcohol relapse, in line with other studies [22]. This could be explained by the higher risk of liver-related disease and mortality after alcohol relapse, which could occur before the development of DNM [1]. Age at LT was an independent risk factor for developing DNM. In our cohort and other centers [1], over the last decades, patients have become older at the time of LT due to a switch in focus from chronological to biological age as an eligibility criterium for LT listing [1]. Transplanting older patients will only increase DNM incidence post-LT in the future, underscoring the relevance of our findings and the need for measures to lower DNM risk.

In our study, lung carcinomas were frequently diagnosed in a metastatic setting, whereas oropharyngeal were not. Screening could be implemented in clinical practice to diagnose lung carcinoma in curative stages, which was the focus of several studies. Renaud et al. compared an intensive screening program (yearly chest CT and clinical examination by an otorhinolaryngologist versus chest CT every 5 years) in patients transplanted for ALD who continued to smoke after LT [23]. They found that 63.6% of patients underwent a curative treatment of lung carcinoma in the intensive screening program versus only 26.3% in the standard screening program ($p = 0.062$) [23]. There was no difference in curative treatment of oropharyngeal tumors between the groups [100% vs. 87.5% ($p = 0.498$)] [23]. These findings are comparable with our results, where in a clinical setting without systematic post-LT screening, all diagnoses of oropharyngeal tumors were made with a possibility of curative treatment. Other studies analyzing the impact of malignancy screening after LT also showed that screening led to diagnosing DNM in earlier stages with higher rates of curative treatment [24, 25]. However, these studies were not limited to ALD LT recipients, therefore caution is warranted to extrapolate these findings. We propose that future studies assessing the benefit of DNM screening post-LT should primarily focus on ALD patients who have a proportionally higher risk for DNM. Based on our data and those of Renaud et al. a yearly screening with chest CT for lung carcinoma might be beneficial in active smokers [23], and potentially in all patients with a smoking history.

Although we provided a detailed assessment of the effect of TDEL and smoking habits on the risk of DNM in patients transplanted for ALD, the retrospective nature of our study is a limitation. On the other hand, the single-center approach enables assessment of DNM risk in ALD patients that underwent similar work-up, treatment and follow-up regarding LT, yet this also implies that our data need external validation.

In conclusion, our study identified high tacrolimus drug exposure levels in the first year post-LT and smoking as significant risk factors for early DNM after LT for ALD.

Therefore, tacrolimus overexposure should be avoided and more efforts for smoking cessation should be initiated in these patients. Future studies are needed to assess the value and cost-benefit of systematical DNM screening after LT.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving humans were approved by Ethische commissie onderzoek UZ/KU Leuven. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because of the long-term retrospective nature of the study.

AUTHOR CONTRIBUTIONS

BV and JV participated in research design, writing of the paper and data analysis. HvM, MS-B, IJ, DC, DM, SvM, JP, and FN critically revised the manuscript. All authors contributed to draft finalization and approved the final version of the manuscript.

FUNDING

The study was supported by the Maag Lever Darm Stichting (Dutch Digestive Foundation)—Grant number D 18-19.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

ACKNOWLEDGMENTS

Graphical abstract was made using BioRender.com.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2024.12055/full#supplementary-material

REFERENCES

1. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Liver Transplantation. *J Hepatol* (2016) 64(2):433–85. doi:10.1016/j.jhep.2015.10.006
2. Dumortier J, Guillaud O, Adham M, Boucaud C, Delafosse B, Bouffard Y, et al. Negative Impact of De Novo Malignancies Rather Than Alcohol Relapse on Survival After Liver Transplantation for Alcoholic Cirrhosis: A Retrospective Analysis of 305 Patients in a Single Center. *Am J Gastroenterol* (2007) 102(5):1032–41. doi:10.1111/j.1572-0241.2007.01079.x
3. Verbeek J, Cassiman D, Nevens F. De Novo Malignancy and Recurrent Alcoholic Cirrhosis Account for 70% of Deaths in Patients Transplanted for End-Stage Alcoholic Liver Disease. *Am J Gastroenterol* (2016) 111(3):436–7. doi:10.1038/ajg.2016.10
4. Dumortier J, Dharancy S, Cannesson A, Lassailly G, Rolland B, Pruvot FR, et al. Recurrent Alcoholic Cirrhosis in Severe Alcoholic Relapse After Liver Transplantation: A Frequent and Serious Complication. *Am J Gastroenterol* (2015) 110(8):1160–6. doi:10.1038/ajg.2015.204
5. Chandok N, Watt KD. Burden of De Novo Malignancy in the Liver Transplant Recipient. *Liver Transpl* (2012) 18(11):1277–89. doi:10.1002/lt.23531
6. Boffetta P, Hashibe M. Alcohol and Cancer. *Lancet Oncol* (2006) 7(2):149–56. doi:10.1016/s1470-2045(06)70577-0
7. Pasala S, Barr T, Messaoudi I. Impact of Alcohol Abuse on the Adaptive Immune System. *Alcohol Res* (2015) 37(2):185–97.
8. MacLean RR, Sofuoglu M, Rosenheck R. Tobacco and Alcohol Use Disorders: Evaluating Multimorbidity. *Addict Behav* (2018) 78:59–66. doi:10.1016/j.addbeh.2017.11.006
9. Dantal J, Soulillou JP. Immunosuppressive Drugs and the Risk of Cancer After Organ Transplantation. *N Engl J Med* (2005) 352(13):1371–3. doi:10.1056/NEJMe058018
10. Geissler EK. Post-Transplantation Malignancies: Here Today, Gone Tomorrow? *Nat Rev Clin Oncol* (2015) 12(12):705–17. doi:10.1038/nrclinonc.2015.186
11. Scalea JR, Levi ST, Ally W, Brayman KL. Tacrolimus for the Prevention and Treatment of Rejection of Solid Organ Transplants. *Expert Rev Clin Immunol* (2016) 12(3):333–42. doi:10.1586/1744666x.2016.1123093
12. Buell JF, Gross TG, Woodle ES. Malignancy After Transplantation. *Transplantation* (2005) 80(2 Suppl. l):S254–64. doi:10.1097/01.tp.0000186382.81130.ba
13. Rodríguez-Perálvarez M, Colmenero J, González A, Gastaca M, Curell A, Caballero-Marcos A, et al. Cumulative Exposure to Tacrolimus and Incidence of Cancer After Liver Transplantation. *Am J Transpl* (2022) 22(6):1671–82. doi:10.1111/ajt.17021
14. Carenco C, Assenat E, Faure S, Duny Y, Danan G, Bismuth M, et al. Tacrolimus and the Risk of Solid Cancers After Liver Transplant: A Dose Effect Relationship. *Am J Transpl* (2015) 15(3):678–86. doi:10.1111/ajt.13018
15. Bardou FN, Guillaud O, Erard-Poinsot D, Chambon-Augoyard C, Thimonier E, Vallin M, et al. Tacrolimus Exposure After Liver Transplantation for Alcohol-Related Liver Disease: Impact on Complications. *Transpl Immunol* (2019) 56:101227. doi:10.1016/j.trim.2019.101227
16. Vivarelli M, Cucchetti A, La Barba G, Ravaioli M, Del Gaudio M, Lauro A, et al. Liver Transplantation for Hepatocellular Carcinoma Under Calcineurin Inhibitors: Reassessment of Risk Factors for Tumor Recurrence. *Ann Surg* (2008) 248(5):857–62. doi:10.1097/SLA.0b013e3181896278
17. de Fijter JW. Cancer and mTOR Inhibitors in Transplant Recipients. *Transplantation* (2017) 101(1):45–55. doi:10.1097/tp.0000000000001447
18. Kirubakaran R, Stocker SL, Hennig S, Day RO, Carland JE. Population Pharmacokinetic Models of Tacrolimus in Adult Transplant Recipients: A Systematic Review. *Clin Pharmacokinet* (2020) 59(11):1357–92. doi:10.1007/s40262-020-00922-x
19. Woillard JB, Labriffe M, Debord J, Marquet P. Tacrolimus Exposure Prediction Using Machine Learning. *Clin Pharmacol Ther* (2021) 110(2):361–9. doi:10.1002/cpt.2123
20. Ursic-Bedoya J, Donnadieu-Rigole H, Faure S, Pageaux GP. Alcohol Use and Smoking After Liver Transplantation; Complications and Prevention. *Best Pract Res Clin Gastroenterol* (2017) 31(2):181–5. doi:10.1016/j.bpg.2017.03.005

21. Bagnardi V, Rota M, Botteri E, Tramacere I, Islami F, Fedirko V, et al. Alcohol Consumption and Site-Specific Cancer Risk: A Comprehensive Dose-Response Meta-Analysis. *Br J Cancer* (2015) 112(3):580–93. doi:10.1038/bjc.2014.579
22. Dumortier J, Maucort-Boulch D, Poinsot D, Thimonier E, Chambon-Augoyard C, Ducroux E, et al. Immunosuppressive Regimen and Risk for De Novo Malignancies After Liver Transplantation for Alcoholic Liver Disease. *Clin Res Hepatol Gastroenterol* (2018) 42(5):427–35. doi:10.1016/j.clinre.2018.04.011
23. Renaud L, Hilleret MN, Thimonier E, Guillaud O, Arbib F, Ferretti G, et al. De Novo Malignancies Screening After Liver Transplantation for Alcoholic Liver Disease: A Comparative Opportunistic Study. *Liver Transpl* (2018) 24(12):1690–8. doi:10.1002/lt.25336
24. Herrero JI, Alegre F, Quiroga J, Pardo F, Iñarrairaegui M, Sangro B, et al. Usefulness of a Program of Neoplasia Surveillance in Liver Transplantation. A Preliminary Report. *Clin Transpl* (2009) 23(4):532–6. doi:10.1111/j.1399-0012.2008.00927.x
25. Finkenstedt A, Graziadei IW, Oberaigner W, Hilbe W, Nachbaur K, Mark W, et al. Extensive Surveillance Promotes Early Diagnosis and Improved Survival of De Novo Malignancies in Liver Transplant Recipients. *Am J Transpl* (2009) 9(10):2355–61. doi:10.1111/j.1600-6143.2009.02766.x

ESOT | Transplant International

ORIGINAL RESEARCH
published: 26 February 2024
doi: 10.3389/ti.2024.11614

Incidence of *De Novo* Post-Transplant Malignancies in Thai Adult Kidney Transplant Recipients: A Single-Center, Population-Controlled, Retrospective Cohort Study at the Highest Volume Kidney Transplant Center in Thailand

Praopilad Srisuwarn[1]*, *Napun Sutharattanapong*[2,3], *Sinee Disthabanchong*[2], *Surasak Kantachuvesiri*[2,3], *Chagriya Kitiyakara*[2], *Bunyong Phakdeekitcharoen*[2], *Atiporn Ingsathit*[1,3,4] *and Vasant Sumethkul*[2]

[1]*Department of Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand,* [2]*Division of Nephrology, Department of Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand,* [3]*Excellence Center for Organ Transplantation, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand,* [4]*Department of Clinical Epidemiology and Biostatistics, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand*

OPEN ACCESS

Correspondence
Praopilad Srisuwarn,
psrisuwarn@gmail.com

Received: *25 May 2023*
Accepted: *14 February 2024*
Published: *26 February 2024*

Citation:
Srisuwarn P, Sutharattanapong N, Disthabanchong S, Kantachuvesiri S, Kitiyakara C, Phakdeekitcharoen B, Ingsathit A and Sumethkul V (2024) Incidence of De Novo Post-Transplant Malignancies in Thai Adult Kidney Transplant Recipients: A Single-Center, Population-Controlled, Retrospective Cohort Study at the Highest Volume Kidney Transplant Center in Thailand. Transpl Int 37:11614. doi: 10.3389/ti.2024.11614

Kidney transplant recipients (KTRs) are at increased risk of developing *de novo* post-transplant malignancies (PTMs), with regional differences in types with excess risk compared to the general population. A single-center, population-controlled, retrospective cohort study was conducted at a tertiary care center in Thailand among all adults who underwent their first kidney transplant from 1986 to 2018. Standardized incidence ratios (SIRs) of malignancy by age, sex, and place of residence were obtained using data from the National Cancer Registry of Thailand as population control. There were 2,024 KTRs [mean age, 42.4 years (SD 11.4); female patients, 38.6%] during 16,495 person-years at risk. Of these, 125 patients (6.2%) developed 133 *de novo* PTMs. The SIR for all PTMs was 3.85 (95% CI 3.22, 4.56), and for pooled solid and hematologic PTMs, it was 3.32 (95% CI 2.73, 3.99). Urothelial malignancies had the largest excess risk, especially in women [female SIR 114.7 (95% CI 66.8, 183.6); male SIR 17.5 (95% CI 8.72, 31.2)]. The next two most common cancers were non-Hodgkin's lymphoma

Abbreviations: BCC, Basal cell carcinoma; CI, Confident interval; CIF, Cumulative incidence functions; CNI, Calcineurin inhibitor; E, Expected; EBV, Epstein-Barr virus; HL, Hodgkin's lymphoma; HPV, Human papillomavirus; KDIGO, Kidney Disease Improving Global Outcomes; KTR, Kidney transplant recipient; NCI, National Cancer Institute; NHL, Non-Hodgkin's lymphoma; ICD-10, International classification of diseases 10; IQR, Interquartile range; O, Observed; PTM, Post-transplant malignancies; SIR, Standardized incidence ratio; SCC, Squamous cell carcinoma; SD, Standard deviation; Y, Year.

and skin cancer [SIR 20.3 (95% CI 13.6, 29.1) and 24.7 (95% CI 15.3-37.8), respectively]. Future studies are needed to identify the risk factors and assess the need for systematic screening among PTMs with excess risk in KTRs.

Keywords: kidney transplantation, cancer, adult, incidence, Thailand

INTRODUCTION

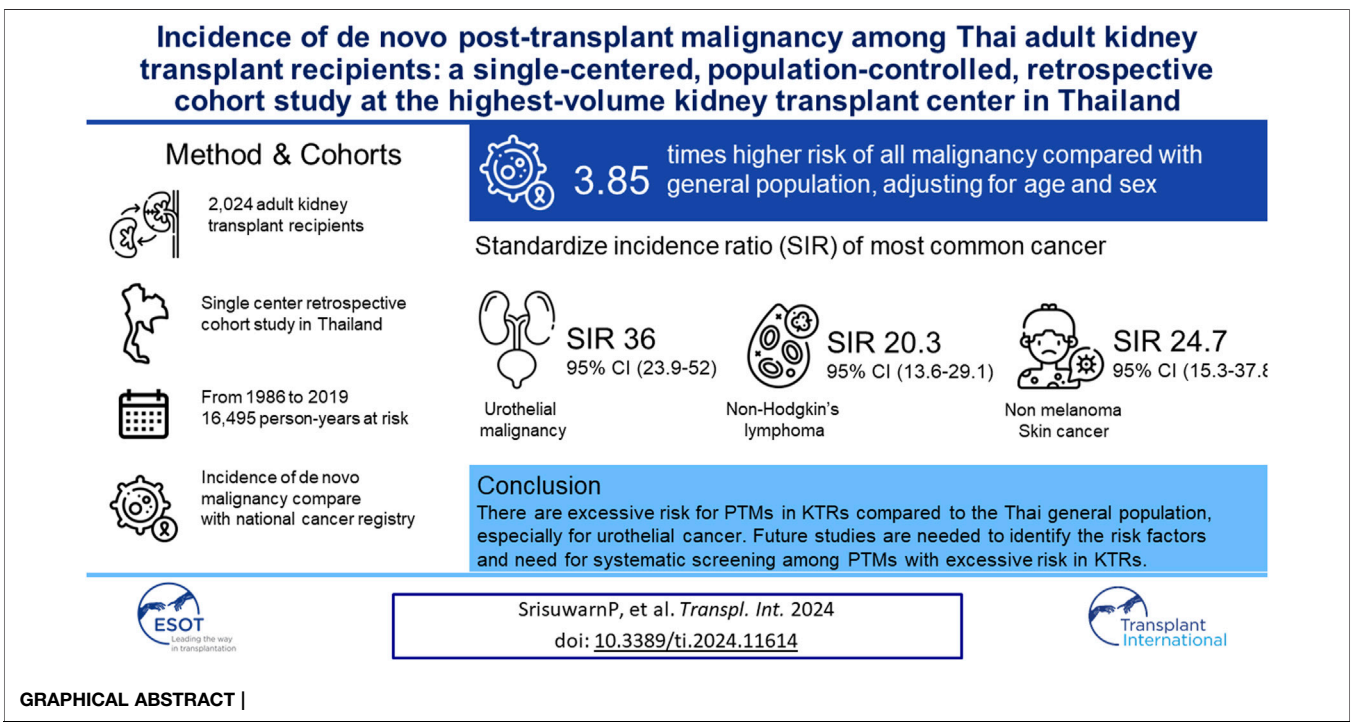
Post-transplant malignancy (PTM) is one of the most devastating long-term complications for kidney transplant recipients (KTRs), leading to death with a functioning graft [1]. The excess risk of PTMs in KTRs is 2.9–3.9 times that of the general population. The risk is even higher for virus-related cancers, such as Kaposi's sarcoma, post-transplant lymphoproliferative disorder, and non-melanoma skin cancer [2–7]. The excess risk is mainly due to immunosuppressive agents that increase vulnerability to oncogenic viral infection, disrupt the ability of the immune surveillance systems to detect and remove abnormal cells, and interfere with cell repair mechanisms [8]. However, the risk of each cancer may vary by geographical area due to site-specific environmental exposures and genetics.

Therefore, the incidence of PTMs among KTRs in each region must be estimated to allow policymakers to plan for appropriate service provision. To date, no study has estimated the excess risk of PTMs in Thai KTRs compared with the Thai general population. Thus, we aimed to estimate the incidence of PTMs in adult Thai KTRs at the highest-volume transplant center in Thailand.

PATIENTS AND METHODS

Study Design, Patients, and Setting

This was a single-center, retrospective cohort study conducted at Ramathibodi Hospital, a tertiary care university hospital that performs the highest volume of kidney transplants in the country, accounting for one-quarter of the cumulative kidney transplant surgeries in Thailand. This study included consecutive adult patients aged ≥18 years who received a first kidney transplant between 1 January 1986 and 30 July 2018 and had ≥1 month of follow-up. All recipients were followed up from the date of kidney transplantation to the date of a diagnosis of *de novo* incident cancer, all-cause death, graft failure, loss to follow-up, or administrative censoring on 31 December 2019, whichever occurred first. The exclusion criteria were cancer occurring after graft failure and cancer occurring before or ≤1 month following transplantation. The study was approved by the Institutional Review Board, Faculty of Medicine, Ramathibodi Hospital (MURA2022/503). Informed consent was not required due to the de-identification of patient data. This study was conducted in accordance with the tenets of the Declaration of Helsinki.



GRAPHICAL ABSTRACT |

Data Collection

Data were collected from three sources. First, incidence data for the Thai general population were obtained from the Thai National Cancer Institute's (NCI) nationwide cancer data registry. We chose to compare incident malignancy rates between our KTRs and the Thai general population between 2013 and 2015. We only selected the 2013–2015 period because the place of residence to be matched with that of our KTRs in the registry had been validated by cross-checking with the Ministry of Interior's National Civil Registration records [9]. Additionally, data after 2016 were not available when we conducted the analysis. Moreover, the national coverage of the Thai NCI has gradually grown since the establishment of the first population-based only on data from Chiangm Mai province in 1986 [10]. Thus, adjusting for calendar year using historical subnational coverage would have reduced our sample size and power to detect any significant results. Diagnoses were initially coded by registry personnel using the International Classification of Diseases for Oncology (ICD-O, third edition), and the coding demonstrated good reliability [9]. These codes were then transformed to the International Classification of Diseases, Tenth Revision (ICD 10) for analysis. Second, we collected baseline patient data from the Ramathibodi KTR database, including age, sex, region of residence, and type and date of transplantation. Third, we manually reviewed hospital electronic medical records to collect outcomes and the date of outcomes. Diagnoses of *de novo* PTMs were ascertained by histopathologic confirmation or compatible radiographic studies with serologic testing. These were then categorized according to the ICD-10.

Immunosuppressive Regimens

Immunosuppressive regimens for induction and maintenance therapy in KTRs were carefully selected based on the immunologic risks of the patients. Induction regimens included methylprednisolone with or without an interleukin-2 receptor antagonist or anti-thyroglobulin. The maintenance medications were mainly calcineurin inhibitor (CNI)-based regimens. A typical combination of these regimens before 2000 was cyclosporine-azathioprine-prednisolone, which gradually changed to tacrolimus-mycophenolate mofetil-prednisolone. Other regimens were used much less frequently, and they included CNI-mTOR inhibitor-prednisolone and CNI-prednisolone.

Cancer Screening and Surveillance in Kidney Transplant Candidates and Recipients

At our center, age-appropriate pre-transplant cancer screening and abdominal ultrasound have been performed since January 2013. Post-transplant cancer surveillance was opportunistic and consistent with standard cancer screening recommended for the general population [11].

Outcomes

The outcome was the standardized incidence ratio (SIR), which represents the excess risk of malignancy compared to the Thai general population.

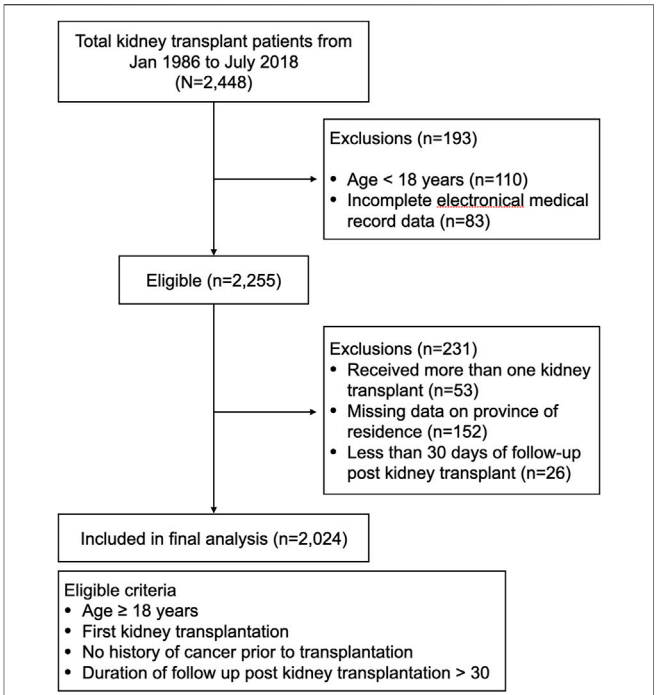


FIGURE 1 | Flowchart of patients in the study.

Statistical Analysis

Patient characteristics were analyzed descriptively. Continuous data are presented as mean (SD) or median (interquartile range), as appropriate. Categorical data are presented as frequencies (%).

The excess risk of *de novo* PTM in KTRs compared to the general population was estimated by SIR by indirect standardization of the Thai general population. Confidence intervals were estimated using the Poisson distribution. We selected the 2013–2015 data from the Thai NCI, which used the projected Thai population in mid-2014 based on the 2010 national population census. We defined the start of the time at risk as 1 month after the date of the kidney transplant to exclude non-*de novo* PTMs. We defined the end of the time at risk as incident *de novo* PTM, loss to follow-up, all-cause mortality, or administrative censoring at the end of the study period, whichever happened first. We also reported the incidence and SIRs stratified by sex, age at kidney transplant, duration of follow-up after kidney transplant, and transplant era of the top three cancers with the most excess risk. To avoid underestimating the incidence due to multiple *de novo* PTMs, if a second or third *de novo* PTM occurred, we generated time at risk from 1-month post-transplant to the date of the second or third incident PTM. Statistical analyses were performed using Stata 15.1 (StataCorp. 2017. College Station, TX). A non-null 95% confidence interval (CI) was considered significant.

RESULTS

Characteristics of the Kidney Transplant Recipients

During the 32-year period from January 1986 to July 2018, there were 2,448 kidney transplantations. After exclusions, a total of

TABLE 1 | Characteristics of all kidney transplants.

Characteristic	All kidney transplants
Total number	2,024
Female patients, *n* (%)	781 (38.6)
Deceased donor	998 (49.3)
Age at transplantation, mean ± SD, y	42.4 ± 11.4
Male patients	42.6 ± 11.7
Female patients	42.2 ± 11.0
Region of residence in Thailand, *n* (%)	
Central	1,273 (63.1)
North-eastern	210 (10.4)
Northern	162 (8.0)
Eastern	220 (10.9)
Southern	151 (7.5)
Total person-time-at-risk, y	16,382
Male patients	10,127
Female patients	6,254
Year of transplantation, *n* (%)	
Before 1989	15 (0.7)
1989–1998	302 (14.9)
1999–2008	534 (26.4)
2009–2018	1,173 (58.0)
Length of follow-up in years, *n* (%)	
<1	82 (4.0)
1–4	706 (34.9)
5–9	618 (30.5)
10–14	313 (15.5)
15–19	178 (8.8)
≥20	127 (6.3)
Length of follow-up, median (IQR), y	6.35 (3.21, 11.5)
Male patients	6.39 (3.32, 11.6)
Female patients	6.19 (3.15, 11.4)

Abbreviations: IQR, interquartile range; SD, standard deviation.

2,024 cases were included in the final analysis, contributing to 16,495 patient-years of risk time in the follow-up (**Figure 1**; **Table 1**). The mean age at transplantation was 42.4 years (SD 11.4), and 38.6% of the subjects were women (**Table 1**). The median follow-up time was 6.4 years (interquartile range 3.21, 11.5) (**Table 1**).

Incidence of *De Novo* Post-Transplant Malignancy

A total of 133 *de novo* PTMs were identified in 125 (6.2%) patients. In total, eight (6%) patients developed secondary cancer, including 2 non-melanoma skin cancers, 2 liver and biliary cancers, 1 prostate cancer, 1 kidney cancer, 1 urothelial cancer, and 1 colorectal cancer. The incidence by type of PTMS, age at diagnosis, and time from transplantation to diagnosis are shown in **Table 2**. The most common PTM was urothelial cancer (n = 28), accounting for one-fifth of all PTMs in the cohort, followed by non-Hodgkin's lymphoma (NHL) at 22% and non-melanoma skin cancer at 16%.

Table 3 shows the SIRs adjusted for age, sex, and place of residence, comparing the KTRs to the Thai general population. The excess risk of *de novo* PTMs in KTRs was nearly fourfold compared with the general population. The top three cancers with significantly increased risk were consistent across genders. This risk was more pronounced for urothelial cancer, NHL, and non-melanoma skin cancer, all of which had more than a 20-fold excess risk. In particular, urothelial cancer showed the highest significant excess risk in women with a SIR of 114.7 (95% CI 66.8, 183.6). The risk of the most common cancers in the Thai general population, including lung, colorectal, breast, ovarian, and cervical cancers was comparable. The SIR for prostate cancer was significantly increased [SIR 8.11 (95% CI 3.71, 15.4)]. The SIR calculations considering only the first *de novo* PTM are shown in **Supplementary Table S1**.

Table 4 shows the SIRs for all PTMs stratified by age at transplant, duration of follow-up, and era of transplantation. The excess risk in KTRs compared to the general population by age at transplant was greatest in KTRs aged 45–64 years, and there was a comparable risk in KTRs transplanted at <20 years of age. By duration of follow-up, there was a decreasing trend over the duration of follow-up until the risk was comparable to the general population at 15 years or more of follow-up.

Table 5 shows the incidence rates and SIRs for the top three most common PTMs in Thai KTRs, which were urothelial cancer, NHL, and non-melanoma skin cancer, stratified by age at transplant, duration of follow-up, and era of transplant. All three cancers showed no excess risk in KTRs aged ≥65 years at transplantation. For urothelial cancer, age at transplant between 20 and 64 years old showed significant excess risk with the greatest excess between 45–64 years old [SIR 28.4 (95% CI 17.1, 44.4)], and duration of follow-up showed the greatest significant excess risk between 1 and 5 years of follow-up. There was still a significant excess risk at ≥20 years of follow-up. NHL had the greatest excess risk by age at transplant in KTRs aged less than 20 years at transplant [SIR 362 (95% 9.15, 2,015)], and the excess risk decreased with increasing age at transplant. There was a significant excess risk of NHL at all follow-up periods, with the risk decreasing over time. For non-melanoma skin cancer, the greatest excess risk according to age at transplantation was between 20 and 44 years old [SIR 1,820 (95% CI 46.1, 10,139)], and there was excess risk up to >20 years of follow-up.

Supplementary Figures S1–S3 show the cumulative incidence functions (CIF) of the three most common cancers adjusted for competing risks. After adjusting for all-cause death, graft failure, loss to follow-up, or administrative censoring, the odds of developing any of the three cancers were mostly low, at less than 5% over a period of nearly 20 years post-kidney transplantation.

DISCUSSION

We conducted the largest study of the excess risk of *de novo* PTMs in Thai KTRs at the highest volume transplant center in Thailand, accounting for a quarter of all historic kidney transplants in Thailand. The excess risk of *de novo* PTMs in our KTRs was approximately four times that of the general population after adjusting for age, sex, and region of residence, which is similar to the excess risk reported in other East Asian countries [2–4]. Furthermore, the top three cancers with excess risk among KTRs were urothelial cancer, NHL, and non-melanoma skin cancer.

TABLE 2 | Distribution and clinical characteristics of malignancies following kidney transplantation by sex.

	Male patients	Female patients	All	Percentage	Age at transplantation, mean ± SD, y	Age at diagnosis of PTM, mean ± SD, y	Time from transplant to PTM, median (IQR), y
Solid							
Urothelial	11	17	28	35.0	49.7 ± 9.93	58.7 ± 12.7	6.63 (4.55, 10.4)
Prostate	9		9	11.3	56.3 ± 7.22	68.8 ± 7.32	11.8 (8.70, 13.0)
Liver and bile duct	5	4	9	11.3	46.0 ± 11.2	53.5 ± 14.1	4.96 (3.15, 9.34)
Breast		8	8	10.0	47.3 ± 7.31	53.0 ± 7.92	5.72 (2.64, 9.03)
Colorectal	2	4	6	7.5	47.8 ± 9.91	62.8 ± 7.80	13.0 (12.2, 14.4)
Trachea, lung, bronchus	5	1	6	7.5	57.0 ± 6.04	61.4 ± 6.73	4.67 (3.24, 6.23)
Other solid malignancies, unspecified	1	1	2	2.5	54.8 ± 5.59	58.7 ± 6.54	3.79 (3.12, 4.46)
Cervix		3	3	3.8	57.1 ± 2.77	61.5 ± 5.53	3.49 (1.89, 7.85)
Gallbladder	1	0	1	1.3	38.6	40.5	1.96
Kidney	3	0	3	3.8	55.0 ± 6.77	62.9 ± 4.29	9.36 (4.43, 9.94)
Thyroid	0	2	2	2.5	49.6 ± 23.8	53.1 ± 21.3	3.43 (1.64, 5.22)
Stomach	1	0	1	1.3	63.7	77.0	13.3
Ovary		1	1	1.3	60.9	63.3	2.43
Uterus, part unspecified		1	1	1.3	35.6	47.4	11.8
Total	38	42	80	100			
Hematologic							
NHL							
Monomorphic B cell	15	8	23	71.9	47.1 ± 10.2	57.2 ± 11.1	11.4 (4.11, 15.4)
Polymorphic	1	3	4	12.5	49.0 ± 12.7	54.6 ± 11.0	4.16 (4.11, 4.57)
Monomorphic T cell	2	0	2	6.3	37.3 ± 13.7	44.5 ± 19.6	4.84 (1.61, 12.7)
Leukemia, all types	1	1	2	6.3	54.1 ± 6.52	58.4 ± 6.23	4.36 (4.16, 4.57)
HL	1	0	1	3.1	52.3	60.1	7.78
Total	20	12	32	100			
Skin							
SCC	12	4	16	76.2	50.5 ± 7.31	63.0 ± 7.02	10.7 (7.10, 18.8)
BCC	4	1	5	23.8	52.4 ± 14.4	62.4 ± 8.73	7.62 (3.15, 15.3)
Total non-melanoma	16	5	21	100			

Abbreviations: BCC, basal cell carcinoma; HL, Hodgkin's lymphoma; IQR, interquartile range; NHL, non-Hodgkin's lymphoma; PTM, post-transplant malignancy; SCC, squamous cell carcinoma; SD, standard deviation.

The subgroup of KTRs with the greatest excess risk of one type of PTM were female KTRs with urothelial cancer, who had a greater than 100-fold excess risk.

KTRs are susceptible to new viral infections or the reactivation of a latent one. The risk of oncogenic virus-related cancers, such as Kaposi's sarcoma, NHL, and lip cancer, has been reported to be up to 10- to 100 times higher in KTRs than in the end-stage renal disease population [6, 7]. In the present study, urothelial cancer, NHL, and non-melanoma skin cancer all showed a more than 20-fold significant excess risk, and these have been associated with infection with BK virus or human papillomavirus (HPV), Epstein-Barr virus (EBV), and human papillomavirus infection, respectively [12–14]. Conversely, cervical cancer, associated with HPV infection, was not significant. Hepatitis B infection has been estimated to affect up to 6%–9% of the general Thai population born before the national hepatitis B vaccination program was rolled out in 1992 [15]. Unfortunately, the excess risk in KTRs of hepatocellular carcinoma associated with hepatitis B or C virus infection was uninterpretable in our study because it was coded together with bile duct cancer in some of our data sources.

In non-oncogenic virus-related cancers, susceptible KTRs with genetic risk factors or exposure to carcinogens may have preferential cancer cell transformation and growth due to immunosuppressive agents that affect DNA repair, immune surveillance, and pro- or anti-inflammatory cytokines [16, 17]. In the present study, we found just over a 10-fold excess risk for kidney cancer. Goh et al. reported that long dialysis vintage and native renal cysts predicted an increased risk of this cancer, which may be due to prolonged exposure to uremic toxin-induced oncogenic changes of epithelial cells [18]. With regard to prostate cancer, we are not aware of any pathophysiologic mechanism related to KTRs. The significance of the finding may be due to more opportunistic screening of prostate-specific antigen testing by urologists following up on KTR patients to find *de novo* PTMs than in the general population, or random sampling error.

With regard to urothelial cancer, we found that excess risk was observed in both sexes, but the excess risk was much more pronounced in female KTRs at more than 100-fold. Similar excess risks have been reported in population-based studies in Korea, Hong Kong, and particularly Taiwan, where the SIR for urothelial cancer was also greater than 100-fold [2–4]. In Europe, Australia, New Zealand, and the United States, although the absolute risk seems to be higher in male KTRs, the SIRs remain higher in female KTRs (SIRs 2.7–6.9), but they have been reported to be much higher in Asia [19, 20]. The reasons for

TABLE 3 | Standardized incidence ratios of different types of malignancies in kidney transplant patients by sex.

Cancer site	ICD-10	Male patients		Female patients		All	
		O/E	SIR (95% CI)	O/E	SIR (95% CI)	O/E	SIR (95% CI)
Prostate	C61	9/1.109145	8.11 (3.71, 15.4)*				
Breast	C50			8/5.166225	1.56 (0.67, 3.08)		
Ovary	C56			1/0.7406286	1.35 (0.36, 5.07)		
Cervix	C53			3/1.728333	1.73 (0.86, 4.91)		
Bronchus, lung, trachea	C33, C34	5/4.185616	1.20 (0.39, 2.79)	1/1.232264	0.81 (0.02, 4.52)	6/5.41788	1.11 (0.41, 2.41)
Stomach	C16	1/0.8211308	1.22 (0.03, 6.79)	0/0.4394963	0.0 (0.0, 6.82)	1/1.260627	0.79 (0.02, 4.42)
Liver and bile duct	C22, C24	5/6.909814	0.73 (0.24, 1.55)	4/1.381054	2.90 (0.79, 7.42)	9/8.290868	1.09 (0.50, 2.06)
Gallbladder	C23	1/0.0948561	10.5 (0.27, 58.7)	0/0.0948561	0 (0.0, 27.1)	1/0.2053207	4.87 (0.12, 27.1)
Colorectal	C18 - C20	2/3.178986	0.63 (0.08, 2.27)	4/1.370327	2.92 (0.80, 7.47)	6/4.549313	1.32 (0.48, 2.87)
Kidney	C64	3/0.2353302	12.7 (2.63, 37.3)*	0/0.0575237	0.0 (0.0, 52.1)	3/0.2928539	10.2 (2.11, 29.9)*
Urothelial	C65 - C67	11/0.6300718	17.5 (8.72, 31.2)*	17/0.1482415	114.7 (66.8, 183.6)*	28/0.6227172	36.0 (23.9, 52.0)*
Thyroid	C73	0/0.2594859	0 (0.0, 11.5)	2/0.5199386	3.85 (0.47, 13.9)	2/0.7794246	2.57 (0.31, 9.27)
Uterus, part unspecified	C55			1/0.0882458	11.3 (0.29, 63.1)		
Other solid malignancies: unspecified	O & U	1/1.03719	0.96 (0.02, 5.37)	1/0.3765939	2.66 (0.07, 14.8)	2/1.413784	1.42 (0.17, 5.11)
All solid malignancies		38/18.461626	2.06 (1.46, 2.83)*	42/13.343727	3.15 (2.27, 4.26)*	80/31.805353	2.52 (1.99, 3.13)*
NHL**	C82-85, C96	18/0.9139875	19.7 (11.7, 31.1)*	11/0.5157974	21.3 (10.6, 38.2)*	29/1.429785	20.3 (13.6, 29.1)*
HL	C81	1/0.0270835	36.9 (0.94, 205.7)	0/0.0121523	0 (0.0, 246.5)	1/0.0392358	25.5 (0.65, 142.0)
Leukemia	C91, C92-C94	1/0.3327671	3.01 (0.08, 16.7)	1/0.136444	7.33 (0.19, 40.8)	2/0.4692111	4.26 (0.52, 15.4)
All hematologic malignancies		20/1.2738381	15.7 (9.59, 24.2)*	12/0.6643937	18.1 (9.33, 31.6)*	32/1.9382318	16.5 (11.3, 23.3)*
Non-melanoma skin cancer***	C44	16/0.5000404	32.0 (18.3, 52.0)*	5/0.3501561	14.3 (4.64, 33.3)*	21/0.8501965	24.7 (15.3, 37.8)*
All solid and hematologic malignancies		58/19.735464	2.94 (2.23, 3.80)*	54/14.008121	3.86 (2.90, 5.03)*	112/33.743585	3.32 (2.73, 3.99)*
All cancers		74/20.235504	3.66 (2.87, 4.59)*	59/14.358277	3.76 (2.82, 4.91)*	133/34.593781	3.85 (3.22, 4.56)*

*Notes: *Significant results at 95% confidence interval. ** Includes monomorphic B cells, and polymorphic, monomorphic T cells. *** Includes squamous cell carcinoma and basal cell carcinoma. The total risk time for the cohort was 16,495 person-years for standardized incidence ratio calculations.*
Abbreviations: CI, confidence interval; E, expected; HL, Hodgkin's lymphoma; ICD-10, international classification of diseases 10; NHL, non-Hodgkin's lymphoma; O, observed; SIR, standardized incidence ratio.

TABLE 4 | Standardized incidence ratios for all malignancies stratified by age at transplantation, duration of follow-up, and year of transplantation.

Parameter	Person-years	O/E	SIR (95% CI)
Age at transplant, y			
<20	191.9535	1/0.0729803	13.7 (0.35, 76.3)
20–44	9,859.359	38/14.12602	2.69 (1.90, 3.69)
45–64	6,247.127	88/27.16186	3.24 (2.60, 3.99)
≥ 65	196.1123	6/1.928599	3.11 (1.14, 6.77)
Duration of follow-up, y			
<1	31.59206	6/0.069681	86.1 (31.6, 187)
1–5	2,100.715	39/4.575053	8.52 (6.06, 11.7)
5–10	4,465.733	39/11.0498	3.53 (2.51, 4.83)
10–15	3,839.713	24/10.8994	2.20 (1.41, 3.28)
15–19	3,067.138	14/8.118509	1.72 (0.94, 2.89)
≥20	2,989.662	11/8.577023	1.28 (0.64, 2.30)
Year of transplant			
Before 1989	191.2663	0/0.4592726	0
1989–1998	4,544.882	38/12.89968	2.95 (2.09, 4.04)
1999–2008	6,207.307	57/16.68373	3.42 (2.59, 4.43)
2009–2018	5,551.097	38/13.24678	2.87 (2.03, 3.94)

Abbreviations: CI, confidence interval; E, expected; O, observed; SIR, standardized incidence ratio.

this difference between the sexes remain to be elucidated. Of note, the majority of urothelial cancers in our KTRs were upper tract cancers, similar to the Taiwanese and Korean KTRs [21, 22]. The main risk factors contributing to this cancer in Taiwanese KTRs were exposure to herbal remedies containing Aristolochia and heavy metals in groundwater [22]. In the present study, we suspect that local Thai/Chinese herbal remedies may have been a contributing factor, although we did not collect data on such herbal remedies in this retrospective study. The hypothesis of a link with these herbal remedies is plausible because up to 45% of Thai patients with chronic kidney disease reported using local Thai/Chinese herbal remedies in the previous year [23]. Although the active ingredients of Thai/Chinese herbal remedies are not well documented, at least one herb, *Aristolochia acuminata,* known as "Krai-Krue," has been identified by sampling polyherbal pills from pharmacies in Bangkok [24]. Furthermore, unregulated local Thai/Chinese herbal products may be contaminated with toxic heavy metals and analgesic agents, posing additional risks to users [25]. However, further study of these possible etiologic factors in Thai KTRs is needed to estimate the increased risk.

TABLE 5 | Incidence rates per 100000 person-years at risk and standardized incidence ratios of selected cancers.

	Cancer type								
	Urothelial cancer			Non-Hodgkin's lymphoma			Non-melanoma skin cancer		
	No. of events	Incidence rate per 100,000 person-years at risk (95% CI)	SIR (95% CI)	No. of events	Incidence rate per 100,000 person-years at risk (95% CI)	SIR (95% CI)	No. of events	Incidence rate per 100,000 person-years at risk (95% CI)	SIR (95% CI)
Age at transplant									
<20	0		0	1	521 (73, 3,698)	362 (9.15, 2,015)*	0	0	0
20–44	8	81 (41, 162)	18.7 (8.09, 36.9)*	11	112 (62, 201)	25.5 (12.8, 45.7)*	5	51 (21, 122)	1,820 (46.1, 10,139)*
45–64	19	306 (195, 480)	28.4 (17.1, 44.4)*	16	256 (157, 418)	19.2 (11.0, 31.1)*	15	240 (145, 398)	28.5 (16.0, 47.0)*
≥65	1	371 (52, 2,640)	15.3 (0.39, 85.4)	1	510 (72, 3,620)	17.4 (0.44, 96.8)	1	510 (72, 3,620)	22.3 (0.57, 124)
Duration of follow-up, y									
<1	0		0	4	12,661 (4,752, 33,735)	1,903 (518, 4,872)*	1	3,165 (446, 22,471)	915 (23.2, 5,100)*
1–5	8	381 (190, 761)	86.2 (37.2, 170)*	6	286 (128, 635)	42.5 (15.6, 92.4)*	2	95 (24, 381)	30.1 (3.65, 109)*
5–10	13	291 (169, 501)	51.8 (27.6, 88.6)*	4	89.6 (34, 239)	12.0 (3.27, 30.7)*	7	157 (75, 329)	39.5 (15.9, 81.5)*
10–15	2	52 (13.0, 208)	7.29 (0.88, 26.3)	8	208 (104, 417)	23.9 (10.3, 47.1)*	2	52 (13, 208)	10.5 (1.27, 38.0)*
15–19	2	65 (16, 261)	11.8 (1.43, 42.5)*	7	228 (109, 479)	28.5 (11.5, 58.8)*	5	163 (68, 392)	34.6 (11.2, 80.8)*
≥20	3	100 (32, 311)	13.8 (2.84, 40.3)*	0		0	4	134 (50, 356)	25.0 (6.81, 64.0)*
Year of transplant									
Before 1989	0		0	0		0	0		0
1989–1998	8	176 (88, 352)	25.4 (11.0, 50.0)*	6	132 (59, 294)	15.0 (5.50, 32.6)*	9	198 (103, 381)	38.9 (17.8, 73.8)*
1999–2008	14	226 (134, 381)	37.5 (20.5, 62.9)*	15	242 (146, 401)	29.9 (16.7, 49.3)*	6	97 (43, 215)	20.3 (7.46, 44.3)*
2009–2018	6	108 (49, 241)	20.7 (7.59, 45.0)*	8	144 (72, 288)	19.8 (8.56, 39.1)*	6	108 (49, 241)	29.0 (10.6, 63.1)*

*Notes: *Significant results at 95% confidence interval.*
Abbreviations: CI, confidence interval; E, expected; O, observed; SIR, standardized incidence ratio; Y, year.

The excess risk of hematologic malignancies in KTRs is well-established. Epstein-Barr virus infection, along with the administration of T cell-depleting agents, can lead to the early development of post-transplant lymphoproliferative disorders (PTLD) [26]. In Asia, late-onset PTLD, defined as >1 year, was more common and was associated with an increased proportion of EBV-negative PTLD [27, 28]. Current KDIGO guidelines suggest EBV serologic testing before transplantation and monitoring for EBV reactivation in high-risk EBV mismatch recipients. Immunosuppression is suggested to be reduced if the EBV viral load increases during the follow-up [29]. Although no standard chemoprophylaxis regimen for EBV exists, a cohort study of 4,765 organ transplant recipients reported that no participant receiving a rituximab-containing induction regimen developed PTLD [30]. Reducing the dose of T cell-depleting agents was also found to reduce the risk of EBV reactivation, and

showed a trend toward reducing the incidence of early PTLD without compromising graft survival over 2 years of follow-up [31].

The three most common skin cancers reported in KTRs are melanoma, non-melanoma, and Kaposi's sarcoma, and this has been shown to be a significantly increased risk compared to the general population worldwide [32]. In the present study, *de novo* incident cases of non-melanoma skin cancer were observed while neither melanoma nor Kaposi's sarcoma occurred. The risk of developing non-melanoma skin cancer can be reduced by educating patients about lifestyle modifications, such as smoking cessation and reducing exposure to ultraviolet light. In addition, in patients with a history of cancer, the physician may consider avoiding the prescription of azathioprine or the use of high-dose mycophenolate and may prefer to prescribe an mTOR inhibitor instead if the patient's condition is appropriate [33, 34].

In general, the excess risk of PTMs rises in the first year post-transplantation, after which it falls over time. Highly elevated excess risk in the early post-transplantation period may not be truly *de novo* cancers, but rather cancers that developed prior to transplantation that were missed by preoperative screening. Furthermore, it is noteworthy that not all cancer types behave similarly. Krishnan et al. found that urinary tract cancer, melanoma, and post-transplant lymphoproliferative disease were the three most common incident cancers in the first year post-transplantation. In addition, incident lung and colorectal cancers were less common but were at a more advanced stage at the time of diagnosis [35].

Early detection of *de novo* PTM in KTRs through systematic cancer screening may provide a window of opportunity for effective early cancer treatment. Regarding the current cancer screening program in Thailand, the Thai Ministry of Public Health offers a 5-year PAP smear, bi-annual fecal occult blood, and opportunistic mammogram as population cancer screenings [11]. However, cancer screening among KTRs at a tertiary care center may be more intensive because specialists are likely to order screening tests that comply with international society recommendations [36]. This practice is deemed to be in line with the clinical practice guidelines of transplant organizations, which suggest that screening of KTRs should follow the provisions for systematic screening in the general population, with additional screening for other common cancers seen in KTRs, such as skin cancer [37]. Although this policy may seem to help detect common cancers, it may not cause survival benefits and may not be cost-effective due to the decreased life expectancy in KTRs, or it may inadvertently cause harm due to false-positive results, leading to over-investigation and psychological distress [38, 39].

The extremely high excess risk of urothelial cancer in KTRs in our study highlights the need for future action. Despite the aforementioned limited benefit of systematic screening programs in the general population, screening may be beneficial if the cancer incidence is high, the screened candidate has a high risk of cancer with a low risk of graft failure, and the screening tools are low-cost with high sensitivity [40]. From the results of the present study, we suggest that the special KTR subpopulation of women aged 45–65 years with an extremely high excess risk of urothelial cancer may be an initial candidate subgroup for systematic screening, especially in those who have been exposed to carcinogens, such as exposure to aromatic amines (e.g., benzidine and β-naphthylamine), high-dose cyclophosphamide, arsenic from contaminated drinking water, and HPV or BK viral infection [22, 41]. The high incidence of upper tract cancers may require urinalysis and cytology in combination with contrast-enhanced computed tomography of the kidneys, ureters, and bladder as the primary screening test. Abdominal ultrasound should not be used in this setting as it has low sensitivity for detecting early-stage disease [42]. Of note, if the patient has aristolochic nephropathy, the most effective way to improve the cancer outcome may be prophylactic bilateral nephrectomy, followed by annual surveillance cystoscopy and urine cytology [43, 44]. Due to the widespread use of unregulated Thai/Chinese medicinal herbs in the Thai population, we suggest that, if possible, a urothelial sample be obtained during the surgical procedure for a kidney transplant to test it for aristolochic acid-adducted DNA, which is a hallmark biomarker of aristolochic acid exposure [45]. This may identify very high-risk patients, allowing for appropriate management.

Strengths and Limitations

There are strengths and limitations to our study. One strength is that this is the first study to demonstrate the excess *de novo* cancer risk among the Thai KTRs in a large sample size with a long period of follow-up for most of the KTRs. In addition, all pathologic diagnoses were confirmed by retrospective chart review, and the stratification of the excess incidence based on subnational regional risk in the Thai general population adjusted for different underlying risk factors in each subnational region. However, there are also limitations. One limitation is the use of the 2013–2015 Thai general population. We would have preferred to adjust our statistics for excess risk in KTRs compared to the Thai general population incidence by calendar year. However, there is a limitation as we have mentioned in the methodology section. The reasons for potential bias in our estimated standardized incidence ratio due to our choice of Thai general population comparison group can be divided into differences in age and sex distribution in the Thai population in mid-2014 and differences in cancer incidence between 2013 and 2015 independent of age and sex (e.g., changes in the prevalence of other cancer risk factors or national/subnational systematic cancer screening) compared with an ideal comparison group adjusting for age, sex, and cancer incidence by calendar year. The age structure of the Thai population has changed in recent years toward an aging society [46]. Due to the association of older age with higher cancer incidence in most PTMs, recent calendar year data with an older population may have higher cancer incidence, creating a bias in our estimates toward lower SIRs. The incidence of different types of cancer has changed at different rates. For example, cancers of the liver, lung, stomach, and Hodgkin's lymphoma have had declining incidence trends, while cancers of the colon, breast, ovary, prostate, kidney, and non-Hodgkin's lymphoma have had increasing trends. Hence, the expected directions of bias are upward bias in SIRs for the former group of cancers with decreasing trends and downward bias for those with increasing trends. Given the strong magnitudes of the strength of association at the lower bounds

of the 95% CIs for cancers with known viral etiologies, which are known to be more likely in KTRs due to long-term maintenance immunosuppression, we suggest that there are truly significantly greater risks of these types of PTMs, regardless of bias due to choice of population for indirect standardization and other methods of adjusting for confounders [47]. We also acknowledge that the lack of standardized mortality ratios in our study may not allow for the interpretation of the data as to whether Thai KTRs are genuinely an appropriate, special, and very high-risk population that requires service provision for systematic screening for some cancers. Only cancers with significant excess risk, adjusted for confounders, compared to the Thai general population are attractive targets for systematic screening service provision. This issue should be investigated in future studies, but such studies may be challenging due to historical vital statistics data quality issues [9].

CONCLUSION

The risk of *de novo* cancer increased after kidney transplantation in Thai adults, especially oncogenic virus-related cancers. The post-transplant malignancies with the greatest excess risk, such as urothelial cancer, warrant further investigation of risk factors to establish whether a systematic screening program is needed for any special, very high-risk subgroups of KTRs.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The study was approved by the Institutional Review Board, Faculty of Medicine, Ramathibodi Hospital (MURA2022/503). Needing informed consent was waived due to de-identification of the patients' data. This study was performed in accordance with the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

PS collected data. PS, NS, and VS designed the study. PS analyzed the data. PS, NS, and VS wrote the manuscript. SD, SK, CK, BP, and AI conceptualized and critically reviewed the study. All authors contributed to the article and approved the submitted version.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

ACKNOWLEDGMENTS

We extend our sincere gratitude to the dedicated staff at the Thai National Cancer Institute for generously providing access to the invaluable Thai National Cancer Registry data. Special appreciation goes to Dr. Suchin Woawichawong and the Department of Pathology at Ramathibody Hospital for their invaluable guidance during the tissue histology review process. Additionally, we express our thanks to Dr. Anthony Tan for his meticulous editing of the English language and insightful statistical advice.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2024.11614/full#supplementary-material

Supplementary Figure S1 | Cumulative incidence functions (cif) of all urothelial cancers.

Supplementary Figure S2 | Cumulative incidence functions (cif) of all non-Hodgkin's lymphomas.

Supplementary Figure S3 | Cumulative incidence functions (cif) of non-melanoma skin cancer.

Supplementary Table S1 | Standardized incidence ratios of different types of first *de novo* malignancy in post-kidney transplant patients by sex.

REFERENCES

1. Ying T, Shi B, Kelly PJ, Pilmore H, Clayton PA, Chadban SJ. Death After Kidney Transplantation: An Analysis by Era and Time Post-Transplant. *J Am Soc Nephrol* (2020) 31(12):2887–99. Epub 20200909. doi:10.1681/ASN.2020050566
2. Cheung CY, Lam MF, Chu KH, Chow KM, Tsang KY, Yuen SK, et al. Malignancies After Kidney Transplantation: Hong Kong Renal Registry. *Am J Transpl* (2012) 12(11):3039–46. Epub 20120806. doi:10.1111/j.1600-6143.2012.04209.x
3. Jeong S, Lee HS, Kong SG, Kim DJ, Lee S, Park MJ, et al. Incidence of Malignancy and Related Mortality After Kidney Transplantation: A Nationwide, Population-Based Cohort Study in Korea. *Sci Rep* (2020) 10(1):21398. Epub 2020/12/10. doi:10.1038/s41598-020-78283-5
4. Yeh CC, Khan A, Muo CH, Yang HR, Li PC, Chang CH, et al. De Novo Malignancy After Heart, Kidney, and Liver Transplant: A Nationwide Study in Taiwan. *Exp Clin Transpl* (2020) 18(2):224–33. Epub 20200304. doi:10.6002/ect.2019.0210
5. Benoni H, Eloranta S, Dahle DO, Svensson MHS, Nordin A, Carstens J, et al. Relative and Absolute Cancer Risks Among Nordic Kidney Transplant Recipients-A Population-Based Study. *Transpl Int* (2020) 33(12):1700–10. Epub 20200925. doi:10.1111/tri.13734
6. Vajdic CM, McDonald SP, McCredie MR, van Leeuwen MT, Stewart JH, Law M, et al. Cancer Incidence Before and After Kidney Transplantation. *JAMA* (2006) 296(23):2823–31. doi:10.1001/jama.296.23.2823
7. Yanik EL, Clarke CA, Snyder JJ, Pfeiffer RM, Engels EA. Variation in Cancer Incidence Among Patients With Esrd During Kidney Function and Nonfunction Intervals. *J Am Soc Nephrol* (2016) 27(5):1495–504. Epub 20151112. doi:10.1681/ASN.2015040373
8. Sprangers B, Nair V, Launay-Vacher V, Riella LV, Jhaveri KD. Risk Factors Associated With Post-Kidney Transplant Malignancies: An Article From the Cancer-Kidney International Network. *Clin Kidney J* (2018) 11(3):315–29. Epub 2018/06/27. doi:10.1093/ckj/sfx122

9. Sirirungreung A, Buasom R, Jiraphongsa C, Sangrajrang S. Data Reliability and Coding Completeness of Cancer Registry Information Using Reabstracting Method in the National Cancer Institute: Thailand, 2012 to 2014. *J Glob Oncol* (2018) 4:1–9. doi:10.1200/JGO.17.00147
10. Insamran WPA, Supattagron P, Chiawiriyabunya I, Namthaisong K, Wongsena K, Puttawibul P, et al. *Cancer in Thailand Vol.Ix, 2013-2015* (2018).
11. Insamran W, Sangrajrang S. National Cancer Control Program of Thailand. *Asian Pac J Cancer Prev* (2020) 21(3):577–82. Epub 20200301. doi:10.31557/APJCP.2020.21.3.577
12. Cantalupo PG, Katz JP, Pipas JM. Viral Sequences in Human Cancer. *Virology* (2018) 513:208–16. Epub 20171105. doi:10.1016/j.virol.2017.10.017
13. Manole B, Damian C, Giusca SE, Caruntu ID, Porumb-Andrese E, Lunca C, et al. The Influence of Oncogenic Viruses in Renal Carcinogenesis: Pros and Cons. *Pathogens* (2022) 11(7):757. Epub 20220702. doi:10.3390/pathogens11070757
14. Opelz G, Daniel V, Naujokat C, Dohler B. Epidemiology of Pretransplant Ebv and Cmv Serostatus in Relation to Posttransplant Non-Hodgkin Lymphoma. *Transplantation* (2009) 88(8):962–7. doi:10.1097/TP.0b013e3181b9692d
15. Posuwan N, Wanlapakorn N, Sintusek P, Wasitthankasem R, Poovorawan K, Vongpunsawad S, et al. Towards the Elimination of Viral Hepatitis in Thailand by the Year 2030. *J Virus Erad* (2020) 6(3):100003. Epub 20200627. doi:10.1016/j.jve.2020.100003
16. Herman M, Weinstein T, Korzets A, Chagnac A, Ori Y, Zevin D, et al. Effect of Cyclosporin a on DNA Repair and Cancer Incidence in Kidney Transplant Recipients. *J Lab Clin Med* (2001) 137(1):14–20. doi:10.1067/mlc.2001.111469
17. Morteau O, Blundell S, Chakera A, Bennett S, Christou CM, Mason PD, et al. Renal Transplant Immunosuppression Impairs Natural Killer Cell Function *In Vitro* and *In Vivo*. *PLoS One* (2010) 5(10):e13294. Epub 2010/10/23. doi:10.1371/journal.pone.0013294
18. Goh A, Vathsala A. Native Renal Cysts and Dialysis Duration Are Risk Factors for Renal Cell Carcinoma in Renal Transplant Recipients. *Am J Transpl* (2011) 11(1):86–92. Epub 20101025. doi:10.1111/j.1600-6143.2010.03303.x
19. Stewart JH, Buccianti G, Agodoa L, Gellert R, McCredie MR, Lowenfels AB, et al. Cancers of the Kidney and Urinary Tract in Patients on Dialysis for End-Stage Renal Disease: Analysis of Data From the United States, Europe, and Australia and New Zealand. *J Am Soc Nephrol* (2003) 14(1):197–207. Epub 2002/12/31. doi:10.1097/01.asn.0000039608.81046.81
20. Kasiske BL, Snyder JJ, Gilbertson DT, Wang C. Cancer After Kidney Transplantation in the United States. *Am J Transpl* (2004) 4(6):905–13. doi:10.1111/j.1600-6143.2004.00450.x
21. Yu J, Lee CU, Kang M, Jeon HG, Jeong BC, Seo SI, et al. Incidences and Oncological Outcomes of Urothelial Carcinoma in Kidney Transplant Recipients. *Cancer Manag Res* (2019) 11:157–66. Epub 2019/01/15. doi:10.2147/CMAR.S185796
22. Wu MJ, Lian JD, Yang CR, Cheng CH, Chen CH, Lee WC, et al. High Cumulative Incidence of Urinary Tract Transitional Cell Carcinoma After Kidney Transplantation in Taiwan. *Am J Kidney Dis* (2004) 43(6):1091–7. Epub 2004/05/29. doi:10.1053/j.ajkd.2004.03.016
23. Tangkiatkumjai M, Boardman H, Praditpornsilpa K, Walker DM. Prevalence of Herbal and Dietary Supplement Usage in Thai Outpatients With Chronic Kidney Disease: A Cross-Sectional Survey. *BMC Complement Altern Med* (2013) 13:153. Epub 2013/07/03. doi:10.1186/1472-6882-13-153
24. Thongkhao K, Tungphatthong C, Sukrong S. A Pcr-Lateral Flow Immunochromatographic Assay (Pcr-Lfa) for Detecting Aristolochia Species, the Plants Responsible for Aristolochic Acid Nephropathy. *Sci Rep* (2022) 12(1):12188. Epub 20220716. doi:10.1038/s41598-022-16528-1
25. Ernst E. Toxic Heavy Metals and Undeclared Drugs in Asian Herbal Medicines. *Trends Pharmacol Sci* (2002) 23(3):136–9. doi:10.1016/S0165-6147(00)01972-6
26. Ali H, Soliman K, Daoud A, Elsayed I, Fulop T, Sharma A, et al. Relationship Between Rabbit Anti-Thymocyte Globulin and Development of Ptld and its Aggressive Form in Renal Transplant Population. *Ren Fail* (2020) 42(1):489–94. doi:10.1080/0886022X.2020.1759636
27. Petrara MR, Giunco S, Serraino D, Dolcetti R, De Rossi A. Post-Transplant Lymphoproliferative Disorders: From Epidemiology to Pathogenesis-Driven Treatment. *Cancer Lett* (2015) 369(1):37–44. Epub 20150813. doi:10.1016/j.canlet.2015.08.007
28. Cheung CY, Ma MKM, Chau KF, Chak WL, Tang SCW. Posttransplant Lymphoproliferative Disorders in Kidney Transplant Recipients: A Retrospective Cohort Analysis Over Two Decades in Hong Kong. *Oncotarget* (2017) 8(57):96903–12. Epub 20170630. doi:10.18632/oncotarget.18890
29. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. Kdigo Clinical Practice Guideline for the Care of Kidney Transplant Recipients. *Am J Transpl* (2009) 9(3):S1–155. Epub 2009/10/23. doi:10.1111/j.1600-6143.2009.02834.x
30. Walti LN, Mugglin C, Sidler D, Mombelli M, Manuel O, Hirsch HH, et al. Association of Antiviral Prophylaxis and Rituximab Use With Posttransplant Lymphoproliferative Disorders (PTLDs): A Nationwide Cohort Study. *Am J Transpl* (2021) 21(7):2532–42. Epub 20201222. doi:10.1111/ajt.16423
31. Ashoor IF, Beyl RA, Gupta C, Jain A, Kiessling SG, Moudgil A, et al. Low-Dose Antithymocyte Globulin Has No Disadvantages to Standard Higher Dose in Pediatric Kidney Transplant Recipients: Report From the Pediatric Nephrology Research Consortium. *Kidney Int Rep* (2021) 6(4):995–1002. Epub 20210117. doi:10.1016/j.ekir.2021.01.007
32. Au E, Wong G, Chapman JR. Cancer in Kidney Transplant Recipients. *Nat Rev Nephrol* (2018) 14(8):508–20. doi:10.1038/s41581-018-0022-6
33. Shao EX, Betz-Stablein B, Marquat L, Campbell S, Isbel N, Green AC, et al. Higher Mycophenolate Dosage Is Associated With an Increased Risk of Squamous Cell Carcinoma in Kidney Transplant Recipients. *Transpl Immunol* (2022) 75:101698. Epub 20220819. doi:10.1016/j.trim.2022.101698
34. Thet Z, Lam AK, Ranganathan D, Aung SY, Han T, Khoo TK. Reducing Non-Melanoma Skin Cancer Risk in Renal Transplant Recipients. *Nephrology (Carlton)* (2021) 26(11):907–19. Epub 20210728. doi:10.1111/nep.13939
35. Krishnan A, Wong G, Teixeira-Pinto A, Lim WH. Incidence and Outcomes of Early Cancers After Kidney Transplantation. *Transpl Int* (2022) 35:10024. Epub 20220503. doi:10.3389/ti.2022.10024
36. Pausawasdi N, Tongpong P, Geeratragool T, Charatcharoenwitthaya P. An Assessment of Physicians' Recommendations for Colorectal Cancer Screening and International Guidelines Awareness and Adherence: Results From a Thai National Survey. *Front Med (Lausanne)* (2022) 9:847361. Epub 20220429. doi:10.3389/fmed.2022.847361
37. Acuna SA, Huang JW, Scott AL, Micic S, Daly C, Brezden-Masley C, et al. Cancer Screening Recommendations for Solid Organ Transplant Recipients: A Systematic Review of Clinical Practice Guidelines. *Am J Transpl* (2017) 17(1):103–14. Epub 20160830. doi:10.1111/ajt.13978
38. Boenink R, Astley ME, Huijben JA, Stel VS, Kerschbaum J, Ots-Rosenberg M, et al. The Era Registry Annual Report 2019: Summary and Age Comparisons. *Clin Kidney J* (2022) 15(3):452–72. Epub 20211215. doi:10.1093/ckj/sfab273
39. Wong G, Chapman JR, Craig JC. Cancer Screening in Renal Transplant Recipients: What Is the Evidence?. *Clin J Am Soc Nephrol* (2008) 3(2):S87–S100. doi:10.2215/CJN.03320807
40. Wong G, Howard K, Webster AC, Chapman JR, Craig JC. Screening for Renal Cancer in Recipients of Kidney Transplants. *Nephrol Dial Transpl* (2011) 26(5):1729–39. Epub 2010/10/22. doi:10.1093/ndt/gfq627
41. Pradere B, Schuettfort V, Mori K, Quhal F, Aydh A, Sari Motlagh R. Management of De-Novo Urothelial Carcinoma in Transplanted Patients. *Curr Opin Urol* (2020) 30(3):467–74. Epub 2020/04/03. doi:10.1097/MOU.0000000000000749
42. Kliem V, Thon W, Krautzig S, Kolditz M, Behrend M, Pichlmayr R, et al. High Mortality From Urothelial Carcinoma Despite Regular Tumor Screening in Patients With Analgesic Nephropathy After Renal Transplantation. *Transpl Int* (1996) 9(3):231–5. doi:10.1007/BF00335391
43. Lemy A, Wissing KM, Rorive S, Zlotta A, Roumeguere T, Muniz Martinez MC, et al. Late Onset of Bladder Urothelial Carcinoma After Kidney Transplantation for End-Stage Aristolochic Acid Nephropathy: A Case Series With 15-Year Follow-Up. *Am J Kidney Dis* (2008) 51(3):471–7. doi:10.1053/j.ajkd.2007.11.015
44. Kanaan N, Hassoun Z, Raggi C, Jadoul M, Mourad M, De Meyer M, et al. Long-Term Outcome of Kidney Recipients Transplanted for Aristolochic Acid Nephropathy. *Transplantation* (2016) 100(2):416–21. doi:10.1097/TP.0000000000000941
45. Jelakovic B, Karanovic S, Vukovic-Lela I, Miller F, Edwards KL, Nikolic J, et al. Aristolactam-DNA Adducts Are a Biomarker of Environmental Exposure to Aristolochic Acid. *Kidney Int* (2012) 81(6):559–67. Epub 20111109. doi:10.1038/ki.2011.371

46. United Nation Department of Economic and Social Affairs Population Division. *World Population Prospective 2022* (2022). Available From: https://population.un.org/wpp/Graphs/DemographicProfiles/Pyramid/764 (Accessed February 1, 2023).
47. Blair A, Stewart P, Lubin JH, Forastiere F. Methodological Issues Regarding Confounding and Exposure Misclassification in Epidemiological Studies of Occupational Exposures. *Am J Ind Med* (2007) 50(3):199–207. doi:10.1002/ajim.20281

ESOT | Transplant International

REVIEW
published: 25 July 2024
doi: 10.3389/ti.2024.12969

Paraneoplastic Syndrome After Kidney Transplantation: Frequency, Risk Factors, Differences to Paraneoplastic Occurrence of Glomerulonephritis in the Native Kidney, and Implications on Long-Term Kidney Graft Function

*Izabela Zakrocka[1], Gayatri Nair[2,3], Maria Jose Soler[4,5], Kenar D. Jhaveri[2,3] and Andreas Kronbichler[6]**

[1]Department of Nephrology, Medical University of Lublin, Lublin, Poland, [2]Northwell Health, New York, NY, United States, [3]Division of Kidney Diseases and Hypertension, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Glomerular Center at Northwell Health, New York, NY, United States, [4]Nephrology Department, Vall d'Hebron University Hospital, Universitat Autònoma de Barcelona, Barcelona, Spain, [5]Nephrology Research Group, Vall d'Hebron Research Institute (VHIR), Barcelona, Spain, [6]Department of Internal Medicine IV, Nephrology and Hypertension, Medical University Innsbruck, Innsbruck, Austria

OPEN ACCESS

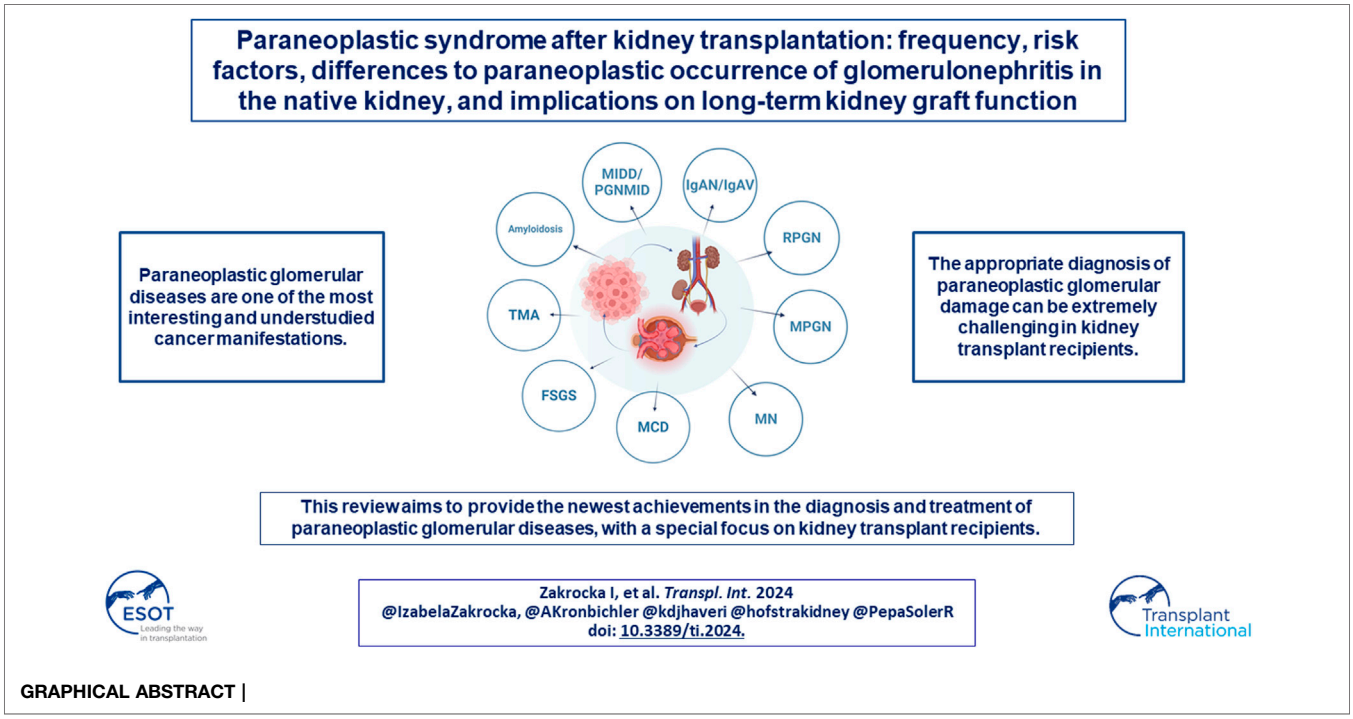
***Correspondence**
Andreas Kronbichler,
andreas.kronbichler@i-med.ac.at

Received: 09 March 2024
Accepted: 12 July 2024
Published: 25 July 2024

Citation:
Zakrocka I, Nair G, Soler MJ, Jhaveri KD and Kronbichler A (2024) Paraneoplastic Syndrome After Kidney Transplantation: Frequency, Risk Factors, Differences to Paraneoplastic Occurrence of Glomerulonephritis in the Native Kidney, and Implications on Long-Term Kidney Graft Function. Transpl Int 37:12969. doi: 10.3389/ti.2024.12969

Posttransplant malignancies are an important complication of solid organ transplantation. Kidney transplant recipients are at particularly high risk of cancer development. The most relevant risk factors of carcinogenesis are the use of immunosuppressive agents and oncogenic viral infections. Additionally, immune dysregulation caused by these factors may predispose to various types of organ damage. Paraneoplastic glomerular diseases are one of the most interesting and understudied cancer manifestations. The appropriate diagnosis of paraneoplastic glomerular damage can be challenging in kidney transplant recipients, due to factors inherent to concomitant medication and common comorbidities. Recent advances in the field of molecular and clinical nephrology led to a significant improvement in our understanding of glomerular diseases and their more targeted treatment. On the other hand, introduction of novel anticancer drugs tremendously increased patients' survival, at the cost of kidney-related side effects. Our review aims to provide insights into diagnosis and treatment of paraneoplastic glomerular diseases, with a special attention to kidney transplant recipients.

Keywords: kidney, transplantation, cancer, paraneoplastic syndrome, glomerulonephritis



GRAPHICAL ABSTRACT |

INTRODUCTION

Kidney transplantation is the preferred form of kidney replacement therapy as it offers significant improvement in quality of life and overall survival of patients with end stage kidney disease (ESKD) [1]. Introduction of novel immunosuppressive agents, together with advances in organ preservation and surgical techniques lead to greater 1-year allograft survival [2, 3]. Unfortunately, the rate of long-term complications remains high, reducing overall survival of transplant recipients in comparison to the general population. A plethora of immune- and nonimmune-related factors are known to contribute to late posttransplant complications, with malignancies being one of the most relevant one.

Diagnosis and management of malignancies pose specific challenges in transplant patients. A non-specific presentation of cancer mimicking chronic infectious complications, limited availability of anticancer therapies due to potential nephrotoxic side effects and interactions with immunosuppression are among the main challenges in kidney transplant recipient. Identified risk factors of posttransplant malignancies are older age at the time of transplantation, male gender, white ethnicity, time spent on dialysis, longer term follow-up after transplantation, and higher cumulative exposure to immunosuppression [4]. Malignancies are reported as the second most common cause of death in kidney allograft recipients and the overall cancer risk is estimated to be 2- to 4- fold higher than in the general population [5].

Paraneoplastic syndromes, defined as cancer clinical manifestations triggered by tumor products, but not by the neoplasm itself, may precede cancer diagnosis or occur even many years thereafter [6]. The diagnostic processes of paraneoplastic syndrome in kidney transplant patients can be difficult due to its non-characteristic clinical picture and often require invasive procedures to make a final diagnosis. One of such paraneoplastic syndromes are glomerular diseases. Appropriate diagnosis is of special importance, since glomerular diseases in kidney transplant recipients are claimed to be the second most common cause of kidney graft failure [7]. Among possible triggers of glomerular damage after kidney transplantation, a complex interplay between genetic predisposition and especially immunological factors seems to play a leading role. Three types of glomerular damage can occur: donor-derived, *de novo* and recurrent. *De novo* glomerulonephritis is mainly immune complex mediated, being highly dependent on the immune status of the graft recipient [8]. In contrast, recurrent glomerular diseases are mainly found in kidney transplant recipients with an established glomerular disease before transplantation, often resulting in significant graft function impairment and eventually its loss [9]. Adding to that, a specific type of glomerular damage, classified as paraneoplastic glomerular disease, remains intriguing and an understudied kidney allograft complication. Although one of the first reports connecting the presence of nephrotic syndrome with malignant tumors was already published in 1966 [10], data about paraneoplastic glomerular diseases in kidney transplant patients remain obscure.

In this review, we aim to describe the epidemiology of paraneoplastic glomerular diseases after kidney transplantation, differences in their management in

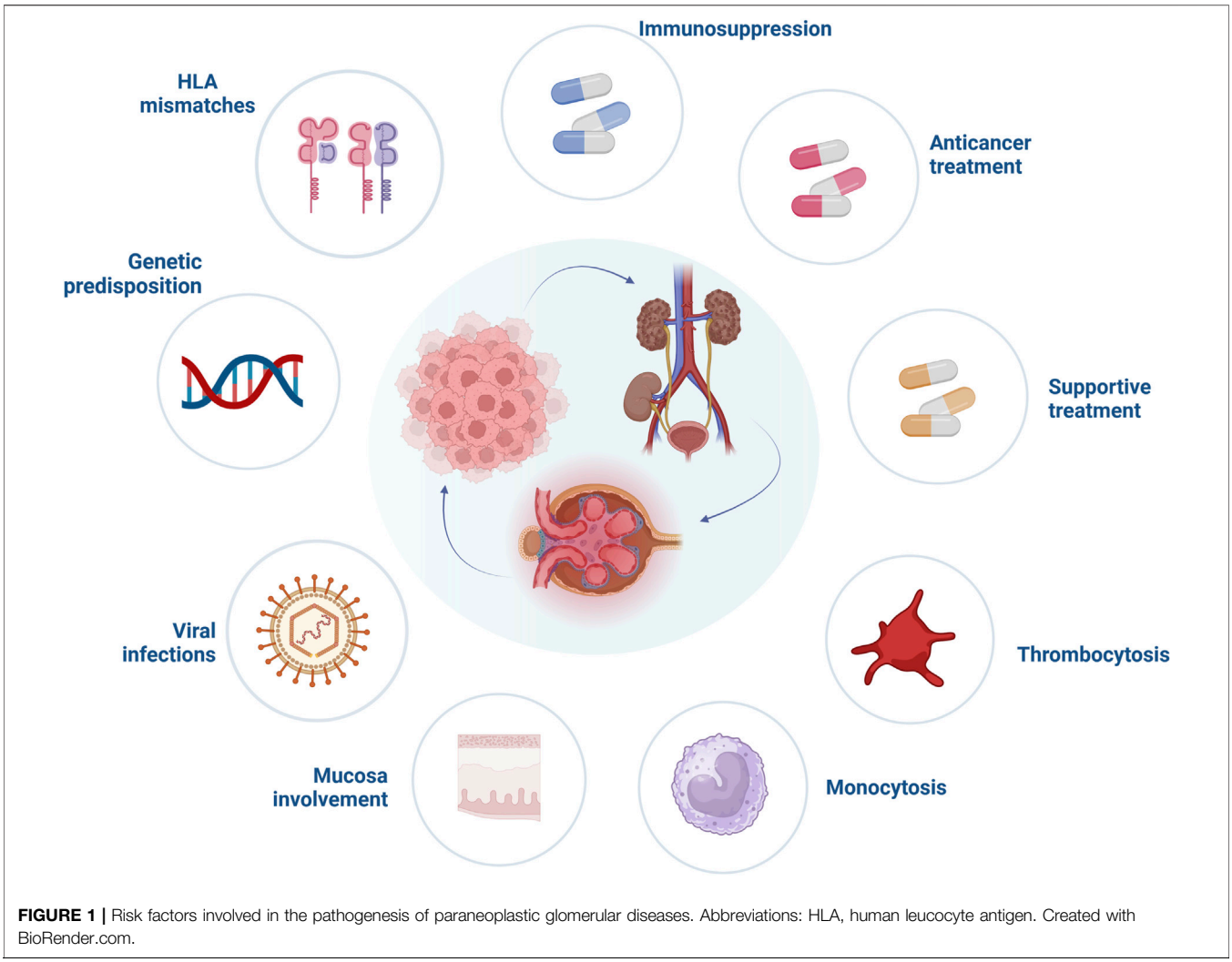


FIGURE 1 | Risk factors involved in the pathogenesis of paraneoplastic glomerular diseases. Abbreviations: HLA, human leucocyte antigen. Created with BioRender.com.

comparison with non-transplant patients, their impact on graft survival and difficulties regarding immunosuppressive and anticancer treatment. The paucity of data in the posttransplant setting requires in-depth discussions of paraneoplastic glomerular diseases in the native kidney.

PARANEOPLASTIC GLOMERULAR DISEASES

Paraneoplastic glomerular diseases are defined as disorders that are not attributable to invasion or compression by the tumor or by metastasis caused by the tumor [11]. The production and secretion of hormones or peptides by the tumor or immune cross-reactivity with the host's renal tissue are considered to lead to paraneoplastic glomerular diseases. A paraneoplastic origin is likely when the occurrence of glomerular disease has a temporal relationship to the occurrence of cancer and the severity of kidney disease follows the course of cancer, i.e., deteriorates when the tumor burden increases or *vice versa*. This has been nicely demonstrated for a case with thrombospondin type-1 domain-containing 7A (THSD7A)-associated membranous nephropathy (MN) who had a concomitant gallbladder carcinoma. After surgery of the carcinoma, THSD7A antibodies became negative, and a subsequent significant reduction of proteinuria indicated a partial response of MN to anti-cancer measures [12].

RISK FACTORS OF PARANEOPLASTIC GLOMERULAR DISEASES AFTER KIDNEY TRANSPLANTATION

Drugs

Little is known whether one specific agent is responsible for an increased frequency of paraneoplastic glomerular disease (**Figure 1**). Alemtuzumab, a monoclonal antibody directed against the CD52 antigen, is known to cause autoimmunity after its use. Post-marketing surveillance in patients with multiple sclerosis found that one out of three will develop another autoimmune disorder after alemtuzumab is used, but

these cases are mainly restricted to thyroid dysfunction and only a minority (<10%) thereof are considered serious [13]. Nonetheless, severe autoimmunity such as the development of anti-glomerular basement membrane (GBM) disease has been reported in single cases [14]. Associations between administration of other potent induction immunosuppressants and systemic autoimmunity are much weaker, but single cases of Guillain-Barre syndrome with the use of anti-thymocyte globulin exist in the literature [15]. It should be noted, that induction therapy itself with antithymocyte globulin or alemtuzumab significantly increases the risk of malignancy development, especially posttransplant lymphoproliferative disorder [16]. Taken together, a paucity of data on the prevalence of paraneoplastic glomerular disease development with the use of agents to prevent allograft rejections hinders strong conclusions, but it is likely that certain agents such as alemtuzumab at least influence the occurrence of glomerular diseases independent of cancer development.

HLA Matching

Besides the possible role of immunosuppression in paraneoplastic glomerular diseases pathogenesis, other specific factors related to solid organ transplantation should be mentioned (**Figure 1**). It is widely accepted that human leukocyte antigen (HLA) matching is essential for optimal graft function, however, it is not required for cancer prevention. Khurram et al. inoculated rats with kidney tumor cells and started them on cyclosporine. The animals showed stronger anti-tumor response when a higher degree of major histocompatibility complex (MHC) mismatch was present in comparison to a well-matched group [17]. Moreover, after withdrawal of immunosuppression all rats in the mismatch group eliminated cancer cells, compared to only a 50% reduction in well-matched animals, suggesting a significant impact of immunosuppression reduction and higher mismatch levels on cancer prognosis. Unfortunately, data from human studies are less conclusive. In a large study analyzing data from 166,256 adult kidney transplant recipients, who survived 1 year without episodes of graft rejection or malignancy, recipients with 4–6 HLA mismatches had higher risk of solid organ cancer development (hazard ratio [HR] = 1.11, 95% CI = 1.00–1.34) compared to well-matched individuals. This, however, might have also been related to other risk factors, such as male sex or prior transplant history [18]. On the contrary, an analysis focusing on the incidence and risk factors of melanoma in a cohort of 105,174 kidney transplant recipients from the United States Renal Data System database observed that less than 4 HLA mismatches significantly increased the risk of melanoma development (44.9% vs. 37.1%) [19]. This finding was supported by another study performed on 10,649 heart and lung transplant recipients, which indicated that the higher level of HLA mismatching revealed a protective effect on occurrence of posttransplant skin cancers [20]. However, little is known whether higher levels of HLA mismatches provide protection against recurrence or *de novo* occurrence of glomerular disease. Fewer HLA mismatches have been postulated as a potential risk factor of glomerulonephritis reoccurrence, particularly IgA nephropathy [21]. The significance of HLA mismatch in the pathogenesis of paraneoplastic glomerular diseases remain to be established by future studies.

T cell Subpopulations

A study in kidney transplant recipients with cancer found a significantly higher frequency of Tregs together with higher level of soluble HLA-G (sHLA-G) [22]. Tregs have been shown to exert immunosuppressive features, thereby potentially preventing the occurrence of paraneoplastic autoimmunity [23]. A subsequent reduction of Treg activity, eventually developing an exhaustive phenotype, may thereby provoke specific glomerular damage as well.

Beyond the crucial role of specific T cells on alloantigen recognition and antibody production, other cells, i.e., natural killer (NK) cells exhibit alloreactive properties, relevant to control viral infections after kidney transplantation, such as cytomegalovirus (CMV) or Ebstein-Barr (EBV) infections [24]. This alloreactivity may in turn result in glomerular damage. Xiao et al. reported a case of histiocytic glomerulopathy related with extranodal NK/T-cell lymphoma [25]. On the other hand, NK cells have been postulated as potential biomarkers of idiopathic MN, their levels significantly increased after rituximab treatment [26] and were associated with remission of MN [27]. In a recently published study, antigen-specific chimeric autoantibody receptor (CAAR) NK cells have been used to eliminate cells producing antibodies involved in MN, especially against THSD7A [28]. The specific role of immune cells in the development of paraneoplastic glomerulopathies requires further studies.

Viruses

Viral infections are another important factor related to impaired graft function and cancerogenesis in kidney transplant recipients (**Figure 1**). In addition, it was suggested that viruses may induce glomerular damage. One of these, Kaposi's sarcoma herpesvirus (KSHV)/human herpesvirus 8 (HHV8) has high tropism for endothelial cells, thereby inducing vIL-6 [29] and vascular endothelial growth factor (VEGF) [30] as angiogenic factors. vIL-6 has been proposed as one of the molecular links between KSHV and glomerular diseases, especially amyloidosis, thrombotic microangiopathy (TMA) and membranoproliferative glomerulonephritis (MPGN) [31]. Interestingly, KSHV gene sequences have been found in patients with multiple myeloma and primary amyloidosis [32]. Other viral infections may contribute to glomerular damage after kidney transplantation as well. Cases of immunotactoid [33] and crescentic glomerulopathy [34] secondary to CMV infection have been documented.

Genes

Underlying genetic predisposition is of relevance for paraneoplastic glomerular diseases. Mutations of more than 70 genes are already identified to be associated with increased risk of glomerular damage, however often a "second hit" is necessary to evoke the full clinical picture of kidney disease, frequently manifesting as focal segmental glomerulosclerosis (FSGS), a non-specific pattern of kidney injury, in a kidney biopsy [35]. Bonilla et al. suggested that mutations of genes

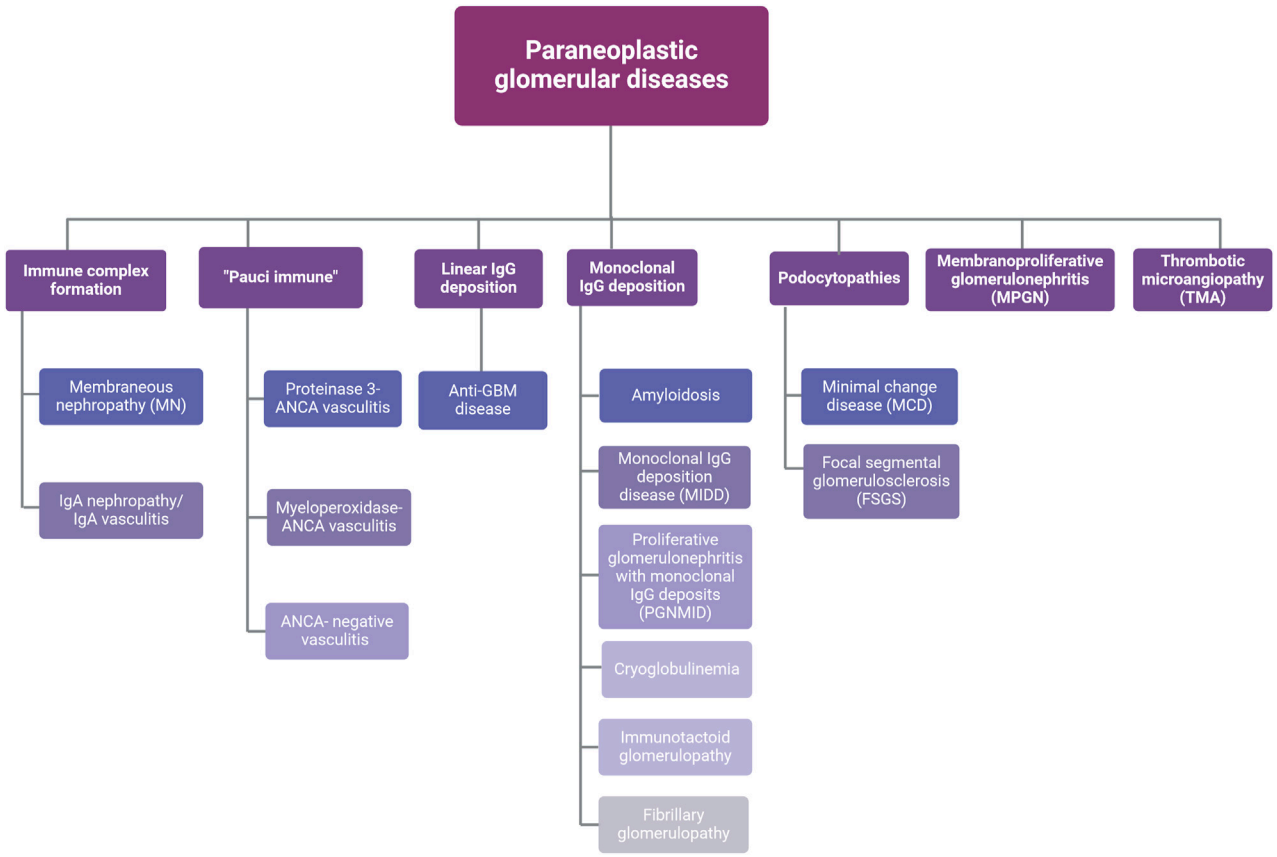


FIGURE 2 | Types of paraneoplastic glomerular diseases. Abbreviations: ANCA, anti-neutrophil cytoplasmic antibodies; GBM, glomerular basement membrane; IgA, immunoglobulin A; IgG, immunoglobulin G. Created with BioRender.com.

crucial for podocyte function, namely, protocadherin FAT1 gene, may be one of the unrecognized triggers of immune-mediated glomerular damage, especially in the transplant setting [36]. Moreover, mutations of podocyte genes may predispose to glomerulopathies secondary to anticancer treatment. Czogalla et al. presented another "multi-hit" case of FSGS in a patient with chronic lymphocytic leukemia, in whom an unrecognized podocin mutation was exacerbated by ibrutinib administration [37]. Additionally, a specific role of genotyping the donor has been highlighted in other studies. This is particularly relevant in donors of African-American decent, where apolipoprotein L1 (APOL1) gene polymorphisms play a crucial role, and a risk constellation (G1/G2) is related to collapsing FSGS in kidney transplant recipients, which in turn might rapidly progress to ESKD [38].

Complement System

The role of complement system activation in cancerogenesis remains a controversial issue. It was postulated that local complement activation in the microenvironment of melanoma is responsible for lower immune responsiveness to neoplastic cells through inhibition of $CD8^+$ T cells [39]. On the other hand, reduced C3 and C5 production or the blockade of the C5 receptor reduced tumor growth in animal models of cancer, indicating their crucial role in cancerogenesis [40]. Cancer or treatment-related complement activation may also result in TMA, a rare form of glomerular damage, and is in some cases more amenable to anticomplement treatment than therapeutic plasma exchange (TPE) [41].

TYPES OF PARANEOPLASTIC GLOMERULAR DISEASES

Several patterns of glomerular injury have been linked with cancer occurrence (**Figure 2**). In the next sections the most common histological types of paraneoplastic glomerular diseases will be discussed.

Membranous Nephropathy (MN)

MN is the most common type of paraneoplastic glomerular disease related to solid tumors and is less prevalent in hematological malignancies. The prevalence of paraneoplastic cases of MN was reported to be approximately 20% [42]. Importantly, the diagnosis of MN may precede the occurrence of malignancy [43]. Gastrointestinal cancers, followed by lung,

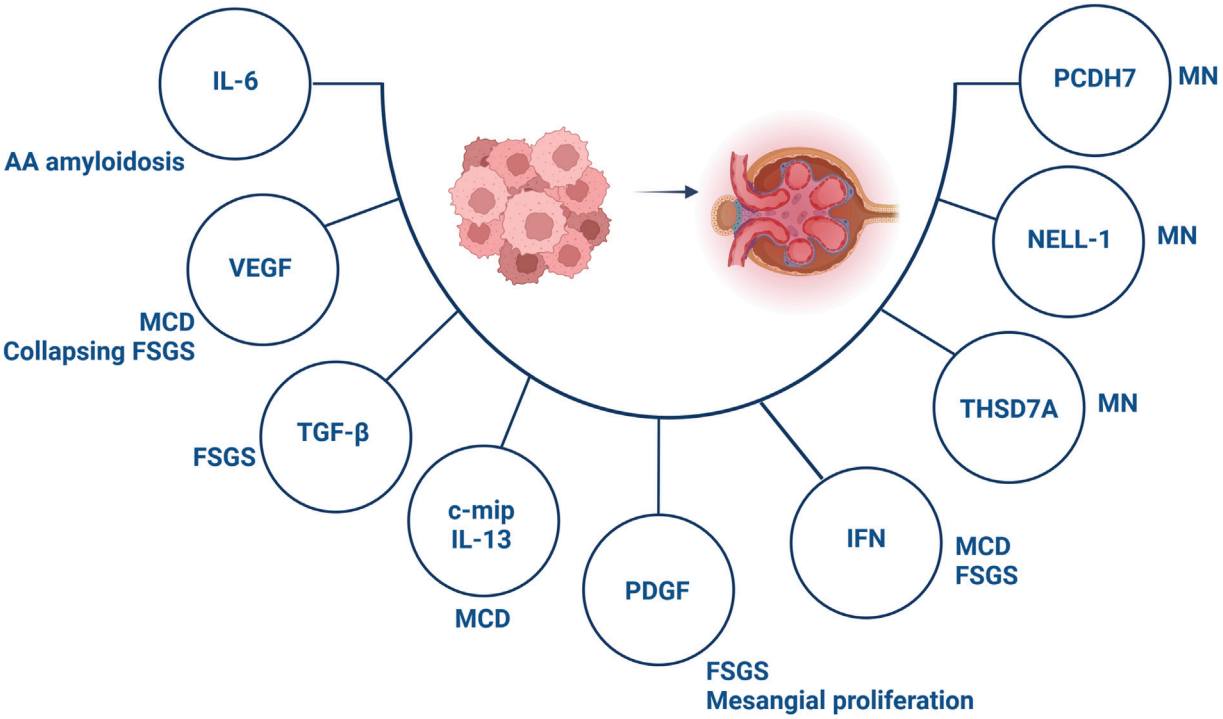


FIGURE 3 | Involved components in the pathogenesis of paraneoplastic glomerular diseases. Abbreviations: c-mip, c-maf inducing protein; FSGS, focal segmental glomerulosclerosis; IFN, interferon; IL, interleukin; MCD, minimal change disease; MN, membranous nephropathy; NELL-1, neural epidermal growth factor-like 1; PCDH7, protocadherin 7; PDGF, platelet-derived growth factor; TGF-β, transforming growth factor-β; THSD7A, thrombospondin type 1 domain containing 7A; VEGF, vascular endothelial growth factor. Created with BioRender.com.

kidney and prostate cancer are the most frequently reported malignancies to cause MN [6]. MN usually manifests as nephrotic syndrome, with formation of immune complexes leading to its onset. However, it should be noted that although glomerular immune deposits were found in the autopsy of 30% of cancer patients, their significance remains unclear [44]. A higher deposition of IgG1 and IgG2 was found in patients with paraneoplastic MN [45], whereas IgG4 prevalence was related with the primary form of MN [42]. Additionally, a switch in the IgG subclass was shown to predict MN progression, especially in secondary MN [46]. Other findings, such as >8 inflammatory cells affecting the glomerulus, mesangial proliferation and segmental MN, especially in the presence of neural epidermal growth factor-like 1 (NELL-1) antigen, support the diagnosis of paraneoplastic MN [47]. The discovery of novel antigens involved in MN pathogenesis significantly improved our diagnostic understanding of glomerular damage in these patients. Antibodies against the M-type phospholipase A2 receptor (PLA2R) are known to be highly indicative for primary MN. Recently discovered antigens, i.e., THSD7A, FAT1, NELL-1 and protocadherin 7 (PCDH7) have been postulated as potential antigens in paraneoplastic MN [48]. Importantly, the diagnosis of PLA2R positive MN does not exclude paraneoplastic occurrence of MN, since reports of cases with positive PLA2R staining are available [49]. Moreover, dual antigen-positive MN cases have been reported, with predominant IgG1 staining in the kidney tissue and clinically a longer time to achieve remission [50]. Despite great advances in diagnostic techniques, the course of MN in kidney transplant recipients remains understudied. Solà-Porta et al. reported an unusual case of a 72-year old kidney transplant patient with THSD7A-positive MN and positive C4d capillary wall staining, without anti-THSD7A antibodies and lesions suggestive for malignancy [51]. In another study, Münch et al. presented a case of NELL-1-positive MN in a 56-year old kidney transplant recipient, again without underlying malignancy, in whom the level of serum anti-NELL-1 antibodies correlated with the proteinuria intensity [52]. Since NELL-1 was found in noncancerous MN cases, i.e., after exposure to lipoic acid [53], tiopronin [54] or mercury [55], more data are needed to predict the role of MN antigens on the kidney graft function and outcome, especially in the presence of malignancy.

Minimal Change Disease (MCD)

Hematological malignancies, especially Hodgkin's lymphoma, non-Hodgkin's lymphoma and leukemias have often been associated with MCD, although single cases of solid tumors affecting gastrointestinal tract, lung, kidney and thymus have been described [56]. The role of cytokines secreted by cancer cells is of special importance in the pathogenesis of paraneoplastic MCD (**Figure 3**).

Nephrotic syndrome evoked by paraneoplastic MCD occurs early, around the time of malignancy diagnosis. High levels of

circulating cytokines released by lymphocytes and macrophages are responsible for a generalized inflammatory condition, resulting in systemic symptoms. Paraneoplastic MCD was reported to remit after successful anti-cancer treatment, resulting in either complete [57, 58] or partial remission [59]. MCD occurs frequently after hematopoietic stem cell transplantation, likely as a limited form of graft *versus* host disease manifesting in the kidney [60]. Data on MCD occurrence after kidney transplantation are scarce. Yamada et al. reported a case of a patient 25 years after transplantation, who presented with nephrotic syndrome due to minimal change like podocyte injury evoked by coronavirus disease-2019 infection and with high-risk APOL1 alleles in the kidney donor, that improved after glucocorticoid administration [61]. Another case of a combined heart-kidney transplant recipient developing *de novo* MCD more than 1 year after transplantation was reported who responded to glucocorticoids [62].

Immunoglobulin a (IgA) Nephropathy

The association between IgA nephropathy and malignancies has first been reported in 1984 [63]. Among the most common cancers, respiratory tract and buccal cavity cancers have been reported [6], although rare cases of hematological malignancies are published [64, 65]. IgA nephropathy has emerged as the most common glomerular disease when kidney biopsies were performed in cancer patients, with a frequency of 7.4%, followed by MN in 6.1% [66]. The time of paraneoplastic glomerulopathy manifestation can also differ in various cancers. In a case presented by Melandro et al., the diagnosis of IgA nephropathy preceded kidney graft cancer occurrence by 6 months [67]. Interestingly, mesangial IgA deposits have been found in the autopsy of 17% of patients with mainly gastrointestinal malignancies, and without prior evidence of kidney damage [68]. Tumor antigens and abnormal IgA production by cancer cells, together with abnormal immune system reactivity against tumor antigens have been suggested to be involved in paraneoplastic IgA nephropathy [69]. Tumor removal remains the standard therapy in cancer-related IgA nephropathy [70].

Anti-Neutrophil Cytoplasmic Antibodies (ANCA)-Associated Vasculitis

Patients with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis are at higher risk to develop malignancies, with frequencies reported from 10% to 26%, with a significant increase 5 years after diagnosis [71]. These estimates largely stem from the cyclophosphamide- and azathioprine-era, both known to be carcinogenic. Recent investigations have found a standardized incidence ratio which is comparable to a background population [72]. Cyclophosphamide is still used by many practicing centers in the management of severe kidney failure due to ANCA-associated vasculitis. This was linked to increased frequency of several malignancies, including prostate [73], breast [74], respiratory tract [75] and chronic lymphocytic leukemia [76]. Removal of malignancy is not sufficient to control active vasculitis, as has been highlighted in a case report where an intensive immunosuppressive treatment including TPE was shown to be effective in a 85-year old patient with prostate cancer and ANCA-negative pauci-immune glomerulonephritis [77].

Anti-Glomerular Basement Membrane (Anti-GBM) Disease

Anti-GBM disease is a rare but severe kidney disease, frequently presenting with dialysis-dependent kidney failure. Due to the severity of symptoms, immediate care is required to optimize renal and overall outcome of patients. Paraneoplastic anti-GBM disease has been reported in patients with renal cell carcinoma [78, 79], lung [80] and rectal cancer [81]. Although different therapeutic approaches were shown, immunosuppression alongside TPE was effective in achieving partial remission of paraneoplastic anti-GBM disease [82].

Focal Segmental Glomerulosclerosis (FSGS)

FSGS describes a lesion encountered by different triggers. The pathogenesis of paraneoplastic FSGS is, in line with MCD, based on VEGF expression and secretion of profibrotic factors (**Figure 3**). Several malignancies have been linked to FSGS, although mainly of hematological origin [83, 84]. Importantly, essential thrombocythemia and polycythemia have been associated with FSGS, which has been assumed to occur secondary to cytokine release responsible for glomerulosclerosis [85, 86]. Data on the effectiveness of anticancer treatment and concomitant immunosuppression in paraneoplastic FSGS remain elusive, indicating achievement of FSGS remission in some cases [87].

Thrombotic Microangiopathy (TMA)

TMA is another rare presentation of paraneoplastic glomerular injury. The correlation between the TMA and cancers has been shown in mucin-producing neoplasms, especially stomach, breast and lung [88]. Patients are exposed to TMA risk factors after kidney transplantation [89], and most *de novo* cases were observed in the graft [90, 91]. Of note, paraneoplastic TMA diagnosis after kidney transplantation remains a huge challenge, since its histological picture often mimics antibody-mediated or T-cell mediated rejection [92, 93]. However, lack of laboratory indicators of generalized intravascular thrombosis, *de novo* TMA localized in the graft, lack of donor specific antibodies (DSAs) and/or C4d deposition in peritubular capillaries and time between occurrence of cancer and TMA may help to distinguish primary and posttransplant TMA from its paraneoplastic form. Treatment of paraneoplastic TMA is also a matter of debate. It has been reported that TPE is less effective in cancer-derived TMA, due to lower rate of reduced ADAMTS13 activity [88]. Additionally, single reports emerged about the effectiveness of eculizumab in cancer-associated TMA [94]. More studies are necessary to analyze the pathogenesis of paraneoplastic TMA and to expand the armamentarium of

therapies that can be safely used, especially in kidney transplant recipients.

NEWER ANTICANCER DRUGS AND GLOMERULAR DAMAGE

Onconephrology, and in particular transplant medicine are rapidly evolving fields, providing targeted treatment in kidney transplant recipients diagnosed with cancer. Up to date, various anticancer agents have been shown to induce glomerular damage (**Figure 1**) [36]. Novel anticancer drugs have revolutionized oncological treatment and significantly improved patient survival. Immune checkpoint inhibitors (ICIs) block cytotoxic T-lymphocyte antigen 4 (CTLA-4), programmed cell death 1 receptor (PD-1) or its ligand (PD-L1), main targets responsible for downregulation of T cells. As a result, an anticancer response after ICIs is augmented, at the cost of immune-mediated events [95]. A broad spectrum of glomerular disorders has been linked with ICIs use, with both nephrotic and nephritic presentation. In a systematic review performed by Kitchlu et al. the most common form of glomerular damage found after ICIs administration was pauci-immune glomerulonephritis, followed by MCD, C3 glomerulonephritis, amyloid A amyloidosis and IgA nephropathy [96]. Most patients presenting with glomerular lesions related to ICIs have been successfully treated with corticosteroids or a combination of rituximab or cyclophosphamide and corticosteroids (the latter especially in cases with pauci-immune glomerulonephritis) [97], nonetheless, critical questions remain largely unanswered. First, reintroduction of ICIs is challenging, especially when pauci-immune glomerulonephritis was induced by ICIs, as of recurrence of glomerular diseases might be expected. Second, patients after kidney transplantation are at high risk of immune-mediated disorders, especially due to immunotherapy. In general, kidney transplant recipients treated with ICIs experience more often episodes of antibody mediated as well as T cell mediated rejections. Increasing the dose of corticosteroids and switching calcineurin inhibitors (CNIs) to mammalian target of rapamycin (mTOR) inhibitors prior to ICIs initiation are one of the proposed resolutions to reduce the risk of immune-related episodes of graft injury in kidney transplant recipients [98]. However, one needs to emphasize that mTOR inhibitors may induce glomerular damage in the form of TMA or FSGS, probably due to overexpression of VEGF in podocytes [56].

Beyond anticancer drugs and their potential to induce glomerular damage, the role of supportive treatment of glomerulopathies should be mentioned (**Figure 1**). Potent stimulators of granulocyte and macrophage activity, granulocyte-colony stimulating factors filgrastim and its derivative pegfilgrastim were associated with glomerular damage in patients with hematological malignancies [56, 99, 100].

PARANEOPLASTIC GLOMERULAR DISEASE AND IMPLICATIONS ON LONG-TERM GRAFT FUNCTION IN KIDNEY TRANSPLANT RECIPIENTS

The immunological risk related to conversion of immunosuppression at the time of cancer diagnosis in kidney transplant recipients is challenging. Lack of recommendations regarding the management of immunosuppression in cancer patients after organ transplantation enforces clinicians to balance between the risk of graft rejection (also due to paraneoplastic glomerulopathy) and effective anticancer treatment [101]. Owing to limited effectiveness of standard treatment (immunosuppression, TPE) of paraneoplastic glomerular diseases, which mostly depends on cancer removal and adequate anticancer pharmacotherapy, long-term graft function preservation can be challenging, especially in kidney transplant recipients.

CONCLUSION

To the best of our knowledge, this is the first comprehensive narrative review of paraneoplastic glomerular diseases, with special focus on patients after kidney transplantation. Our article highlights further areas of research, as such cases are underreported and in clinical routine pose challenges for the treating physicians. Close cooperation between nephrologists, specialists in transplantation and hemato-oncologists should ensure appropriate medical care of kidney transplant recipients diagnosed with cancer. Large inter-center studies are crucial to determine the significance of paraneoplastic glomerular diseases after kidney transplantation.

AUTHOR CONTRIBUTIONS

IZ and AK contributed to conception and design of the study, performed literature search, wrote the first draft of the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

The authors declare that financial support was received for the research, authorship, and/or publication of this article. MS is supported by grants from Fondo de Investigación Sanitaria-FEDER, ISCIII, PI17/00257, PI20/00744, PI21/01292, Marató TV3 2020 421/C/2020, Marató TV3 2021 215/C/2021, RD16/0009/0030 (REDINREN), BECA SENFRO 2021, RD21/0005/0016 (RICORS 2040), and ERA-PerMed-JTC 2022 (ONAKI-ICI AC22/00029).

CONFLICT OF INTEREST

IZ received grant support by Chiesi, Sanofi and Takeda and received consultancy fees from Astra Zeneca, Boehringer Ingelheim, Chiesi, Sandoz and Sanofi. AK received grant support by CSL Vifor and Otsuka, and received consultancy fees from CSL Vifor, Otsuka, Walden Biosciences, Catalyst Biosciences, AstraZeneca, Glaxo Smith Kline, Roche and Delta 4. He is Editorial Board member of Nephrology Dialysis Transplantation, Glomerular Diseases and Current Rheumatology Reports. KJ reports consultancy agreements with PMV pharmaceuticals, ChemoCentryx, GlaxoSmithKline, George Clinicals and Travere Therapeutics; reports honoraria from the American Society of Nephrology and Lexicomp; is a paid contributor to UpToDate.com and is section editor for onconephrology for Nephrology Dialysis Transplantation; serves on the editorial boards of American Journal of Kidney Diseases, CJASN, Clinical Kidney Journal, Frontiers in Nephrology, Journal of Onco-Nephrology, and Kidney International; serves as the Editor-in-Chief of ASN Kidney News. MS reports personal fees and consultancy agreements with NovoNordisk, Jansen, Mundipharma, AstraZeneca, Esteve, Fresenius, Ingelheim Lilly, Vifor, ICU, Pfizer, Bayer, Travere Therapeutics, GE Healthcare and grants and personal fees from Boehringer Ingelheim. She is Editorial Board member of Clinical Kidney Journal, vice-president of the Spanish Society of Nephrology and Co-Chair of the Western Europe Regional Board of the International Society of Nephrology.

The remaining author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

REFERENCES

1. Tonelli M, Wiebe N, Knoll G, Bello A, Browne S, Jadhav D, et al. Systematic Review: Kidney Transplantation Compared With Dialysis in Clinically Relevant Outcomes. *Am J Transpl* (2011) 11:2093–109. doi:10.1111/j.1600-6143.2011.03686.x
2. Lentine KL, Smith JM, Miller JM, Bradbrook K, Larkin L, Weiss S, et al. OPTN/SRTR 2021 Annual Data Report: Kidney. *Am J Transpl* (2023) 23: S21–S120. doi:10.1016/j.ajt.2023.02.004
3. Astley ME, Boenink R, Abd ElHafeez S, Trujillo-Alemán S, Arribas F, Åsberg A, et al. The ERA Registry Annual Report 2020: A Summary. *Clin Kidney J* (2023) 16:1330–54. doi:10.1093/ckj/sfad087
4. Au E, Wong G, Chapman JR. Cancer in Kidney Transplant Recipients. *Nat Rev Nephrol* (2018) 14:508–20. doi:10.1038/s41581-018-0022-6
5. Serkies K, Dębska-Ślizień A, Kowalczyk A, Lizakowski S, Małyszko J. Malignancies in Adult Kidney Transplant Candidates and Recipients: Current Status. *Nephrol Dial Transpl* (2023) 38:1591–602. doi:10.1093/ndt/gfac239
6. Bacchetta J, Juillard L, Cochat P, Droz J-P. Paraneoplastic Glomerular Diseases and Malignancies. *Crit Rev Oncol Hematol* (2009) 70:39–58. doi:10.1016/j.critrevonc.2008.08.003
7. El-Zoghby ZM, Stegall MD, Lager DJ, Kremers W, Amer H, Gloor JM, et al. Identifying Specific Causes of Kidney Allograft Loss. *Am J Transpl* (2009) 9: 527–35. doi:10.1111/j.1600-6143.2008.02519.x
8. Khairallah P, Kamal J, Crew RJ, Serban G, Vasilescu E-R, Dube GK, et al. The Association Between Post–Kidney Transplant De Novo Glomerulonephritis and Alloimmunity. *Kidney Int Rep* (2021) 6:813–6. doi:10.1016/j.ekir.2020.12.028
9. Zanoni F, Khairallah P, Kiryluk K, Batal I. Glomerular Diseases of the Kidney Allograft: Toward a Precision Medicine Approach. *Semin Nephrol* (2022) 42: 29–43. doi:10.1016/j.semnephrol.2022.01.005
10. Lee JC, Yamauchi H, Hopper J. The Association of Cancer and the Nephrotic Syndrome. *Ann Intern Med* (1966) 64:41–51. doi:10.7326/0003-4819-64-1-41
11. Amarapurkar P, Bou-Slaiman S, Madrid B, Ladino M. Paraneoplastic Glomerular Disease: The Struggle Is Real. *J Onco-nephrology* (2019) 3: 31–8. doi:10.1177/2399369319828732
12. Hoxha E, Wiech T, Stahl PR, Zahner G, Tomas NM, Meyer-Schwesinger C, et al. A Mechanism for Cancer-Associated Membranous Nephropathy. *N Engl J Med* (2016) 374:1995–6. doi:10.1056/NEJMc1511702
13. Coles AJ, Jones JL, Vermersch P, Traboulsee A, Bass AD, Boster A, et al. Autoimmunity and Long-Term Safety and Efficacy of Alemtuzumab for Multiple Sclerosis: Benefit/Risk Following Review of Trial and Post-Marketing Data. *Mult Scler* (2022) 28:842–6. doi:10.1177/13524585211061335
14. Clatworthy MR, Wallin EF, Jayne DR. Anti-Glomerular Basement Membrane Disease After Alemtuzumab. *N Engl J Med* (2008) 359:768–9. doi:10.1056/NEJMc0800484
15. Tavakoli F, Dalil D, Yaghoubi F, Hosseini SM. Guillain-Barre Syndrome After Antithymocyte Globulin Administration in a Kidney Transplant Recipient: A Case Report and Literature Review. *Clin Case Reports* (2023) 11:e8184. doi:10.1002/ccr3.8184
16. Attieh RM, Wadei HM, Mao MA, Mao SA, Pungpapong S, Taner CB, et al. The Impact of Induction Therapy on the Risk of Post-Transplant Lymphoproliferative Disorder in Adult Kidney Transplant Recipients With Donor-Recipient Serological Epstein-Barr Virus Mismatch. *Am J Transpl* (2024). doi:10.1016/j.ajt.2024.02.028
17. Khurram MA, Stamp S, Sheerin NS, Rix D, Cunningham AC, Carter N, et al. Behaviour of Transplanted Tumours and Role of Matching in Rejection. *Transpl Immunol* (2015) 32:121–5. doi:10.1016/j.trim.2015.02.006
18. Santos AH, Mehta R, Ibrahim H, Leghrouz MA, Alquadan K, Belal A, et al. Role of Standard HLA Mismatch in Modifying Associations Between Non-Pharmacologic Risk Factors and Solid Organ Malignancy After Kidney Transplantation. *Transpl Immunol* (2023) 80:101885. doi:10.1016/j.trim.2023.101885
19. Ascha M, Ascha MS, Tanenbaum J, Bordeaux JS. Risk Factors for Melanoma in Renal Transplant Recipients. *JAMA Dermatol* (2017) 153:1130–6. doi:10.1001/jamadermatol.2017.2291
20. Gao Y, Twigg AR, Hirose R, Roll GR, Nowacki AS, Maytin EV, et al. Association of HLA Antigen Mismatch With Risk of Developing Skin Cancer After Solid-Organ Transplant. *JAMA Dermatol* (2019) 155:307–14. doi:10.1001/jamadermatol.2018.4983
21. Li Y, Tang Y, Lin T, Song T. Risk Factors and Outcomes of IgA Nephropathy Recurrence After Kidney Transplantation: A Systematic Review and Meta-Analysis. *Front Immunol* (2023) 14:1277017. doi:10.3389/fimmu.2023.1277017
22. Własiuk P, Steć A, Świder R, Durlik M, Giannopoulos K, Książek A. Association Between Increased Levels of Regulatory T Cells and Soluble Human Leukocyte Antigen G With the Prevalence of Cancer in Kidney Transplant Recipients. *Pol Arch Med Wewn* (2015) 125:779–82. doi:10.20452/pamw.3123
23. Herrnstadt GR, Steinmetz OM. The Role of Treg Subtypes in Glomerulonephritis. *Cell Tissue Res* (2021) 385:293–304. doi:10.1007/s00441-020-03359-7
24. López-Botet M, Vilches C, Redondo-Pachón D, Muntasell A, Pupuleku A, Yélamos J, et al. Dual Role of Natural Killer Cells on Graft Rejection and Control of Cytomegalovirus Infection in Renal Transplantation. *Front Immunol* (2017) 8:166. doi:10.3389/fimmu.2017.00166
25. Xiao F, Hou S, Kui K, Wang X, Bai L, Dai H. Case Report of Extranodal Natural Killer/T-Cell Lymphoma That Induced Secondary Hemophagocytic

Syndrome-Related Histiocytic Glomerulopathy. *J Int Med Res* (2023) 51: 3000605231158952. doi:10.1177/03000605231158952
26. Rosenzwajg M, Languille E, Debiec H, Hygino J, Dahan K, Simon T, et al. B- and T-Cell Subpopulations in Patients With Severe Idiopathic Membranous Nephropathy May Predict an Early Response to Rituximab. *Kidney Int* (2017) 92:227–37. doi:10.1016/j.kint.2017.01.012
27. Chen W, Cai J, Raffetseder U, Zhu B, Chen J, Song N, et al. Association Between High NK-Cell Count and Remission of Primary Membranous Nephropathy: A Retrospective Chart Review and Pilot Study. *Clin Ther* (2023) 45:364–74. doi:10.1016/j.clinthera.2023.03.002
28. Seifert L, Riecken K, Zahner G, Hambach J, Hagenstein J, Dubberke G, et al. An Antigen-Specific Chimeric Autoantibody Receptor (CAAR) NK Cell Strategy for the Elimination of Anti-PLA2R1 and Anti-THSD7A Antibody-Secreting Cells. *Kidney Int* (2024) 105:886–9. doi:10.1016/j.kint.2024.01.021
29. Giraudo E, Arese M, Toniatti C, Strasly M, Primo L, Mantovani A, et al. IL-6 Is an *In Vitro* and *In Vivo* Autocrine Growth Factor for Middle T Antigen-Transformed Endothelial Cells. *J Immunol* (1996) 157:2618–23. doi:10.4049/jimmunol.157.6.2618
30. Cornali E, Zietz C, Benelli R, Weninger W, Masiello L, Breier G, et al. Vascular Endothelial Growth Factor Regulates Angiogenesis and Vascular Permeability in Kaposi's Sarcoma. *Am J Pathol* (1996) 149: 1851–69.
31. Ronco PM. Paraneoplastic Glomerulopathies: New Insights Into an Old Entity. *Kidney Int* (1999) 56:355–77. doi:10.1046/j.1523-1755.1999.00548.x
32. Raje N, Kica G, Chauhan D, Zhang Y, Teoh G, Treon SP, et al. Kaposi's Sarcoma-Associated Herpesvirus Gene Sequences Are Detectable at Low Copy Number in Primary Amyloidosis. *Amyloid* (2000) 7:126–32. doi:10.3109/13506120009146250
33. Rao KV, Hafner GP, Crary GS, Anderson WR, Crosson JT. De Novo Immunotactoid Glomerulopathy of the Renal Allograft: Possible Association With Cytomegalovirus Infection. *Am J Kidney Dis* (1994) 24: 97–103. doi:10.1016/s0272-6386(12)80167-3
34. Detwiler RK, Singh HK, Bolin P, Jennette JC. Cytomegalovirus-Induced Necrotizing and Crescentic Glomerulonephritis in a Renal Transplant Patient. *Am J Kidney Dis* (1998) 32:820–4. doi:10.1016/s0272-6386(98)70139-8
35. De Vriese AS, Sethi S, Nath KA, Glassock RJ, Fervenza FC. Differentiating Primary, Genetic, and Secondary FSGS in Adults: A Clinicopathologic Approach. *J Am Soc Nephrol* (2018) 29:759–74. doi:10.1681/ASN.2017090958
36. Bonilla M, Gudsoorkar P, Wanchoo R, Herrmann SM, Jhaveri KD. Onconephrology 2022: An Update. *Kidney360* (2023) 4:258–71. doi:10.34067/KID.0001582022
37. Czogalla J, Schliffke S, Lu S, Schwerk M, Petereit H, Zhang T, et al. Ibrutinib-Associated Focal Segmental Glomerulosclerosis and the Impact of Podocin Mutations in Chronic Lymphocytic Leukemia. *Kidney Int* (2024) 105:877–81. doi:10.1016/j.kint.2024.02.001
38. Chang J-H, Husain SA, Santoriello D, Stokes MB, Miles CD, Foster KW, et al. Donor's APOL1 Risk Genotype and "Second Hits" Associated With De Novo Collapsing Glomerulopathy in Deceased Donor Kidney Transplant Recipients: A Report of 5 Cases. *Am J Kidney Dis* (2019) 73:134–9. doi:10.1053/j.ajkd.2018.05.008
39. Afshar-Kharghan V. The Role of the Complement System in Cancer. *J Clin Invest* (2017) 127:780–9. doi:10.1172/JCI90962
40. Kolev M, Das M, Gerber M, Baver S, Deschatelets P, Markiewski MM. Inside-Out of Complement in Cancer. *Front Immunol* (2022) 13:931273. doi:10.3389/fimmu.2022.931273
41. Jones-Carr ME, Fatima H, Kumar V, Anderson DJ, Houp J, Perry JC, et al. C5 Inhibition With Eculizumab Prevents Thrombotic Microangiopathy in a Case Series of Pig-To-Human Kidney Xenotransplantation. *J Clin Invest* (2024) 134:e175996. doi:10.1172/JCI175996
42. Jeyabalan A, Trivedi M. Paraneoplastic Glomerular Diseases. *Adv Chronic Kidney Dis* (2022) 29:116–26.e1. doi:10.1053/j.ackd.2022.02.009
43. Rosner MH, Jhaveri KD, McMahon BA, Perazella MA. Onconephrology: The Intersections Between the Kidney and Cancer. *CA Cancer J Clin* (2021) 71: 47–77. doi:10.3322/caac.21636
44. Davison AM. Renal Diseases Associated With Malignancies. *Nephrol Dial Transpl* (2001) 16(Suppl. 6):13–4. doi:10.1093/ndt/16.suppl_6.13
45. Ohtani H, Wakui H, Komatsuda A, Okuyama S, Masai R, Maki N, et al. Distribution of Glomerular IgG Subclass Deposits in Malignancy-Associated Membranous Nephropathy. *Nephrol Dial Transpl* (2004) 19:574–9. doi:10.1093/ndt/gfg616
46. Huang CC, Lehman A, Albawardi A, Satoskar A, Brodsky S, Nadasdy G, et al. IgG Subclass Staining in Renal Biopsies With Membranous Glomerulonephritis Indicates Subclass Switch during Disease Progression. *Mod Pathol* (2013) 26:799–805. doi:10.1038/modpathol.2012.237
47. Cambier J-F, Ronco P. Onco-Nephrology: Glomerular Diseases With Cancer. *Clin J Am Soc Nephrol* (2012) 7:1701–12. doi:10.2215/CJN.03770412
48. Sethi S, Beck LH, Glassock RJ, Haas M, De Vriese AS, Caza TN, et al. Mayo Clinic Consensus Report on Membranous Nephropathy: Proposal for a Novel Classification. *Mayo Clin Proc* (2023) 98:1671–84. doi:10.1016/j.mayocp.2023.08.006
49. Al-Khazraji M, Al-Mufti IA, Al-Khazraji Y. Large B-Cell Lymphoma-Associated Membranous Nephropathy With Positive PLA2R on Kidney Biopsy. *Cureus* (2023) 15:e48902. doi:10.7759/cureus.48902
50. Yang L, Wang G, Ye N, Xu X, Cheng W, Sun L, et al. Clinicopathological and Prognostic Characteristics of Idiopathic Membranous Nephropathy With Dual Antigen Positivity. *Front Immunol* (2023) 14:1297107. doi:10.3389/fimmu.2023.1297107
51. Solà-Porta E, Buxeda A, Lop J, Naranjo-Hans D, Gimeno J, Lloveras-Rubio B, et al. THSD7A-Positive Membranous Nephropathy After Kidney Transplantation: A Case Report. *Nefrologia* (2023) 43:85–90. doi:10.1016/j.nefroe.2022.09.005
52. Münch J, Krüger BM, Weimann A, Wiech T, Reinhard L, Hoxha E, et al. Posttransplant Nephrotic Syndrome Resulting From NELL1-Positive Membranous Nephropathy. *Am J Transpl* (2021) 21:3175–9. doi:10.1111/ajt.16610
53. Nassar R, Kadhem SA, Shakir M. Lipoic Acid as a Trigger for NELL-1 Positive Membranous Nephropathy. *Kans J Med* (2023) 16:297–8. doi:10.17161/kjm.vol16.20996
54. Santoriello D, Ramaswamy R, Kudose S, Markowitz GS. Segmental NELL-1 Membranous Nephropathy Complicating Tiopronin Therapy. *Kidney Int Reports* (2023) 8:1683–6. doi:10.1016/j.ekir.2023.05.023
55. Sultan A, Mamankar D, Thakare S, Rojekar A, Jamale T. Mercury-Associated Neural Epidermal Growth Factor-Like 1 Protein (NELL-1) Positive Membranous Nephropathy After Use of Skin Lightening Creams. *Clin Toxicol (Phila)* (2023) 61:387–91. doi:10.1080/15563650.2023.2188141
56. Jhaveri KD, Shah HH, Calderon K, Campenot ES, Radhakrishnan J. Glomerular Diseases Seen With Cancer and Chemotherapy: A Narrative Review. *Kidney Int* (2013) 84:34–44. doi:10.1038/ki.2012.484
57. Yu C-Y, Liu J, Qi C-H, Wu Z-Y, Xiao Y-F, Zhang X-G. Minimal Change Disease Associated With Gastrointestinal Stromal Tumor Accompanied by Significantly Elevated Serum IgE Level: A Case Report. *BMC Nephrol* (2022) 23:139. doi:10.1186/s12882-022-02775-x
58. Nakano Y, Yoshida M, Muraki N, Sugita K, Ishihara S, Kumagai J, et al. Prostate Cancer Associated With Minimal Change Disease: A Case Report. *Glomerular Dis* (2022) 2:145–50. doi:10.1159/000525040
59. Ribas A, Puche A, Gimeno J, Sans L, Barrios C, Márquez E, et al. Podocytopathy in Patients With Monoclonal Gammopathy: Three Patients and Literature Review. *Clin Kidney J* (2022) 15:417–24. doi:10.1093/ckj/sfab176
60. Huskey J, Rivard C, Myint H, Lucia S, Smith M, Shimada M, et al. Minimal Change Disease in Graft Versus Host Disease: A Podocyte Response to the Graft? *Clin Nephrol* (2013) 80:469–73. doi:10.5414/CN107420
61. Yamada M, Rastogi P, Ince D, Thayyil A, Adela Mansilla M, Smith RJH, et al. Minimal Change Disease With Nephrotic Syndrome Associated With Coronavirus Disease 2019 After Apolipoprotein L1 Risk Variant Kidney Transplant: A Case Report. *Transpl Proc* (2020) 52:2693–7. doi:10.1016/j.transproceed.2020.08.012
62. Hussain Z, Chhabra D. Late-Onset De Novo Minimal Change Disease Presenting With Nephrotic Range Proteinuria More Than 1 Year After

Combined Heart-Kidney Transplant: A Case Report. *Transpl Proc* (2019) 51: 3099–102. doi:10.1016/j.transproceed.2019.04.031
63. Mustonen J, Pasternack A, Helin H. IgA Mesangial Nephropathy in Neoplastic Diseases. *Contrib Nephrol* (1984) 40:283–91. doi:10.1159/000409763
64. Ng MSY, Francis L, Pillai E, Mallett AJ. Paraneoplastic Immunoglobulin A Nephropathy and Associated Focal Segmental Glomerulosclerosis in Asymptomatic Low Volume B-Cell Lymphoma - A Case Report. *BMC Nephrol* (2018) 19:224. doi:10.1186/s12882-018-1034-y
65. Wang X, Yang N, Lu C, Xu F, Wang J. Clinical Characterization of Polycythemia Vera Associated With IgA Nephropathy in a Single Chinese Center: A Case Series. *Medicine (Baltimore)* (2023) 102:e33493. doi:10.1097/MD.0000000000033493
66. Bolufer M, García-Carro C, Blasco M, Quintana LF, Shabaka A, Rabasco C, et al. Kidney Biopsy in Patients With Cancer along the Last Decade: A Multicenter Study. *J Clin Med* (2022) 11:2915. doi:10.3390/jcm11102915
67. Melandro F, Guglielmo N, Nudo F, Pretagostini R, Mennini G, Poli L, et al. Renal Papillary Carcinoma Developed in a Kidney Transplant Recipient With Late IgA-Nephropathy. *Exp Clin Transpl* (2016) 14:445–6. doi:10.6002/ect.2014.0124
68. Beaufils H, Jouanneau C, Chomette G. Kidney and Cancer: Results of Immunofluorescence Microscopy. *Nephron* (1985) 40:303–8. doi:10.1159/000183483
69. Pertuiset E, Lioté F, Launay-Russ E, Kemiche F, Cerf-Payrastre I, Chesneau AM. Adult Henoch-Schönlein Purpura Associated With Malignancy. *Semin Arthritis Rheum* (2000) 29:360–7. doi:10.1053/sarh.2000.6988
70. Lien Y-HH, Lai L-W. Pathogenesis, Diagnosis and Management of Paraneoplastic Glomerulonephritis. *Nat Rev Nephrol* (2011) 7:85–95. doi:10.1038/nrneph.2010.171
71. Thet Z, Lam AK, Ranganathan D, Aung SY, Khoo TK. Cancer Risks Along the Disease Trajectory in Antineutrophil Cytoplasmic Antibody Associated Vasculitis. *Clin Rheumatol* (2020) 39:2501–13. doi:10.1007/s10067-020-05055-x
72. van Daalen EE, Rizzo R, Kronbichler A, Wolterbeek R, Bruijn JA, Jayne DR, et al. Effect of Rituximab on Malignancy Risk in Patients With ANCA-Associated Vasculitis. *Ann Rheum Dis* (2017) 76:1064–9. doi:10.1136/annrheumdis-2016-209925
73. Haskell LP, Fusco MJ, Wadler S, Sablay LB, Mennemeyer RP. Crescentic Glomerulonephritis Associated With Prostatic Carcinoma: Evidence of Immune-Mediated Glomerular Injury. *Am J Med* (1990) 88:189–92. doi:10.1016/0002-9343(90)90473-q
74. Mohammed BT, Uzodi N, Gotimukul A, Kokebie R. Case Report of MPO^+ ANCA Vasculitis With Pauci-Immune GN Associated With Invasive Ductal Carcinoma of the Breast. *Curr Rheumatol Rev* (2023) 20:213–8. doi:10.2174/0115733971246438230924163114
75. Edgar JD, Rooney DP, McNamee P, McNeill TA. An Association Between ANCA Positive Renal Disease and Malignancy. *Clin Nephrol* (1993) 40:22–5.
76. Dussol B, Brunet P, Vacher-Coponat H, Bouabdallah R, Chetaille P, Berland Y. Crescentic Glomerulonephritis With Antineutrophil Cytoplasmic Antibodies Associated With Chronic Lymphocytic Leukaemia. *Nephrol Dial Transpl* (1997) 12:785–6. doi:10.1093/ndt/12.4.785
77. Saladi L, Shaikh D, Saad M, Cancio-Rodriguez E, D'Agati VD, Medvedovsky B, et al. Pulmonary Renal Syndrome: A Case Report of Diffuse Alveolar Hemorrhage in Association With ANCA Negative Pauci-Immune Glomerulonephritis. *Medicine (Baltimore)* (2018) 97:e10954. doi:10.1097/MD.0000000000010954
78. Rivedal M, Haaskjold YL, Berge H, Knoop T. Antiglomerular Basement Membrane Disease Possibly Triggered by Undiagnosed Renal Cell Carcinoma: A Case Report. *Kidney Med* (2023) 5:100709. doi:10.1016/j.xkme.2023.100709
79. Khor C, Wong MG, Reagh J. Anti-Glomerular Basement Membrane Disease and IgA Nephropathy in a Patient With Previous Renal Cell Carcinoma. *BMJ Case Rep* (2021) 14:e236555. doi:10.1136/bcr-2020-236555
80. McGregor C, Yeo R. An Observed Association Between Lung Cancer and the Presence of Anti-Glomerular Basement Membrane Antibodies. *Nephrology (Carlton)* (2022) 27:290–2. doi:10.1111/nep.14006
81. Li X, Huang M, Liu J. ANCA-Associated Vasculitis With Anti-GBM Disease and Two Types of Tumors: A Case Report. *Front Med* (2021) 8:810680. doi:10.3389/fmed.2021.810680
82. Gao C, Xie J, Pan X, Chen X. Anti-Glomerular Basement Membrane Nephritis With Bronchial Carcinoma: A Case Report. *J Int Med Res* (2020) 48:300060519892397. doi:10.1177/0300060519892397
83. Komisarof J, Forman J, Goldman B, Syposs C, Passero F, Garbade E. A Rare Case of Renal Thrombotic Microangiopathy and Focal Segmental Glomerulosclerosis Secondary to Plasma Cell Leukemia. *Case Rep Hematol* (2023) 2023:7803704. doi:10.1155/2023/7803704
84. Karakus V, Atas U, Uzuntas S, Dere Y, Meteoglu I. A Rare Nephrotic Syndrome Related to Chronic Lymphocytic Leukemia: Focal Segmental Glomerulosclerosis. *Cureus* (2022) 14:e31545. doi:10.7759/cureus.31545
85. Sugimoto H, Sawa N, Yamagiwa H, Kawada M, Ikuma D, Oba Y, et al. Focal Segmental Glomerulosclerosis Associated With Essential Thrombocythemia. *Intern Med* (2023) 62:1789–94. doi:10.2169/internalmedicine.0767-22
86. Au WY, Chan KW, Lui SL, Lam CC, Kwong YL. Focal Segmental Glomerulosclerosis and Mesangial Sclerosis Associated With Myeloproliferative Disorders. *Am J Kidney Dis* (1999) 34:889–93. doi:10.1016/S0272-6386(99)70047-8
87. Choi SB, Kim KM, Park MH, Kang KP. Collapsing Focal Segmental Glomerulosclerosis in a Patient With Oral Cavity Cancer: A Case Report. *Medicine (Baltimore)* (2021) 100:e25857. doi:10.1097/MD.0000000000025857
88. Jhaveri KD, Shah HH, Patel C, Kadiyala A, Stokes MB, Radhakrishnan J. Glomerular Diseases Associated With Cancer, Chemotherapy, and Hematopoietic Stem Cell Transplantation. *Adv Chronic Kidney Dis* (2014) 21:48–55. doi:10.1053/j.ackd.2013.08.003
89. Von Tokarski F, Fillon A, Maisons V, Thoreau B, Bayer G, Gatault P, et al. Thrombotic Microangiopathies After Kidney Transplantation in Modern Era: Nosology Based on Chronology. *BMC Nephrol* (2023) 24:278. doi:10.1186/s12882-023-03326-8
90. Dessaix K, Bontoux C, Aubert O, Grünenwald A, Soussan RS, Zuber J, et al. De Novo Thrombotic Microangiopathy After Kidney Transplantation in Adults: Interplay Between Complement Genetics and Multiple Endothelial Injury. *Am J Transpl* (2024). doi:10.1016/j.ajt.2024.01.029
91. Hsiung C-Y, Chen H-Y, Wang S-H, Huang C-Y. Unveiling the Incidence and Graft Survival Rate in Kidney Transplant Recipients With De Novo Thrombotic Microangiopathy: A Systematic Review and Meta-Analysis. *Transpl Int* (2024) 37:12168. doi:10.3389/ti.2024.12168
92. Afrouzian M, Kozakowski N, Liapis H, Broecker V, Truong L, Avila-Casado C, et al. Thrombotic Microangiopathy in the Renal Allograft: Results of the TMA Banff Working Group Consensus on Pathologic Diagnostic Criteria. *Transpl Int* (2023) 36:11590. doi:10.3389/ti.2023.11590
93. Naesens M, Roufosse C, Haas M, Lefaucheur C, Mannon RB, Adam BA, et al. The Banff 2022 Kidney Meeting Report: Reappraisal of Microvascular Inflammation and the Role of Biopsy-Based Transcript Diagnostics. *Am J Transpl* (2023) 24:338–49. doi:10.1016/j.ajt.2023.10.016
94. Perrier Q, Noble J, Grangé S, Bedouch P, Tetaz R, Rostaing L. Atypical Evolution of Secondary Hemolytic Uremic Syndrome Defined as Paraneoplastic Syndrome Under Eculizumab and Palbociclib Therapies. *Case Rep Oncol* (2021) 14:676–80. doi:10.1159/000514982
95. Bermejo S, Bolufer M, Riveiro-Barciela M, Soler MJ. Immunotherapy and the Spectrum of Kidney Disease: Should We Individualize the Treatment? *Front Med* (2022) 9:906565. doi:10.3389/fmed.2022.906565
96. Kitchlu A, Jhaveri KD, Wadhwani S, Deshpande P, Harel Z, Kishibe T, et al. A Systematic Review of Immune Checkpoint Inhibitor-Associated Glomerular Disease. *Kidney Int Reports* (2021) 6:66–77. doi:10.1016/j.ekir.2020.10.002

97. Rao Ullur A, Côté G, Pelletier K, Kitchlu A. Immunotherapy in Oncology and the Kidneys: A Clinical Review of the Evaluation and Management of Kidney Immune-Related Adverse Events. *Clin Kidney J* (2023) 16:939–51. doi:10.1093/ckj/sfad014
98. Hanna GJ, Dharanesswaran H, Giobbie-Hurder A, Harran JJ, Liao Z, Pai L, et al. Cemiplimab for Kidney Transplant Recipients With Advanced Cutaneous Squamous Cell Carcinoma. *J Clin Oncol* (2024) 42:1021–30. doi:10.1200/JCO.23.01498
99. Batal I, Markowitz GS, Wong W, Avasare R, Mapara MY, Appel GB, et al. Filgrastim-Induced Crescentic Transformation of Recurrent IgG2λ GN. *J Am Soc Nephrol* (2016) 27:1911–5. doi:10.1681/ASN.2016010061
100. Villegas-Gamas JM, Márquez-Macedo SE, Jiménez-Franco B, Fonseca-Correa JI, Mejía-Vilet JM. Proliferative Glomerulonephritis With Monoclonal IgG Deposits Triggered by Filgrastim in a Patient With Multiple Myeloma. *J Nephrol* (2023) 36:1209–12. doi:10.1007/s40620-022-01555-y
101. Lizakowski S, Dębska-Ślizień A, Kurnatowska I, Zaucha MJ, Matuszewski M, Naumnik B, et al. Nephro-Oncology: Clinical and Biochemical Aspects of Kidney Disease and Cancer. *Acta Biochim Pol* (2023) 70:347–61. doi:10.18388/abp.2020_6588

GLOSSARY

ANCA Anti-neutrophil cytoplasmic antibody
APOL1 Apolipoprotein L1
CAAR Chimeric autoantibody receptor
c-mip c-maf inducing protein
CMV Cytomegalovirus
CNI Calcineurin inhibitor
CTLA4 Cytotoxic T-lymphocyte antigen 4
DSA Donor specific antibody
EBV Ebstein-Barr virus
ESKD End stage kidney disease
FSGS Focal segmental glomerulosclerosis
GBM Glomerular basement membrane
HHV-8 Human herpesvirus-8
HLA Human leukocyte antigen
ICI Immune checkpoint inhibitor
IgA Immunoglobulin A
IL Interleukin
KSHV Kaposi's sarcoma herpesvirus
MCD Minimal change disease
MHC Major histocompatibility complex
MN Membranous nephropathy
MPGN Membranoproliferative glomerulonephritis
mTOR Mammalian target of rapamycin
NELL-1 Neural epidermal growth factor-like 1
NK Natural killer
PCDH7 Protocadherin 7
PD-1 Programmed cell death 1
PLA2R Phospholipase A2 receptor
sHLA-G Soluble HLA-G
TGF-β Transforming growth factor β
THSD7A Thrombospondin type-1 domain-containing 7A
TMA Thrombotic microangiopathy
TPE Therapeutic plasma exchange
VEGF Vascular endothelial growth factor

ESOT | Transplant International

ORIGINAL RESEARCH
published: 20 August 2024
doi: 10.3389/ti.2024.13220

Post-Kidney Transplant Cancer: A Real-World Retrospective Analysis From a Single Italian Center

***Correspondence**
Carlo Alfieri,
carlo.alfieri1@gmail.com,
carlo.alfieri@unimi.it

†ORCID:
Giulia Vanessa Re Sartò
orcid.org/0009-0004-6615-6216
Carlo Alfieri
orcid.org/0000-0003-3860-5219
Laura Cosmai
orcid.org/0000-0002-9474-4232
Emilietta Brigati
orcid.org/0000-0001-7678-8488
Mariarosaria Campise
orcid.org/0000-0002-4804-3996
Anna Regalia
orcid.org/0000-0001-7040-0761
Simona Verdesca
orcid.org/0009-0000-3468-9799
Paolo Molinari
orcid.org/0000-0001-6196-5656
Anna Maria Pisacreta
orcid.org/0000-0003-1538-5225
Marta Pirovano
orcid.org/0000-0002-9737-7052
Luca Nardelli
orcid.org/0000-0002-1749-7100
Maurizio Gallieni
orcid.org/0000-0002-2011-2160
Giuseppe Castellano
orcid.org/0000-0002-0153-3795

‡These authors have contributed equally to this work

Giulia Vanessa Re Sartò[1†‡], Carlo Alfieri[2,3†‡], Laura Cosmai[1†], Emilietta Brigati[2†], Mariarosaria Campise[2†], Anna Regalia[2†], Simona Verdesca[2†], Paolo Molinari[2,4†], Anna Maria Pisacreta[2,4†], Marta Pirovano[1,4†], Luca Nardelli[2,3†], Maurizio Gallieni[1,5†] and Giuseppe Castellano[2,3†]*

[1]Nephrology and Dialysis Unit, ASST Fatebenefratelli Sacco, Milano, Italy, [2]Department of Nephrology, Dialysis and Renal Transplantation, Fondazione IRCCS Ca' Granda Ospedale Policlinico, Milan, Italy, [3]Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy, [4]Post-Graduate School of Specialization in Nephrology, University of Milan, Milan, Italy, [5]Department of Biomedical and Clinical Sciences, Università di Milano, Milano, Italy

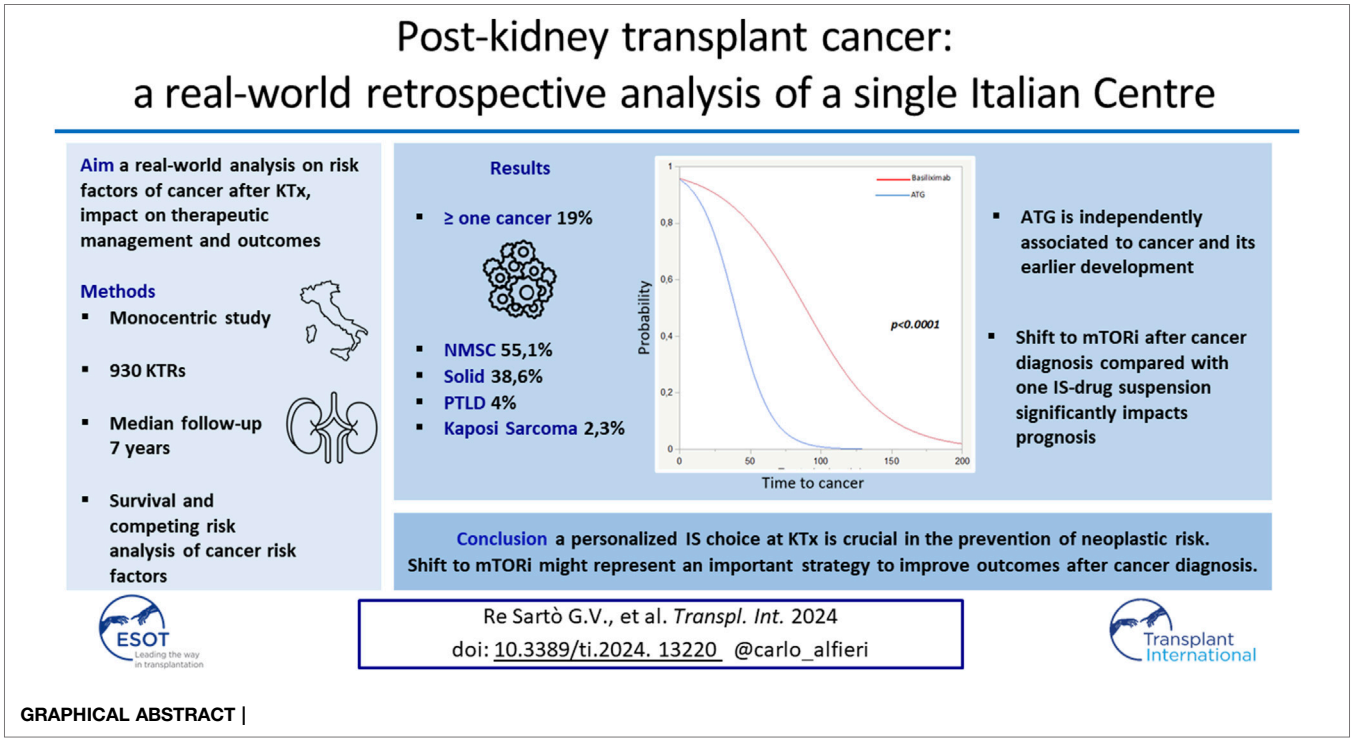
Received: 02 May 2024
Accepted: 06 August 2024
Published: 20 August 2024

Citation:
Re Sartò GV, Alfieri C, Cosmai L, Brigati E, Campise M, Regalia A, Verdesca S, Molinari P, Pisacreta AM, Pirovano M, Nardelli L, Gallieni M and Castellano G (2024) Post-Kidney Transplant Cancer: A Real-World Retrospective Analysis From a Single Italian Center. Transpl Int 37:13220. doi: 10.3389/ti.2024.13220

We describe the epidemiology of cancer after kidney transplantation (KTx), investigating its risk factors and impact on therapeutic management and survival in KTx recipients (KTRs). The association between modification of immunosuppressive (IS) therapy after cancer and survival outcomes was analyzed. We collected data from 930 KTRs followed for 7 [1–19] years. The majority of KTRs received KTx from a deceased donor (84%). In total, 74% of patients received induction therapy with basiliximab and 26% with ATG. Maintenance therapy included steroids, calcineurin inhibitors, and mycophenolate. Patients with at least one cancer (CA+) amounted to 19%. NMSC was the most common tumor (55%). CA+ were older and had a higher BMI. Vasculitis and ADPKD were more prevalent in CA+. ATG was independently associated with CA+ and was related to earlier cancer development in survival and competing risk analyses (p = 0.01 and <0.0001; basiliximab 89 ± 4 vs. ATG 40 ± 4 months). After cancer diagnosis, a significant prognostic impact was derived from the shift to mTOR inhibitors compared to a definitive IS drug suspension (p = 0.004). Our data confirm the relevance of cancer as a complication in KTRs with ATG as an independent risk factor. An individualized choice of IS to be proposed at the time of KTx is crucial in the prevention of neoplastic risk. Finally, switching to mTORi could represent an important strategy to improve patient survival.

Keywords: kidney transplant, post-kidney transplant cancer, immunosuppressive therapy, mTOR inhibitors, induction therapy

Abbreviations: ADPKD, Autosomal dominant polycystic kidney disease; BMI, Body mass index; CA-, Patients with no cancer diagnosis; CA+, Patients with at least one cancer; CNI, Calcineurin inhibitors; IS, Immunosuppressive therapy; KTRs, Kidney transplant recipients; KTx, Kidney transplant; MMF, Mycophenolate/mycophenolic acid; mTORi, mTOR inhibitors; NMSC, Non-melanoma skin cancer; PTLD, Post-transplant lymphoproliferative disorder.



GRAPHICAL ABSTRACT |

INTRODUCTION

Post-kidney (KTx) transplant cancer is an increasing risk for kidney transplant recipients (KTRs), with incidence rates 2-4 times higher than the general population of similar age and sex [1–3]; this risk escalates with time since transplantation [4]. Malignancies are the second or third leading cause of death in many registries, accounting for up to 56% of deaths in patients with functioning grafts [5]. Recent Italian research identifies cancer as the primary cause of death, accounting for 32.4% of all KTR deaths [6, 7] Variations in mortality suggest differing tumor biology and aggressiveness, and the potential undertreatment of KTRs [8].

Post-KTx malignancy depends on several factors that are related to the patient's previous individual history and the therapeutic characteristics of the KTx [9]. Cumulative pre-KTx immunosuppressive therapy (IS), advanced age, dialysis vintage, and reduced immunocompetence are relevant risk factors. This setting motivates a challenging evaluation of IS therapy at KTx and individualization of the IS regimen according to patient risk [10]. However, according to the literature, the most appropriate IS management after cancer diagnosis is still lacking in terms of indication quality and evidence level [11].

Our retrospective observational study aimed to describe the epidemiology of post-KTx cancer, investigate its risk factors and impact on management and survival, and provide a real-world long-term analysis from our center.

MATERIALS AND METHODS

Patients and Study Characteristics

We retrospectively analyzed a cohort of 930 kidney transplant recipients at the Fondazione IRCCS Ca' Granda Ospedale Policlinico Maggiore, Milan, Italy, who underwent transplantation between 2004 and 2021. Patients were followed until September 2023 with a median observation period of 7 [1–19] years. Data were recorded from both paper and electronic hospital records.

Clinical and Biochemical Evaluations

According to our protocols, blood and urine analyses were performed after a 12-h fast by the nursing staff of the Transplantation Outpatient Clinic.

For each of the 930 KTRs, the following data were recorded:

- at the time of KTx, anthropometric and clinical characteristics: age, sex, type of transplant, dialysis vintage and type, basic nephropathy, presence of diabetes mellitus, body mass index (BMI), steroid use before KTx, and HCV serology.
- at 1 month (T1) and 12 months (T12) after KTx, clinical and biochemical parameters: systolic and diastolic blood pressure, BMI, serum creatinine, hemoglobin, serum albumin, blood glucose, serum uric acid, total cholesterol, HDL cholesterol, triglycerides, 25-OH-vitamin D, and 24-h proteinuria.

Biochemical parameters were measured according to the routine methodology used by our central laboratory. Serum creatinine was assessed by Jaffe's reaction, whereas urinary protein excretion was assessed by measuring 24-h urine collection protein using the immunoturbidimetric method.

Data on the IS therapy regimen were collected during the first year after KTx; specifically, both the induction IS therapy with basiliximab or ATG and the subsequent maintenance regimen at T1 and T12 with steroids, calcineurin inhibitors (CNI), mycophenolate/mycophenolic acid (MMF), and/or mTORi were fully evaluated. For ATG use, the cumulative dose was expressed in mg/kg; for steroid use, the overall exposure of patients at T1 and T12 was calculated in mg. According to our internal protocol, basiliximab was used in cases of first KTx and low immunologic risk based on donor type and recipient immunologic status. ATG was administered to patients with high immunologic risk or in cases of re-transplantation.

Cancer Screening and Evaluation

At our center, KTRs undergo regular cancer screening, including an annual abdominal ultrasound and graft examination, along with skin, urological, and gynecological exams. Colorectal cancer screening follows general guidelines. We recorded the time of cancer onset, tumor details, recurrence, staging, management, and therapy. The cohort was divided into CA+ (KTRs who developed cancer) and CA- (KTRs who did not develop cancer). Cancer types included NMSC (graded according to Broder's system [12]), solid tumors, PTLD, and Kaposi's sarcoma. We analyzed survival from cancer and KTx, along with patient and graft outcomes post-cancer.

Principal Outcomes Considered

Patients were followed up for a median time of 7 [1–19] years. At the end of the follow-up, we evaluated as principal outcomes graft loss and death with functioning graft both globally and related to IS modifications after cancer diagnosis.

Statistical Analysis

Continuous variables were presented as mean and standard deviation or median [25°–75° percentile] for non-normally distributed data. Qualitative data were presented as frequencies and percentages. Group differences were assessed using the Student's t-test and the Wilcoxon-Mann-Whitney test for normally and non-normally distributed continuous variables, respectively. The nominal variable analysis employed the χ^2 and Fisher tests. Logistic regression models were used for multivariate analysis of cancer risk factors. Survival analysis utilized Kaplan-Meier curves with the Log-Rank test, a multivariable time-dependent Cox model, and competing risk analysis to assess the mortality risk associated with IS induction therapy. The multivariate analysis variables were determined based on univariate testing. ROC curve analyses with the evaluation of the Youden Index were used for discriminatory analyses. Statistical significance was set at $p < 0.05$. All the statistical analyses in this manuscript were conducted using SPSS 27® software and JMP Pro 15®. Treatments and procedures reported herein were in accordance with the ethical standards of the institutional committee where the study was conducted (Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico Ethical Committee, Protocol ID 4759-1837/19), and with the tenets of the Helsinki declaration of 1964 and its later amendments, or comparable ethical standards.

TABLE 1 | Clinical characteristics at the time of kidney transplantation in the total cohort.

Clinical variables		Values
Patients - n		930
Sex - n (%)	Male patients	537 (57.7%)
Recipient age at KTx - years		49 ± 13
Transplant donor - n (%)	Deceased	778 (83.6%)
Dialysis type - n (%)	HD	672 (72.2%)
	PD	181 (19.4%)
	No	78 (8.4%)
Dialysis vintage - months		52 ± 51
Diabetes pre-KTx - n (%)	Yes	54 (5.8%)
	No	850 (91.3%)
	NA	27 (2.9%)
History of HCV infection - n (%)	Yes	37 (3.9%)
	No	565 (61.8%)
	NA	328 (35.3%)
Steroids pre-KTx - n (%)	Yes	332 (35.7%)

HD, hemodialysis; PD, peritoneal dialysis; NA, not available.

RESULTS

Overall Patient Characteristics

The cohort consisted of 930 KTRs, 537 of them men, with a mean age at KTx of 49 ± 13 years. The main clinical characteristics of KTRs are summarized in **Table 1**.

The majority of patients were on dialysis prior to KTx, with a higher prevalence of hemodialysis and a mean dialysis vintage of 52 ± 51 months. The majority of patients received KTx from a deceased donor. The most common cause of kidney disease in the overall cohort was glomerulonephritis (20.5%) (**Figure 1**).

Data regarding induction and maintenance IS are shown in **Supplementary Table S1**. The majority of patients who received induction therapy had been treated with basiliximab (74%) while ATG was administered in 26% of cases, with the latter having a mean individual dose of 4.8 ± 1.1 mg. Of note, between 2004 and December 2015 (KTRs, n = 576), only 10.4% (KTRs, n = 60) of patients received ATG, whereas between 2016 and 2021 (KTRs, n = 355), ATG and basiliximab were used in 53.8% (KTRs, n = 191) and 46.2% of cases, respectively. Maintenance therapy included, in the majority of cases, the use of steroids with a cumulative dose of 1094 ± 438 mg at T1 and 2915 ± 1004 mg at T12; CNI (tacrolimus 91.9%, ciclosporin 7.7%) and mycophenolate/mycophenolic acid (94.6%) were the most represented categories. Only 2.6% of patients were prescribed mTORi. No significant differences were observed in the distribution of IS regimens from T1 to T12.

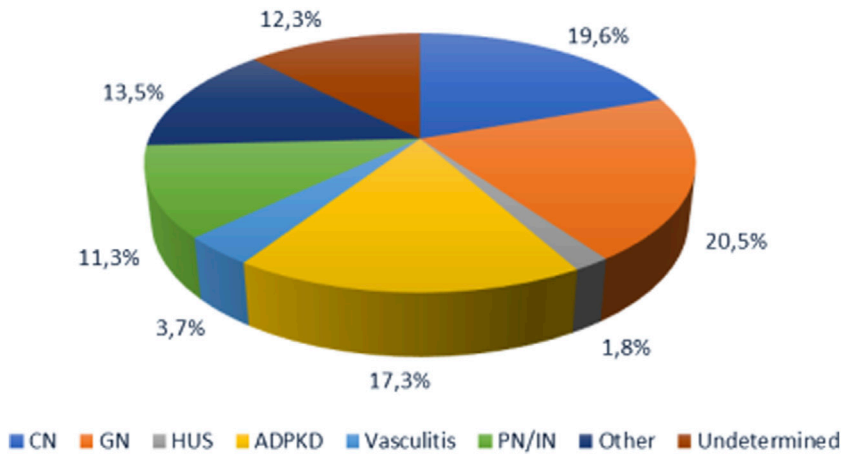


FIGURE 1 | Causes of end-stage renal disease in the cohort (n = 930). CN, chronic nephropathy (diabetic nephropathy, hypertensive renal injury, vasculopathy); GNF, glomerulonephritis; HUS, hemolytic uremic syndrome; ADPDK, autosomal dominant polycystic kidney disease; PN/NI, pyelonephritis and interstitial nephritis.

Biochemical and Anthropometric Parameters of the Entire Cohort

The biochemical and anthropometric parameters of the entire cohort at T1 and T12 are summarized in **Table 2**. Among the anthropometric characteristics, BMI at T1 showed a substantial increase during the first year post-KTx. No differences were found in blood pressure control. Kidney function did not differ significantly between T1 and T12. Regarding the biochemical data, the levels of hemoglobin, albumin, uric acid, and 25-OH-vitamin D increased during the 12 months; lipid control remained stable during the first year after KTx.

Post-Kidney Transplant Cancer

During the follow-up, 177 KTRs (19%) were diagnosed with at least one cancer, with a mean time to development from KTx of 83 ± 48 months.

Available data showed the occurrence of *de novo* cancer in 113 patients and the recurrence of a pre-KTx tumor in 9 cases; in 55 subjects, cancer could not be defined as *de novo* nor recurrent. NMSC was the most common cancer type (55.1%), while solid tumors were observed in 69 patients (38.6%); PTLD and Kaposi's sarcoma were diagnosed in 4% and 2.3% of cases, respectively (**Supplementary Table S2**).

In one-third of the KTRs (n = 58), a second cancer further developed (specifically 36 NMSC, 19 solid tumors, 2 PTLD and 1 Kaposi's sarcoma), with recurrence in half of the cases (50% *de novo* cancer). The mean time to the onset of the second neoplasia after KTx was 122 ± 53 months. For both first and second tumors, the most prevalent grade of NMSC was G2; among solid cancers, the most frequent primary cancer sites were breast (13.2%), prostate (11.7%), cervix (10.3%), lung (10.3%), and urothelial carcinoma (8.8%). Considering first malignancies, 6% of cases were diagnosed with lymph node involvement and 4% with metastatic disease at diagnosis.

TABLE 2 | Anthropometric and biochemical characteristics of the total cohort at T1 and T12.

Variables	T1	T12
Patients – n = 930		
BMI - kg/m^2	23 ± 3	24 ± 3
SBP - mmHg	130 ± 16	131 ± 17
DBP - mmHg	80 ± 10	80 ± 10
Creatinine - mg/dL	1.5 ± 0.63	1.4 ± 0.46
Proteinuria - g/24 h	0.2 [0.14–0.3]	0.17 [0.1–0.25]
Hb - g/dL	10.9 ± 1.35	12.7 ± 1.6
Albumin - g/dL	4.1 ± 0.42	4.4 ± 0.45
Glucose - mg/dL	89 ± 24	89 ± 24
Uric acid - mg/dL	5.8 ± 1.6	6.6 ± 2.7
Total cholesterol - mg/dL	211 ± 50	195 ± 43
HDL cholesterol - mg/dL	61 ± 19	56 ± 17
Triglycerides - mg/dL	165 ± 84	160 ± 83
25-OH-vitamin D - ng/mL	14.8 ± 8.2	19.9 ± 12.1

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; Hb, hemoglobin.

Comparison Between CA+ and CA-: Clinical and Biochemical Risk Factors for Cancer

Table 3 and **Supplementary Table S3** summarize the clinical, biochemical, and anthropometric differences observed between CA+ and CA- during follow-up.

CA+ exhibited a statistically significant difference in age, being older than CA- ($p < 0.001$). The incidence of malignancy was higher in men, with a mean age at diagnosis of 54 ± 10 years. Although not of causal meaning, CA+ correlated significantly with KTx from a deceased donor ($p = 0.04$) and dialysis treatment by any method ($p = 0.06$) with a mean dialysis vintage of 57.8 ± 57.1 months. There was no statistically significant difference between the two groups regarding diabetes, steroids pre-KTx or HCV positivity before KTx.

TABLE 3 | Clinical differences from the comparison of KTRs who developed cancer (CA+) and KTRs without cancer diagnosis (CA-).

Clinical variables		CA- (n = 753)	CA+ (n = 177)	*p*-value
Sex - n (%)	Male patients	426 (79.3%)	111 (20.7%)	0.08
	Female patients	327 (83.2%)	66 (16.8%)	
Transplant donor - n (%)	Deceased	620 (79.9%)	156 (20.1%)	**0.04**
	Living	131 (86.2%)	21 (13.8%)	
Age at KTx - years		47.5 ± 13	54.6 ± 10.6	**<0.001**
Dialysis type - n (%)	HD	522 (80.6%)	125 (19.4%)	0.17
	PD	139 (76.8%)	42 (23.2%)	
	No	68 (87.2%)	10 (12.8%)	
Dialysis vintage - months		51.2 ± 49	57.8 ± 57.1	0.06
Diabetes pre-KTx - n (%)	Yes	44 (81.5%)	10 (18.5%)	0.51
	No	684 (80.5%)	166 (19.5%)	
History of HCV infection - n (%)	Yes	26 (70.3%)	11 (29.7%)	0.33
	No	422 (74.7%)	143 (25.3%)	
Steroids pre-KTx - n (%)	Yes	269 (81%)	63 (19%)	0.50
	No	417 (80.8%)	99 (19.2%)	
Causes of ESRD – n (%)	CN	145 (79.7%)	37 (20.3%)	**0.011**
	GN	154 (80.6%)	37 (19.4%)	
	HUS	16 (94.1%)	1 (5.9%)	
	ADPKD	118 (73.3%)	43 (26.7%)	
	Vasculitis	23 (67.6%)	11 (32.4%)	
	PN/NI	91 (86.7%)	14 (13.3%)	
	Other	107 (84.9%)	19 (15.1%)	
	Undetermined	99 (86.8%)	15 (13.2%)	

HD, hemodialysis; PD, peritoneal dialysis; CN, chronic nephropathy; GN, glomerulonephritis; HUS, hemolytic uremic syndrome; ADPDK, autosomal dominant polycystic kidney disease; PN/NI, pyelonephritis and interstitial nephritis.
Bold value indicates the statistic significance ($p < 0.05$*).*

TABLE 4 | Differences in induction and maintenance of immunosuppressive therapy from the comparison at T1 and T12 of KTRs who developed cancer (CA+) and KTRs without cancer diagnosis (CA-).

Drugs		CA- (n = 753)	CA+ (n = 177)
Induction of immunosuppression			
Basiliximab - % ATG - % ATG dose - mg/kg		522 (56.3%)	142 (15.3%)
		186 (20%)	29 (3.1%)
		4.92 ± 1.1	4.44 ± 1.2
2016–2021 interval			
Basiliximab - %		148 (41.7%)	8 (2.2%)
ATG - %		155 (43.6%)	17 (4.7%)
ATG dose - mg/kg		4.8 ± 0.7	4.66 ± 0.7
Maintenance of immunosuppression			
Ciclosporin - %	T1	41 (4.8%)	24 (2.8%)
Tacrolimus - %		635 (74.4%)	151 (17.7%)
No - %		1 (0.1%)	2 (0.2%)
Ciclosporin - %	T12	46 (5.7%)	19 (2.4%)
Tacrolimus - %		579 (71.8%)	145 (18%)
No - %		9 (1.1%)	8 (1%)
MMF-MPA - %	T1	645 (75.5%)	164 (19.2%)
	T12	579 (71.8%)	156 (19.4%)
mTORi - %	T1	17 (2%)	5 (0.6%)
	T12	34 (4.2%)	13 (1.6%)
Cumulative steroid dose - mg	T1	1109 ± 422	1040 ± 492
	T12	2941 ± 983	2817 ± 1076

ATG, antithymocyte polyclonal immunoglobulins; MMF-MPA, mycophenolate-mycophenolic acid; mTORi, inhibitors of the mTOR system.

CA+ showed a higher prevalence of vasculitis and ADPKD, as well as basal nephropathy.

Moreover, CA+ correlated with significantly higher BMI values at T1 and T12 ($p = 0.018$ and $p = 0.08$, respectively). No other anthropometric differences were found.

When comparing biochemical variables, no significant differences were found between CA+ and CA- for renal function values such as serum creatinine and proteinuria at T1 and T12. In addition, no significant difference was found for the values of hemoglobin, albumin, blood glucose and uric

TABLE 5 | Multivariate analysis using logistic regression models. Independent variable: development of cancer after KTx.

Variables	Regression coefficient	Std error	Hazard ratio	Confidence interval	*p*-value
Recipient age	0.061	0.009	1.063	1.045–1.081	<0.001
BMI T1	0.005	0.026	1.005	0.956–1.056	0.851
Steroids T12	0	0	1.0	1.0–1.0	0.690
ATG	1.233	0.5	3.432	1.287–9.153	**0.014**
Basiliximab	0.313	0.505	1.368	0.508–3.683	0.535

Bold value indicates the statistic significance (p < 0.05).

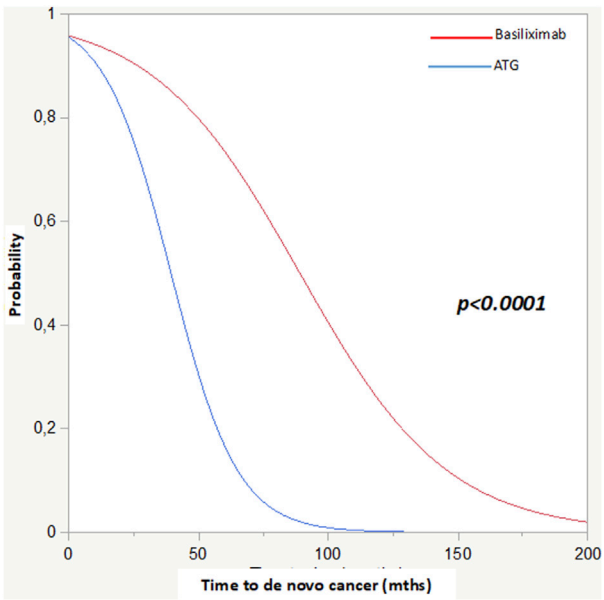


FIGURE 2 | Competing risk analysis: Basiliximab and ATG in relation to time to cancer diagnosis post-KTx.

acid at T1 and T12. However, during the regular management of KTRs, higher levels of total cholesterol at T12 (p = 0.034) and lower levels of 25-OH-vitamin D at T1 and T12 (p = 0.08 and p = 0.033) were reported in CA+ compared to CA-.

Comparison Between CA+ and CA-: Immunosuppressive Regimen as a Risk Factor for Cancer

In the first year after KTx (**Table 4**), a significant correlation with higher cumulative therapy with steroids at T1 was found in CA- (p = 0.03), a result that was not confirmed at T12. Furthermore, the significance of the results of the IS regimen containing CNI at T1 and T12 remains difficult to interpret considering the almost ubiquitous use of tacrolimus in the maintenance regimens of the entire cohort.

Regarding induction IS therapy, in the entire follow-up cohort, basiliximab showed a significant correlation with cancer development, a result that was not confirmed when the induction therapy was evaluated between 2016 and 2021. In this specific period, characterized by a homogeneous and comparable administration of two different drugs in induction, the use of ATG proved to be significantly associated with cancer development after KTx.

We did not detect a significant difference in the average individual dose of ATG between the groups, which, according to the Center's strategy, we attempted to maintain as a target of <5 mg/kg.

ATG as an Independent Cancer Risk Factor: Multivariate Survival Analysis

In the multivariate analysis, BMI at T1, cumulative exposure to steroid therapy at T12, and use of basiliximab or ATG were included as dependent variables, with post-KTx cancer as the independent variable.

Induction therapy with ATG emerged as an independent and modifiable risk factor with a statistically significant association with cancer development after KTx (p = 0.014, HR 3.43, CI 1.287–9.153) (**Table 5**).

The critical role of ATG in oncological risk was confirmed by survival analyses. This was first demonstrated in the Kaplan-Meier analysis (p < 0.0001) and subsequently confirmed by both the Cox (p < 0.01 HR 3.4) and competing risk (p < 0.0001, time to cancer onset: basiliximab 89 ± 4 vs. ATG 40 ± 4 months) analyses (**Figure 2**; **Table 6**).

Therapeutic Strategies for Cancer After KTx: Oncological Treatment

Oncological management for the different types of cancer included a surgical approach (75.1%), radiotherapy (8.4%), and/or active oncological treatment (17.5%). In the majority of individuals who underwent active systemic treatment, cytotoxic chemotherapy (61.3%) was the leading indication, while some CA+ patients started targeted therapy, immunotherapy or a combination of different classes of drugs (**Figure 3**). In the subgroup with second post-KTx neoplasia, active oncological treatment was initiated in 7 cases. Of note, at least 10 patients did not receive the optimal oncological treatment because of the potential risk of toxicity for the transplanted graft (i.e., no treatment or choice of less nephrotoxic drugs).

At cancer diagnosis, the mean serum creatinine was 1.53 ± 0.74 mg/dL. There were no reports of nephrotoxicity or renal adverse events directly associated with oncological therapy

TABLE 6 | Cox analysis.

Variables	Regression coefficient	Std error	Hazard ratio	Confidence interval	*p*-value
BMI T1	0.019	0.027	1.019	0.967–1.074	0.480
Steroids T12	0	0	1.0	1.0–1.0	0.981
ATG	1.437	0.556	4.208	1.414–12.521	**0.010**
Basiliximab	–0.207	0.552	0.813	0.276–2.397	0.707

Bold value indicates the statistic significance (p < 0.05).

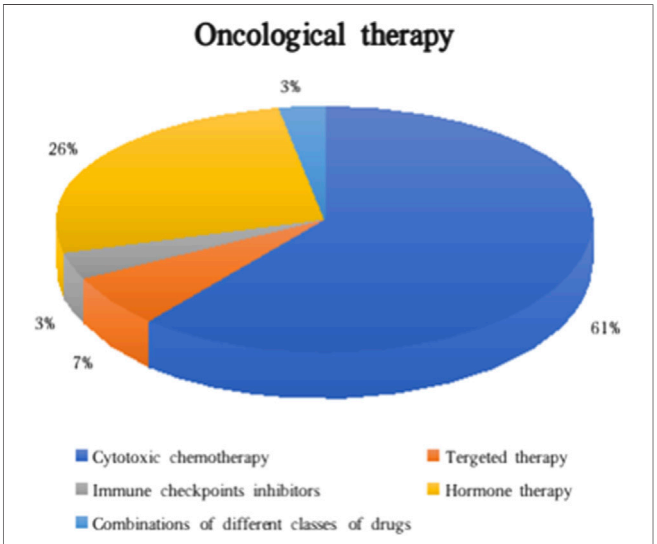


FIGURE 3 | Classes of oncological therapies administered in CA+.

(acute kidney injury, proteinuria, electrolyte imbalance, microangiopathy, etc.); in two cases, acute renal failure of pre-renal origin occurred.

Therapeutic Strategies in Cancer After KTx: Immunosuppressive Treatment

In 113 cases (65.7%), no major changes in the IS maintenance therapy regimen were made after cancer diagnosis, except for a general reduction in trough levels (trough levels: tacrolimus 3–5 μg/L–cyclosporine 80 μg/L). In total, 39.3% of CA+ subjects were subjected to modifications of the IS therapy, 12.2% of them in combination with the start of an active oncological therapy. These modifications consisted of the introduction in 38 cases (64.4%) of the mTORi regimen, which allowed the serum levels of CNI to be consensually minimized. In 16 cases (27.1%) an antimetabolite drug was permanently discontinued to achieve a dual IS regimen; of the available data, five patients (8.4%) underwent both therapeutic indications.

Patient Clinical Outcomes

A total of 125 patients (13.4%) experienced graft failure and returned to dialysis after a median time from KTx of 57.3 [8.4–103.1] months. Of these, 9.6% were CA+ and in four cases a cancer-related cause was associated with the return to dialysis (in most cases due to explantation for cancer involving the graft).

During follow-up, 124 patients (13.3%) died, of whom 31.6% were CA+ and 9% CA-. Mortality was mainly due to septic shock (24.1%), cancer-related causes (23.3%), or cardiovascular events (18.5%). Median survival from cancer diagnosis to death was 23 [7.9–59.4] months, with a higher prevalence of cancer-related causes of mortality (51.7%) than all other causes in CA+.

Comparing CA+ and CA-, the median survival from KTx to the end of the follow-up was 148 [88–191] months in CA+ and 82 [45–147] months in CA-, confirming that tumor development and cancer-related mortality are common complications in long-term transplantation. Using competing risk analyses, we investigated the possible relationship between induction therapy and mortality. Interestingly, we found a significantly lower survival in the ATG-treated group (148 ± 2 vs. 89 ± 3 months, $p < 0.0001$).

We investigated the correlation between IS therapy strategies following cancer diagnosis and survival outcomes in CA+. Although no significant differences were observed when comparing various modifications in IS therapy, with no change in median survival (60.3 ± 47 vs. 63.3 ± 43 months, $p = 0.339$), a significant prognostic impact was identified regarding changes in the type of IS therapy regimen. Specifically, switching to mTORi and reducing CNI were associated with prolonged overall survival post-cancer diagnosis compared to patients who definitively discontinued one drug, while maintaining a dual therapy approach (67.4 ± 40 vs. 34.4 ± 40 months, $p = 0.004$). This was also investigated, by non-parametric analyses taking into account the type of cancer, dividing our cohort into NMSC and other cancers. Both in the NMSC group and the other cancers group, switching to mTORi and reducing CNI were associated with prolonged post-cancer overall survival: NMSC: 61 ± 35 vs. 34 ± 48 months, $p = 0.002$; other cancers: 61 ± 35 vs. 34 ± 40 months, $p = 0.01$.

No differences in principal anamnestic and biochemical parameters were found between those patients who switched to mTORi and those who did not.

DISCUSSION

This study aimed to perform a real-world analysis of post-KTx cancer at our transplant Center. The development of at least one cancer occurred in 19% of the KTRs. In an Italian multicenter study with a 25-year follow-up [13], an incidence rate of post-

KTx cancer of approximately 13% was reported. In a single-center experience, Gioco et al. reported a cancer incidence of 7.2% with a 7.8 years follow-up [14]. In a recent paper by Srisuwarn et al, an incidence of 6.2% post-transplant cancer was reported [15]. Our results are in line with the trend and the standardized incidence rates of international registries which vary between 1.5 and 3.8 for any post-KTx tumor [1, 3, 6].

According to data reported in the literature, NMSC was the most frequent cancer [11]. The incidence of Kaposi's sarcoma and PTLD was comparable to other KTR cohorts [16, 17].

A second cancer occurred in 32.7% of CA+ patients at 122 ± 53 months after KTx. Two consecutive NMSCs accounted for more than half of the cases and the majority of recurrences. This suggests a reevaluation of IS maintenance therapy after NMSC, considering the positive impact of switching to mTORi on reducing the first recurrence of squamous cell carcinoma [18, 19].

Age at KTx was a major risk factor. Older age at KTx is associated with a higher absolute risk of cancer because of immune system senescence with reduced immunosurveillance and the greater need for IS in marginal donors [20]. Dialysis vintage, although longer compared to CA-, was not significant ($p = 0.06$) for CA+. However, an increasing dialysis vintage was identified by Wong et al. as a significant risk factor for post-KTx solid tumors with a linear relationship [10].

Among kidney diseases, a greater presence of vasculitis was observed in CA+ subjects. This association, with a limited description in the literature, could be a consequence of the cumulative potency of prior IS treatment added to IS for KTx [21, 22]. In a paper recently published by our group, we observed a significant incidence of post-transplant cancer in vasculitis, which may be due to decreased immunosurveillance caused by a stronger immunosuppressive therapy administered before and after the transplantation [23]. In addition, we demonstrated a correlation between ADPKD and CA+, confirming some findings reported in the literature [24, 25].

A higher BMI at T1 appeared to be statistically significant; one observational study reported higher exposure to tacrolimus in obese KTRs with a substantial dose reduction required at 3 months [26]. Thus, the risk of overexposure to IS therapy may contribute to the increased risk of cancer in KTRs with a high BMI. In any case, since obesity may be independently linked to cancer development [27, 28], we explored this relationship further. We divided our cohort according to the median BMI T1 (23.6 kg/m^2). No statistical differences were found between those patients above or below the median BMI T1 in terms of time to *de novo* cancer (81 ± 49 vs. 83 ± 46 months, $p = 0.87$) and survival from *de novo* cancer (64 ± 41 vs. 61 ± 46 months, $p = 0.32$). BMI T1 also showed no influence on the type of cancer developed by the patients ($p = 0.25$). We also examined the discriminatory power of BMI T1. The ROC curve analysis, showed a significant ability to identify patients at high risk of developing *de novo* cancer ($p = 0.003$- BMI T1 23.67 Youden index 0.103, with an AUC of 0.56).

Our study shows that ATG significantly affects the risk of cancer post-KTx compared to Basiliximab. ATG use is linked to an increased risk of NMSC, kidney, and lung cancer. [29]; in other studies, ATG use was associated with an increased risk of PTLD [30, 31]. The possible reason for these findings is related to the ability of ATG to accelerate immunosenescence and the decline of cell-mediated immune responses [32]. Careful, individualized choice of induction therapy is essential to mitigate cancer risk, especially in younger recipients, those with a neoplastic history, and considering the immunologic risk profile of both recipient and donor.

We found a high mortality rate among CA+ individuals, with cancer being the leading cause of death in this group and the second leading cause in the entire cohort. Among deceased CA+ individuals, 23% had advanced or metastatic cancer at diagnosis, leading to death within 2 years. These findings highlight cancer as a major cause of death in kidney transplant recipients. The variance in median survival post-transplantation supports international registry observations of increasing long-term cancer-related mortality, which represents a cumulative risk [33]. International registries have already established that cancer represents the second or third cause of death in KTRs, a consequence of better management of infections and cardiovascular disease in the last decades [34, 35]. Our study confirms the negative impact of post-KTx cancer on outcomes and emphasizes the importance of proper screening and surveillance to enable early cancer diagnosis and more effective treatment.

In recent decades, cancer treatments have significantly improved survival and outcomes. However, KTRs are often excluded from pharmacokinetic studies and oncology trials, complicating their treatment. Nonetheless, new drug opportunities should not be dismissed. We observed active oncological treatment in only 17.5% of CA+ cases, mostly with cytotoxic chemotherapy. Contrary to reports in the literature, our study did not record any renal adverse events or rejections due to oncological therapy [36, 37]. The monocentric and retrospective nature of the study limited our ability to gather complete information on the oncological appropriateness of indications, the feasibility of optimal oncological treatment, and data to evaluate outcomes in KTRs. We hypothesized that the lack of precise indications in KTRs and limited nephrology expertise led to a conservative approach. Rousseau et al. described that, according to current guidelines, 11% of cases indicated that KTx and IS interfere with optimal specific cancer treatment [38].

According to our data, a significant improvement in survival, in both the NMSC group and other cancers was observed with the switch to mTORi compared with the second group, although the therapeutic impact of each cancer treatment could not be separated. The indication of mTORi remains controversial; some data recommend mTORi to reduce the risk of the first recurrence of NMSC [39]. In solid malignancies, highly variable data are available [40]; however, one small study found no significant difference in the mTORi group for cancer recurrence, patient survival, and graft function [41]. A meta-analysis of 56 studies reported a positive association between sirolimus and a 40% reduction in cancer risk, particularly a 56% reduction in NMSC risk [42]; however, an unexpected correlation between sirolimus and an increased risk of mortality was described [43]. To date, the introduction of mTORi along with optimal anticancer treatment are the two factors that appear to markedly improve CA+ survival. Further studies will be crucial to identify high-risk cancer patients who will benefit from the use of mTORi.

While our study has a large sample size and extended follow-up in its monocentric design, limitations exist. Nonetheless, our findings could inspire broader multicenter studies to aid in KTx-patient cancer management. Notably, initiating mTORi after cancer diagnosis correlated with improved patient survival. However, the size of our cohort limits us to basic univariate analyses, precluding in-depth examination across various cancer types. Future multicenter investigations may delve into this area of interest.

Our analysis excluded episodes of rejection: no one received ATG therapy for rejection. The retrospective nature of this study limited comprehensive data collection on post-KTx cancer management, including treatment duration, dose adjustments, therapeutic indications based on graft function, and potential no-treatment. Consequently, we could not evaluate the impact of oncological treatment on long-term clinical outcomes in KTRs.

CONCLUSION

Post-KTx cancer is a significant complication with notable mortality. Although primarily descriptive, our monocentric study includes a large number of patients. Administering ATG significantly influences early cancer development post-KTx and must be an individualized choice, taking into account recipient and donor characteristics and previous cancer history. If cancer develops, variations in IS therapy and initiations of mTORi should be considered for better outcomes.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving humans were approved by Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico Ethical Committee. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

GR, CA, LC, and GC were responsible for study concept and design; GR, LC, CA, MC, AR, SV, PM, AP, MP, LN, MG, and GC wrote the main manuscript; GR, CA, and EB performed the statistical analyses.

FUNDING

The authors declare that financial support was received for the research, authorship, and/or publication of this article. This research was funded by the Italian Ministry of Health—current research Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

ACKNOWLEDGMENTS

The authors thank Marina Balderacchi for their kind collaboration in the health research and the realization of this study.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2024.13220/full#supplementary-material

REFERENCES

1. Au E, Wong G, Chapman JR. Cancer in Kidney Transplant Recipients. *Nat Rev Nephrol* (2018) 14(8):508–20. doi:10.1038/s41581-018-0022-6
2. Vajdic CM, McDonald SP, McCredie MR, van Leeuwen MT, Stewart JH. Law Met Al. Cancer Incidence Before and After Kidney Transplantation. *JAMA* (2006)) 296(23):2823–31. doi:10.1001/jama.296.23.2823
3. Au EH, Chapman JR, Craig JC, Lim WH, Teixeira-Pinto A, Ullah S, et al. Overall and Site-Specific Cancer Mortality in Patients on Dialysis and After Kidney Transplant. *J Am Soc Nephrol* (2019) 30(3):471–80. doi:10.1681/ASN.2018090906
4. Villeneuve PJ, Schaubel DE, Fenton SS, Shepherd FA, Jiang Y, Mao Y. Cancer Incidence Among Canadian Kidney Transplant Recipients. *Am J Transpl* (2007) 7(4):941–8. doi:10.1111/j.1600-6143.2007.01736.x
5. van de Wetering J, Roodnat JI, Hemke AC, Hoitsma AJ, Weimar W. Patient Survival After the Diagnosis of Cancer in Renal Transplant Recipients: A Nested Case-Control Study. *Transplantation* (2010) 90(12):1542–6. doi:10.1097/TP.0b013e3181ff1458
6. Taborelli M, Serraino D, Cimaglia C, Furian L, Biancone L, Busnach G, et al. Cancer Mortality After Kidney Transplantation: A Multicenter Cohort Study in Italy. *Int J Cancer* (2023) 154(Nov 4):842–51. doi:10.1002/ijc.34787
7. Taborelli M, Serraino D, Cimaglia C, Furian L, Biancone L, Busnach G, et al. The Impact of Cancer on the Risk of Death With a Functioning Graft of Italian Kidney Transplant Recipients. *Am J Transpl* (2022) 22(2):588–98. doi:10.1111/ajt.16825
8. Schreiber B, Abdelrahim M, Abudayyeh A, Murakami N. Emerging Concepts in Managing Malignancy in Kidney Transplant Patients. *Semin Nephrol* (2022) 42(1):63–75. doi:10.1016/j.semnephrol.2022.01.003
9. Massicotte-Azarniouch D, Detwiler RK, Hu Y, Falk RJ, Saha MK, Hogan SL, et al. Malignancy Risk in Kidney Transplant Recipients Exposed to Immunosuppression Pre-Transplant for the Treatment of Glomerulonephritis. *Nephrol Dial Transpl* (2023) 38(9):2009–18. doi:10.1093/ndt/gfac337
10. Chukwu CA, Wu HHL, Pullerits K, Garland S, Middleton R, Chinnadurai R, et al. Incidence, Risk Factors, and Outcomes of *De Novo* Malignancy Following Kidney Transplantation. *J Clin Med* (2024) 13(7):1872. doi:10.3390/jcm13071872

11. Blosser CD, Haber G, Engels EA. Changes in Cancer Incidence and Outcomes Among Kidney Transplant Recipients in the United States Over a Thirty-Year Period. *Kidney Int* (2021) 99(6):1430–8. doi:10.1016/j.kint.2020.10.018
12. Broders AC. Squamous-Cell Epithelioma of the Skin: A Study of 256 Cases. *Ann Surg* (1921) 73(2):141–60. doi:10.1097/00000658-192102000-00001
13. Piselli P, Serraino D, Cimaglia C, Furian L, Biancone L, Busnach G, et al. Variation in Post-Transplant Cancer Incidence Among Italian Kidney Transplant Recipients Over a 25-Year Period. *Cancers (Basel)* (2023)) 15(4):1347. doi:10.3390/cancers15041347
14. Gioco R, Corona D, Agodi A, Privitera F, Barchitta M, Giaquinta A, et al. *De Novo* Cancer Incidence and Prognosis After Kidney Transplantation: A Single Center Analysis. *Transpl Proc* (2019) 51(9):2927–30. doi:10.1016/j.transproceed.2019.04.096
15. Srisuwarn P, Sutharattanapong N, Disthabanchong S, Kantachuvesiri S, Kitiyakara C, Phakdeekitcharoen B, et al. Incidence of *De Novo* Post-Transplant Malignancies in Thai Adult Kidney Transplant Recipients: A Single-Center, Population-Controlled, Retrospective Cohort Study at the Highest Volume Kidney Transplant Center in Thailand. *Transpl Int* (2024) 37:11614. doi:10.3389/ti.2024.11614
16. Opelz G, Henderson R. Incidence of Non-Hodgkin Lymphoma in Kidney and Heart Transplant Recipients. *Lancet* (1993)) 342(8886-8887):1514–6. doi:10.1016/s0140-6736(05)80084-4
17. Fuhrmann JD, Valkova K, von Moos S, Wüthrich RP, Müller TF, Schachtner T. Cancer Among Kidney Transplant Recipients >20 Years After Transplantation: Post-Transplant Lymphoproliferative Disorder Remains the Most Common Cancer Type in the Ultra Long-Term. *Clin Kidney J* (2022)) 15(6):1152–9. doi:10.1093/ckj/sfac013
18. Euvrard S, Morelon E, Rostaing L, Goffin E, Brocard A, Tromme I, et al. Sirolimus and Secondary Skin-Cancer Prevention in Kidney Transplantation. *N Engl J Med* (2012) 367(4):329–39. doi:10.1056/NEJMoa1204166
19. Dantal J, Morelon E, Rostaing L, Goffin E, Brocard A, Tromme I, et al. Sirolimus for Secondary Prevention of Skin Cancer in Kidney Transplant Recipients: 5-Year Results. *J Clin Oncol* (2018)) 36(25):2612–20. doi:10.1200/JCO.2017.76.6691
20. Webster AC, Craig JC, Simpson JM, Jones MP, Chapman JR. Identifying High Risk Groups and Quantifying Absolute Risk of Cancer After Kidney Transplantation: A Cohort Study of 15,183 Recipients. *Am J Transpl* (2007) 7(9):2140–51. doi:10.1111/j.1600-6143.2007.01908.x
21. Westman KW, Bygren PG, Olsson H, Ranstam J, Wieslander J. Relapse Rate, Renal Survival, and Cancer Morbidity in Patients With Wegener's Granulomatosis or Microscopic Polyangiitis With Renal Involvement. *J Am Soc Nephrol* (1998) 9(5):842–52. doi:10.1681/ASN.V95842
22. Thet Z, Lam AK, Ranganathan D, Aung SY, Khoo TK. Cancer Risks Along the Disease Trajectory in Antineutrophil Cytoplasmic Antibody Associated Vasculitis. *Clin Rheumatol* (2020) 39(9):2501–13. doi:10.1007/s10067-020-05055-x
23. Perna A, Campise M, Alfieri CM, Regalia A, Cresseri D, Gandolfo MT, et al. Kidney Transplantation in Patients With ANCA-Associated Vasculitis Is Associated With a High Incidence of Post-Transplant Cancer. *J Nephrol* (2024). Epub ahead of print. doi:10.1007/s40620-024-01951-6
24. Yu TM, Chuang YW, Yu MC, Chen CH, Yang CK, Huang ST, et al. Risk of Cancer in Patients With Polycystic Kidney Disease: A Propensity-Score Matched Analysis of a Nationwide, Population-Based Cohort Study. *Lancet Oncol* (2016) 17(10):1419–25. doi:10.1016/S1470-2045(16)30250-9
25. Schrem H, Schneider V, Kurok M, Goldis A, Dreier M, Kaltenborn A, et al. Independent Pre-Transplant Recipient Cancer Risk Factors After Kidney Transplantation and the Utility of G-Chart Analysis for Clinical Process Control. *PLoS One* (2016)) 11(7):e0158732. doi:10.1371/journal.pone.0158732
26. Robert V, Manos-Sampol E, Manson T, Robert T, Decourchelle N, Gruliere AS, et al. Tacrolimus Exposure in Obese Patients: and A Case-Control Study in Kidney Transplantation. *Ther Drug Monit* (2021)) 43(2):229–37. doi:10.1097/FTD.0000000000000820
27. Renehan AG, Tyson M, Egger M, Heller RF, Zwahlen M. Body-Mass Index and Incidence of Cancer: A Systematic Review and Meta-Analysis of Prospective Observational Studies. *Lancet* (2008) 371(9612):569–78. doi:10.1016/S0140-6736(08)60269-X
28. Jiménez-Cortegana C, Gutiérrez-García C, Sánchez-Jiménez F, Vilariño-García T, Flores-Campos R, Pérez-Pérez A, et al. Impact of Obesity-Associated Myeloid-Derived Suppressor Cells on Cancer Risk and Progression (Review). *Int J Oncol* (2024) 65(2):79. doi:10.3892/ijo.2024.5667
29. Wang L, Motter J, Bae S, Ahn JB, Kanakry JA, Jackson J, et al. Induction Immunosuppression and the Risk of Incident Malignancies Among Older and Younger Kidney Transplant Recipients: A Prospective Cohort Study. *Clin Transpl* (2020) 34(12):e14121. doi:10.1111/ctr.14121
30. Cherikh WS, Kauffman HM, McBride MA, Maghirang J, Swinnen LJ, Hanto DW. Association of the Type of Induction Immunosuppression With Posttransplant Lymphoproliferative Disorder, Graft Survival, and Patient Survival After Primary Kidney Transplantation. *Transplantation* (2003) 76(9):1289–93. doi:10.1097/01.TP.0000100826.58738.2B
31. Ali H, Soliman K, Daoud A, Elsayed I, Fülöp T, Sharma A, et al. Relationship Between Rabbit Anti-Thymocyte Globulin and Development of PTLD and Its Aggressive Form in Renal Transplant Population. *Ren Fail* (2020) 42(1):489–94. doi:10.1080/0886022X.2020.1759636
32. Crepin T, Carron C, Roubiou C, Gaugler B, Gaiffe E, Simula-Faivre D, et al. ATG-Induced Accelerated Immune Senescence: Clinical Implications in Renal Transplant Recipients. *Am J Transpl* (2015) 15(4):1028–38. doi:10.1111/ajt.13092
33. Johansen KL, Chertow GM, Foley RN, Gilbertson DT, Herzog CA, Ishani A, et al. US Renal Data System 2020 Annual Data Report: Epidemiology of Kidney Disease in the United States. *Am J Kidney Dis* (2021) 77(4 Suppl. 1):A7–A8. doi:10.1053/j.ajkd.2021.01.002
34. Rosales BM, De La Mata N, Vajdic CM, Kelly PJ, Wyburn K, Webster AC. Cancer Mortality in Kidney Transplant Recipients: An Australian and New Zealand Population-Based Cohort Study, 1980-2013. *Int J Cancer* (2020)) 146(10):2703–11. doi:10.1002/ijc.32585
35. D'Arcy ME, Coghill AE, Lynch CF, Koch LA, Li J, Pawlish KS, et al. Survival After a Cancer Diagnosis Among Solid Organ Transplant Recipients in the United States. *Cancer* (2019) 125(6):933–42. doi:10.1002/cncr.31782
36. Murakami N, Mulvaney P, Danesh M, Abudayyeh A, Diab A, Abdel-Wahab N, et al. A Multi-Center Study on Safety and Efficacy of Immune Checkpoint Inhibitors in Cancer Patients With Kidney Transplant. *Kidney Int* (2021) 100(1):196–205. doi:10.1016/j.kint.2020.12.015
37. Perazella MA, Shirali AC. Immune Checkpoint Inhibitor Nephrotoxicity: What Do We Know and What Should We Do? *Kidney Int* (2020) 97(1):62–74. doi:10.1016/j.kint.2019.07.022
38. Rousseau B, Guillemin A, Duvoux C, Neuzillet C, Tlemsani C, Compagnon P, et al. Optimal Oncologic Management and mTOR Inhibitor Introduction Are Safe and Improve Survival in Kidney and Liver Allograft Recipients With *De Novo* Carcinoma. *Int J Cancer* (2019) 144(4):886–96. doi:10.1002/ijc.31769
39. Opelz G, Unterrainer C, Süsal C, Döhler B. Immunosuppression With Mammalian Target of Rapamycin Inhibitor and Incidence of Post-Transplant Cancer in Kidney Transplant Recipients. *Nephrol Dial Transpl* (2016) 31(8):1360–7. doi:10.1093/ndt/gfw088
40. Hellemans R, Pengel LHM, Choquet S, Maggiore U, for ESOT Workstream 3 of the TLJ Transplant Learning Journey Project. Managing Immunosuppressive Therapy in Potentially Cured Post-Kidney Transplant Cancer (Excluding Non-Melanoma Skin Cancer): An Overview of the Available Evidence and Guidance for Shared Decision-Making. *Transpl Int* (2021) 34(10):1789–800. doi:10.1111/tri.13952
41. Cheung CY, Man Ma MK, Chak WL, Chau KF, Tang SCW. Conversion to Mammalian Target of Rapamycin Inhibitors in Kidney Transplant Recipients With *De Novo* Cancers. *Oncotarget* (2017)) 8(27):44833–41. doi:10.18632/oncotarget.14908
42. Knoll GA, Kokolo MB, Mallick R, Beck A, Buenaventura CD, Ducharme R, et al. Effect of Sirolimus on Malignancy and Survival After Kidney Transplantation: Systematic Review and Meta-Analysis of Individual Patient Data. *BMJ* (2014)) 349:g6679. Erratum in: BMJ. 2014;349:g7543. doi:10.1136/bmj.g6679
43. Badve SV, Pascoe EM, Burke M, Clayton PA, Campbell SB, Hawley CM, et al. Mammalian Target of Rapamycin Inhibitors and Clinical Outcomes in Adult Kidney Transplant Recipients. *Clin J Am Soc Nephrol* (2016)) 11(10):1845–55. doi:10.2215/CJN.00190116

ESOT | Transplant International

ORIGINAL RESEARCH
published: 09 September 2024
doi: 10.3389/ti.2024.12127

Malignancies After Lung Transplantation

Caroline Stenman[1], *Andreas Wallinder*[1,2], *Erik Holmberg*[3,4], *Kristjan Karason*[1,5,6], *Jesper Magnusson*[1,7,6] *and Göran Dellgren*[1,2,6]*

[1]Transplant Institute, Sahlgrenska University Hospital, Gothenburg, Sweden, [2]Department Cardiothoracic Surgery, Sahlgrenska University Hospital, Gothenburg, Sweden, [3]Regional Cancer Center West, Region Västra Götaland, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden, [4]Department of Oncology, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden, [5]Department Cardiology, Sahlgrenska University Hospital, Gothenburg, Sweden, [6]Department of Molecular and Clinical Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden, [7]Department of Internal Medicine/Respiratory Medicine and Allergology, Sahlgrenska University Hospital, Gothenburg, Sweden

Lung transplantation (LTx) is a well-known treatment for end-stage lung disease. This study aimed to report the incidence of cancer after LTx and long-term outcome among lung transplant recipients with a pretransplant diagnosis of cancer. Patients who underwent LTx between 1990–2016 were included in the study. Detection of cancer was obtained by cross-checking the study population with the Swedish Cancer Registry and the Cause-of-Death registry. A total of 614 patients were followed for a median of 5.1 years. In all, 159 malignancies were diagnosed. The excess risk of cancer or standardized incidence ratio (SIR) following LTx was 5.6-fold compared to the general Swedish population. The most common malignancies were non-melanoma skin cancer (NMSC) (SIR 76.5 (95%CI 61.7–94.8); non-Hodgkin lymphoma (SIR 23.5, 95%CI 14.8–37.2); and lung cancer (SIR 8.89, 95%CI 5.67–13.9). There was no significant difference in overall survival between those with and without a history of cancer before LTx ($p = 0.56$). In total, 159 malignancies were identified after LTx, which was a 5.6-fold higher relative to the general population. A history of previous cancer yields similar survival in selected recipients, compared to those without cancer prior to LTx.

Keywords: cancer, immunosuppression, heart transplantation, epidemiology, cohort study

OPEN ACCESS

***Correspondence**
Göran Dellgren,
goran.dellgren@vgregion.se,
caroline.stenman@vgregion.se

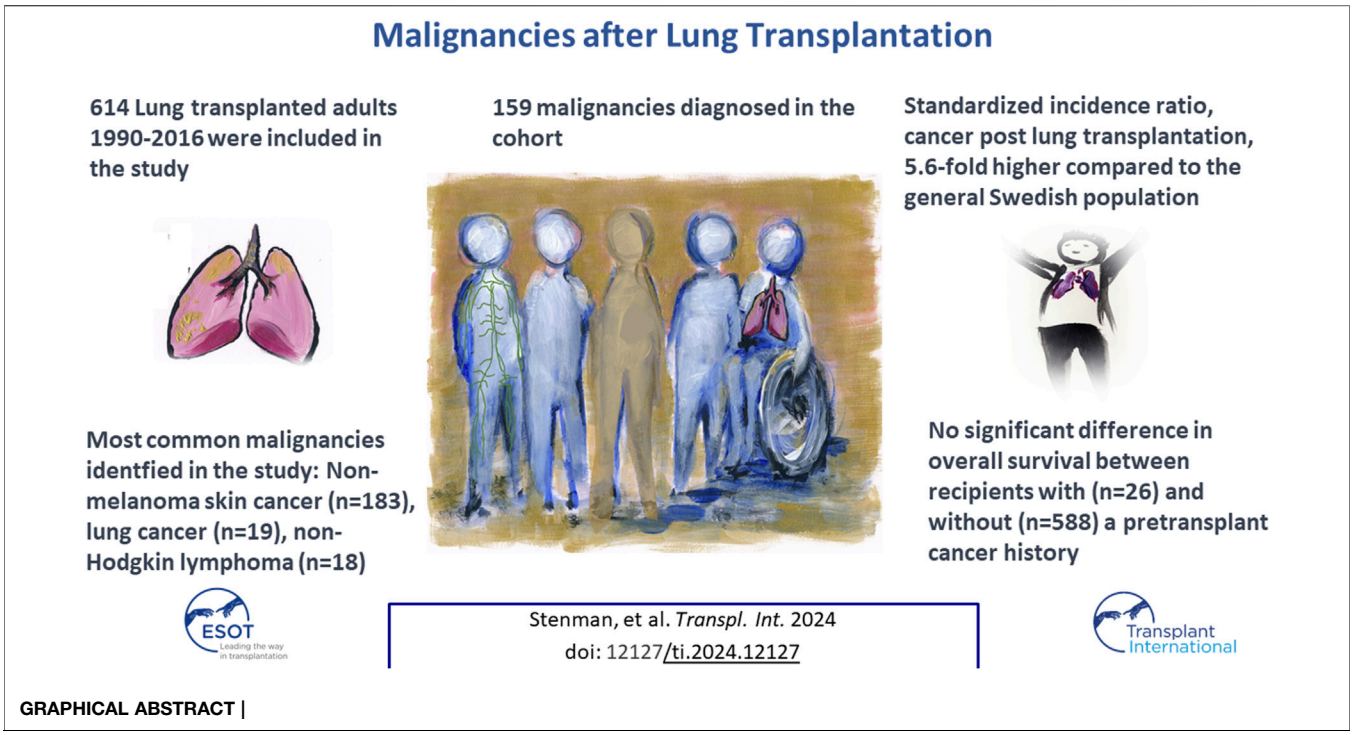
Received: *26 September 2023*
Accepted: *01 August 2024*
Published: *09 September 2024*

Citation:
Stenman C, Wallinder A, Holmberg E, Karason K, Magnusson J and Dellgren G (2024) Malignancies After Lung Transplantation. Transpl Int 37:12127. doi: 10.3389/ti.2024.12127

INTRODUCTION

Lung transplantation (LTx) is nowadays an established treatment for patients with end-stage respiratory disease [1]. The immunosuppression is a crucial component to prevent graft rejection after LTx. However, there is a well-known risk of developing cancer in immunosuppressed transplant recipients [2, 3] above all thoracic transplants [4]. After solid organ transplantation, the risk has been reported to increase 2-4-fold compared with the general

Abbreviations: BCC, basal cell carcinoma; BMI, body mass index; CI, confidence interval; CMV, cytomegalo virus; COPD, chronic obstructive pulmonary disease; GVHD, graft versus host disease, HR, hazard ratio; ICD, International Statistical Classification of Diseases; ISHLT, International Society for Heart and Lung Transplantation; LAM, lymphangioleiomyomatosis; LTx, lung transplantation; NMSC, non-melanoma skin cancer; MMF, mycophenolate mofetil; PTLD, post-transplant lympho-proliferative disease; SCR, Swedish cancer registry; SIR, standardized incidence ratio; SUH, Sahlgrenska University Hospital.



GRAPHICAL ABSTRACT |

population [5, 6]. Lung cancer has been reported to be the most common malignancy, excluding non-melanoma skin cancer (NMSC), after LTx [7]. There are several factors associated with the increased risk of developing cancer after LTx, such as: higher age of both donor and recipient; type of immunosuppression; and type of LTx (single or bilateral) [8, 9] but also likely the fact that the 5-year survival rate after LTx has increased from 46% in 1990 to 57% in 2015 [10, 11].

Our study aims to report the incidence and long-term outcome of malignancies after LTx, and to report the outcome in those treated for cancer before LTx.

MATERIALS AND METHODS

From February 1990 to December 2016, 685 LTx were performed in 633 patients at Sahlgrenska University Hospital (SUH) in Gothenburg, Sweden. We used the local patient registry at the Transplant Institute to identify those patients. We excluded those who were not Swedish citizens, and thus did not receive follow-up in Sweden after LTx (n = 19), and those who underwent re-transplantation (n = 52). The remaining 614 patients [266 (43%) men, 348 (57%) women, mean age of 50.0 years] had a median follow-up time of 5.1 years and were included in the study. Baseline characteristics for the cohort are shown in **Table 1**, also stratified for time era. Chronic obstructive pulmonary disease (177, 29%), pulmonary fibrosis (139, 23%), alfa-1-deficiency (104, 17%) and vascular disease (69, 11%) were the leading indications for lung transplantation in this cohort (**Figure 1**).

Digital and scanned medical records from the transplantation unit were reviewed for all the patients. The Swedish Population Registry, which contains complete data about population changes, such as the number of births, deaths, immigration, and emigration, was used. The cancer diagnoses were obtained from the Swedish Cancer Registry (SCR) of the National Board of Health and Welfare, which contains data on all cancers diagnosed among the Swedish population since 1958. Since the start of the registry, it has been mandatory for pathologists and clinicians in Sweden to report cancer diagnosis to the SCR. Therefore, the registry has a very high coverage rate, and all our patients were crosschecked with the SCR [12] and the national Swedish cause-of-death registry to identify all patient's survival and specifically those with a diagnosis of cancer after LTx. We did not investigate whether the patients have had basal cell carcinoma (BCC), since it is not reported in the SCR, but also since the BCC carcinoma type tends to grow slowly and metastases rarely occur [13].

At our centre, cancer, in general, has been a contraindication for listing for LTx with a few exceptions (n = 26) outlined in **Table 1**. We have followed International Society for Heart and Lung Transplantation (ISHLT) recommendations, and those with a cancer-free interval of at least 5 years, have been eligible for waitlisting [14]. All of the cancer diagnoses were histopathologically verified. The International Statistical Classification of Diseases (ICD-10) code was used to classify cancers. Our study was conducted in accordance with the Declaration of Helsinki and was approved by the Regional Ethical Review Board at University of Gothenburg (EPN no. 019-09, approval date 22nd Oct 2009, amendments approved 29th Nov 2010, 10th Dec 2012, 17th Dec 2013, 10th May 2017).

The immunosuppressive agents were administered according to a local protocol and has remained relatively unchanged over time. Most of the patients that underwent transplantation at SUH

TABLE 1 | Patient characteristics.

	Total	1985–2000	2001–2010	2011–2016	p-value
	N = 614	N = 162	N = 237	N = 215	
Sex					0.87
Males	266 (43%)	70 (43%)	100 (42%)	96 (45%)	
Females	348 (57%)	92 (57%)	137 (58%)	119 (55%)	
Age at LTx, mean (SD)	50.0 (13.7)	44.5 (12.9)	50.8 (13.2)	53.3 (13.6)	<0.001
Age at LTx, median (IQR)	54.0 (44.0,60.0)	48.5 (36.0–54.0)	55.0 (44.0,60)	56.0 (48.0,63)	<0.001
Age-group at LTx					<0.001
<18	19 (3%)	7 (4%)	7 (3%)	5 (2%)	
18–29	51 (8%)	20 (12%)	16 (7%)	15 (7%)	
30–39	53 (9%)	21 (13%)	21 (9%)	11 (5%)	
40–49	102 (17%)	39 (24%)	37 (16%)	26 (12%)	
50–59	230 (37%)	66 (41%)	94 (40%)	70 (33%)	
≥60	159 (26%)	9 (6%)	62 (26%)	88 (41%)	
Diagnoses					<0.001
COPD	177 (29%)	41 (25%)	78 (33%)	58 (27%)	
α-1-antitrypsin	104 (17%)	42 (26%)	34 (14%)	28 (13%)	
Eisenmenger	26 (4%)	21 (13%)	4 (2%)	1 (0%)	
Pulmonary arterial hypertension	43 (7%)	18 (11%)	14 (6%)	11 (5%)	
Cystic fibrosis	53 9%)	14 (9%)	20 (8%)	19 (9%)	
Pulmonary fibrosis	139 (23%)	16 (10%)	57 (24%)	66 (31%)	
Sarcoidosis	16 (3%)	2 (1%)	8 (3%)	6 (3%)	
Sclerodermia	9 (1%)	0 (0%)	7 (3%)	2 (1%)	
LAM	8 (1%)	0 (0%)	3 (1%)	5 (2%)	
GVHD	7 (1%)	0 (0%)	4 (2%)	3 (1%)	
Bronchiectasis	7 (1%)	0 (0%)	2 (1%)	5 (2%)	
Other	163 (27%)	23 (14%)	63 (27%)	77 (36%)	
Previous malignancy, and type					
Mycosis Fungoides 5	5 (19%)				
Lung	5 (19%)				
Breast	4 (15%)				
Lymphosarcoma/reticulosarcoma	2 (7%)				
Prostate	2 (7%)				
Brain and nervous system	1 (4%)				
Kidney	1 (4%)				
Bladder and urinary organs	1 (4%)				
Female genital organs	1 (4%)				
Lip	1 (4%)				
Lymphoma (reticulosis)	1 (4%)				
Skin (reticulosis)	1 (4%)				
Cervix uteri	1 (4%)				
Total	26				
Smoking					0.15
No, never	201 (33%)	57 (35%)	68 (29%)	76 (35%)	
No, stopped<6 mo. before LTx	5 (1%)	3 (2%)	1 (0%)	1 (0%)	
No, stopped>6 mo. before LTx	391 (64%)	98 (60%)	164 (69%)	129 (60%)	
Missing	17 (3%)	4 (2%)	4 (2%)	9 (4%)	
Transplant type					<0.001
Single transplant	235 (38%)	86 (53%)	126 (53%)	23 (11%)	
Double transplant	379 (62%)	76 (47%)	111 (47%)	192 (89%)	
Donor sex					0.045
Males	296 (48%)	85 (52%)	122 (51%)	89 (41%)	
Females	318 (52%)	77 (48%)	115 (49%)	126 (59%)	
Donor age (median)	46 (30, 57)	34 (21, 47)	46 (33, 57)	53 (40, 63)	<0.001
CMV mismatch					0.11
No (0)	408 (66%)	123 (76%)	153 (65%)	132 (61%)	
Yes (1)	80 (13%)	15 (9%)	36 (15%)	29 (13%)	
Missing	126 (21%)	24 (15%)	48 (20%)	54 (25%)	
BMI	22.1 (19.3, 25.6)	20.5 (18.7, 22.9)	22.4 (19.3, 26.0)	23.2 (19.9, 26.5)	<0.001
Recipient blood group					0.69
0	221 (36%)	59 (36%)	81 (34%)	81 (38%)	
A	294 (48%)	75 (46%)	117 (49%)	102 (47%)	
AB	28 (5%)	11 (7%)	8 (3%)	9 (4%)	
B	71 (12%)	17 (10%)	31 (13%)	23 (11%)	
Follow-up (years) median (IQR)	5.1 (2.2, 9.9)	8.9 (2.0, 17.0)	8.3 (2.8, 11.5)	3.7 (2.0, 5.3)	<0.001

COPD, chronic obstructive pulmonary disease; LAM, lymphangioleiomyomatosis; GVHD, graft versus host disease; CMV, cytomegalo virus.

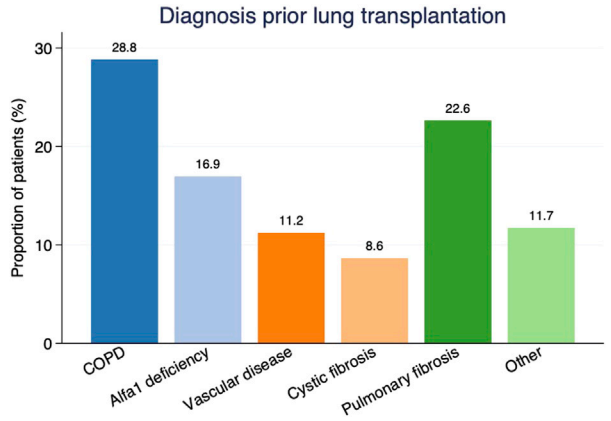


FIGURE 1 | Etiology of lung failure as proportions of patients by diagnosis prior to lung transplantation. COPD, Chronic obstructive pulmonary disease.

were treated with induction therapy (n = 599) using a t-cell antibody to minimize the risk of early acute rejection [15]. In general, all patients then received a triple combination of a calcineurin inhibitor (tacrolimus or cyclosporine), an antiproliferative agent, (mycophenolate mofetil (MMF) or Azathioprine), and steroids (Prednisone) [16]. The most used calcineurin inhibitor has been cyclosporine, and Azathioprine was replaced as the antiproliferative agent by MMF in 2004-2005.

Data are presented as means and standard deviations, medians and interquartile ranges, or numbers and percentages. Overall survival curves were generated using Kaplan-Meier estimates and comparisons between groups were performed with the log rank test. Relative survival was calculated using the Ederer II method [17]. Mortality data for the general population in Sweden was used to estimate expected survival rates. The mortality data comprised the probability of death for single-year age groups in 1-year calendar period. Cumulative incidence of cancer was analyzed using competing risk methods with death as a competing event [18]. When analyzing cancer incidence for different cancer types, person-years were calculated from date of the transplantation to the first of the following events: diagnosis of the cancer site; death; or end of surveillance period, i.e., 31 December 2018. The standardized incidence ratio (SIR) was defined as the observed number of cancers during the observation time divided by the expected number of cases, using incidence rates from the Swedish population stratified for 5-year age groups (0–4, 5–9, . . . 80–84, 85-), sex and calendar year. Incidence rates for different cancer sites were used from the NORDCAN project. Furthermore, the coding of cancer followed definitions according to international rules for multiple primary cancers [19]. Univariable and multivariable risk factor analyses were performed by Cox proportional hazards regression model for the development of posttransplant malignancy. The following parameters were tested by univariable analyses: age (per 10 years), sex, body mass index (BMI, <20; 20–30; >30), smoking (never; cessation >6 months before LTx listing; cessation <6 months before LTx listing), diagnostic groups, donor age (per 10 years), donor cytomegalo virus (CMV) +/−, recipient CMV+/−, CMV mismatch and recipient blood group. Significant risk factors identified in the univariate models were tested also in a multivariable model. All statistical tests were two-sided, and a p-value of <0.05 was considered statistically significant. Statistical analyses were carried out with Stata/IC 16.1.

RESULTS

Mortality for the whole patient cohort within 30 days and 1-year post-transplant was 36/614 (6%) and 107/614 (17%), respectively. Overall survival for the whole cohort at 1, 5, and 10 years was: 82% (95%CI 79%–85%); 61% (95%CI 57%–65%); and 43% (95% CI 38%–47%), respectively. Five-year overall survival for those who underwent LTx: was 59% (95%CI: 51%–66%) between 1990 and 2000; 65% (95%CI: 59%–71%) between 2001 and 2010; and 57% (95%CI: 49%–64%) between 2011 and 2016 (**Figures 2A–D**). There was no significant difference in overall survival over time (p = 0.52). However, risk profile has dramatically changed over time, as illustrated by recipients above 60 years of age were only 6% in the first compared to 41% in the last time-era (p < 0.001) (**Table 1**).

A total of 159 *de novo* cancers were diagnosed in 111 LTx patients (48 men and 63 women) during follow-up, which corresponds to 18% of the total study population (**Table 2**). In comparison, 28.6 cancers would have been detected in a cohort from the general population matched by age, sex, and time period. The resulting SIR was 5.56 (95%CI 4.76–6.50) for all cancers after LTx, and 2.76 (95%CI: 2.21–3.46) after excluding NMSC.

Our study's cumulative incidence of death was 16.4% at 1 year, 33.3% at 5 years, 46.8% at 10 years and 56.1% at 15 years post-transplantation. Corresponding numbers for the cumulative incidence of cancer were: 2.7% at 1 year; 10.6% at 5 years; 17.9% at 10 years; 22.5% at 15 years; and 23.6% at 20 years (**Figures 2A, B**). The cumulative incidence of *de novo* malignancy after LTx showed no significant difference between time eras (p = 0.40) (**Figure 2C**). There was no significant difference in overall mortality (p = 0.29) between the three time periods (**Figure 2D**).

The type and frequency of solid tumors for the total group, and shown separately for men and women, are listed in **Table 2**. The most common type of cancer after LTx was non-melanoma skin cancer (NMSC) (52.2% of all cancers), lung cancer (11.9% of all cancers), and non-Hodgkin Lymphoma (11.3% of all cancers). Of those 19 lung cancers that we found after LTx, the majority (n = 13) were developed in the transplanted lung, four in the native lung and two were unknown.

The SIR for cancer types diagnosed in 4 or more individuals are shown in **Table 3**. The excess risk of all cancers for the total population was 5.6 and similar between men and women (SIR 4.90 and SIR 6.17, respectively).

The overall incidences of cancers in the cohort were higher than expected for: NMSC SIR 76.5 (95%CI 61.7–94.8); non-Hodgkin Lymphoma (SIR 23.5, 95%CI 14.8–37.2); lung cancer

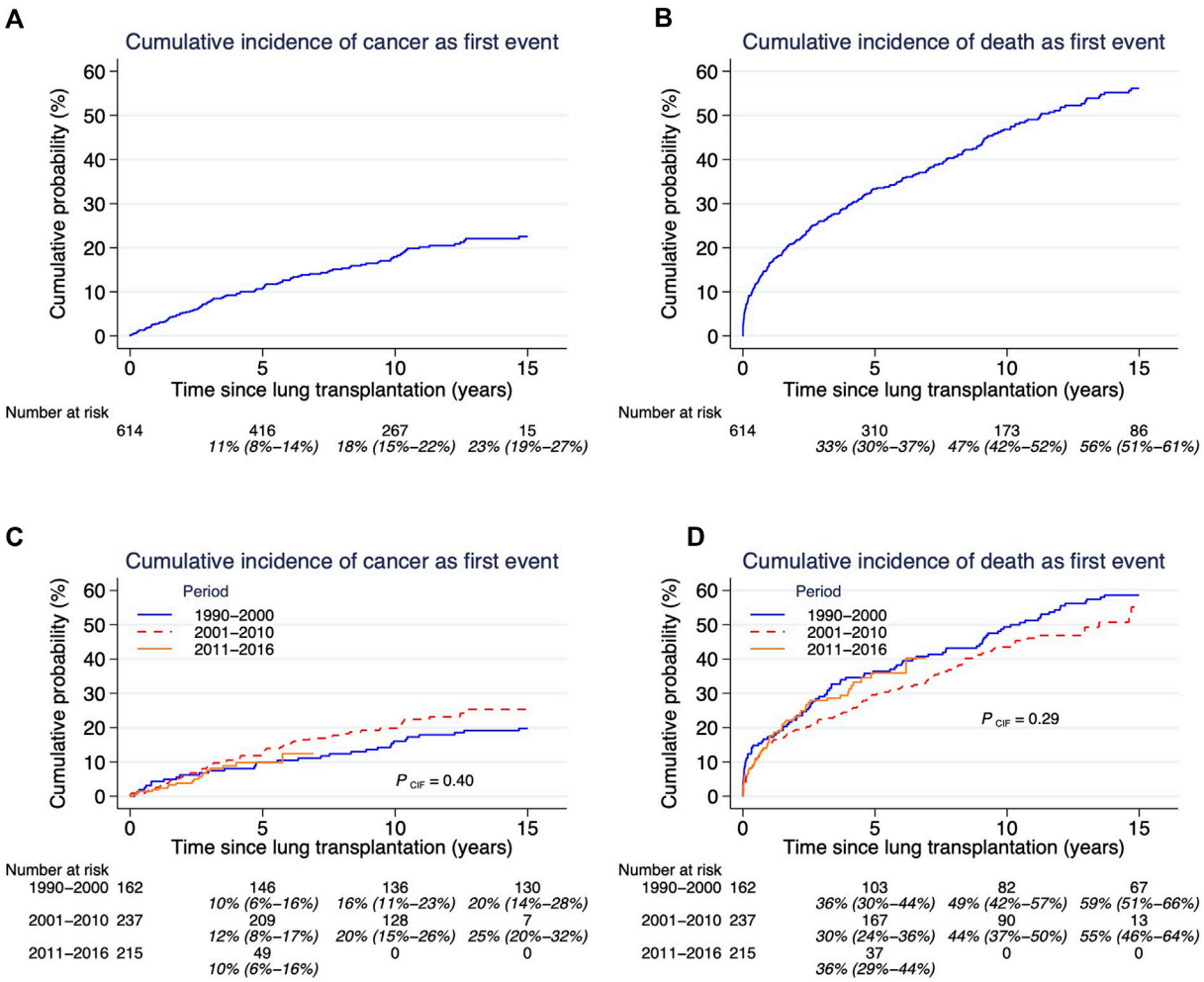


FIGURE 2 | (A–D) Cumulative probability of cancer and cumulative incidence of death. Cumulative incidence of competing risks cancer (panel **(A)**] and death [panel **(B)**], and related to time-era after lung transplantation. Both outcomes cancer and death need to be assessed together since they are competing outcomes. Estimates and 95% confidence intervals are shown under the number of patients at risk.

(SIR 8.89, 95%CI 5.67–13.9); and malignant melanoma (SIR 3.24, 95%CI 0.35–7.78).

Univariable and multivariable analysis between baseline characteristics and NMSC only is shown in **Table 4**. Significant risk factors in the multivariable model predicting NMSC only were: age per 10 years [HR 2.23, (95%CI 1.51–3.42), $p < 0.001$] and recipient blood group A [HR 2.36, (95%CI 1.01–5.53), $p < 0.001$].

We found 26 (4%) malignancies in 26 patients that had occurred 9.1 years (IQR 2.3–18.3) before LTx. Three of these were actually lung cancers detected at LTx. The median age at their first tumor before LTx was 42 years (IQR 33–53 years), and at LTx the recipient median age was 53 years (IQR 44–59). The most common cancers were: lung, breast, prostate, lymphosarcoma and reticulosarcoma which are shown in **Table 1**. There was no significant difference in overall survival between those with and without a history of cancer before LTx ($p = 0.80$) (**Figure 3**). Furthermore, there was no significant difference ($p = 0.73$) in post-LTx relative survival between cancer-free patients *versus* those who had experienced cancer before LTx (**Figure 4**).

We have no data regarding recurrence of cancers in patients who had malignancy before LTx.

DISCUSSION

This Swedish cohort of lung transplanted patients was studied through national obligatory cancer and cause of death registries, and we observed an overall 5.6-fold excess risk of cancer relative to the general population after a median of 5.1 years of follow-up. The majority of these cancers were NMSC, and when we excluded them from analysis, the risk relative to the general population was reduced to a 2.8-fold excess risk of developing

TABLE 2 | Cancer following LTx 1990–2016.

Cancer site (ICD-10)	Sex		Total
	Males	Females	
Extrahepatic bile duct (C24)	0	1	1
Bladder (C67)	2	1	3
Breast (C50)	0	2	2
Colon (C18)	1	1	2
Cervix uteri (C53)	0	1	1
Gallbladder (C23)	1	0	1
Gastric (C16)	1	1	2
Hodgkin lymphoma (C81)	0	2	2
Isthmus uteri (C54)	0	1	1
Lip (C00)	0	2	2
Lung (C34)	6	13	19
Liver cell carcinoma (C22)	1	1	2
Malignant melanoma (C43)	2	3	5
Mouth (C06)	1	0	1
Non-Hodgkin Lymphoma (C83-C85)	4	14	18
Other malignant neoplasms of skin (C44)	39	44	83
Pancreas (C25)	0	1	1
Penis (C60)	1	0	1
Prostate (C61)	8	0	8
Thyroid gland (673)	0	2	2
Vulva (C51)	0	2	2
Total	**68**	**92**	**159**

cancer. We also noted, that there was no significantly different survival in patients who had a cancer before LTx, compared to those without a cancer.

Transplanted patients have a higher risk of developing skin cancer. It is also known that those tumors are more aggressive compared to immunocompetent patients [20]. We identified NMSC as the most common cancer, with 83 cancers in a total cohort of 614 patients (13.5%) after LTx. Rashtag et al. identified skin tumors in approximately 28% (47/166 patients) after a median follow-up of 3 years. Berastegui et al. found 39 cases of NMSC in their cohort of 1100 patients (3.5%) after a follow-up of 3 years. However, the data from these studies were not obtained from a national population registry or cancer registry, as in our study, but from individual hospital databases, which might result in missing cancer diagnoses during follow-up. In our study, among NMSC only, age and blood group were identified as independent predictors of developing NMSC after LTx. In concordance Rashtak et al. reported that age per 10 years [HR 1.54 (95%CI 1.14–2.09), p = 0.005] but also male sex [HR 2.79 (95%CI 1.48–5.28), p = 0.002] and a history of NMSC [HR 4.23 (95%CI 1.93–9.26), p =<0.001] were associated with the development of NMSC after lung transplantation [21].

In our study, when we excluded NMSC, the excess risk was 2.8 -fold to develop cancer in relation to the general population. In comparison, a large American study by Magruder et al. observed a 3.26-fold excess risk to develop cancer. In a Spanish study with 1353 patients by Berastegui et al. 125 (9.2%) developed cancer after a mean of 3.7 years, which resulted in a 5-fold higher risk compared to the general population [22]. The cumulative incidence of a *de novo*

TABLE 3 | Observed and expected cancer risks following LTx[a].

Site (ICDO-10)	Observer number	Expected number	Person years	SIR (95% CI)
All sites				
Total	159	28.6	3903	5.56 (4.7–6.50)
Males	67	13.7	1722	4.90 (3.8–6.23)
Females	92	14.9	2181	6.17 (5.03–7.57)
All sites (exluding NMSC)				
Total	76	27.5	3903	2.76 (2.21–3.46)
Males	28	13.1	1722	2.14 (1.48–3.10)
Females	19	14.4	2181	3.34 (2.51–4.43)
Lung (C33, C34)				
Total	19	2.14	3903	8.89 (5.67–13.9)
Males	6	0.90	1722	6.64 (2.98–14.8)
Females	13	1.23	2181	10.5 (6.12–18.1)
Malignant melanoma (C43)				
Total	5	1.54	3903	3.24 (0.35–7.78)
Males	2	0.71	1722	2.82 (0.70–11.3)
Females	3	0.83	2181	3.60 (1.16–11.1)
Skin, exkl. malignant melanoma (C44)				
Total	83	1.09	3903	76.5 (61.7–94.8)
Males	39	0.58	1722	68.6 (50.1–93.9)
Females	44	0.52	2181	85.1 (63.3–114)
Prostate (C61)	8	5.12	1696	1.56 (0.78–3.13)
Males				
Non-Hodgkin Lymphoma (C81-C85)				
Total	18	0.77	3903	23.5 (14.8–37.2)
Males	4	0.40	1722	10.0 (3.76–26.7)
Females	5	0.17	2180	38.1 (22.5–64.3)

[a]*Observed and expected number of cancers, person years in follow-up and Standardized Mortality Ratio (SIR) per site after lung transplantation. NMSC, nonmelanoma skin cancer (not including basal cancer).*

TABLE 4 | Uni- and multivariable Cox proportional hazard regression for developing NMSC after LTx[a].

Variable	Number of persons with cancer/N	Cox proportional hazard regression			
		Univariable		Multivariable	
		HR (95% CI)	p	HR (95% CI)	p
Age at LTx, per 10 years	36/614	2.25 (1.51–3.36)	<0.001	2.23 (1.51–3.42)	<0.001
Sex					
Male	16/266	1.0 (ref.)			
Female	20/348	0.98 (0.50–1.88)	0.94		
BMI					
<20	13/196	1.0 (ref.)			
20–30	22/363	1.06 (0.54–2.12)	0.86		
>30	1/50	0.42 (0.05–3.12)	0.40		
Smoking					
No, ended >6 mon before LTx	9/206	1.0 (ref.)			
No, ended <6 mon before LTx	27/391	1.67 (0.78–3.55)	0.50		
Diagnosis group					
COPD	15/177	1.0 (ref.)			
Alfa1 deficiency	9/104	0.96 (0.42–2.19)	0.92		
Vascular disease	0/69	-	-		
Cystic fibrosis	1/53	0.21 (0.03–1.56)	0.13		
Pulmonary fibrosis	9/139	0.96 (0.42–2.19)	0.92		
Other	2/72	0.94 (0.40–2.22)	0.89		
Donor age, per 10 years	36/614	0.34 (0.08–1.50)	0.16		
Recipient blood group					
0	7/221	1.0 (ref.)		1.0 (ref)	
A	22/294	2.46 (1.05–5.76)	0.038	2.36 (1.01–5.53)	0.048
AB	2/28	2.45 (0.51–11.8)	0.18	2.96 (0.61–14.3)	0.18
B	5/71	1.95 (0.62–6.16)	0.72	1.73 (0.55–5.46)	0.35
CMV mismatch					
No	24/408	1.0 (ref.)			
Yes	8/80	1.92 (0.86–4.28)	0.11		

[a]*Time from date of lung transplantation (LTx) to first cancer analyzed. Twenty years follow-up.*

LTx, lung transplantation; NMSC, non-melanoma skin cancer; BMI, body mass index; CMV, cytomegalo virus; COPD, chronic obstructive pulmonary disease.

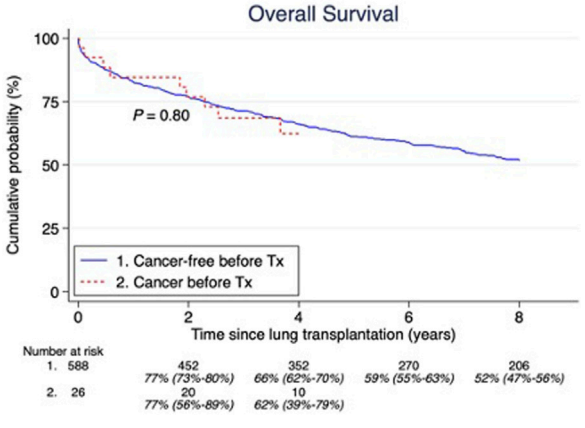


FIGURE 3 | Pretransplant malignancy overall survival compared to those without. Estimates and 95% confidence intervals are shown under the number of patients at risk.

malignancy between 1 and 5 years after LTx was 7.9%. The most common cancer was NMSC, followed by non-Hodgkin Lymphoma and lung cancer, very similar to our observations. There were no independent predictors of cancer (excluding NMSC) in our study. Predictors of *de novo* malignancies following LTx presented by Magruder et al. were age, male sex and single-lung transplantation. The cumulative incidence of death was in our study 16.4% at 1 year 33.3% at 5 years, 46.8% at 10 years and 56.1% at 15 years post transplantation. Although some report limited survival among lung transplant recipients, Rashtak et al. reported a 53% mortality at 5 years and 86% at 10 years post-LTx. Our survival was better, but clearly lower than for other organ transplants [21]. Corresponding numbers, in a study with over 4000 patients, 5 years and 10 years after liver transplantation was 21% and 33% respectively [23]. A study on kidney transplantation showed a 11% mortality at 5 years and 22% after 10 years. [24]. Obviously, death as an event is a competing outcome to developing cancer, and particularly in LTx with a relatively high cumulative early death rate, the assessment of survival and cancer incidence needs to be analyzed together. Clearly, our study also shows that there was no difference in cumulative incidence of cancer between time eras, and considering that recipients have become older and sicker when accepted for LTx, this might even imply a better screening and detection of cancer in modern era.

After NMSC, non-Hodgkin lymphoma had the highest incidence (SIR 23) of cancer after LTx. A well-known complication after lung transplantation is post-transplant lympho-proliferative disease (PTLD) [25], however this entity

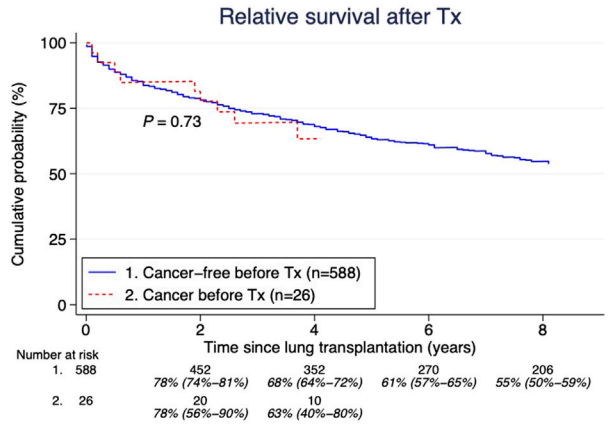


FIGURE 4 | Pretransplant malignancy relative survival compared to those without. Estimates and 95% confidence intervals are shown under the number of patients at risk.

does not have its own ICD number, and we account them as non-Hodgkin lymphoma since they are registered in that way by the SCR. In a study by Zaffiri et al. using ISHLT database with more than 19,000 lung transplant procedures registered they were able to identify 454 PTLD, resulting in a cumulative incidence of about 1% during the first year [26]. However, data from this registry was from an international community with a high risk of missing data and not compared to population in general, but our data indicate similar figures, although we cannot discriminate between PTLD and non-Hodgkin lymphomas.

We found a total of 19 lung cancers in 19 patients (3.1%), resulting in a 8.9-fold increased risk after LTx. Corroborating our findings, a French study by Chatron et al. found a total of 19 lung cancers in 463 patients after LTx (4.10%) after a median follow-up time of 21.5 months. [27]. Out of 633 lung transplant patients Pérez-Callejo et al. found that lung cancer was detected in 23 of them (3.63%), with a median follow-time of 3.5 years. [28]. Magruder et al. found the most common cancer after LTx was lung cancer (26.2% of all malignancies, SIR 6.49, 95% CI: 5.04–8.45) after a median follow-up time of 2.97 years. In a large study from the United States, Engels et al. also found an increased risk of developing lung cancer after LTx, resulting in a SIR not very different from ours SIR6.13 (95% CI, 5.18–7.21) [29]. The ISHLT reported that cancer was the 2nd most common cause of death in patients who underwent LTx five to 10 years out from transplant (17.3%) and for patients who were more than 10-year after the procedure (17.9%) [11]. In our cohort, 65% of the patients confirmed a smoking history. Earlier studies have reported that smoking history and older age have been shown to increase the risk of lung cancer after LTx, which are the same risk factors as for the general population. Interestingly, previous smoking was not identified in our study as a predictor of cancer, neither by univariable nor by multivariable testing. Those patients who received a single lung have been reported to be at a higher risk for lung cancer (compared to those who underwent double lung transplantation). The native lung left behind has with inherent risk from the underlying disease, been claimed as a possible explanation [7, 28–32]. Predictors of *de novo* malignancies following LTx presented by Magruder et al. were age, male sex, and single-lung transplantation [7].

CONCLUSION

In total 159 malignancies were identified after LTx, which was a 5.6-fold higher relative to the general population. A history of previous cancer yields similar survival in selected recipients, compared to those without cancer prior to LTx.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

Our study was conducted in accordance with the Declaration 79 of Helsinki and was approved by the Regional Ethical Review Board at University of Gothenburg (EPN no. 019-09, approval date 22nd Oct 2009, amendments approved 29th 80 Nov 2010, 10th Dec 2012, 17th Dec 2013, 10 81th May 2017).

AUTHOR CONTRIBUTIONS

CS: conceived and designed the analysis, collected the data, wrote the paper. AW: conceived and designed the analysis. EH: collected the data, performed the analysis, wrote the paper. KK: conceived and designed the analysis, collected the data, wrote the paper. JM: collected the data, wrote the paper. GD: conceived and designed the analysis, collected the data, performed the analysis, wrote the paper. All authors contributed to the article and approved the submitted version.

FUNDING

The author(s) declare(s) that no financial support was received for the research, authorship, and/or publication of this article.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

ACKNOWLEDGMENTS

The aim of this article is to investigate cancer after lung transplantation. My colleagues and I published a paper entitled "Sun protection behaviour in organ transplant recipients and non-transplant patients attending a dermatology outpatient clinic in Sweden: A questionnaire survey." Photodermatol Photoimmunol Photomed. 2022 Mar; 38(2):132-140. doi: 10.1111/phpp.12726. Epub 2021 Aug 30.PMID: 34416022 This article included a survey among 696 organ transplant recipients (lung, heart, kidney, liver, and pancreas) focused on sun habits after transplantation.

REFERENCES

1. Yusen RD, Edwards LB, Dipchand AI, Goldfarb SB, Kucheryavaya AY, Levvey BJ, et al. The Registry of the International Society for Heart and LUNG Transplantation: Thirty-Third Adult LUNG and Heart-Lung Transplant Report-2016; Focus Theme: Primary Diagnostic Indications for Transplant. *J Heart Lung Transpl* (2016) 35(10):1170–84. doi:10.1016/j.healun.2016.09.001
2. Adami J, Gabel H, Lindelof B, Ekström K, Rydh B, Glimelius B, et al. Cancer RISK Following Organ Transplantation: A Nationwide Cohort Study in Sweden. *Br J Cancer* (2003) 89(7):1221–7. doi:10.1038/sj.bjc.6601219
3. Hall EC, Pfeiffer RM, Segev DL, Engels EA. Cumulative Incidence of Cancer After Solid Organ Transplantation. *Cancer* (2013) 119(12):2300–8. doi:10.1002/cncr.28043
4. Krynitz B, Edgren G, Lindelof B, Baecklund E, Brattström C, Wilczek H, et al. RISK of SKIN Cancer and Other Malignancies in Kidney, Liver, Heart and LUNG Transplant Recipients 1970 to 2008--a Swedish Population-Based Study. *Int J Cancer* (2013) 132(6):1429–38. doi:10.1002/ijc.27765
5. Collett D, Mumford L, Banner NR, Neuberger J, Watson C. Comparison of the Incidence of Malignancy in Recipients of Different Types of Organ: A UK Registry Audit. *Am J Transplant : official J Am Soc Transplant Am Soc Transpl Surgeons* (2010) 10(8):1889–96. doi:10.1111/j.1600-6143.2010.03181.x
6. Ippoliti G, Rinaldi M, Pellegrini C, Vigano M. Incidence of Cancer After Immunosuppressive Treatment for Heart Transplantation. *Crit Rev Oncol Hematol* (2005) 56(1):101–13. doi:10.1016/j.critrevonc.2005.03.013
7. Magruder JT, Crawford TC, Grimm JC, Kim B, Shah AS, Bush EL, et al. RISK Factors for De NOVO Malignancy Following LUNG Transplantation. *Am J Transpl* (2017) 17(1):227–38. doi:10.1111/ajt.13925
8. Dickson RP, Davis RD, Rea JB, Palmer SM. HIGH Frequency of Bronchogenic Carcinoma After Single-Lung Transplantation. *J Heart Lung Transpl* (2006) 25(11):1297–301. doi:10.1016/j.healun.2006.09.009
9. Opelz G, Dohler B. Lymphomas After Solid Organ Transplantation: A Collaborative Transplant Study Report. *Am J Transplant : official J Am Soc Transplant Am Soc Transpl Surgeons* (2004) 4(2):222–30. doi:10.1046/j.1600-6143.2003.00325.x
10. Yusen RD, Edwards LB, Kucheryavaya AY, Benden C, Dipchand AI, Goldfarb SB, et al. The Registry of the International Society for Heart and LUNG Transplantation: Thirty-Second Official Adult LUNG and Heart-Lung Transplantation Report--2015; Focus Theme: Early Graft Failure. *J Heart Lung Transpl* (2015) 34(10):1264–77. doi:10.1016/j.healun.2015.08.014
11. Chambers DC, Yusen RD, Cherikh WS, Goldfarb SB, Kucheryavaya AY, Khusch K, et al. The Registry of the International Society for Heart and LUNG Transplantation: Thirty-Fourth Adult LUNG and Heart-Lung Transplantation Report-2017; Focus Theme: Allograft Ischemic TIME. *J Heart Lung Transpl* (2017) 36(10):1047–59. doi:10.1016/j.healun.2017.07.016
12. Barlow L, Westergren K, Holmberg L, Talbäck M. The Completeness of the Swedish Cancer Register: A Sample Survey for YEAR 1998. *Acta Oncol* (2009) 48(1):27–33. doi:10.1080/02841860802247664
13. Rubin AI, Chen EH, Ratner D. Basal-Cell Carcinoma. *N Engl J Med* (2005) 353(21):2262–9. doi:10.1056/NEJMra044151
14. Weill D, Benden C, Corris PA, Dark JH, Davis RD, Keshavjee S, et al. A Consensus Document for the Selection of LUNG Transplant Candidates: 2014—An Update FROM the Pulmonary Transplantation Council of the International Society for Heart and LUNG Transplantation. *The J Heart Lung Transplant* (2015) 34(1):1–15. doi:10.1016/j.healun.2014.06.014
15. Van den Hoogen MW, Hoitsma AJ, Hilbrands LB. Anti-T-cell Antibodies for the Treatment of Acute Rejection After Renal Transplantation. *Expert Opin Biol Ther* (2012) 12(8):1031–42. doi:10.1517/14712598.2012.689278
16. Gilljam M, Nystrom U, Dellgren G, Skog I, Hansson L. Survival After LUNG Transplantation for Cystic Fibrosis in Sweden. *Eur J Cardiothorac Surg* (2017) 51(3):571–6. doi:10.1093/ejcts/ezw328
17. Ederer F, Axtell LM, Cutler SJ. The Relative Survival RATE: A Statistical Methodology, *Natl Cancer Inst Monogr* (1961) 6:101–21.
18. Fine JP, Gray RJ. A Proportional Hazards Model For the Subdistribution of A Competing RISK. *J Am Stat Assoc* (1999) 94(446):496–509. doi:10.1080/01621459.1999.10474144
19. International rules for multiple primary cancers (ICD-0 third edition). International Rules for Multiple Primary Cancers (ICD-0 Third Edition). *Eur J Cancer Prev: official J Eur Cancer Prev Organisation (Ecp)* (2005) 14(4):307–8. doi:10.1097/00008469-200508000-00002
20. Euvrard S, Kanitakis J, Pouteil-Noble C, Disant F, Dureau G, Finaz de Villaine J, et al. Aggressive Squamous CELL Carcinomas in Organ Transplant Recipients. *Transplant Proc* (1995) 27(2):1767–8.
21. Rashtak S, Dierkhising RA, Kremers WK, Peters SG, Cassivi SD, Otley CC. Incidence and RISK Factors For SKIN Cancer Following LUNG Transplantation. *J Am Acad Dermatol* (2015) 72(1):92–8. doi:10.1016/j.jaad.2014.09.010
22. Berastegui C, LaPorta R, López-Meseguer M, Romero L, Gómez-Ollés S, Riera J, et al. Epidemiology and RISK Factors For Cancer After LUNG Transplantation. *Transpl Proc* (2017) 49(10):2285–91. doi:10.1016/j.transproceed.2017.09.043
23. Jain A, Reyes J, Kashyap R, Dodson SF, Demetris AJ, Ruppert K, et al. Long-Term Survival After Liver Transplantation in 4,000 Consecutive Patients At A Single Center. *Ann Surg* (2000) 232(4):490–500. doi:10.1097/00000658-200010000-00004
24. Scheffner I, Gietzelt M, Abeling T, Marschollek M, Gwinner W. Patient Survival After Kidney Transplantation: Important Role of Graft-Sustaining Factors as Determined By Predictive Modeling Using Random Survival Forest Analysis. *Transplantation* (2020) 104(5):1095–107. doi:10.1097/TP.0000000000002922
25. Penn I, Hammond W, Brettschneider L, Starzl TE. Malignant Lymphomas in Transplantation Patients. *Transpl Proc* (1969) 1(1):106–12.
26. Zaffiri L, Long A, Neely ML, Cherikh WS, Chambers DC, Snyder LD. Incidence and Outcome of Post-transplant Lymphoproliferative Disorders in Lung Transplant Patients: Analysis of ISHLT Registry. *J Heart Lung Transpl* (2020) 39(10):1089–99. doi:10.1016/j.healun.2020.06.010
27. Chatron E, Dégot T, Salvaterra E, Dumazet A, Porzio M, Hirschi S, et al. Lung Cancer After LUNG Transplantation: An Analysis of 25 Years of Experience in a Single Institution. *Clin Transplant* (2019) 33(1):e13446. doi:10.1111/ctr.13446
28. Pérez-Callejo D, Torrente M, Parejo C, Laporta R, Ussetti P, Provencio M. Lung Cancer in LUNG Transplantation: Incidence and Outcome. *Postgrad Med J* (2018) 94(1107):15–9. doi:10.1136/postgradmedj-2017-134868
29. Engels EA, Pfeiffer RM, Fraumeni JF, Jr., Kasiske BL, Israni AK, Snyder JJ, et al. Spectrum of Cancer RISK Among US Solid Organ Transplant Recipients. *Jama* (2011) 306(17):1891–901. doi:10.1001/jama.2011.1592
30. Triplette M, Crothers K, Mahale P, Yanik EL, Valapour M, Lynch CF, et al. Increased RISK of LUNG Cancer in LUNG Transplant Recipients in the United States. *Am J Of Respir And Crit Care Med* (2017) 195.

31. Raviv S, Hawkins KA, DeCamp MM, Jr., Kalhan R. LUNG Cancer in Chronic Obstructive Pulmonary Disease: Enhancing Surgical Options and Outcomes. *Am J Respir Crit Care Med* (2011) 183(9):1138–46. doi:10.1164/rccm.201008-1274CI
32. Brown SW, Dobelle M, Padilla M, Agovino M, Wisnivesky JP, Hashim D, et al. Idiopathic Pulmonary Fibrosis and LUNG Cancer. A Systematic Review and Meta-Analysis. *Ann Am Thorac Soc* (2019) 16(8):1041–51. doi:10.1513/AnnalsATS.201807-481OC

ESOT | Transplant International

ORIGINAL RESEARCH
published: 09 September 2024
doi: 10.3389/ti.2024.12109

Malignancies After Heart Transplantation

Caroline Stenman[1], Andreas Wallinder[1,2], Erik Holmberg[3,4], Kristjan Karason[1,5,6], Jesper Magnusson[1,7,6] and Göran Dellgren[1,2,6]*

[1]Transplant Institute, Sahlgrenska University Hospital, Gothenburg, Sweden, [2]Department of Cardiothoracic Surgery, Sahlgrenska University Hospital, Gothenburg, Sweden, [3]Regional Cancer Center West, Region Västra Götaland, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden, [4]Department of Oncology, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden, [5]Department of Cardiology, Sahlgrenska University Hospital, Gothenburg, Sweden, [6]Department of Molecular and Clinical Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden, [7]Department of Internal Medicine/Respiratory Medicine and Allergology, Sahlgrenska University Hospital, Gothenburg, Sweden

Heart transplant patients have an increased risk of developing cancer. Patients who underwent HTx between 1985 and 2017 were included. Detection of cancer was obtained by cross-checking the study population with the Swedish Cancer-Registry and the Cause-of-Death-Registry. A total of 664 patients were followed for a median of 7.7 years. In all, 231 malignancies were diagnosed in 138 patients. Compared to the general population the excess risk of cancer following HTx was 6.2-fold calculated as the standardized incidence ratio (SIR) and 2.9-fold after exclusion of non-melanoma skin cancer (NMSC). The most common malignancies were NMSC, non-Hodgins lymphoma, and lung cancer. There was no significant difference in overall survival between those with and without a history of cancer before HTx ($p = 0.53$). During a median follow-up of 7.7 years, 19% of HTx recipients developed cancer, 6.2-fold higher relative to the general population, and 2.9-fold higher when excluding NMSC. Risk factors for malignancies (excluding NMSC) included previous smoking, hypertension and prolonged ischemic time; and for NMSC, increasing age, seronegative CMV-donors, and azathioprine. A previous cancer in selected recipients results in similar survival compared to those without cancer prior to HTx.

Keywords: cancer, heart transplantation, epidemiology, cohort study, single center study

***Correspondence**
Caroline Stenman,
caroline.stenman@vgregion.se

***Received:** 24 September 2023*
***Accepted:** 01 August 2024*
***Published:** 09 September 2024*

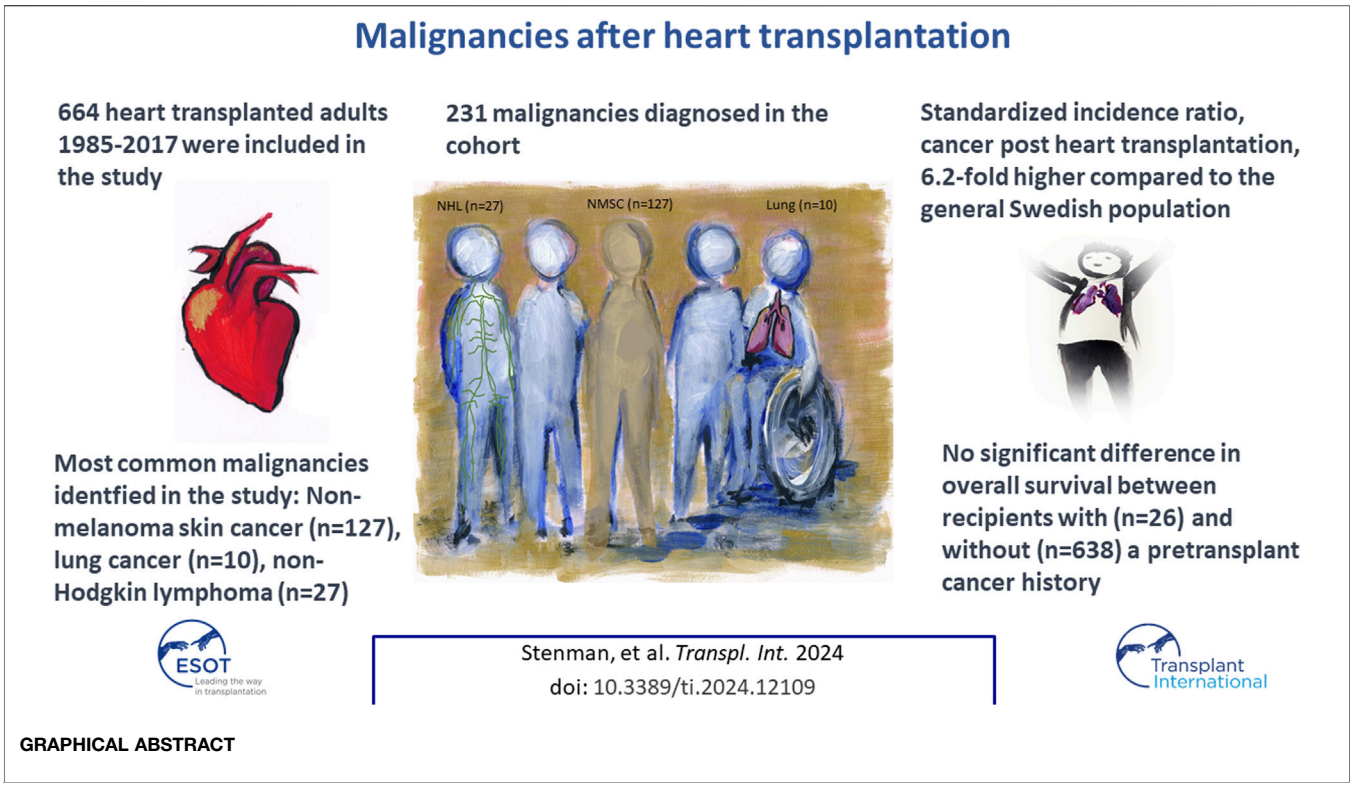
Citation:
Stenman C, Wallinder A, Holmberg E, Karason K, Magnusson J and Dellgren G (2024) Malignancies After Heart Transplantation. Transpl Int 37:12109. doi: 10.3389/ti.2024.12109

INTRODUCTION

Heart transplantation (HTx) is a life-saving treatment for end-stage heart failure. Long-term survival after HTx is limited by several risk factors.; one of them being malignancies. As compared with the general population, solid organ recipients have a 2-4-fold higher risk of developing cancer [1–3], a major cause of morbidity and mortality [4].

Compared with recipients of abdominal organs, thoracic transplant recipients have a higher risk of developing cancer. The leading cause is the higher doses of immunosuppressive agents needed to prevent organ rejection [5–7]. The most frequent cancers after HTx have been reported to be non-melanoma skin cancer (NMSC), lung cancer and lymphomas [8].

The present study examines the incidence of post-transplant cancer and the survival rate among HTx recipients diagnosed with cancer at the Sahlgrenska University Hospital (SUH). Survival rates are compared with the general population in Sweden. It was also studied if a history of treated cancer before HTx affected post-transplant cancer incidence and survival.



GRAPHICAL ABSTRACT

PATIENTS AND METHODS

Between June 1985 and December 2017, 708 HTx were performed at the SUH. After exclusion of patients treated with re-transplantation (n = 21) and patients followed abroad (n = 23), a total of 664 patients were included in the study. Baseline characteristics are shown in **Table 1**. The mean age was 48 years and 74% of the cohort were men**.** The median follow-up time was 7.7 years generating a total of 5,668 patient-years. **Figure 1** depicts the etiology of heart failure in the study population. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Regional Ethical Review Board at University of Gothenburg (EPN no. 019-09, approval date 22nd October 2009, amendments approved 29th November 2010, 10th December 2012, 17th December 2013, 10th May 2017). The main outcome was the detection of cancer among participants, by cross-checking the study cohort with the Swedish Cancer Register (SCR) [9] and the Swedish Cause of Death Register (SCDR), which both are operated by the Swedish National Board of Health and Welfare. The following cancer diagnosis codes were used: 140-239 (International Classification of Diseases-9 until 1996) and codes C00-D48 (International Classification of Diseases-10 from 1997). Data on basal cell carcinoma (BCC) were not available from these registers, and are, therefore, not included in our NMSC population.

All Swedish citizens have a specific personal identity number that is registered at all healthcare contacts. This allows tracking of how the Swedish population interacts with the healthcare system [10]. The SCR, that originates from 1958 holds information on all citizens registered in Sweden with a cancer diagnosis. The SCDR, which stems from 1961, registers the cause of death, including cancer, for all deceased citizens registered in Sweden. All cancer diagnoses in this report were verified by a histopathological examination. The International Rules for Multiple Primary Cancers (IARC, ICD-0 Third Edition) were applied to ensure correct numbers of cancer tumors reported [11]. These rules enable comparison of cancer risk and outcome between different populations.

Listing criteria for HTx were coherent with established international guidelines [12]. Recipients and donors were matched for ABO blood group compatibility. Complement-dependent cytotoxicity assays were performed to assess the recipient serum's ability to lyse a panel of T or B cells and, if positive above a certain level, a prospective donor-specific cross-match was performed. At the beginning of our HTx program, bi-atrial technique was initially used but this was slowly changed to bi-caval technique during the period as formerly described [13]. Over time, the complexity of surgery has increased, and the number of patients bridged with mechanical circulatory support has risen. Survival has improved over time, which has previously been reported [14].

Induction therapy has been applied throughout our HTx program (n = 573), mainly anti-thymocyte globulin. All patients received a regime with three different immunosuppressive agents, including a calcineurin inhibitor (cyclosporine or tacrolimus), an antimetabolite (azathioprine or mycophenolate mofetil (MMF) and a corticosteroid, tapered

TABLE 1 | Patient characteristics*.

Characteristics	
Age, years	48 (33–57)
Follow-up time, years	7.7 (3.0–13.6)
Gender	
Males	494 (74)
Females	170 (26)
Smoking	
Previous, cessation <6 months before HTx	57 (9)
Previous, cessation >6 months before HTx	227 (34)
Never	355 (53)
Missing data	25 (4)
Previous malignancy, and type	
Acute lymphoblastic leukemia (ALL)	3 (11.1)
Adrenal gland	1 (3.7)
Breast	2 (7.4)
Corpus uteri	1 (3.7)
Hodgkin lymphoma	3 (7.4)
Connective and soft tissue of lower limb including hip	1 (3.7)
Connective and soft tissue of thorax	1 (3.7)
Lymphosarcoma	3 (11.1)
Ovary	1 (3.7)
Other primary malignant neoplasm of lymphoid tissue	1 (3.7)
Other skin of other and unspecified parts of face	1 (3.7)
Pelvic bones, sacrum and coccyx	1 (3.7)
Prostate	1 (3.7)
Stomach	2 (3.7)
Testis	1 (3.7)
Unspecified axilla and upper limb lymph nodes	1 (3.7)
Unspecified part of bronchus or lung	1 (3.7)
Vertebral column	1 (3.7)
Total	26 (100)
Donors	
Males	405 (61%)
Females	255 (38%)
Missing data	4 (1%)
Median age of the donor, years	40.0 (23–51)

Values are presented as medians with interquartile ranges or numbers and percentages within parenthesis.

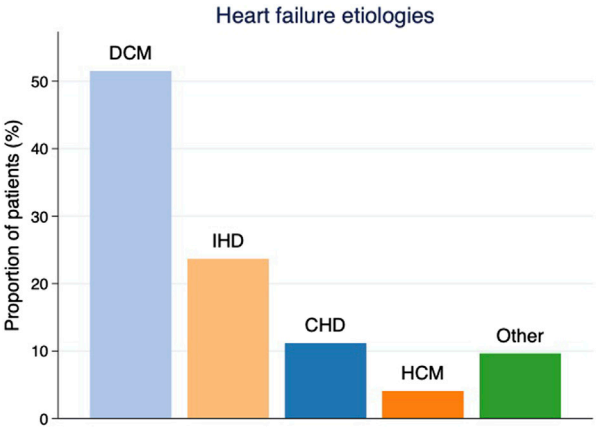


FIGURE 1 | Etiology of heart failure as proportions of patients by diagnosis prior to heart transplantation. DCM = dilated cardiomyopathy, IHD = ischemic heart disease, CHD = congenital heart disease, HCM = hypertrophic cardiomyopathy.

during the first year. Previously, cyclosporine and azathioprine constituted the primary immunosuppressive treatment but were replaced with tacrolimus and MMF during the 2000s. According to a routine protocol, percutaneous transvenous myocardial biopsies were used for rejection monitoring. All patients received acetylsalicylic acid and a statin as a preventive measure for graft vasculopathy.

Data are presented as means and standard deviations, medians and interquartile ranges, or numbers and percentages. Overall survival curves were generated using Kaplan-Meier estimates and comparisons between groups were performed with the log rank test. Relative survival was calculated using the Ederer II method [15]. Mortality data for the general population in Sweden were used to estimate expected survival rates. The mortality data comprised the probability of death for single-year age groups in 1-year calendar period. Cumulative incidence of cancer was analyzed using competing risk methods with death as a competing event [16]. When analyzing cancer incidence for different cancer types, person-years were calculated from date of the transplantation to the first of the following events: diagnosis of the cancer site; death; or end of surveillance period, i.e., 31 December 2018 The standardized incidence ratio (SIR) was defined as the observed number of cancers during the observation time divided by the expected number of cases, using incidence rates from the Swedish population stratified for 5-year age groups (0–4, 5–9, ... 80–84, 85-), gender and calendar year. Incidence rates for different cancer sites were used from the NORDCAN project. Furthermore, the coding of cancer followed definitions according to International rules for multiple primary cancers [11]. Univariable and multivariable risk factor analyses by Cox proportional hazards regression model for the development of posttransplant malignancy were performed. The following parameters were tested by univariable analyses: age (per 10 years), sex, BMI (<20; 20–30; >30), smoking (never; cessation >6 months before HTx listing; cessation <6 months before HTx listing), hypertension, diabetes mellitus, TIA/stroke, previous cardiac surgery, donor age (per 10 years), CMV+/− donor, CMV+/− recipients, CMV mismatch, ventricular assist device (VAD), ischemic time (<3; 3–4; >4 h), total induction dose with ATG (<200; 200–800; >800 mg) and proliferation inhibitors (azathioprine vs. MMF). Significant risk factors in the univariate models for all cancers and NMSC, respectively (**Supplementary Tables S1, S2**) were tested also in a multivariable model. All statistical tests were two-sided, and a p-value of <0.05 was considered statistically significant. Statistical analyses were carried out with Stata/IC 16.1.

RESULTS

Mortality for the whole patient cohort within 30 days and 1-year was 51/664 (8%) and 78/664 (12%), respectively. Overall survival was for the whole cohort at 1, 5, 10, 15 and 20 years was: 88% (95% CI 86%–90%); 80% (95% CI 76%–83%); 67% (95% CI 63%–71%); 53% (95% CI 48%–58%) and 37% (95% CI 32%–43%), respectively. Overall survival for HTx patients increased

TABLE 2 | Number of cancers after HTx according to ICD-10.

Site (ICD-10)	Sex		Total
	Males	Females	
Acute myeloblastic leukemia (AML) (C92)		1	1
Anus (C21)	1		1
Bladder (C67)	1		1
Breast (C50)		3	3
Brain (C71)	2		2
Colon (C18)	1		1
Cerebral meninges (C70)	2	1	3
Cervix uteri (C53)		1	1
Connective and soft tissue (C49)	1		1
Extrahepatic bile duct (C24)	1		1
Gastric (C16)	4	1	5
Glottis (C32)	1	1	2
Hodgkin lymphoma (C81)		1	1
Kidney (C64)	3		3
Lip (C00)	7		7
Lung (C34)	8	2	10
Lymph nodes (C77)	1		1
Malignant melanoma (C43)	4	2	6
Malignant of other and ill-defined sites (C76)	1		1
Multiple Myeloma (C90)	4		4
Non-Hodgkin lymphoma (C83-C85)	22	5	27
Nasal cavity (C30)	1		1
Penis (C60)	2		2
Prostate (C61)	12		12
Oral cavity (C03,C08)	2		2
Other malignant neoplasms of skin (C44)	110	17	127
Tonsil (C09)	1		1
Upper respiratory tract (C39)	1		1
Urethra (C66)	1		1
Vulva (C51)		2	2
Total	195	36	231

significantly over time ($p < 0.001$). Five-year overall survival for those who underwent HTx between 1985 and 2000 was: 70% (95% CI: 64%–75%); between 2001 and 2010 81% (95% CI: 75%–86%); and between 2011 and 2017 92% (95% CI: 85%–96%) (**Supplementary Figure S1**).

A total of 231 *de novo* cancers were diagnosed in 138 HTx patients during follow-up, which corresponds to 19.6% of the total study population (**Table 2**). In contrast 37.5 detected cancers would have been in a cohort from the general population matched by age, sex and time period. This resulted in a SIR of 6.2 (95% CI 5.4–7.0) for all cancers and a SIR of 2.9 (95% CI: 2.4–3.5) after exclusion of NMSC.

The cumulative incidence of a *de novo* malignancy between 1 and 5 years after transplant was 4.6%. The cumulative incidence of cancer for the total cohort at 1, 5, 10, 15 and 20 years was 2.4% (95% CI 1.5–3.9), 7.0% (95% CI 5.2–9.3), 19% (95% CI 15.8–23), 26% (95% CI 22–31) and 33% (95% CI 28–38), respectively.

Cumulative incidence of post-HTx cancers by three prespecified time periods showed no difference over time (**Figure 2A**). During these same eras there was a significant decrease in overall cumulative mortality (**Figure 2B**).

The type and frequency of solid tumors for the total group, and for men and women separately, are listed in **Table 2**. The most common type of cancer was NMSC (55% of all cancers), non-Hodgin's lymphoma (11.7% of all cancers) and lung cancer (4.3% of all cancers).

Among the patients who developed lung cancer (eight men and two women), 80% had a smoking history. Among them, four patients had stopped smoking <6 months before HTx listing and four had stopped >6 months before HTx listing.

A total of 44 patients (32%) had multiple tumors; 18 patients had 2 tumors, 6 patients had 3 tumors, 3 patients had 4 tumors and 5 patients had 5 tumors. Two patients developed 7 tumors each. One had 5 NMSC, one lip tumor and one salivary gland tumor, and the other had 5 NMSC, 1 anal cancer and 1 salivary gland tumor.

The SIR for cancer types diagnosed in four persons or more, are shown in **Table 3**. The excess risk of all cancers for the total population was 6.2 and similar between men and women (SIR 6.39 and SIR 5.18, respectively).

The overall incidences of cancers in the cohort were higher than expected for: NMSC (SIR 82.6, 95% CI 69.4–98.3); non-Hodgkin lymphoma (SIR 24.8, 95% CI 17–36.1); malignant

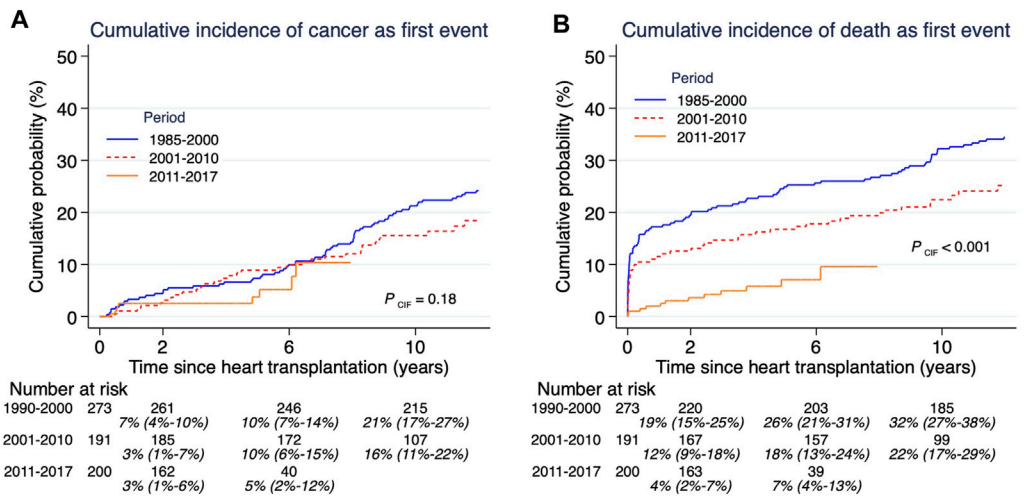


FIGURE 2 | Cumulative incidence of competing risks cancer **(A)** and death **(B)**, and related to time-era after heart transplantation. Both outcomes cancer and death need to be assessed together since they are competing outcomes. Estimates and 95% confidence intervals are shown under the number of patients at risk.

TABLE 3 | Observed and expected cancer risks following HTx.*

Site (ICDO-10)	Observed number	Expected number	Person years	SIR (95% CI)
All sites				
Total	231	37.5	5,668	6.16 (5.42–7.01)
Males	195	30.5	4,175	6.39 (5.55–7.35)
Females	36	6.95	1,493	5.18 (3.74–7.18)
All sites (except NMSC)				
Total	104	35.9	5,668	2.89 (2.39–3.51)
Males	85	29.2	4,175	2.91 (2.35–3.60)
Females	19	6.73	1,493	2.82 (1.80–4.43)
Lip (C00)				
Total	7	0.10	5,668	72.6 (34.6–152)
Males	7	0.08	4,175	83.0 (39.6–174)
Females	0	0.01	1,493	—
Stomach (C16)				
Total	5	0.64	5,668	7.86 (3.27–18.9)
Males	4	0.56	4,175	7.13 (2.68–19.0)
Females	1	0.08	1,493	13.3 (1.87–94.5)
Breast (C32)				
Total	3	2.38	5,668	1.26 (0.41–3.91)
Males	0	0.05	4,175	
Females	3	2.33	1,493	1.28 (0.41–3.98)
Lung (C33, C34)				
Total	10	2.72	5,668	3.68 (1.98–6.84)
Males	8	2.21	4,175	3.62 (1.81–7.25)
Females	2	0.51	1,493	3.93 (0.98–15.7)
Malignant melanoma (C43)				
Total	6	0.64	5,668	9.43 (4.24–21.0)
Males	4	0.56	4,175	7.13 (2.68–19.0)
Females	2	0.08	1,493	26.6 (6.66–106)
Skin, NMSC (C44)				
Total	127	1.54	5,668	82.6 (69.4–98.3)
Males	110	1.31	4,175	84.0 (69.7–101)
Females	17	0.23	1,493	74.7 (46.4–120)
Prostate (C61)				
Males	12	10.6	4,110	1.13 (0.64–1.99)
Kidney (C64)				
Total	3	0.94	5,668	3.20 (1.03–9.92
Males	3	0.82	4,175	3.65 (1.18–11.3)
Females	0	0.12	1,493	
Non-Hodgkin lymphoma (C81-C85)				
Total	27	1.09	5,668	24.8 (17.0–36.1)
Males	22	0.92	4,175	23.9 (15.7–36.3)
Females	5	0.17	1,493	29.4 (12.2–70.6)
Myeloma (C90)				
Total	4	0.44	5,628	9.08 (3.41–24.2)
Males	4	0.38	4,135	10.6 (3.99–28.3)
Females	0	0.06	1,493	

**Observed and expected number of cancers, person years in follow-up and Standardized Mortality Ratio (SIR) per site after heart transplantation. NMSC, non-melanoma skin cancer (not including basal cancer).*

melanoma (SIR 9.42, 95% CI 4.24–21.0); multiple myeloma (SIR 9.08, 95% CI 3.41–24.2); gastric (SIR 7.86, 95% CI 3.27–18.9); lung (SIR 3.68, 95% CI 1.98–6.84); and kidney (SIR 3.20, 95% CI 1.03–9.92).

Among the 138 HTx patients who developed post-HTx cancer, 29 died from their malignancy: non-Hodgkin lymphoma (n = 13), lung cancer (n = 8), NMSC (n = 5), and gastric (n = 3).

Univariable and multivariable associations between baseline factors and cancer (omitting NMSC) are shown in **Table 4**. Independent predictors of cancer development included: smoking cession <6 months before HTx listing [HR 3.46 (95% CI 1.69–7.07), $p < 0.001$]; hypertension [HR 2.16 (95% CI 1.10–4.26), $p < 0.026$]; ischemic time (reference: <3 h) 3–4 h [HR 1.93 (95% CI 1.09–3.40), $p = 0.024$]; and treatment with azathioprine (vs. MMF) [HR 1.69 (95% CI 0.99–2.90), $p < 0.055$]. Interestingly, CMV mismatch was not significantly associated with cancer [HR 0.79 (95% CI 0.39–1.62), $p = 0.53$].

Significant risk factors in the multivariable model predicting NMSC only (**Table 4**) were: age per 10 years [HR 2.90 (95% CI 1.85–4.55), $p < 0.001$]; hypertension [HR 1.87 (95% CI 0.91–3.84), $p < 0.091$], seronegative CMV-donor [HR 2.14 (95% CI 1.11–4.14), $p = 0.024$], and treatment with Azathioprine [HR 2.53 (95% CI 1.20–5.36), $p < 0.015$].

TABLE 4 | Uni- and multivariable Cox proportional hazard regression for developing cancer.*

Risk factors for any cancer except skin cancer after HTx					
Variable	**Number of persons with cancer/N**	**Cox proportional hazard regression**			
		Univariable		**Multivariable**	
		HR (95% CI)	***p***	**HR (95% CI)**	***p***
Smoking					
No, never	23/355	1.0 (ref.)		1.0 (ref.)	
No, stopped >6 months before HTx	27/227	1.84 (1.05–3.21)	0.032	1.70 (0.96–3.02)	0.070
No, stopped < 6 months before HTx	12/57	3.12 (1.55–6.27	0.001	3.46 (1.69–7.07)	0.001
Hypertension					
No	51/565	1.0 (ref.)		1.0 (ref.)	
Yes	11/74	1.92 (1.00–3.68)	0.050	2.16 (1.10–4.26)	0.026
Ischemic time (hours)					
<3	23/285	1.0 (ref.)		1.0 (ref.)	
3–4	30/274	1.44 (0.84–2.48)	0.19	1.93 (1.09–3.40)	0.024
>4	10/97	1.59 (0.75–3.34)	0.22	1.92 (0.87–4.24)	0.11
Proliferation inhibitors					
MMF	23/355	1.0 (ref.)		1.0 (ref.)	
Azathioprine	40/288	1.68 (1.00–2.83)	0.050	1.69 (0.99–2.90)	0.055
Risk factors for skin cancer after HTx					
Age, per 10 years	40/664	2.53 (1.77–3.62)	<0.001	2.90 (1.85–4.55)	<0.001
Hypertension					
No	29/565	1.0 (ref.)		1.0 (ref.)	
Yes	11/74	3.74 (1.86–7.49)	<0.001	1.87 (0.91–3.84)	0.091
CMV donor					
Positive	19/400	1.0 (ref.)		1.0 (ref.)	
Negative	18/205	2.01 (1.05–3.83)	0.034	2.14 (1.11–4.14)	0.024
Proliferation inhibitors					
MMF	13/355	1.0 (ref.)		1.0 (ref.)	
Azathioprine	27/288	1.54 (0.79–3.01)	0.20	2.53 (1.20–5.36)	0.015

HTx, heart transplantation; CMV, cytomegalo virus; MMF, mycophenolate mofetil.
**Time to first cancer analyzed. Twenty years follow-up.*

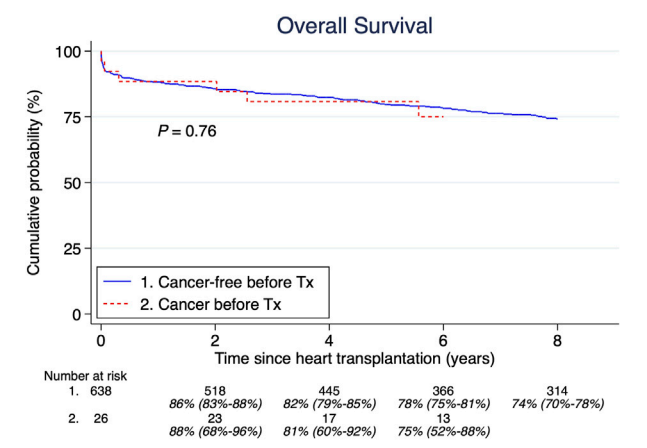


FIGURE 3 | Pretransplant malignancy overall survival compared to those without. Estimates and 95% confidence intervals are shown under the number of patients at risk.

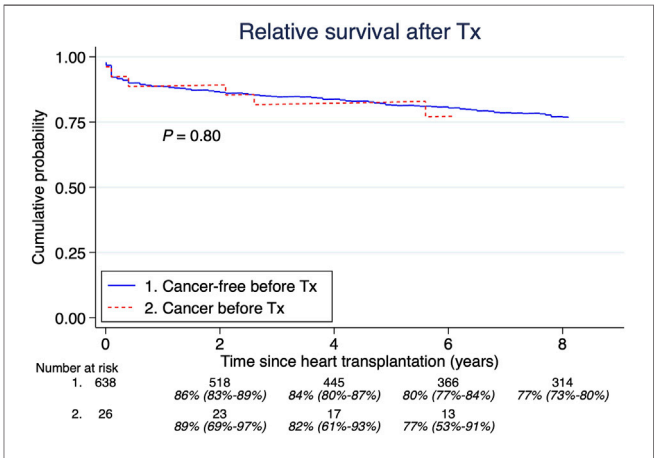


FIGURE 4 | Pretransplant malignancy relative survival compared to those without. Estimates and 95% confidence intervals are shown under the number of patients at risk.

A total of 26 patients (4%) had a malignancy history >5 years before HTx. The median age at their first tumor was 34 years (IQR; 11.3–52.2 years). The most common cancers were: acute lymphoblastic leukemia, lymphosarcoma, and Hodgkin lymphoma, shown in **Table 1**. There were no significant differences in overall survival between those with and without cancer before HTx (**Figure 3**). Furthermore, there was no significant difference in post-HTx relative survival between patients who were cancer-free before and after HTx (**Figure 4**).

DISCUSSION

In the current study, we observed a 6.2-fold excess risk of cancer following HTx relative to the general population. When excluding NMSC, the excess risk was 2.9-fold. The cumulative incidence of a *de novo* malignancy between 1 and 5 years after HTx was 4.6%, which is lower compared to previous studies. In a study by Yoan et al., including over 17,000 patients [17] the corresponding incidence rate of *de novo* malignancy was 10.7%, which is considerably higher than the 4.6% rate observed in the present study. Yoan et al., derived data from the ISHLT registry, with a high rate of missing data supported by the fact that 24,000 HTx patients were excluded from the analyses. We therefore argue that they overestimated the risk of cancer due to positive selection. In contrast, we have derived data from national full coverage registries with a very low risk of missing any cancer. Data extraction from complete registries with detailed information on individual level makes this study unique. An improved post-HTx survival was observed during later eras, this could not be explained by a reduction in cancer incidence, which remained stable over the study period. This could indicate earlier detection and/or improved post-HTx cancer treatment.

It is well known that transplanted patients, as compared to the general population, have a higher incidence of NMSC, and the detected tumors are more aggressive [18]. It is also acknowledged that the incidence of NMSC increases with the intensity and duration of immunosuppression [19]. The SIR for NMSC of 82.6 in our cohort was more than four times higher as compared to the SIR of 18.5 reported by Collett et al. [3]. However, Collett et al. noted that their results might have been underestimated, since lesions might have been removed without a histological examination. A study from Finland, including 479 patients reported a SIR of 51.9 for squamous cell carcinoma (SCC) [20], which is also lower than we observed. Crespo Leiro et al. [21] and Vaan Keer et al. [22] studied the incidence of NCSC in a Spanish and Belgian population, but didn´t compare the cancer incidence to the general population, why SIR could not be calculated. In our study, almost 55% of the tumors (127 of 231) were NMSC. Corresponding numbers in the studies by Crespo-Leiro et al. and Vann Keer et al. were 51% (324 of 490) and 22% (58 of 263). The median duration of patient follow-up was 7.7 years in the present study compared to with 5.8 years in the study by Crespo-Leiro et al. and 10.7 years in the study by Vaan Keer et al.

While lung cancer in men has declined in Sweden since the 1980s, the opposite trend has been observed in women, to the point where more women than men now develop lung cancers [23]. The overall SIR for lung cancer (3.68) was higher than observed in other comparable studies (2.0–2.79) [3, 24–27]. There was no significant increased risk for lung cancer in transplanted women presented in a Spanish study by Crespo-Lieiro et al. [25], with over four thousand patients. Among patients with a history of smoking in our study, 284 patients (43%) had stopped smoking 6 months or more before being listed for transplantation. Crespo-Lieiro et al [25] showed an association between previous smoking and development of post-HTx lung cancer. In that study the median time between HTx and the lung cancer diagnosis was 6.4 years, compared to 7.8 years (IQR: 4.1–12.2) in our study. In addition to hypertension and longer ischemic time, previous smoking was also a risk factors for the development of NMSC in the present study.

The SIR for prostate cancer in our cohort was low (1.13), indicating that immunosuppression after HTx was not associated with a significantly increased prostate cancer risk. Similar findings have also been reported in a meta-analysis including six independent studies, with over 21,000 heart transplant patients [28]. Why immunosuppression does not increase the risk for prostate cancer remains largely unknown, but this may in part be explained by intensive screening before HTx, and the possibility that male HTX recipients don't survive long enough to develop prostate cancer, which mostly occurs after the age of 70 years [23]. These findings support that patients with low-grade prostate cancer could be accepted for HTx without the often applied 5-year cancer free waiting period.

An excess risk of lip cancer was demonstrated (SIR 72.6) corroborating findings by Collet et al (SIR 60) and Jääma-Holmberg et al (SIR 47.4). The reason remains unclear, but may be related to the fact that this is a NMSC, and therefore can be classified as skin cancer. There is an association between smoking and lip cancer and the fact that two patients diagnosed with lip cancer (seven lip cancers among four persons) had a history of smoking may partially explain our findings. Sun exposure is also a well-established risk factor for the development of lip cancer [29]. Among the seven patients with a lip cancer, five (71%) also had a NMSC.

A history of malignancy within 5 years has been considered to be a contraindication for transplantation because of the increased risk of recurrence following initiation of immunosuppressive therapy. Sigurdardottir et al. [30] reported a cancer recurrence rate of 63%, if the disease-free interval between malignancy and HTx was less than 1 year, but only 6% if the HTx recipient had been cancer free for more than 5 years. However, prostate cancer was not presented as a separate entity, why the post-HTx relapse of prostate cancer remains unclear. In a review article by Mistiaen et al [31], patients with localized prostate cancer before transplantation had no increased risk of reduced survival post-HTx [31]. At present, there is no consensus regarding the optimal time interval between cancer treatment and HTx [32, 33], but a relapse free period of ≥5 years is a common criterion, which has also been applied at our center. However, when post HTx survival is constantly improving, at the same time as cancer incidence remains unchanged, it might be time to revise and consider individualization of these criteria.

Limitations

The current study did not investigate whether the patients had BCC before or after HTx, since this cancer form has been considered rather benign and, therefore, not reported in the SCR. The growth rate of BCC is slow and this cancer rarely metastasizes [34]. Post-transplant lymphoproliferative disease (PTLD), a well-known complication after HTx [35] is not recorded as a specific entity in the SCR, why the exact number of patients with PTLD is cannot be reported. Instead, such cases are presented as lymphomas.

There are multiple primary cancer coding rules to count incident cases. Cancer registries in the U.S. and Canada use, for example, SEER multiple primary rules. In this study, the International Rules for Multiple Primary Cancers (IARC/IACR, ICD-0 Third Edition) was applied. Compared to SEER rules, IARC/IACR recognizes fewer multiple primary cancers [36], which may explain the differences compared to other studies [26].

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

Regional Ethical Review Board at University of Gothenburg (EPN no. 019-09) approved the study and waived the need for individual consent.

AUTHOR CONTRIBUTIONS

CS: Conceived and designed the analysis, collected the data, wrote the paper. AW: Conceived and designed the analysis. EH: Collected the data, performed the analysis, wrote the paper. KK: Conceived and designed the analysis, collected the data, wrote the paper JM: Collected the data, wrote the paper. GD: Conceived and designed the analysis, collected the data, performed the analysis, wrote the paper. All authors contributed to the article and approved the submitted version.

FUNDING

The authors declare that financial support was received for the research, authorship, and/or publication of this article. This work was supported by grants from the Swedish Heart and Lung Foundation, and from the Swedish state under the agreement between the Swedish government and the county councils, the ALF-agreement (ALFGBG-717811 to GD).

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

ACKNOWLEDGMENTS

We would like to thank all participants of the heart transplant team for their dedicated clinical work.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2024.12109/full#supplementary-material

REFERENCES

1. Hall EC, Pfeiffer RM, Segev DL, Engels EA. Cumulative Incidence of Cancer After Solid Organ Transplantation. *Cancer* (2013) 119(12):2300–8. doi:10.1002/cncr.28043
2. Adami J, Gabel H, Lindelof B, Ekström K, Rydh B, Glimelius B, et al. Cancer Risk Following Organ Transplantation: A Nationwide Cohort Study in Sweden. *Br J Cancer* (2003) 89(7):1221–7. doi:10.1038/sj.bjc.6601219
3. Collett D, Mumford L, Banner NR, Neuberger J, Watson C. Comparison of the Incidence of Malignancy in Recipients of Different Types of Organ: A UK Registry Audit. *Am J Transplant* (2010) 10(8):1889–96. doi:10.1111/j.1600-6143.2010.03181.x
4. Vajdic CM, van Leeuwen MT. Cancer Incidence and Risk Factors After Solid Organ Transplantation. *Int J Cancer* (2009) 125(8):1747–54. doi:10.1002/ijc.24439
5. Krynitz B, Edgren G, Lindelof B, Baecklund E, Brattström C, Wilczek H, et al. Risk of Skin Cancer and Other Malignancies in Kidney, Liver, Heart and Lung Transplant Recipients 1970 to 2008--A Swedish Population-Based Study. *Int J Cancer* (2013) 132(6):1429–38. doi:10.1002/ijc.27765
6. Roithmaier S, Haydon AM, Loi S, Esmore D, Griffiths A, Bergin P, et al. Incidence of Malignancies in Heart and/or Lung Transplant Recipients: A Single-Institution Experience. *J Heart Lung Transplant* (2007) 26(8):845–9. doi:10.1016/j.healun.2007.05.019
7. Jensen P, Hansen S, Møller B, Leivestad T, Pfeffer P, Geiran O, et al. Skin Cancer in Kidney and Heart Transplant Recipients and Different Long-Term Immunosuppressive Therapy Regimens. *J Am Acad Dermatol* (1999) 42(2):307–186. doi:10.1016/S0190-9622(00)90154-3
8. Crespo-Leiro MG, Alonso-Pulpón L, Vázquez de Prada JA, Almenar L, Arizón JM, Brossa V, et al. Malignancy After Heart Transplantation: Incidence, Prognosis and Risk Factors. *Am J Transplant* (2008) 8(5):1031–9. doi:10.1111/j.1600-6143.2008.02196.x
9. Barlow L, Westergren K, Holmberg L, Talbäck M. The Completeness of the Swedish Cancer Register: A Sample Survey for Year 1998. *Acta Oncol* (2009) 48(1):27–33. doi:10.1080/02841860802247664
10. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbom A. The Swedish Personal Identity Number: Possibilities and Pitfalls in Healthcare and Medical Research. Research Support, Non-U.S. Gov't. *Eur J Epidemiol* (2009) 24(11):659–67. doi:10.1007/s10654-009-9350-y
11. International Rules for Multiple Primary Cancers (ICD-0 Third Edition). International Rules for Multiple Primary Cancers (ICD-0 Third Edition). *Eur J Cancer Prev* (2005) 14(4):307–8. doi:10.1097/00008469-200508000-00002
12. Mehra MR, Kobashigawa J, Starling R, Russell S, Uber PA, Parameshwar J, et al. Listing Criteria for Heart Transplantation: International Society for Heart and Lung Transplantation Guidelines for the Care of Cardiac Transplant Candidates--2006. *J Heart Lung Transpl* (2006) 25(9):1024–42. doi:10.1016/j.healun.2006.06.008
13. Carlstrom M, Dahlin S, Gabel J, Doanhu R, Hörlinge J, Jeppsson A, et al. 265 Tricuspid Regurgitation and Surgical Technique Influences Outcome After Heart Transplantation. *J Heart Lung Transplant* (2012) 31(4):S96. doi:10.1016/j.healun.2012.01.272
14. Dellgren G, Westerlind A, Liden H, Gäbel J, Bartfay SE, Bollano E, et al. Continuous Improvement in Outcome After Heart Transplantation — Long-Term Follow-Up After Three Decades of Experience. *Int J Cardiol* (2017) 231:188–94. doi:10.1016/j.ijcard.2016.12.186

15. Ederer F, Axtell LM, Cutler SJ. The Relative Survival Rate: A Statistical Methodology. *Natl Cancer Inst Monogr* (1961) 6:101–21.
16. Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. *J Am Stat Assoc* (1999) 94(446):496–509. doi:10.1080/01621459.1999.10474144
17. Youn J-C, Stehlik J, Wilk AR, Cherikh W, Kim IC, Park GH, et al. Temporal Trends of *De Novo* Malignancy Development After Heart Transplantation. *J Am Coll Cardiol* (2018) 71(1):40–9. doi:10.1016/j.jacc.2017.10.077
18. Euvrard S, Kanitakis J, Pouteil-Noble C, Disant F, Dureau G, Finaz de Villaine J, et al. Aggressive Squamous Cell Carcinomas in Organ Transplant Recipients. *Transplant Proc* (1995) 27(2):1767–8.
19. Fortina AB, Piaserico S, Caforio AL, Abeni D, Alaibac M, Angelini A, et al. Immunosuppressive Level and Other Risk Factors for Basal Cell Carcinoma and Squamous Cell Carcinoma in Heart Transplant Recipients. *Arch Dermatol* (2004) 140(9):1079–85. doi:10.1001/archderm.140.9.1079
20. Jäämaa-Holmberg S, Salmela B, Lemström K, Pukkala E, Lommi J. Cancer Incidence and Mortality After Heart Transplantation - A Population-Based National Cohort Study. *Acta Oncologica* (2019) 58(6):859–63. doi:10.1080/0284186X.2019.1580385
21. Crespo-Leiro MG, Paniagua-Martin MJ, Muniz J, Marzoa-Rivas R, Rodriguez JA, Franco R, et al. Malignancy After Heart Transplantation. Incidence and Survival From a Cohort of 378 Patients. *Eur Heart J* (2007) 28:352.
22. Van Keer J, Droogne W, Van Cleemput J, Vörös G, Rega F, Meyns B, et al. Cancer After Heart Transplantation: A 25-Year Single-Center Perspective. *Transplant Proc* (2016) 48(6):2172–7. doi:10.1016/j.transproceed.2016.03.037
23. Socialstyrelsen. *Statistics on Cancer Incidence 2018 (2018-6-10)*. Stockholm: Socialstyrelsen (2018). p. 6. Available from: https://www.socialstyrelsen.se/publikationer2018/2018-6-10 (Accessed February 20, 2019).
24. Jiang Y, Villeneuve PJ, Wielgosz A, Schaubel DE, Fenton SS, Mao Y. The Incidence of Cancer in a Population-Based Cohort of Canadian Heart Transplant Recipients. *Am J Transpl* (2010) 10(3):637–45. doi:10.1111/j.1600-6143.2009.02973.x
25. Crespo-Leiro MG, Villa-Arranz A, Manito-Lorite N, Paniagua-Martin MJ, Rábago G, Almenar-Bonet L, et al. Lung Cancer After Heart Transplantation: Results From a Large Multicenter Registry. *Am J Transpl* (2011) 11(5):1035–40. doi:10.1111/j.1600-6143.2011.03515.x
26. Kellerman L, Neugut A, Burke B, Mancini D. Comparison of the Incidence of *De Novo* Solid Malignancies After Heart Transplantation to That in the General Population. *Am J Cardiol* (2009) 103(4):562–6. doi:10.1016/j.amjcard.2008.10.026
27. Secnikova Z, Gopfertova D, Hoskova L, Hercogova J, Dzambova M, Jirakova A, et al. Significantly Higher Incidence of Skin Cancer Than Other Malignancies in Patients After Heart Transplantation. A Retrospective Cohort Study in the Czech Republic. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub* (2015) 159(4):648–51. doi:10.5507/bp.2015.011
28. Bao J-M, Zhu H-L, Yang G-S, Chen PL, Dang Q, Chen XX, et al. No Significant Association Between Immunosuppression in Solid Organ Transplantation and Prostate Cancer Risk: A Meta-Analysis of Cohort Studies. *Translational Cancer Res* (2019) 8(3):939–49. doi:10.21037/tcr.2019.06.03
29. Perea-Milla López E, Miñarro-Del Moral RM, Martínez-García C, Zanetti R, Rosso S, Serrano S, et al. Lifestyles, Environmental and Phenotypic Factors Associated With Lip Cancer: A Case-Control Study in Southern Spain. *Br J Cancer* (2003) 88(11):1702–7. doi:10.1038/sj.bjc.6600975
30. Sigurdardottir V, Bjortuft O, Eiskjær H, Ekmehag B, Gude E, Gustafsson F, et al. Long-Term Follow-Up of Lung and Heart Transplant Recipients With Pre-transplant Malignancies. *J Heart Lung Transplant* (2012) 31(12):1276–80. doi:10.1016/j.healun.2012.09.007
31. Peter Mistiaen W. Heart Transplantation in Patients With Previous Malignancy. An Overview. *Acta Cardiol* (2015) 70(2):123–30. doi:10.1080/ac.70.2.3073502
32. Chapman JR, Webster AC, Wong G. Cancer in the Transplant Recipient. *Cold Spring Harb Perspect Med* (2013) 3(7):a015677. doi:10.1101/cshperspect.a015677
33. Mehra MR, Canter CE, Hannan MM, Semigran MJ, Uber PA, Baran DA, et al. The 2016 International Society for Heart Lung Transplantation Listing Criteria for Heart Transplantation: A 10-Year Update. *J Heart Lung Transpl* (2016) 35(1):1–23. doi:10.1016/j.healun.2015.10.023
34. Rubin AI, Chen EH, Ratner D. Basal-Cell Carcinoma. *N Engl J Med* (2005) 353(21):2262–9. doi:10.1056/NEJMra044151
35. Penn I, Hammond W, Brettschneider L, Starzl TE. Malignant Lymphomas in Transplantation Patients. *Transpl Proc* (1969) 1(1):106–12.
36. Weir HK, Johnson CJ, Ward KC, Coleman MP. The Effect of Multiple Primary Rules on Cancer Incidence Rates and Trends. *Cancer Causes Control* (2016) 27(3):377–90. doi:10.1007/s10552-016-0714-9

ESOT | Transplant International

ORIGINAL RESEARCH
published: 20 September 2024
doi: 10.3389/ti.2024.13173

Previous Solid Organ Transplantation Influences Both Cancer Treatment and Survival Among Colorectal Cancer Patients

Henrik Benoni[1,2]*, *Caroline Nordenvall*[3], *Vivan Hellström*[1], *Caroline E. Dietrich*[2], *Anna Martling*[3], *Karin E. Smedby*[2] *and Sandra Eloranta*[2]

[1]*Department of Surgical Sciences, Section of Transplantation Surgery, Uppsala University, Uppsala, Sweden,* [2]*Division of Clinical Epidemiology, Department of Medicine, Solna, Karolinska Institutet (KI), Stockholm, Sweden,* [3]*Department of Molecular Medicine and Surgery, Karolinska Institutet (KI), Stockholm, Sweden*

Previous solid organ transplantation has been associated with worse survival among colorectal cancer (CRC) patients. This study investigates the contribution of CRC characteristics and treatment-related factors to the differential survival. Using the Swedish register-linkage CRCBaSe, all patients with solid organ transplantation before CRC diagnosis were identified and matched with non-transplanted CRC patients. Associations between transplantation history and clinical CRC factors and survival were estimated using the Kaplan-Meier estimator and logistic, multinomial, and Cox regression, respectively. Ninety-eight transplanted and 474 non-transplanted CRC patients were followed for 5 years after diagnosis. Among patients with stage I-III cancer, transplanted patients had lower odds of treatment with abdominal surgery [odds ratio (OR):0.27, 95% confidence interval (CI):0.08–0.90], than non-transplanted patients. Among those treated with surgery, transplanted colon cancer patients had lower odds of receiving adjuvant chemotherapy (OR:0.31, 95% CI:0.11–0.85), and transplanted rectal cancer patients had higher rate of relapse (hazard ratio:9.60, 95% CI:1.84–50.1), than non-transplanted patients. Five-year cancer-specific and overall survival was 56% and 35% among transplanted CRC patients, and 68% and 57% among non-transplanted. Accordingly, transplanted CRC patients were treated less intensely than non-transplanted patients, and had worse cancer-specific and overall survival. These patients might benefit from multidisciplinary evaluation including transplantation specialists.

Keywords: cancer after transplant, colorectal cancer (CRC), organ transplantation, survival, mortality

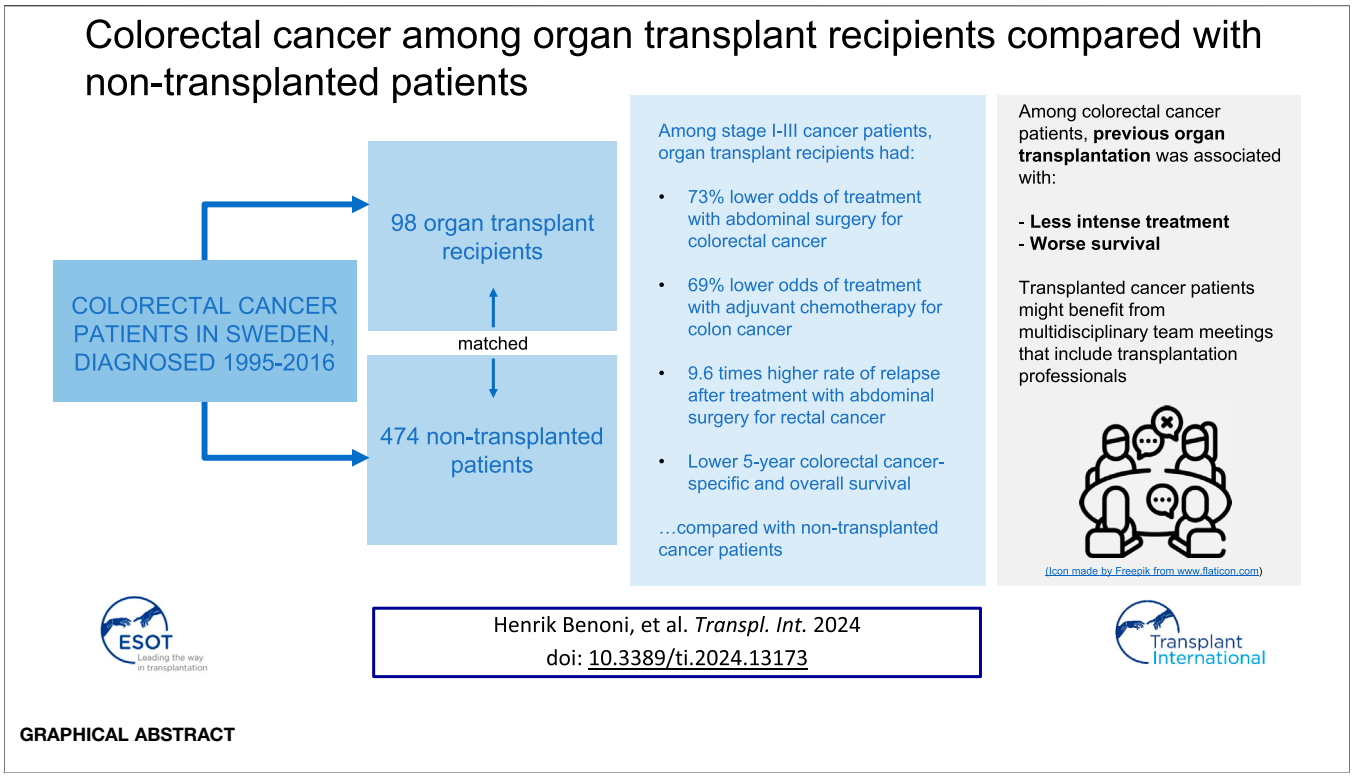
OPEN ACCESS

***Correspondence**
Henrik Benoni,
henrik.benoni@uu.se

Received: *24 April 2024*
Accepted: *09 September 2024*
Published: *20 September 2024*

Citation:
Benoni H, Nordenvall C, Hellström V, Dietrich CE, Martling A, Smedby KE and Eloranta S (2024) Previous Solid Organ Transplantation Influences Both Cancer Treatment and Survival Among Colorectal Cancer Patients. Transpl Int 37:13173. doi: 10.3389/ti.2024.13173

Abbreviations: CCI, Charlson comorbidity index; CI, Confidence interval; CRC, Colorectal cancer; HR, Hazard ratio; MDT, Multidisciplinary team; NPR, National Patient Register; OR, Odds ratio; OS, Overall survival; OTR, Organ transplant recipient; RRR, Relative risk ratio; SCR, Swedish Cancer Register; TNM, Tumor-node-metastasis.



GRAPHICAL ABSTRACT

INTRODUCTION

Solid organ transplantation is associated with both an increased risk of post-transplant cancer, and decreased overall and cancer-specific survival after cancer diagnosis, for numerous cancer types [1–5]. One such example is colorectal cancer (CRC), which has been associated with an increased rate of cancer-specific death among organ transplant recipients (OTRs), compared to CRC patients without transplantation history [4, 5]. Reasons for this difference might include variations in biological cancer characteristics (e.g., tumor grade, aggressiveness), and cancer treatment, where OTRs risk receiving limited treatment due to heavier comorbidity and/or concern for the transplanted organ. End-stage organ failure and organ transplantation are associated with systemic comorbidity to a variable extent during the post-transplant period, which may have implications for primary cancer treatment (e.g., surgery under general anesthesia). Also, neoadjuvant and adjuvant treatments such as chemotherapy or immunotherapy can have detrimental effects on the transplanted organ (e.g., nephrotoxicity), interact with immunosuppressive drugs, or induce rejection of the transplant [6]. Therefore, post-transplant cancer treatment represents a major challenge from both a clinical and scientific perspective, due to the difficulties involved with designing randomized trials of optimal treatments.

The aims of this study were to elucidate reasons for the previously shown excess rate of cancer-specific mortality among post-transplant CRC patients, through examining tumor characteristics, differences in treatment practices and relapse rates among post-transplant and non-transplanted CRC patients, and to confirm associations with survival.

MATERIALS AND METHODS

Data Sources

This matched cohort study utilized data from CRCBaSe, a research database originating from the Swedish Colorectal Cancer Register, which includes rectal cancer diagnoses from 1995 and colon cancer diagnoses from 2007, through 2016 [7]. Reporting to this register, which has been shown to be >98% complete, is done by the treating physicians and the data contain detailed tumor and treatment information (e.g., pathological stage and tumor grade, tumor location, surgery type, and [neo]adjuvant chemo- and radiotherapy) [8]. CRCBaSe includes linkages to several population-based registers, such as the Swedish Cancer Register (SCR), the National Patient Register (NPR) (in- and outpatient specialist care visits and hospitalizations), and the Cause of Death Register. Linkage between the registers is enabled via the unique personal identity number that is assigned to all Swedish residents.

The study was approved by the Regional Ethics Review Board in Stockholm (approval no. 2007/1335-31/4, 2014/71-31 and 2016/876-32).

Study Population

Using transplantation surgery procedure codes (**Supplementary Table S1**), we identified all CRC patients in CRCBaSe who had undergone any solid organ transplantation (kidney, liver, pancreas, heart, lung, bowel, and combinations thereof) prior to first CRC diagnosis (n = 121). CRC patients who were transplanted less than 30 days before their cancer diagnosis were excluded (n = 1), as were CRC patients who had a record of transplantation after their cancer diagnosis (n = 21), since they represent a distinct clinical group, and/or may have been diagnosed with cancer *en passant* around the time of transplantation surgery, in accordance with previous studies [2, 5].

A comparator group was selected, also using CRCBaSe as the source population, by random sampling (with replacement) of up to five matched, non-transplanted CRC patients to each transplanted. The matching was performed on cancer location (colon/rectum), sex, age at CRC diagnosis (±1 year), and year of diagnosis. The first recorded diagnosis of CRC (if more than one was available in CRCBaSe) in each patient was used for matching. Further, patients with synchronous tumors were excluded (1 transplanted patient [together with the corresponding 5 comparators] and 12 comparators).

Comorbidity and Other Potential Confounders

Organ transplantation is heavily associated with comorbidity, which can be difficult to adjust for since the comorbid conditions are often closely related to exposure (e.g., severe kidney disease and kidney transplantation). Careful consideration of how to disentangle confounding from conditions that are interrelated with organ transplantation is thus important in order not to attenuate the effect of the exposure under study. For descriptive purposes, we classified comorbidities at baseline (i.e., at CRC diagnosis) using the Charlson comorbidity index (CCI) based on records of healthcare visits from the NPR (last 5 years before diagnosis) and previous non-CRC diagnoses from the SCR (last 10 years before diagnosis) [9]. Next, to address confounding by comorbidities not directly linked to the indication for the transplantation itself, we created a composite comorbidity variable for cardiovascular and other diseases that could affect choice of surgical and/or oncological treatment (i.e., cerebrovascular disease, hemiplegia, congestive heart failure, myocardial infarction, and peripheral vascular disease). Hypertension, not included in CCI, was assessed separately using ICD-9/10 diagnosis codes (440–447, I10-I15). Furthermore, as a proxy for kidney function at CRC diagnosis, we assessed occurrence of chronic dialysis at or within 180 days before CRC diagnosis using ICD-9/10 diagnosis codes (V45B, Z49, and Z99.2) as well as procedure codes (9912, DR014, and DR016). Since the NPR only includes visits to doctors (and not nurses), the 180 days cutoff was intended to ascertain that patients on dialysis had been registered as having seen a specialist physician in that time period. Naturally, among patients on chronic dialysis, we also ascertained that no kidney transplant procedure had been performed until CRC diagnosis.

Additionally, highest attained level of education (<10 years, 10–12 years, or >12 years) was used as a proxy for socioeconomic status, and administrative region (Stockholm/Gotland, Uppsala/Örebro, South East, South, West, or North) was used to account for potential regional differences in treatment.

Cancer Characteristics, Treatment and Outcome

We studied the association between transplantation history and patient and tumor characteristics, selected based on their clinical relevance for prognosis and treatment selection. These included cancer stage at diagnosis (I-II, III, or IV), case discussion at a pre- or postoperative multidisciplinary team (MDT) meeting (yes/no), and having undergone abdominal surgery (yes/no). For stage I-III CRC patients treated with abdominal surgery, we additionally assessed association with cancer location (right-sided [including transverse colon] or left-sided for colon cancer, and distance [<6 or 6-15 cm] from the anal verge for rectal cancer) [10], low/high tumor grade (well/moderately differentiated or poorly differentiated/undifferentiated), microscopically radical surgery (yes/no), perforations found perioperatively (yes/no), perineural invasion (yes/no), administered neoadjuvant and planned adjuvant treatment (chemo- and/or radiotherapy), number of lymph nodes examined (as a proxy for the extent of surgical dissection), and whether emergency surgery was performed (yes/no) [11, 12]. For patients with palliative disease, clinical TNM (tumor-node-metastasis) status, site of distant metastases, and planned palliative treatment (yes/no, referring to chemo- and/or radiotherapy) were included.

Other outcomes of interest were cancer-specific survival and overall survival (OS) among all patients, and relapse rates among stage I-III CRC patients treated with abdominal surgery. Deaths due to CRC (i.e., cancer-specific deaths) were identified based on recorded cause of death information and the following three conditions: 1) if the diagnosis was colon cancer and the main cause of death was colon or recto-sigmoid cancer; 2) if the diagnosis was rectal cancer and the cause of death was recto-sigmoid or rectal cancer; or 3) if CRC was the only cancer in the patient's medical history, and the recorded cause of death was any cancer, in accordance with previous studies [5, 13]. In addition, we assessed mortality due to infection and cardiovascular disease, as well as other causes.

Statistical Analysis

All regression models were adjusted for the matching factors as well as for healthcare region, cardiovascular comorbidity, highest attained level of education, and chronic dialysis at CRC diagnosis. Logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI) for the association between exposure to transplantation and the various outcomes representing cancer characteristics and treatment. For cancer stage, a non-binary outcome, multinomial regression was used to estimate relative risk ratios (RRR). Individuals with missing data were excluded from the regression analyses.

TABLE 1 | Demographic characteristics of colorectal cancer patients diagnosed in Sweden between 1995 and 2016, by medical history of solid organ transplantation. Organ transplant recipients (OTR) denotes patients with any type of solid organ transplantation prior to their first colon or rectal cancer, and *No Tx* denotes non-transplanted cancer patients.

Characteristics	All colorectal cancer		Colon cancer		Rectal cancer	
	OTRs	No Tx	OTRs	No Tx	OTRs	No Tx
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Total no of patients	98 (100)	474 (100)	73 (100)	352 (100)	25 (100)	122 (100)
Sex						
Male	60 (61)	289 (61)	45 (62)	214 (61)	15 (60)	75 (61)
Female	38 (39)	185 (39)	28 (38)	138 (39)	10 (40)	47 (39)
Age at diagnosis (years)						
40–59	18 (18)	89 (19)	13 (18)	62 (18)	5 (20)	27 (22)
60–69	42 (43)	211 (45)	34 (47)	169 (48)	8 (32)	42 (34)
70–89	38 (39)	174 (37)	26 (36)	121 (34)	12 (48)	53 (43)
Year of diagnosis						
1995–2006	10 (10)	48 (10)	0 (0)	0 (0)	10 (40)	48 (39)
2007–2011	42 (43)	204 (43)	36 (49)	174 (49)	6 (24)	30 (25)
2012–2016	46 (47)	222 (47)	37 (51)	178 (51)	9 (36)	44 (36)
Region						
Stockholm-Gotland	14 (14)	95 (20)	10 (14)	74 (21)	4 (16)	21 (17)
Uppsala-Örebro	24 (24)	108 (23)	19 (26)	82 (23)	5 (20)	26 (21)
South East	8 (8)	46 (10)	6 (8)	30 (9)	2 (8)	16 (13)
South	19 (19)	99 (21)	11 (15)	68 (19)	8 (32)	31 (25)
West	19 (19)	85 (18)	13 (18)	68 (19)	6 (24)	17 (14)
North	14 (14)	41 (9)	14 (19)	30 (9)	0 (0)	11 (9)
Attained level of education						
<10 years	35 (36)	145 (31)	26 (36)	105 (30)	9 (38)	40 (33)
10–12 years	37 (38)	209 (44)	26 (26)	158 (45)	11 (46)	51 (42)
>12 years	25 (26)	116 (25)	21 (29)	86 (25)	4 (17)	30 (25)
Missing	*1*	*4*	*0*	*3*	*1*	*1*
First transplant organ type						
Kidney	75 (77)		54 (74)		21 (84)	
Liver	16 (16)		12 (16)		4 (16)	
Heart and/or lung	4 (4)		4 (5)		0 (0)	
Pancreas and kidney	3 (3)		3 (4)		0 (0)	
Number of transplantations[a]						
1	86 (88)		63 (86)		23 (92)	
2	10 (10)		8 (11)		2 (8)	
3	2 (2)		2 (3)		0 (0)	
Cardiovascular comorbidity[b]						
Yes	30 (31)	64 (14)	23 (32)	50 (14)	7 (28)	14 (11)
No	68 (69)	410 (87)	50 (68)	302 (86)	18 (72)	108 (89)
Chronic dialysis at cancer diagnosis[c]						
Yes	6 (6)	2 (0)				
No	92 (94)	472 (100)				

Abbreviations: OTR, organ transplant recipient; Tx, transplantation; N, number.

[a]*Before first colorectal cancer diagnosis.*

[b]*Composite of pre-CRC diagnosis of cerebrovascular disease, hemiplegia, congestive heart failure, myocardial infarction, and peripheral vascular disease.*

[c]*All OTRs with chronic dialysis had a kidney (including kidney and other) transplant. Frequencies for colon cancer and rectal cancer patients not shown due to single observations.*

In the analyses of cancer-specific survival and OS, patients were followed from the date of first CRC diagnosis (in analyses of all patients) or surgery (in analyses of stage I-III CRC patients treated with abdominal surgery), until date of death or 31st December 2017, as cause of death information was not available after 2017. However, in the relapse rate analysis, as well as in a supplementary OS analysis including stage I-III CRC patients treated with abdominal surgery, administrative censoring was set to 4th June 2022, as information on relapse and vital status was available until this date. In all survival analyses, follow-up was restricted to the first 5 years, as both relapses and cancer-related deaths typically occur within that time frame, and relapses were not systematically registered beyond 5 years after surgery.

The Kaplan-Meier method was used to estimate 5-year cancer-specific (net) survival and OS by transplantation history, and differences were evaluated with the log-rank test. Cox proportional hazards regression was used to estimate hazard ratios (HR) for relapse, and for cancer-specific and overall mortality. Furthermore, we performed sensitivity analyses focusing on survival and relapse that were limited to kidney transplant recipients and their matched comparators. The proportional hazards assumption was evaluated with the Grambsch-Therneau test on the Schoenfeld residuals [14].

TABLE 2 | Characteristics of colorectal cancer patients diagnosed 1995–2016, by medical history of solid organ transplantation. The odds ratios (OR) and relative risk ratios (RRR) compare organ transplant recipients (OTRs) to non-transplanted cancer patients (No Tx) with respect to cancer characteristics and treatment.

Characteristics	All colorectal cancer				Colon cancer				Rectal cancer			
	OTRs	No Tx	OR[a,b] (95% CI)	p-value	OTRs	No Tx	OR[a,b] (95% CI)	p-value	OTRs	No Tx	OR[a,b] (95% CI)	p-value
	N (%)	N (%)			N (%)	N (%)			N (%)	N (%)		
Cancer stage				0.08				0.11				0.47
I-II	33 (40)	187 (43)	Base outcome		25 (37)	138 (40)	Base outcome		8 (50)	49 (53)	Base outcome	
III	19 (23)	134 (31)	0.81 (0.43–1.53)		15 (22)	102 (30)	0.82 (0.39–1.71)		4 (25)	32 (34)	0.90 (0.23–3.55)	
IV	31 (37)	113 (26)	1.53 (0.89–2.64)		27 (40)	101 (30)	1.68 (0.89–3.19)		4 (25)	12 (14)	2.35 (0.52–10.6)	
Missing	*15*	*40*			*6*	*11*			*9*	*29*		
Preoperative MDT meeting				0.64				0.77				0.59
Yes	53 (60)	276 (64)	0.88 (0.52–1.49)		40 (55)	204 (58)	0.91 (0.50–1.67)		13 (81)	72 (88)	0.65 (0.13–3.13)	
No	36 (40)	157 (36)	Base outcome		33 (45)	147 (42)	Base outcome		3 (19)	10 (12)	Base outcome	
Missing	*9*	*41*			*0*	*1*			*9*	*40*		
Abdominal surgery[c]				0.03				0.04				0.32
Yes	47 (90)	306 (96)	0.27 (0.08–0.90)		37 (93)	232 (97)	0.16 (0.03–0.94)		10 (83)	74 (93)	0.33 (0.04–2.98)	
No	5 (10)	14 (4)	Base outcome		3 (8)	8 (3)	Base outcome		2 (17)	6 (8)	Base outcome	
Missing	*0*	*1*			*0*	*0*			*0*	*1*		

Abbreviations: OTR, organ transplant recipient; Tx, transplantation; OR, odds ratio; CI, confidence interval; N, number; MDT, multidisciplinary team.

[a]*All reported ORs and relative risk ratios (RRR) refer to the contrast between OTRs, and non-transplanted cancer patients (No Tx), where the latter constitute the reference group. The regression models were adjusted for the matching factors cancer location (colon or rectum), sex, age at diagnosis (±1 year), and year of CRC, diagnosis, as well as region, cardiovascular comorbidity, attained level of education, and chronic dialysis at cancer diagnosis.*

[b]*RRR from multinomial regression for reporting association with cancer stage.*

[c]*Among stage I-III patients.*

SAS version 9.4 (Copyright © 2002–2012 by SAS Institute Inc., Cary, NC, United States) and Stata version 16 (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC.) were used for data management and statistical analysis.

RESULTS

The final study cohort included 572 CRC patients diagnosed in Sweden 1995-2016 (98 OTRs, 73 with colon cancer and 25 with rectal cancer; and 474 non-transplanted, 352 with colon and 122 with rectal cancer) (**Table 1**). Sixty-one percent were male, and 81% were 60 years or older at CRC diagnosis. The median follow-up time was 3.1 years (interquartile range 1.2–5.0 years). Among the OTRs, 77% had undergone kidney transplantation, 16% liver transplantation, 4% heart or lung transplantation, and 3% combined pancreas and kidney transplantation. Most patients (88%) had undergone one transplantation procedure, 10% two procedures, and 2% three procedures, prior to CRC diagnosis (**Table 1**). The median time from first transplantation to CRC diagnosis was 12 years (range 0.6–45 years). Of OTRs, 31% had cardiovascular comorbidity (compared with 14% among non-transplanted patients), and 6% had chronic dialysis at CRC diagnosis (compared with 0.04% among non-transplanted patients) (**Table 1**).

Cancer Characteristics and Treatment

Overall, the distribution of cancer stage and the odds of case discussion at a preoperative MDT meeting were not statistically different between transplanted and non-transplanted CRC patients (**Table 2**). However, among stage I-III CRC patients, OTRs overall had 73% lower odds (OR:0.27, 95% CI:0.08–0.90), and OTRs with colon cancer had 84% lower odds (OR:0.16, 95% CI: 0.03–0.94), of receiving treatment with abdominal surgery than non-transplanted patients (**Table 2**).

Furthermore, among stage I-III colon cancer patients treated with abdominal surgery, OTRs had higher odds of right-sided colon cancer (OR:3.74, 95% CI:1.59–8.84) compared to non-transplanted patients, and adjuvant chemotherapy was planned for 6 (19%) transplanted and 86 (43%) non-transplanted patients with stage II-III cancer (**Table 3**). This corresponded to OTRs having 69% lower odds of adjuvant treatment than non-transplanted CRC patients (OR:0.31, 95% CI:0.11–0.85). Six (43%) OTRs, compared with 64 (64%) non-transplanted patients, with stage III cancer were treated with adjuvant chemotherapy (OR:0.33, 95% CI:0.07–1.67) (**Table 3**). Among the OTRs with adjuvant treatment, 3 (50%) had right-sided and 3 (50%) left-sided colon cancer, while among the non-transplanted, 41 (48%) had right-sided and 45 (52%) had left-sided cancer.

Among stage I-III rectal cancer patients treated with abdominal surgery, transplanted patients had seven times higher odds of having fewer (0–11 vs. 12–53) lymph nodes extracted and examined pathologically (OR:7.47, 95% CI: 1.17–47.7), while no other differences in cancer characteristics and treatment were found (**Supplementary Table S2**). Adjuvant therapy was only administered to a few stage II-III patients and differences could therefore not be assessed.

In the subset of patients with stage IV CRC treated with abdominal surgery, and among patients who did not undergo potentially curative surgery, only descriptive results were presented due to generally low frequencies and high proportions of missing data (**Supplementary Tables S3, S4**).

TABLE 3 | Characteristics of stage I-III colon cancer patients treated with abdominal surgery, by medical history of solid organ transplantation. The odds ratios (OR) compare organ transplant recipients (OTRs) to non-transplanted cancer patients (No Tx) with respect to colon cancer characteristics (cancer location, tumor grade, number of lymph nodes examined) and treatment.

Characteristics[a]	Colon cancer			
	OTRs	No Tx	OR[2] (95% CI)	p-value
	N (%)	N (%)		
Total	37 (100)	232 (100)		
Cancer location				0.002
Right colon	28 (76)	120 (52)	3.74 (1.59–8.84)	
Left colon	9 (24)	112 (48)	Base outcome	
Tumor grade				0.13
Low	24 (69)	179 (79)	Base outcome	
High	11 (31)	48 (21)	1.94 (0.82–4.62)	
Missing	*2*	*5*		
Perineural invasion				0.56
Yes	3 (10)	35 (18)	0.67 (0.18–2.55)	
No	26 (90)	161 (82)	Base outcome	
Missing	*8*	*36*		
Lymph nodes examined				0.58
0–11	6 (17)	25 (11)	1.37 (0.44–4.23)	
12–78	30 (83)	202 (89)	Base outcome	
Missing	*1*	*5*		
Emergency surgery				0.96
Planned	31 (84)	188 (81)	Base outcome	
Emergent	6 (16)	44 (19)	0.98 (0.36–2.63)	
Postoperative MDT meeting				0.10
Yes	27 (75)	203 (88)	0.34 (0.10–1.23)	
No	9 (25)	28 (12)	Base outcome	
Missing	*1*	*1*		
Neoadjuvant therapy[c]				-
Chemotherapy only	0 (0)	2 (1)	-	
No neoadjuvant therapy	32 (100)	197 (99)	Base outcome	
Adjuvant therapy[c]				0.02
Chemotherapy only	6 (19)	86 (43)	0.31 (0.11–0.85)	
No adjuvant therapy	26 (81)	113 (57)	Base outcome	
Stage II cancer				
Chemotherapy only	0 (0)	22 (22)	-	-
No adjuvant therapy	18 (100)	77 (78)	Base outcome	
Stage III cancer				0.18
Chemotherapy only	6 (43)	64 (64)	0.33 (0.07–1.67)	
No adjuvant therapy	8 (57)	36 (36)	Base outcome	

Abbreviations: OTR, organ transplant recipient. Tx, transplantation. OR, odds ratio; CI, confidence interval. N, number. MDT, multidisciplinary team.

[a]*Virtually all patients underwent microscopically radical surgery, and presented without tumor perforations, regardless of transplantation status; data not shown due to single observations.*

[b]*All reported ORs refer to the contrast between OTRs, and non-transplanted cancer patients (No Tx), where the latter constitute the reference group. The regression models were adjusted for the matching factors sex, age at cancer diagnosis (±1 year), and year of cancer diagnosis, as well as region, cardiovascular comorbidity, attained level of education, and chronic dialysis at cancer diagnosis.*

[c]*Among 32 OTRs and 199 non-transplanted patients with stage II-III cancer.*

No stage IV OTR patients treated with abdominal surgery received neoadjuvant therapy (**Supplementary Table S3**).

Other Comorbidity

As expected, all OTRs had CCI>0 at the time of cancer diagnosis, while 65% of the non-transplanted patients had CCI = 0 (**Supplementary Table S5**). In 33% of the transplanted CRC patients, and 11% of the non-transplanted, at least one other cancer diagnosis was recorded in the SCR before the CRC diagnosis. This difference was mainly explained by a higher frequency of non-melanoma skin cancer among the OTRs. Furthermore, 70 (71%) of the OTRs, and 134 (28%) of the non-transplanted patients, had been diagnosed with hypertension before CRC diagnosis.

Survival and Relapse

Overall, 240 patients (61 transplanted and 179 non-transplanted) died during 5 years of follow-up. Of those, 37 (61%) OTRs died of CRC, 5 (8%) of cardiovascular disease, 4 (7%) of infectious disease, 3 (5%) of diabetes, 3 (5%) of kidney disease, and 9 (15%) of other causes. Among non-transplanted patients 127 (71%) died of CRC, 8 (4%) of cardiovascular disease, 3 (2%) of infectious disease, 3 (2%) of lung disease, 3 (2%) of gastrointestinal disease, and 35 (20%) of other causes. The 5-year cancer-specific survival was 56% among transplanted patients, vs. 68% among non-transplanted patients ($p_{logrank}<0.001$) (**Figure 1A**). The corresponding 5-year OS was 35% among transplanted patients, vs. 57% among non-transplanted patients ($p_{logrank}<0.001$) (**Figure 1B**).

Among stage I-III CRC patients treated with abdominal surgery, 5-year cancer-specific survival was 74% among transplanted patients, vs. 83% among the non-transplanted ($p_{logrank} = 0.02$) (**Figure 1C**), while the corresponding 5-year OS was 43% among transplanted patients, vs. 72% among non-transplanted patients ($p_{logrank}<0.001$) (**Figure 1D**). The 5-year cancer-specific mortality rate was two-fold increased (HR:2.16, 95% CI:1.48–3.15) among transplanted vs. non-transplanted patients overall, and 3.5-fold increased (HR: 3.50, 95% CI: 1.64–7.43) among transplanted vs. non-transplanted stage I-III CRC patients treated with abdominal surgery (**Table 4**). Similarly, the overall mortality rate was two-fold increased (HR:2.11, 95% CI:1.55–2.88) among transplanted vs. non-transplanted CRC patients overall, and three-fold increased (HR:3.02, 95% CI 1.79–5.10) among transplanted vs. non-transplanted stage I-III CRC patients treated with abdominal surgery (**Table 4**). In a supplementary analysis with the date of administrative censoring set to 4th June 2022 (latest available date for vital status), 5-year OS proportions were 53% among OTRs and 79% among non-transplanted patients ($p_{logrank} < 0.001$), with a corresponding almost three-fold increased rate of death (HR: 2.79, 95% CI:1.57–4.95) comparing OTRs to non-transplanted patients.

Also among stage I-III CRC patients treated with abdominal surgery, 12 (26%) OTRs [7 (19%) with colon cancer and 5 (50%) with rectal cancer], and 54 (18%) non-transplanted patients [44 (19%) with colon cancer and 10 (14%) with rectal cancer], developed relapse within 5 years of surgery (**Table 4**). The relapse rate was similar among transplanted and non-transplanted colon cancer patients (HR:1.33, 95% CI: 0.57–3.12), while transplanted rectal cancer patients had a ten times increased relapse rate (HR:9.60, 95% CI:1.84–50.1) compared with non-transplanted patients.

Only including kidney transplant recipients and their comparators in the survival analyses resulted in similar hazard ratios (data not shown). Furthermore, for overall survival, no

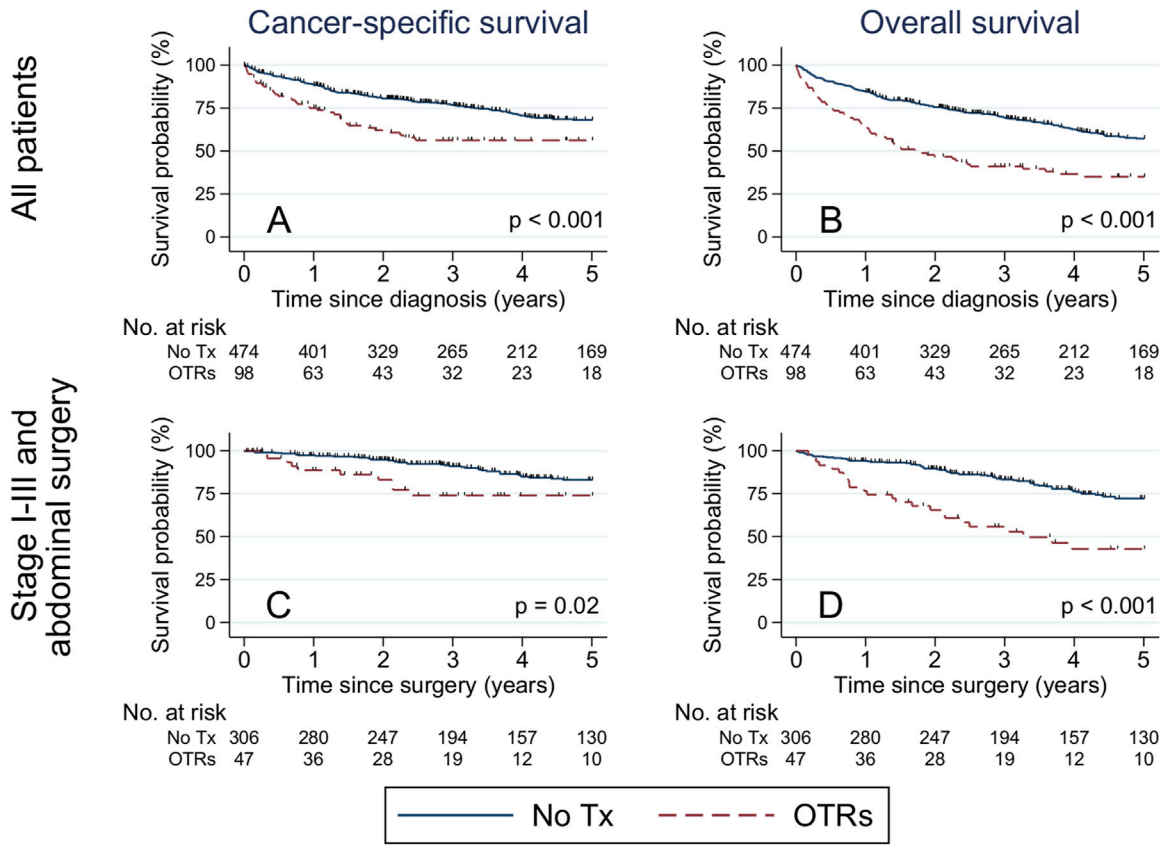


FIGURE 1 | Kaplan-Meier estimates of cancer-specific and overall survival among all patients with colorectal cancer **(A,B)**, and restricted to stage I-III colorectal cancer patients treated with abdominal surgery **(C,D)**, stratified by medical history of solid organ transplantation. Differences were evaluated with the log-rank test. Abbreviations: No., number; Tx, transplantation; OTR, organ transplant recipient.

significant interaction between transplantation status and colon cancer location was found.

DISCUSSION

In this nationwide, population-based study, we observed that transplanted stage I-III CRC patients were less likely than non-transplanted patients to undergo abdominal surgery and to receive adjuvant treatment for colon cancer, and more likely to develop relapse after rectal cancer. However, 90% of transplanted stage I-III CRC patients were treated with abdominal surgery, indicating that most transplanted CRC patients eligible for abdominal surgery actually receive such treatment. The 5-year cancer-specific survival was lower among transplanted compared with non-transplanted patients, both among all patients and among stage I-III CRC patients treated with abdominal surgery. This indicates that the lower cancer-specific survival seen among OTRs could to some extent be due to differences in the likelihood of receiving surgical, adjuvant, and potentially also neoadjuvant, treatment. Nevertheless, stage I-III colon cancer patients treated with abdominal surgery experienced long-term cancer-specific survival that was comparable to non-transplanted individuals, which could indicate that aggressive cancer treatment is justified among OTRs.

While several case reports/series of CRC among OTRs have been published previously, comparative studies of consecutive patients are few. Papaconstantinou et al demonstrated worse OS both for localized and regionally metastasized cancer, but not for cancers with distant metastases, among 150 OTRs with CRC compared with CRC patients in the general population [15]. Kim JY et al compared 17 post-transplant CRC patients to 170 non-transplanted CRC patients matched on closest date of surgery. As in our study, they found no difference in stage and tumor histology, but reported less extensive lymph node dissection and lower frequency of administration of adjuvant therapy (50% vs. 86%) among OTRs than non-transplanted patients, although no formal analyses or adjustments could be made [16]. Among patients with CRC stage III-IV, the 5-year OS was lower among OTRs. Khoury and colleagues demonstrated lower OS and disease-free survival among immunosuppressed CRC patients compared with immunocompetent patients, and argued that the differential

TABLE 4 | Hazard ratios of cancer-specific death, overall death, and relapse, among stage I-III colorectal cancer patients treated with abdominal surgery, stratified by medical history of solid organ transplantation, with 5 years of follow-up. Administrative censoring occurred on Dec 31st, 2017, for cancer-specific and overall death, and on June 4th, 2022, for relapse.

Selection	Start of follow-up	Outcome	All colorectal cancer			Colon cancer			Rectal cancer		
			OTRs	No Tx	HR[a] (95% CI)	OTRs	No Tx	HR[a] (95% CI)	OTRs	No Tx	HR[a] (95% CI)
			N (%)	N (%)		N (%)	N (%)		N (%)	N (%)	
All patients			98 (100)	474 (100)		73 (100)	352 (100)		25 (100)	122 (100)	
	Date of diagnosis	Cancer-specific death	37 (38)	127 (27)	2.16 (1.48–3.15)	30 (41)	102 (29)	2.50 (1.64–3.81)	7 (28)	25 (20)	1.43 (0.58–3.52)
		Overall death	61 (62)	179 (38)	2.11 (1.55–2.88)	50 (68)	137 (39)	2.59 (1.83–3.66)	11 (44)	42 (34)	1.21 (0.59–2.48)
Stage I-III cancer and abdominal surgery[b]			47 (100)	306 (100)		37 (100)	232 (100)		10 (100)	74 (100)	
	Date of surgery	Cancer-specific death	10 (21)	39 (13)	3.50 (1.64–7.43)	6 (16)	29 (13)	2.85 (1.14–7.12)	4 (40)	10 (14)	29.8 (3.77–235)
		Overall death	24 (51)	70 (23)	3.02 (1.79–5.10)	20 (54)	52 (22)	3.70 (2.07–6.62)	4 (40)	18 (24)	5.54 (1.26–24.4)
		Relapse	12 (26)	54 (18)	1.92 (0.98–3.76)	7 (19)	44 (19)	1.33 (0.57–3.12)	5 (50)	10 (14)	9.60 (1.84–50.1)

Abbreviations: OTR, organ transplant recipient; Tx, transplantation; HR, hazard ratio; CI, confidence interval; N, number.

[a]*All reported HRs refer to the contrast between OTRs, and non-transplanted cancer patients (No Tx), where the latter constitute the reference group. The regression models were adjusted for the matching factors cancer location (colon or rectum), sex, age at cancer diagnosis (±1 year), and year of cancer diagnosis, as well as region, cardiovascular comorbidity, attained level of education, and chronic dialysis at cancer diagnosis.*

[b]*Subset of* All patients.

DFS was likely due to increased risk of distant recurrence [17]. Merchea et al reported that OTRs were prone to developing right-sided colon cancer (70%) and present with stage IV disease (25%-30%), with a 5-year OS of 42.5% [18, 19]. In our study, generally higher age at diagnosis might partly explain the higher proportion of stage IV disease (40% for colon cancer) and lower 5-year OS (35%). Finally, Kim M et al matched 33 kidney and liver transplant recipients with CRC to non-transplanted surgically treated CRC patients [20]. Adjuvant chemotherapy proportions (52% of OTRs, and 61% of non-transplanted patients) and 5-year OS (80% among OTRs) were similar.

End-stage organ failure leading to organ transplantation always represents significant comorbidity, which, depending on recipient age, accumulated comorbid conditions, and overall clinical status, has implications for both surgical and neo-/adjuvant cancer treatment. However, comorbidity can also be dramatically improved post-transplant, which is difficult to classify with, e.g., CCI. At cancer diagnosis, the risk of damaging a kidney transplant correlates with (worsening) transplant function, which will influence treatment decisions especially when the expected beneficial effect of chemo-/radiotherapy is moderate. Nevertheless, in our study, adjuvant colon cancer treatment was administered to 0/18 transplanted stage II patients, compared with 22/99 non-transplanted, begging the question whether some OTRs with stage II colon cancer might have been eligible for adjuvant treatment. The low frequency of adjuvant chemotherapy administered to both transplanted and non-transplanted rectal cancer patients is expected, as the benefit of treatment with chemotherapy is lower for rectal cancer than for colon cancer, while such treatment entails substantial risk of morbidity and adverse reactions [10]. Furthermore, radiotherapy may have been deemed contraindicated to a larger extent among transplanted rectal cancer patients, due to possibly harmful effects to the transplanted ureter. However, modern, more precise radiotherapy methods should in many cases enable neoadjuvant radiation for rectal cancer.

Similar to other studies, we found an overrepresentation of right-sided colon cancers among transplanted compared to non-transplanted CRC patients [16, 21]. Right-sided colon cancers have been associated with worse prognosis, and may overall respond to a lower degree to chemotherapy than left-sided; however, this did not impact treatment decisions in the present study [22, 23].

We suggest that MDT meetings should be held whenever an OTR develops a *de novo* cancer where adjuvant treatment would normally be recommended in addition to surgery. Preferably, these MDT meetings would involve not only, e.g., cancer surgeons and oncologists, but also organ transplant specialists, to prevent both over- and undertreating of the cancer. Hellström et al showed that MDT meetings including kidney transplant consultants altered the initial oncological treatment for post-transplant solid or hematological cancer in 52% of the patients, after which 82% were treated in accordance with national guidelines [24]. However, the extra resource allocation required implicates that such conferences need further scientific evaluation.

While strengths of this study include its population-based nature, usage of registers with excellent coverage, and a

comparatively large cohort, we recognize that certain subgroup comparisons should be interpreted within the limitations of available clinical data and statistical power reflected in wide confidence intervals for some contrasts. Information on transplant function and clinical status at cancer diagnosis was available only through proxies of register records of chronic dialysis and cardiovascular comorbidity, and may have been underestimated to some extent. We further adjusted for healthcare region and socioeconomic status through attained education level. We cannot exclude residual confounding by center/surgeon effects although recent Nordic studies on associations between annual hospital volume of CRC surgery and outcome have found either no beneficial effects of centralization, or a small benefit overall that might be confined to certain patient subgroups [25–28]. It was also unclear whether transplantation specialists were involved in the oncological decision-making. Detailed oncological treatment data were not registered and some tumor-specific risk factors, e.g., presence of tumor deposits, were only registered during part of the study period, which limited the ability to fully assess given treatments. Even though we have adjusted for cardiovascular comorbidity and dialysis in our analyses, it might also be argued that transplantation is merely a proxy for comorbidity, which could explain the observed treatment differences. This does not, however, alter our conclusion that OTRs are treated differently, and we have here reported the extent of these differences, which can form the basis for future studies.

CONCLUSION

While most transplanted CRC patients with stage I-III cancer underwent abdominal surgery for their cancer, they were still less likely to undergo abdominal surgery than non-transplanted patients. Furthermore, among stage I-III CRC patients treated with abdominal surgery, transplanted colon cancer patients were less likely to be treated with adjuvant chemotherapy, and transplanted rectal cancer patients had higher rate of relapse, than non-transplanted patients with the same cancer type. Also, transplantation was associated with worse cancer-specific and overall survival among CRC patients. We suggest that MDT meetings, involving organ transplant specialists, should be considered for all post-transplant cancer patients to ensure optimal treatment in the post-transplant setting.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because they are based on detailed pseudonymized health data, the use of which is guided by ethical approval to the principal investigator. Data can only be shared based on additional evaluation and approvals by regulatory authorities in Sweden. Requests to access the datasets should be directed to the corresponding author.

ETHICS STATEMENT

The studies involving humans were approved by the Regional Ethics Review Board in Stockholm (approval no. 2007/1335-31/4, 2014/71-31 and 2016/876-32). The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because this retrospective register study uses pseudonymized data.

AUTHOR CONTRIBUTIONS

HB, CN, VH, KS, and SE formulated the scientific hypotheses. HB, KS, and SE participated in research design; had full access to data and take responsibility for the integrity of the data and the accuracy of the data analyses; performed the analyses and the initial interpretation of data; and drafted the article. HB, CN, VH, CD, AM, KS, and SE participated in the interpretation of data, revised the article for important intellectual content, and approved the final version. SE and KS supervised the study. All authors contributed to the article and approved the submitted version.

FUNDING

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. This study was supported by the Strategic research program in epidemiology at Karolinska Institutet, the Swedish Cancer Society, the Stockholm Cancer Society, the Swedish Cancer and Allergy Foundation, and supported by grants provided by Region Stockholm (ALF project) and Stiftelsen för Njursjukas förening i CUWX-länens forskningsfond.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

ACKNOWLEDGMENTS

This project was made possible by the continuous work of the steering groups of the Swedish Colorectal Cancer Register (SCRCR) and the Colorectal Cancer Base Sweden (CRCBaSe).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2024.13173/full#supplementary-material

REFERENCES

1. Engels EA, Pfeiffer RM, Fraumeni JF, Jr., Kasiske BL, Israni AK, Snyder JJ, et al. Spectrum of Cancer Risk Among US Solid Organ Transplant Recipients. *Jama* (2011) 306(17):1891–901. doi:10.1001/jama.2011.1592
2. Benoni H, Eloranta S, Dahle DO, Svensson MHS, Nordin A, Carstens J, et al. Relative and Absolute Cancer Risks Among Nordic Kidney Transplant Recipients-A Population-Based Study. *Transpl Int : official J Eur Soc Organ Transplant* (2020) 33(12):1700–10. doi:10.1111/tri.13734
3. Miao Y, Everly JJ, Gross TG, Tevar AD, First MR, Alloway RR, et al. De Novo Cancers Arising in Organ Transplant Recipients Are Associated With Adverse Outcomes Compared With the General Population. *Transplantation* (2009) 87(9):1347–59. doi:10.1097/TP.0b013e3181a238f6
4. D'Arcy ME, Coghill AE, Lynch CF, Koch LA, Li J, Pawlish KS, et al. Survival After a Cancer Diagnosis Among Solid Organ Transplant Recipients in the United States. *Cancer* (2019) 125(6):933–42. doi:10.1002/cncr.31782
5. Benoni H, Eloranta S, Ekbom A, Wilczek H, Smedby KE. Survival Among Solid Organ Transplant Recipients Diagnosed With Cancer Compared to Nontransplanted Cancer Patients-A Nationwide Study. *Int J Cancer* (2019) 146:682–91. doi:10.1002/ijc.32299
6. Au E, Wong G, Chapman JR. Cancer in Kidney Transplant Recipients. *Nat Rev Nephrol* (2018) 14(8):508–20. doi:10.1038/s41581-018-0022-6
7. Weibull CE, Boman SE, Glimelius B, Syk I, Matthiessen P, Smedby KE, et al. CRCBaSe: A Swedish Register-Based Resource for Colorectal Adenocarcinoma Research. *Acta oncologica (Stockholm, Sweden)* (2023) 62(4):342–9. doi:10.1080/0284186X.2023.2197121
8. Moberger P, Sköldberg F, Birgisson H. Evaluation of the Swedish Colorectal Cancer Registry: An Overview of Completeness, Timeliness, Comparability and Validity. *Acta oncologica (Stockholm, Sweden)* (2018) 57(12):1611–21. doi:10.1080/0284186X.2018.1529425
9. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A New Method of Classifying Prognostic Comorbidity in Longitudinal Studies: Development and Validation. *J chronic Dis* (1987) 40(5):373–83. doi:10.1016/0021-9681(87)90171-8
10. Glynne-Jones R, Wyrwicz L, Tiret E, Brown G, Rödel C, Cervantes A, et al. Rectal Cancer: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-Up. *Ann Oncol : official J Eur Soc Med Oncol* (2017) 28(Suppl. l_4): iv22–iv40. doi:10.1093/annonc/mdx224
11. Anderson JH, Hole D, McArdle CS. Elective versus Emergency Surgery for Patients With Colorectal Cancer. *The Br J Surg* (1992) 79(7):706–9. doi:10.1002/bjs.1800790739
12. Böckelman C, Engelmann BE, Kaprio T, Hansen TF, Glimelius B. Risk of Recurrence in Patients With Colon Cancer Stage II and III: A Systematic Review and Meta-Analysis of Recent Literature. *Acta oncologica (Stockholm, Sweden)* (2015) 54(1):5–16. doi:10.3109/0284186X.2014.975839
13. Howlader N, Ries LA, Mariotto AB, Reichman ME, Ruhl J, Cronin KA. Improved Estimates of Cancer-Specific Survival Rates From Population-Based Data. *JNCI: J Natl Cancer Inst* (2010) 102(20):1584–98. doi:10.1093/jnci/djq366
14. Grambsch PM, Therneau TM. Proportional Hazards Tests and Diagnostics Based on Weighted Residuals. *Biometrika* (1994) 81(3):515–26. doi:10.2307/2337123
15. Papaconstantinou HT, Sklow B, Hanaway MJ, Gross TG, Beebe TM, Trofe J, et al. Characteristics and Survival Patterns of Solid Organ Transplant Patients Developing De Novo Colon and Rectal Cancer. *Dis colon rectum* (2004) 47(11): 1898–903. doi:10.1007/s10350-004-0674-0
16. Kim JY, Ju MK, Kim MS, Kim NK, Sohn SK, Kim SI, et al. Clinical Characteristics and Treatment Outcomes of Colorectal Cancer in Renal Transplant Recipients in Korea. *Yonsei Med J* (2011) 52(3):454–62. doi:10.3349/ymj.2011.52.3.454
17. Khoury W, Lavery IC, Kiran RP. Effects of Chronic Immunosuppression on Long-Term Oncologic Outcomes for Colorectal Cancer Patients Undergoing Surgery. *Ann Surg* (2011) 253(2):323–7. doi:10.1097/SLA.0b013e3181fc9d36
18. Merchea A, Abdelsattar ZM, Taner T, Dean PG, Colibaseanu DT, Larson DW, et al. Outcomes of Colorectal Cancer Arising in Solid Organ Transplant Recipients. *J Gastrointest Surg : official J Soc Surg Aliment Tract* (2014) 18(3):599–604. doi:10.1007/s11605-013-2402-3
19. Merchea A, Shahjehan F, Croome KP, Cochuyt JJ, Li Z, Colibaseanu DT, et al. Colorectal Cancer Characteristics and Outcomes After Solid Organ Transplantation. *J Oncol* (2019) 2019:5796108. doi:10.1155/2019/5796108
20. Kim M, Kim CW, Hwang S, Kim YH, Lee JL, Yoon YS, et al. Characteristics and Prognosis of Colorectal Cancer After Liver or Kidney Transplantation. *World J Surg* (2021) 45(10):3206–13. doi:10.1007/s00268-021-06219-9
21. Safaeian M, Robbins HA, Berndt SI, Lynch CF, Fraumeni JF, Jr., Engels EA. Risk of Colorectal Cancer After Solid Organ Transplantation in the United States. *Am J Transplant : official J Am Soc Transplant Am Soc Transpl Surgeons* (2016) 16(3):960–7. doi:10.1111/ajt.13549
22. Lee MS, Menter DG, Kopetz S. Right Versus Left Colon Cancer Biology: Integrating the Consensus Molecular Subtypes. *J Natl Compr Cancer Netw JNCCN* (2017) 15(3):411–9. doi:10.6004/jnccn.2017.0038
23. Yahagi M, Okabayashi K, Hasegawa H, Tsuruta M, Kitagawa Y. The Worse Prognosis of Right-Sided Compared With Left-Sided Colon Cancers: A Systematic Review and Meta-Analysis. *J Gastrointest Surg : official J Soc Surg Aliment Tract* (2016) 20(3):648–55. doi:10.1007/s11605-015-3026-6
24. Hellström VC, Enström Y, von Zur-Mühlen B, Hagberg H, Laurell A, Nyberg F, et al. Malignancies in Transplanted Patients: Multidisciplinary Evaluation and Switch to mTOR Inhibitors After Kidney Transplantation - Experiences From a Prospective, Clinical, Observational Study. *Acta oncologica (Stockholm, Sweden)* (2016) 55(6):774–81. doi:10.3109/0284186X.2015.1130855
25. Ljunggren M, Weibull CE, Rosander E, Palmer G, Glimelius B, Martling A, et al. Hospital Factors and Metastatic Surgery in Colorectal Cancer Patients, a Population-Based Cohort Study. *BMC cancer* (2022) 22(1):907. doi:10.1186/s12885-022-10005-8
26. Rosander E, Holm T, Sjövall A, Hjern F, Weibull CE, Nordenvall C. The Impact of Hospital Volume on Survival in Patients With Locally Advanced Colonic Cancer. *BJS open* (2022) 6(6):zrac140. doi:10.1093/bjsopen/zrac140
27. Sarjanoja E, Klintrup K, Ohtonen P, Kauppila JH. Annual Hospital Volume and Colorectal Cancer Survival in a Population-Based Nationwide Cohort Study in Finland. *Eur J Surg Oncol : J Eur Soc Surg Oncol Br Assoc Surg Oncol* (2022) 48(7):1650–5. doi:10.1016/j.ejso.2022.02.017
28. Trewin-Nybråten CB, Larsen IK, Møller B, Heikkilä R. Hospital Surgical Volume and Colorectal Cancer Survival in Norway: A Nationwide Cohort Study. *Cancer Epidemiol* (2023) 85:102404. doi:10.1016/j.canep.2023.102404

ESOT | Transplant International

REVIEW
published: 16 October 2024
doi: 10.3389/ti.2024.13322

Immune Checkpoint Inhibitor Therapy for Kidney Transplant Recipients – A Review of Potential Complications and Management Strategies

Elena Bianca Barbir[1], *Samer Abdulmoneim*[2], *Arkadiusz Z. Dudek*[3] *and Aleksandra Kukla*[1]*

[1]Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN, United States, [2]Department of Surgery, Mayo Clinic, Rochester, MN, United States, [3]Department of Medical Oncology, Mayo Clinic, Rochester, MN, United States

Immune checkpoint inhibitor (ICI) therapy has enabled a paradigm shift in Oncology, with the treatment of metastatic cancer in certain tumor types becoming akin to the treatment of chronic disease. Kidney transplant recipients (KTR) are at increased risk of developing cancer compared to the general population. Historically, KTR were excluded from ICI clinical trials due to concern for allograft rejection and decreased anti-tumor efficacy. While early post-marketing data revealed an allograft rejection risk of 40%–50%, 2 recent small prospective trials have demonstrated lower rates of rejection of 0%–12%, suggesting that maintenance immunosuppression modification prior to ICI start modulates rejection risk. Moreover, objective response rates induced by ICI for the treatment of advanced or metastatic skin cancer, the most common malignancy in KTR, have been comparable to those achieved by immune intact patients. Non-invasive biomarkers may have a role in risk-stratifying patients before starting ICI, and monitoring for rejection, though allograft biopsy is required to confirm diagnosis. This clinically focused review summarizes current knowledge on complications of ICI use in KTR, including their mechanism, risk mitigation strategies, non-invasive biomarker use, approaches to treatment of rejection, and suggestions for future directions in research.

Keywords: immunology, rejection risk, oncology, kidney transplant, biomarkers, immunotherapy

OPEN ACCESS

***Correspondence**
Aleksandra Kukla,
kukla.aleksandra@mayo.edu

Received: *31 May 2024*
Accepted: *01 October 2024*
Published: *16 October 2024*

Citation:
Barbir EB, Abdulmoneim S, Dudek AZ and Kukla A (2024) Immune Checkpoint Inhibitor Therapy for Kidney Transplant Recipients – A Review of Potential Complications and Management Strategies. Transpl Int 37:13322. doi: 10.3389/ti.2024.13322

INTRODUCTION

The last decade has seen a paradigm shift in Oncology with the initial United States Food and Drug Administration approval of immune checkpoint inhibitor (ICI) therapy in 2011 with Ipilimumab. There are currently 10 ICI agents approved (**Figure 1**) with indications in over 85 malignancies [1]. The momentum has been sustained by the demonstrated efficacy of these agents in the treatment of certain aggressive cancers [2]. Post-transplant malignancy represents a leading cause of death with a functional allograft in kidney transplant recipients (KTR) after the first year post transplant [3]. Prior to the era of immunotherapy, there was no significant improvement in cancer related outcomes over three decades [3, 4]. Due to concerns of attenuated anti-tumor responses and increased risk of toxicity related to allograft rejection, KTR were historically excluded from ICI clinical trials. Early retrospective data affirmed initial concerns with kidney allograft rejection rates as high as 40%–50%. More recently, small prospective trials have reported lower rates of 0%–12% [5–7]. This significant discrepancy in outcomes between the early retrospective and recent prospective data has highlighted the need for additional prospective studies to help guide decision making around maintenance

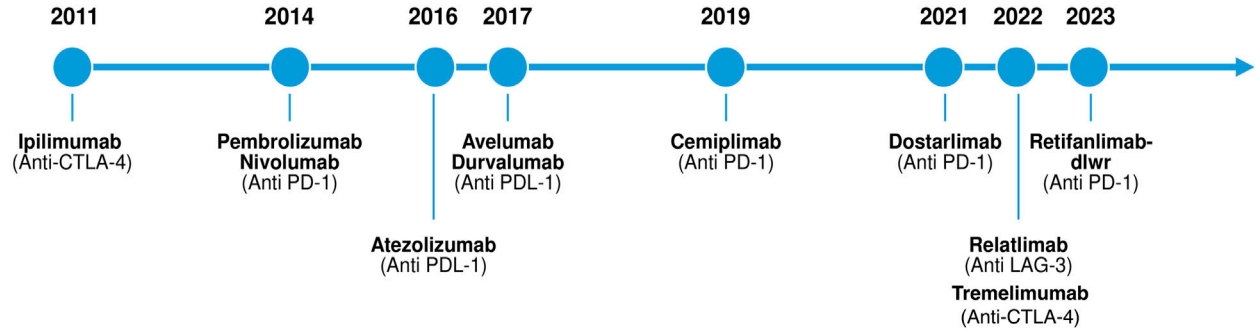


FIGURE 1 | Timeline of immune checkpoint inhibitor approvals by the United States Food and Drug Administration (FDA) from 2011 to 2023.

immunosuppression for these patients. Although there is no definitive data on frequency and grade of immune related adverse events (irAEs), including recurrent glomerulonephritis (GN), retrospective data suggest a decreased frequency of irAEs in KTR [5, 8]. The initial hypothesis that immunotherapy is less effective in immunosuppressed solid organ transplant recipients (SOTR) has been challenged by the accruing data; most recently by results from two small prospective trials that reported objective response rates of about 50% in KTR – similar response rates as seen in the general population [6, 7, 9–12]. This review aims to highlight current knowledge around the risks associated with ICI therapy use in KTR, including their mechanism, risk mitigation strategies, the role of non-invasive biomarkers as well as our proposed approach to the management of these patients.

IMMUNE CHECKPOINT INHIBITOR THERAPY MECHANISM OF ACTION

Cancer immunotherapy as a category encompasses all therapies whose anti-tumor mechanism is exerted via the activation and expansion of the host immune response to tumor antigens [13]. Specifically, ICI's enable amplified tumor-reactive T cell responses by disabling intrinsic attenuation mechanisms which lead to T cell exhaustion. Under normal physiologic conditions "immune checkpoints" exist to regulate T cell responses and prevent excessive activation. However, T cells infiltrating the tumor microenvironment are subject to over-attenuation due to tumor immune escape, allowing tumor cells to evade the host immune response [14]. One of the mechanisms of tumor immune escape is the constitutive expression of immune checkpoint ligands, such as programmed cell death ligand 1 (PDL-1) on tumor cells [14]. This allows peripherally circulating T cells expressing programmed cell death protein 1 (PD1) to bind to PDL-1 and become anergic. The PD1/PDL-1 immune checkpoint pathway provides a mechanism for T cells to recognize "self", as multiple host cells express PDL-1 [15]. Broadly speaking, ICIs are monoclonal antibodies that inhibit immune checkpoint receptors expressed by T-cells from binding to their ligands, and thus enable persistent T cell activation and proliferation. The immune checkpoint pathways that are currently targeted include: 1) the PD1 pathway with its ligands PDL1 and PDL2 which are expressed on lymphoid, myeloid, epithelial cells and tumor cells; 2) the cytotoxic T-lymphocyte antigen 4 (CTLA4) pathway and its ligands CD80/86 which are expressed on myeloid and lymphoid cells, and 3) the lymphocyte-activation gene 3 pathway [15–18]. **Figures 2**, **3** depict the three-signal model of T cell activation, and how the mechanism of action of ICIs ties into this. This review will focus on the use of PD1/PDL-1 and CTLA4 blockade in KTR as, to our knowledge, LAG3 blockade has not yet been reported in SOTR.

There are multiple hypotheses regarding the mechanism by which ICI use can trigger allograft rejection. Pre-clinical studies using murine and porcine models exist which identify the PD1/PDL-1 pathway as a mechanism of peripheral tolerance, with its disruption linked to auto-immunity and alloreactivity [19–23]. Other potential mechanisms include activation of quiescent alloreactive and effector memory T cells with ICI use illustrated by Dunlap et al; tumor and allograft antigen homology leading to the formation of cross-reactive T-cells as has been demonstrated in 2 cases of myocarditis but yet to be demonstrated in SOTR; and functional inhibition of regulatory T-cells via CTLA-4 and PD-1 inhibition [24–26].

INCIDENCE OF ALLOGRAFT REJECTION IN KIDNEY TRANSPLANT RECIPIENTS – A HISTORICAL PERSPECTIVE

Our understanding regarding risk of allograft rejection has been evolving. Initially, rejection risk was reported as 40%–50%. This estimation was based on the results of retrospective studies published up until 2021 [5, 8]. Significant reduction of immunosuppression prior to initiation of ICI was a confounding factor, as demonstrated by Murakami et al.'s multi-center analysis, where 65% of patients underwent changes in maintenance immunosuppression prior to starting ICI, of which 35% had a reduction in the total number of agents [5]. However, discrepancies existed even within early retrospective data with smaller case series reporting rejection

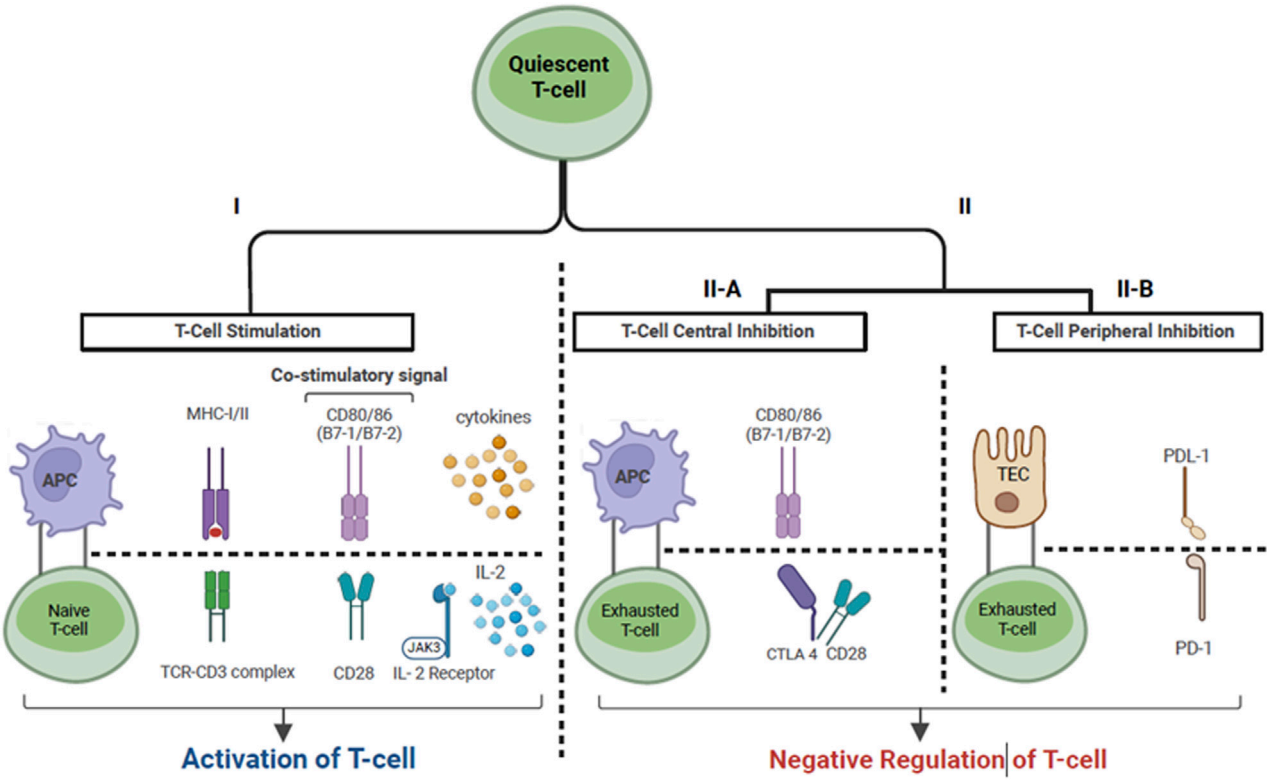


FIGURE 2 | T-cell activation via the three-signal model. Cancer cells express tumor associated antigens which are captured by APCs. Signal 1: Antigen peptide presented by APC on MHC molecule binds to TC on -cell surface. Signal 2: Co-stimulation. The binding of CD28, expressed on T cells, to CD80/86 expressed on APC's describes one of the necessary co- stimulatory signals. Signal 3: Once signal 1 and 2 have been completed, signal 3 denotes cytokine production by T cells, which allows ongoing T cell differentiation and proliferation. This includes the production of IL2 by T-cells leading to IL2-R stimulation on the surface of T cells. II- Immune checkpoints provide a negative feedback mechanism in the setting of T cell activation. In lymphoid tissues, CTLA-4 binds to CD80/86 with higher affinity than CD28, leading to competitive inhibition of signal 2. In the peripheral tissue, PD-L1 which is expressed by epithelial cells (i.e., renal TEC, tumor cells) binds to PD-1, which is expressed by peripherally circulating T cells, inducing T-cell exhaustion. Abbreviations: APC, Antigen presenting cell; MHC, Major histocompatibility complex I/II; TC, T-cell receptor; IL-2, Interleukin-2; IL2-R, Interleukin-2 receptor; CTLA-4, Cytotoxic -lymphocyte associated protein 4; PD-L1, Programmed cell death ligand 1; PD1, Programmed cell death protein 1; TEC, Tubular epithelial cell; JAK-3, Janus Kinase 3.

in only 15% of patients despite decreased immunosuppression [27, 28]. Due to the overall low biopsy rate in the retrospective studies, patients may have been misdiagnosed with rejection given multiple competing risks for acute kidney injury (AKI). Three prospective studies followed which are presented in **Table 1**. Carroll et al. enrolled seventeen KTR who were continued on their baseline maintenance immunosuppression through ICI therapy [7]. Two cases of biopsy-proven acute rejection were reported out of seventeen included patients (12%), with one patient suspected to have had pre-existing subclinical rejection based on an elevated urinary chemokine, C-X-C motif chemokine ligand 10 (CXCL10), prior to starting therapy [7]. Subsequently, in the phase 1 CONTRAC-1 trial, twelve KTR with advanced cSCC received the PD-1 inhibitor, cemiplimab, while maintained on a mammalian target of rapamycin inhibitor (mTORi) and prednisone mini-pulse with each treatment cycle [6]. Selection of this maintenance immunosuppressive strategy was based on reports from retrospective studies suggesting a decreased incidence of rejection with preserved anti-tumor activity when using the combination of mTORi and prednisone [5, 30, 31]. Specifically, everolimus or sirolimus was used with a target trough level of 4–6 ng/mL, and the prednisone mini-pulse consisted of prednisone 40 mg day −1 through day 3 of cemiplimab administration, followed by 20 mg daily days 4–6 and then 10 mg daily from day 7 onwards until the next cycle [6]. The study did not exclude patients based on immunologic risk as Carroll et al. had done [7]. They reported no rejection episodes. Lastly, Schenk et al. published the results of a prospective, multi-center phase I/II trial, in which eight evaluable KTR with multiple advanced skin cancers received PD-1 inhibitor monotherapy with nivolumab, and subsequently had the option of transitioning to dual ICI blockade with PD-1 and CTLA-4 inhibition with ipilimumab and nivolumab (6/8) for progressive disease [29]. Maintenance immunosuppression consisted of tacrolimus (trough target 2–5 ng/mL) and prednisone 5 mg daily. Of eight evaluable patients, three experienced biopsy proven allograft rejection

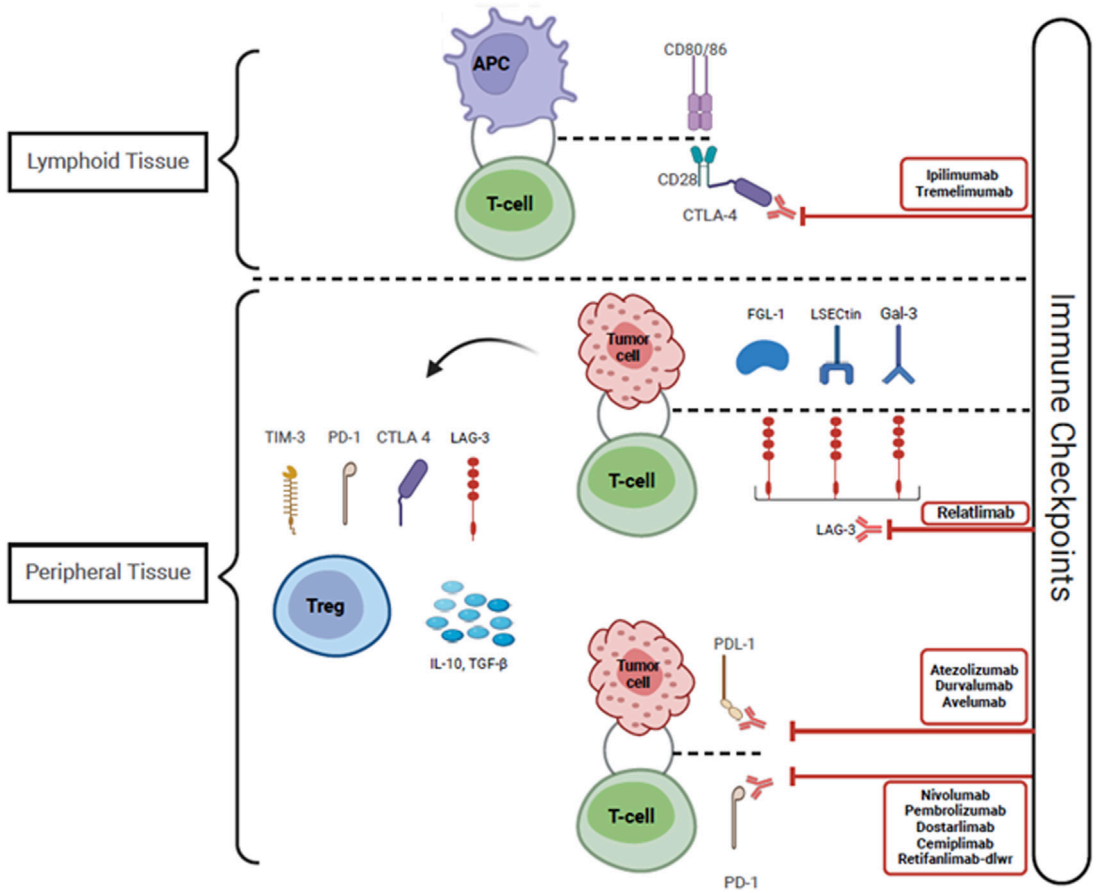


FIGURE 3 | Immune checkpoint inhibitors including Anti CTLA-4, PDL-1 and PD-1 antibodies function by blocking the interactions between checkpoint proteins and their receptors. This disrupts the counter-regulatory negative feedback mechanism that suppresses T-cell activity, leading to persistent T-cell activation and proliferation, allowing T-cells to recognize and eliminate tumor cells. The tumor cells express LECtin, Gal-3, and FGL-1, which bind to LAG-3 expressed on the surface of T-cells and provoke T-cell anergy. Tumor tolerance is also promoted by the infiltration of Tregs within the tumor microenvironment. These Tregs express higher levels of CTLA-4, PD-1, LAG-3, and TIM-3, and they secrete elevated levels of IL-10 and TGF-ß, thus facilitating tumoral resistance. Abbreviations: CTLA-4, Cytotoxic T-Lymphocyte Antigen 4; PDL-1, Programmed cell death ligand 1; PD-1, Programmed cell death protein 1; LSECtin, Liver sinusoidal endothelial cell lectin; Gal-3, Galectin-3; FGL-1, Fibrinogen-like protein-1; LAG-3, Lymphocyte activation gene-3; Treg, Regulatory T-cell; TIM-3, T-cell immunoglobulin and mucin domain-containing protein 3; TGF-ß, Transforming growth factor- beta; CD 80/86 and CD 28, Cluster of differentiation 80/86 and 28; IL-10, Interleukin-10.

(38%); one on ICI monotherapy and two on dual ICI therapy, though the third rejection happened after stopping all treatment, including maintenance immunosuppression [29]. These results suggested that a tacrolimus trough of 2–5 ng/mL and prednisone 5 mg daily may be insufficient to prevent organ rejection.

CHARACTERISTICS OF ICI ASSOCIATED ALLOGRAFT REJECTION

Retrospective data suggest that allograft rejection tends to occur early, with a median time to rejection of 3–4 weeks, and is treatment refractory in 50%–80% of patients [5, 8, 32]. However, in a recent multi-center retrospective study including 30 KTR and 1 lung transplant recipient (LTR), Remon et al. noted a comparatively delayed median time to rejection of 8 weeks [33]. This delay may be the result of less aggressive maintenance immunosuppression reduction prior to ICI start.

The data regarding treatment of ICI associated rejection is limited by low sample sizes, and a significant heterogeneity in treatment approaches. Acute cellular rejection (ACR), either alone or in combination with acute antibody mediated rejection (ABMR), has been reported in all biopsied cases to date [5, 7, 8, 29, 32, 34, 35]. For the cases of biopsy proven allograft rejection included the multi-center retrospective study by Murakami et al., 50% consisted of ACR, and 50% consisted of mixed ACR and ABMR, with nine of fourteen biopsied cases with endothelialitis [5]. In the systematic review by Portuguese et al., which included nineteen cases of biopsy-proven rejection, 74% were reported as ACR and 26% as mixed ACR and ABMR [8]. As the 3 available prospective studies to date have small numbers of patients, with only a few reported episodes of allograft rejections, the data is mixed (**Table 1**).

TABLE 1 | The 3 published prospective trials to date on the use of immune checkpoint inhibitor therapy in kidney transplant recipients.

Study title	Immune checkpoint inhibitors in kidney transplant recipients [7]	CONTRAC-1 [6]	Nivolumab + tacrolimus + prednisone ± ipilimumab for kidney transplant recipients with advanced Cutaneous cancers [29]
Authors, Year	Carroll et al., 2022	Hanna et al., 2024	Schenk et al., 2024
Patient Number	17	12	8
Tumor Group	Any advanced cancer otherwise meeting ICI indication	Advanced cSCC	Advanced Skin Cancers
ICI Type	16 patients on Anti-PD1 therapy 1 patient on Anti-PDL1 therapy	Cemiplimab (Anti PD1)	Initial Nivolumab (Anti PD1) in 8/8 patients Transition to Nivolumab + Ipilimumab (anti-CTLA4) in 6/8 patients
Maintenance Immunosuppression	Maintain prior baseline maintenance immunosuppression	mTORi and dynamic prednisone taper[a]	Tacrolimus (trough 2–5 ng/mL) and Prednisone 5 mg daily
Rejection	2/17, 11.7%	0/12, 0%	3/8, 37.5%
Allograft Biopsy Findings	2 cases of ACR	N/A	1 case of ACR, Mixed Rejection (ACR + ABMR) × 2
Extra-Renal Immune Related Adverse Events	1/17, colitis	1/12, colitis	2/8, arthralgia, maculopapular rash
Objective Response Rate	53%	45%	25%

[a]*Please see text for dosage details. Abbreviations: ICI, immune checkpoint inhibitor; ACR, acute cellular rejection; cSCC, cutaneous squamous cell carcinoma; mTORi, Mammalian Target of Rapamycin Inhibitor; ABMR, antibody mediated rejection.*

ICI ASSOCIATED ALLOGRAFT REJECTION – RISK FACTORS

The data we have to date suggests that significant reduction in baseline immunosuppression is a risk factor for ICI associated allograft rejection though the ideal degree of immunosuppression remains to be defined [5, 8, 36]. Prospective evidence suggests that maintaining patients' prior baseline immunosuppression, or using a dynamic steroid and mTORi reduces the risk of rejection [6–8]. However, despite the encouraging objective response rate noted in these small studies, there remains the concern that maintaining higher degrees of maintenance immunosuppression may blunt the anti-tumor efficacy of ICI. Specifically, high dose steroids have been associated with decreased progression free survival in non-transplant patients with non-small cell lung cancer (NSCLC) [37]. To definitively answer this question, prospective studies comparing allograft and cancer outcomes with different immunosuppressive strategies are needed.

Other risk factors for ICI associated allograft rejection suggested by retrospective data include a prior history of allograft rejection, anti-PD1 therapy or dual ICI therapy, and low dose corticosteroids (<10 mg per day) [5, 8, 24, 31, 35, 36, 38, 39]. Notably, the prospective studies reported by Carroll et al. and Hanna et al. did not exclude patients with a prior history of rejection, and yet low rejection rates were seen [6, 7]. However, Carroll et al. did account for immunologic risk in a different fashion by excluding patients with a donor specific antibody mean fluorescence intensity (DSA MFI) greater than 4,000 [7]. Schenk et al. excluded all patients with any existing DSA or a history of allograft rejection within 3 months prior to enrollment and noted a higher rejection rate [29]. To date, no clear relationship between cancer type and risk of allograft rejection has been established; adequately powered studies are needed to address this question.

ICI ASSOCIATED ALLOGRAFT REJECTION – OPTIMIZING IMMUNOSUPPRESSION

An immunosuppressive strategy with at least 2 agents and a prednisone dose greater than or equal to 10 mg daily is supported by the current body of evidence. The use of mTORi as maintenance immunosuppression has been associated with a decreased rejection risk in retrospective studies, and further supported by the absence of rejection in the CONTRAC-1 study over a median follow up period of 6.8 months, though those patients were on higher doses of prednisone [5, 8, 27, 38]. There are clinical scenarios in which transition to mTORi is either not tolerated by patients due to drug-related toxicities, or not feasible due to the presence of: 1) healing wounds 2) proteinuria with a urine protein to creatinine ratio >0.5 g/g, or 3) high immunologic risk especially within the first 6 months post-transplant [40–42]. In these situations, there is minimal data to guide decision making. The available data would suggest continuing patients on their prior maintenance immunosuppression, as per Carroll et al. [7] Alternatively, pursuing dual maintenance immunosuppression with prednisone 10 mg daily, and tacrolimus with a trough level 5–7 ng/mL can be considered [29]. Two small, single center retrospective studies demonstrated low rates of rejection with tacrolimus use, either as monotherapy or dual therapy with corticosteroids; when available, the reported achieved tacrolimus trough levels were greater than 4 ng/mL [27, 28]. It is also notable that 70% of patients included in Carroll et al.'s study had maintenance immunosuppressive regimens containing a calcineurin inhibitor (CNI) [7]. Moreover, three prior reviews demonstrated a protective effect with CNI use, though the data analysis was done for all SOTR and not KTR alone [8, 35, 36].

ALLOGRAFT REJECTION - TREATMENT

Treatment would ideally be targeted to the histopathologic lesion identified on allograft biopsy. Multiple different approaches to therapy including pulse dose corticosteroids, thymoglobulin, intravenous immunoglobulins, infliximab and plasma exchange to remove circulating ICI have been reported, though no specific treatment approach has consistently demonstrated improved allograft outcomes [5, 7, 29, 35]. The use of lymphodepleting therapies in the treatment of allograft rejection requires careful consideration in the setting of active, advanced malignancies. Allograft irradiation has been trialed for patients with treatment-refractory rejection with limited responses though this may be an option for KTR on ICI wanting to avoid additional immunosuppression and risk tumor progression [43]. It is possible that early recognition of allograft dysfunction and prompt initiation of therapy may improve outcomes, though definitive data is lacking. Ultimately, mortality in this patient population has been attributed to malignancy progression, rather than to organ rejection [5, 8].

ADDITIONAL IMMUNE RELATED ADVERSE EVENTS

The incidence of irAE's in non-transplant patients on ICI therapy has been reported to be as high as 60%–85% [44, 45]. While irAE can affect any organ system, the most common manifestations in non-transplant patients include rash, arthralgias, endocrinopathies such as hypothyroidism, and colitis [46]. Acute tubulointerstitial nephritis can occur in the native kidney, with an estimated incidence of in 1.4%–3% for patients on ICI monotherapy, and up to 5% on ICI dual therapy, with glomerulopathies seen even less frequently [47–51].

A question that has previously arisen is whether we may be mis-identifying hypersensitivity reactions in the allograft, i.e., acute tubulointerstitial nephritis (ATIN), as T cell mediated rejection (TCMR). Both Banff Grade 1 acute TCMR and ATIN consist of a lymphocyte-predominant tubulointerstitial infiltrate [52]. While gene expression profiling confirmed the presence of significant molecular overlap between ICI-ATIN and ICI-TCMR, the most frequently upregulated transcripts were different suggesting different pathophysiologic mechanisms [53]. The highest frequency expressed genes in ICI-TCMR were associated with interferon signaling, T cell and Natural Killer cell functions, and TNF superfamily members, while in ICI-ATIN they were associated with allergic response components (IgE, mast cells and eosinophils) consistent with hypersensitivity responses [53]. The authors also identified an interferon alpha induced transcript, interferon-alpha inducible protein 27, that could serve as a potential biomarker for ICI-TCMR [53]. Moreover, there exist clinical differences between ICI-ATIN and ICI associated allograft rejection suggesting different underlying mechanisms. Median time to occurrence of ICI-ATIN is reported as 12–16 weeks, as compared to 3–4 weeks for rejection [5, 8, 47, 54–56]. Prior or concurrent extra-renal irAEs have been shown to be associated with an increased risk of ICI-ATIN, but the same association has not been noted for rejection [5, 39, 55]. Additionally, ATIN-associated drugs, such as proton pump inhibitors, nonsteroidal anti-inflammatory drugs, and antibiotics have been associated with an increased risk of developing ICI-ATIN in native kidneys in multiple systematic reviews [57–60]. Conversely, a significant association between ICI associated kidney allograft rejection and ATIN-associated drug use was not seen in the largest retrospective study to date [5].

Interestingly, in SOTR a lower incidence of extra-renal irAEs has been documented. Portuguese et al. identified a 13.4% incidence of extra-renal irAEs in their systematic review, of which pneumonitis was the most common (37.5%), followed by dermatitis (31%), colitis (25%) and hepatitis (12.5%) [8]. Looking at KTR alone a 25% incidence of irAEs was reported in a 69 patient retrospective study, and a systematic review similarly reported a 24.5% incidence [5, 35]. When looking at severe irAEs that lead to ICI discontinuation, a 21% incidence was reported in a multi-center cohort of 31 SOTR, of which 30 were KTR and 1 was a lung transplant recipient [33]. Prospective studies have revealed similarly low incidences (**Table 1**) [6, 7, 29].

A question that remains unanswered is the risk of recurrent glomerulonephritis (GN) in KTR on ICI therapy. To our knowledge, no publications on the topic exist to date. In reviewing our single center data at Mayo Clinic Rochester, of 21 patients started on ICI therapy, 9 had end stage kidney disease secondary to a glomerulopathy, and of these, one patient experienced recurrent membranous nephropathy which responded to tacrolimus (**Table 2**) [61].

The occurrence of irAEs in the immune-intact population has been correlated with improved anti-tumor efficacy with multiple retrospective studies demonstrating an improved median overall survival, and one study showing an improved objective response rate (ORR) and progression free survival [62, 63]. Presumably, there is a correlation between the amplitude of the tumor-directed T cell response and the off-target occurrence of irAEs. Despite continuation of maintenance immunosuppression in SOTR and an associated decreased incidence of irAEs, the ORR for certain tumor types, such as advanced cutaneous squamous cell carcinoma (cSCC) and melanoma, has been comparable to that seen in the immune intact population [8].

TABLE 2 | Description of the immune mediated causes of end stage kidney disease included in Mayo Clinic Rochester's single center retrospective study on ICI use in KTR.

Number of cases	Glomerulopathy [61]
2	IgA nephropathy
1	IgA vasculitis
1	Primary focal segmental glomerulosclerosis
1	AA Amyloidosis
2	Anti-neutrophil cytoplasmic antibody associated vasculitis
1	PLA2R positive membranous nephropathy
1	Chronic GN of unclear etiology

Abbreviations: IgA, Immunoglobulin A; PLA2R, Phospholipase A2 receptor; GN, glomerulonephritis.

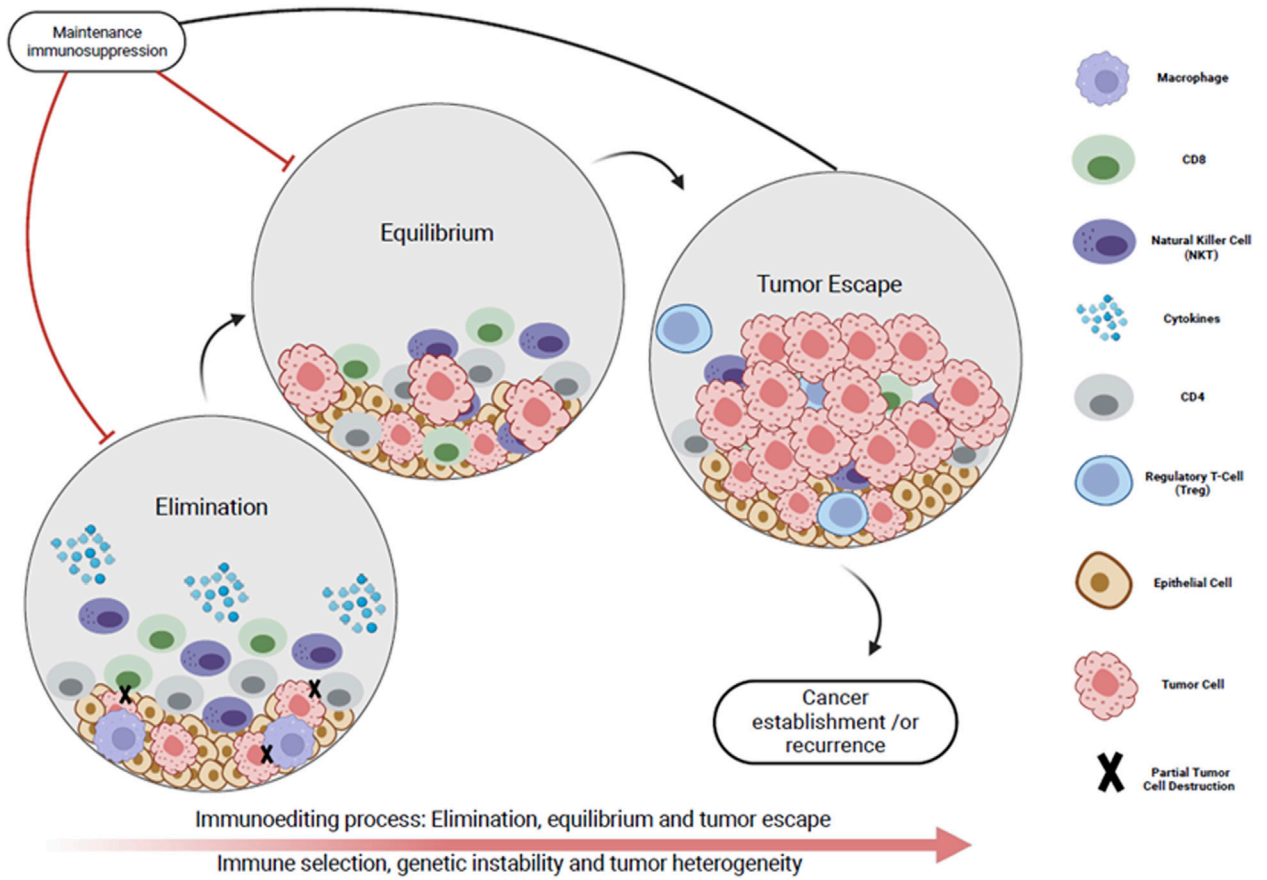


FIGURE 4 | Immunoediting process represented by the dynamic interplay between the tumor micro-environment and the immune system in three phases. Phase I (Elimination): The host immune system initially recognizes the cancer cells as foreign (immune surveillance). Cytotoxic -cells and natural killer cells target tumor cells. Phase I (Equilibrium): A subset of tumor cells develop immune evasion mechanisms (reduced immunogenicity), but there is an overall balance between immune mediated tumor suppression and tumor outgrowth. Phase III (Tumor escape): Tumor cells evade the immune system's surveillance and proliferate uncontrollably. This results in clinically apparent tumor, recurrence and/or metastases. Maintenance immunosuppression impedes initial immune surveillance. This reduces selective pressure on tumor cells which is necessary for the development of mechanisms that allow tumor immune evasion. As a result, tumors that develop in immunosuppressed individuals may be more likely to maintain their initial immunogenicity.

TABLE 3 | Objective response rate by tumor group in retrospective cohort studies focusing on kidney transplant recipients alone, and a systematic review.

Study title	A multi-center study on safety and efficacy of immune checkpoint inhibitors in cancer patients with kidney transplant [5]	Immune-checkpoint inhibitors in renal transplanted patients affected by melanoma: A systematic review [67]	Cemiplimab for advanced cutaneous squamous cell carcinoma in kidney transplant recipients [28]	Immune checkpoint blockers in solid organ transplant recipients and cancer: the INNOVATED cohort[a] [33]
Authors, Year	Murakami et al., 2021	Rossi et al., 2021	Van Meerhaeghe et al., 2022	Remon et al., 2024
Patient Sample Size by Tumor Type	cSCC – 24 Melanoma – 22	Melanoma – 32 Uveal Melanoma - 2	cSCC - 7	NSCLC – 11
Immune Checkpoint Inhibitor Regimen by Tumor Type	cSCC Monotherapy: 87.5% Dual Therapy: 12.5% Melanoma Monotherapy: 64% Dual Therapy: 36%	Monotherapy: 100%	Monotherapy: 100%	Monotherapy: 73% Dual Therapy: 27%
Objective Response Rate by Tumor Group	cSCC – 33% Melanoma – 36%	23.5%	42.8%	45.5%

[a]*The NSCLC sub-group of the INNOVATED cohort consisted of KTR alone. Abbreviations: cSCC, cutaneous squamous cell carcinoma; NSCLC, Non-Small Cell Lung Cancer.*

TUMOR RESPONSE

In the CONTRAC-1 study, an ORR of 46% was shown for KTR treated with cemiplimab for advanced cSCC [6]. Portuguese et al. reported an ORR of 68.2% for SOTR receiving ICI for advanced cSCC [8]. By comparison, the reported ORR in the immune-intact population for advanced cSCC is 34%–50% [9]. With regards to cutaneous melanoma, two recent reviews demonstrated a similar ORR in SOTR receiving ICI therapy (ORR 32%–36%) compared with the immune-intact population (ORR on ICI monotherapy 30%–40%, and ORR 61% with dual CTLA4 and PD1 inhibition) [8, 38, 64]. The theory of tumor-immune editing provides a potential explanation for the similar ORR in immunosuppressed and immune intact patients. This refers to the process by which an intact immune system selects for the survival of less immunogenic cancer cells, which subsequently go on to proliferate by evading both the innate and adaptive host immune responses [65]. Tumor cells proliferating in immunocompromised hosts may not undergo tumor-immune editing to the same extent, potentially rendering them more responsive to ICI (**Figure 4**) [66].

Looking at KTR alone, **Table 3** highlights data regarding objective response rates for cSCC, melanoma and NSCLC from three recent retrospective studies and one systematic review. This data seems to suggest that KTR have worse ORR when looked at individually, compared to ORR data for all SOTR analyzed cumulatively. Currently, prospective data establishing ORR to ICI therapy in kidney transplant recipients with various tumor types is limited, as seen in **Table 1**.

Special considerations with regards to tumor response exist. A literature review which included 94 KTR on ICI found that those with preserved allograft function maintained on CNI have worse tumor response rates than those maintained on mTORi, emphasizing the benefit of a transition to mTORi whenever feasible [38]. This association is suggested in Schenk et al.'s study in which an ORR of 25% was reported despite a low degree of maintenance immunosuppression, suggesting that the use of tacrolimus may impede ICI anti-tumor efficacy [29]. This finding deserves further study as it remains unclear if the difference in outcome is due to: 1) the CNI blunting ICI anti-tumor efficacy, 2) patient selection factors, or 3) the intrinsic anti-neoplastic activity of mTORi. Furthermore, it has not been established if this effect is dependent on tumor type [66]. There is mechanistic evidence suggesting that mTORi can promote the maintenance of the anti-tumor effects of ICI therapy while allowing for the preservation of allograft tolerance [68]. Using peripheral blood immunophenotyping, Esfahani et al. demonstrated that concurrent administration of anti-PD1 therapy and mTORi in a KTR with melanoma led to tolerogenic changes including suppression of global T cell activation and preservation of the regulatory T cell population, while maintaining the circulating levels of a subset of tumor directed T cells (interferon gamma producing $CD4^+$ T cells and cytotoxic $CD8^+$ T cells) [68].

FUTURE CONSIDERATIONS

Additional risk stratification tools would help guide decision making around maintenance immunosuppression optimization prior to ICI initiation. To this end, several biomarkers have been proposed which have not yet been widely clinically validated. A systematic review identified a correlation between positive PDL-1 allograft staining in liver transplant recipients (LTR) and one KTR and ICI associated rejection [8]. All LTR with positive PDL-1 staining experienced rejection (n = 6), and all those without did not (n = 8) [8]. PDL-1 expression has been shown to represent a tolerogenic mechanism in murine cardiac allograft models [19, 69]. Obtaining protocol renal allograft biopsies and staining them for PDL-1 prior to ICI initiation may help risk-stratify patients and help direct decisions around maintenance immunosuppression. This strategy would also allow for the identification and treatment of sub-clinical rejection prior to ICI start. Notably, the patient with treatment refractory allograft rejection described by Carroll et al. may have been experiencing sub-clinical rejection prior to ICI start [7]. In certain clinical situations, allograft biopsies may pose a higher risk, and center-specific resource limitations may also exist. Non-invasive biomarkers may be used to screen for sub-clinical rejection prior to ICI start and once therapy is initiated. These results could subsequently justify indication biopsies and early therapeutic intervention. Urinary chemokines, C-X-C motif chemokine ligand 9 (CXCL9) and ligand 10 (CXCL10), have both been clinically validated as markers of sub-clinical ACR in KTR who are not on ICI therapy [70–73]. Carroll et al. pre-specified an exploratory endpoint utilizing CXCL10 and noted rising levels in both of the patients who experienced allograft rejection [7, 70]. Another non-invasive biomarker, donor-derived cell-free DNA (dd-cfDNA), has been validated for the detection of renal allograft rejection though not in the context of ICI use [74–76]. Schenk et al. trended dd-cfDNA every 2 weeks in their study, but only noted a clear temporal association between dd-cfDNA elevations and allograft rejection in one of three patients [7]. Additional prospective studies to validate non-invasive biomarkers are needed.

From a therapeutic perspective, there is very limited data on dual ICI use in KTR. A phase 2 prospective trial (NCT05896839) is currently underway to determine tumor response and allograft toxicity in patients with advanced cutaneous cancers on dual ICI therapy with mTORi and prednisone maintenance immunosuppression. Additional future considerations include the use of targeted immunotherapies in KTR with solid organ tumors to reduce the risk of allograft rejection, these include chimeric antigen receptor T-cell therapy (CART) in which T cells are engineered to target tumor specific antigens, or use of oncolytic viruses. Recently, the ARTACUS trial demonstrated encouraging results with a 34.8% ORR for the treatment of advanced cSCC in 27 SOTR with intra-tumoral oncolytic viruses, with no allograft rejections [77].

CONCLUSION

Several clear conclusions can be drawn from the existing data: 1) KTR can benefit ICI therapy, 2) KTR are at risk of rejection and treatment related allograft loss while on ICI therapy but this risk can be reduced with optimization of maintenance immunosuppression and potentially with close follow up allowing early intervention, 3) extra-renal irAEs in KTR have been documented less frequently than in the immune-intact population though data on recurrent GN in the allograft is very limited. While we lack high level evidence to direct optimal maintenance immunosuppressive regiments, retrospective data suggests superiority of mTORi over CNI, but no prospective randomized controlled studies comparing the two regiments have been performed. Patients would ideally be risk-stratified prior to ICI therapy initiation. Protocol biopsies and non-invasive biomarkers, such as urine CXCL9, CXCL10 or dd-cfDNA, can be used to screen for sub-clinical rejection. Additional risk stratification with PD-L1 staining of allograft biopsy tissue can be considered. However, all of these interventions require additional clinical validation in the setting of ICI use prior to widespread application. Decisions around timing of ICI therapy initiation, and treatment of allograft complications while on ICI therapy require a patient-centered, multi-disciplinary approach. Transplant centers would benefit from a unified protocol-based approach to the management of KTR with malignancies, co-developed with oncologists. Future research is needed directly comparing different maintenance immunosuppression strategies in a balanced group of patients to help us determine how best to optimize cancer and allograft outcomes.

AUTHOR CONTRIBUTIONS

E-BB and AK were mutually involved in the planning, outline and writing. E-BB wrote the original manuscript. SA designed the graphics. AK and AD reviewed and edited all the revisions of the manuscript, including the graphics. All authors contributed to the article and approved the submitted version.

FUNDING

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

REFERENCES

1. Wang D, Bauersachs J, Berliner D. Immune Checkpoint Inhibitor Associated Myocarditis and Cardiomyopathy: A Translational Review. *Biology (Basel)* (2023) 12(3):472. doi:10.3390/biology12030472
2. Robert C. A Decade of Immune-Checkpoint Inhibitors in Cancer Therapy. *Nat Commun* (2020) 11(1):3801. doi:10.1038/s41467-020-17670-y
3. Hariharan S, Israni AK, Danovitch G. Long-Term Survival After Kidney Transplantation. *New Engl J Med* (2021) 385(8):729–43. doi:10.1056/NEJMra2014530
4. Blosser CD, Haber G, Engels EA. Changes in Cancer Incidence and Outcomes Among Kidney Transplant Recipients in the United States Over a Thirty-Year Period. *Kidney Int* (2021) 99(6):1430–8. doi:10.1016/j.kint.2020.10.018
5. Murakami N, Mulvaney P, Danesh M, Abudayyeh A, Diab A, Abdel-Wahab N, et al. A Multi-Center Study on Safety and Efficacy of Immune Checkpoint Inhibitors in Cancer Patients With Kidney Transplant. *Kidney Int* (2021) 100(1):196–205. doi:10.1016/j.kint.2020.12.015
6. Hanna GJ, Dharanesswaran H, Giobbie-Hurder A, Harran JJ, Liao Z, Pai L, et al. Cemiplimab for Kidney Transplant Recipients With Advanced Cutaneous Squamous Cell Carcinoma. *J Clin Oncol* (2024):JCO2301498. doi:10.1200/JCO.23.01498
7. Carroll RP, Boyer M, Gebski V, Hockley B, Johnston JK, Kireta S, et al. Immune Checkpoint Inhibitors in Kidney Transplant Recipients: A Multicentre, Single-Arm, Phase 1 Study. *Lancet Oncol* (2022) 23(8):1078–86. doi:10.1016/S1470-2045(22)00368-0
8. Portuguese AJ, Tykodi SS, Blosser CD, Gooley TA, Thompson JA, Hall ET. Immune Checkpoint Inhibitor Use in Solid Organ Transplant Recipients: A Systematic Review. *J Natl Compr Canc Netw* (2022) 20(4):406–16.e11. doi:10.6004/jnccn.2022.7009
9. Alberti A, Bossi P. Immunotherapy for Cutaneous Squamous Cell Carcinoma: Results and Perspectives. *Front Oncol* (2022) 11:727027. doi:10.3389/fonc.2021.727027
10. Migden MR, Schmults C, Khushanlani N, Guminski A, Chang A, Lewis K, et al. 814P Phase II Study of Cemiplimab in Patients With Advanced Cutaneous Squamous Cell Carcinoma (CSCC): Final Analysis From EMPOWER-CSCC-1 Groups 1, 2 and 3. *Ann Oncol* (2022) 33:S918–9. doi:10.1016/j.annonc.2022.07.940
11. Maubec E, Boubaya M, Petrow P, Beylot-Barry M, Basset-Seguin N, Deschamps L, et al. Phase II Study of Pembrolizumab As First-Line, Single-Drug Therapy for Patients With Unresectable Cutaneous Squamous Cell Carcinomas. *J Clin Oncol* (2020) 38(26):3051–61. doi:10.1200/JCO.19.03357
12. Grob JJ, Gonzalez R, Basset-Seguin N, Vornicova O, Schachter J, Joshi A, et al. Pembrolizumab Monotherapy for Recurrent or Metastatic Cutaneous Squamous Cell Carcinoma: A Single-Arm Phase II Trial (KEYNOTE-629). *J Clin Oncol* (2020) 38(25):2916–25. doi:10.1200/JCO.19.03054
13. Chen DS, Mellman I. Oncology Meets Immunology: The Cancer-Immunity Cycle. *Immunity* (2013) 39(1):1–10. doi:10.1016/j.immuni.2013.07.012
14. Jiang X, Wang J, Deng X, Xiong F, Ge J, Xiang B, et al. Role of the Tumor Microenvironment in PD-L1/pd-1-Mediated Tumor Immune Escape. *Mol Cancer* (2019) 18(1):10. doi:10.1186/s12943-018-0928-4
15. Kythreotou A, Siddique A, Mauri FA, Bower M, Pinato DJ. PD-L1. *J Clin Pathol* (2018) 71(3):189–94. doi:10.1136/jclinpath-2017-204853
16. Solinas C, Migliori E, De Silva P, Willard-Gallo K. LAG3: The Biological Processes That Motivate Targeting This Immune Checkpoint Molecule in Human Cancer. *Cancers (Basel)* (2019) 11(8):1213. doi:10.3390/cancers11081213
17. Graydon CG, Mohideen S, Fowke KR. LAG3's Enigmatic Mechanism of Action. *Front Immunol* (2021) 11:615317. doi:10.3389/fimmu.2020.615317
18. Oyewole-Said D, Konduri V, Vazquez-Perez J, Weldon SA, Levitt JM, Decker WK. Beyond T-Cells: Functional Characterization of CTLA-4 Expression in Immune and Non-Immune Cell Types. *Front Immunol* (2020) 11:608024. doi:10.3389/fimmu.2020.608024
19. Riella LV, Watanabe T, Sage PT, Yang J, Yeung M, Azzi J, et al. Essential Role of PDL1 Expression on Nonhematopoietic Donor Cells in Acquired Tolerance to Vascularized Cardiac Allografts. *Am J Transpl* (2011) 11(4):832–40. doi:10.1111/j.1600-6143.2011.03451.x
20. Riella LV, Paterson AM, Sharpe AH, Chandraker A. Role of the PD-1 Pathway in the Immune Response. *Am J Transpl* (2012) 12(10):2575–87. doi:10.1111/j.1600-6143.2012.04224.x
21. Borges TJ, Murakami N, Lape IT, Gassen RB, Liu K, Cai S, et al. Overexpression of PD-1 on T Cells Promotes Tolerance in Cardiac

Transplantation via ICOS-Dependent Mechanisms. *JCI Insight* (2021) 6(24): e142909. doi:10.1172/jci.insight.142909
22. Bracamonte-Baran W, Gilotra NA, Won T, Rodriguez KM, Talor MV, Oh BC, et al. Endothelial Stromal PD-L1 (Programmed Death Ligand 1) Modulates CD8(+) T-Cell Infiltration After Heart Transplantation. *Circ Heart Fail* (2021) 14(10):e007982. doi:10.1161/CIRCHEARTFAILURE.120.007982
23. Schmalkuche K, Rother T, Besli S, Voß H, Höffler K, Dogan G, et al. Heart Immunoengineering by Lentiviral Vector-Mediated Genetic Modification During Normothermic *Ex Vivo* Perfusion. *Front Immunol* (2024) 15: 1404668. doi:10.3389/fimmu.2024.1404668
24. Van Meerhaeghe T, Murakami N, Le Moine A, Brouard S, Sprangers B, Degauque N. Fine-Tuning Tumor- and Allo-Immunity: Advances in the Use of Immune Checkpoint Inhibitors in Kidney Transplant Recipients. *Clin Kidney J* (2024) 17(4):sfae061. doi:10.1093/ckj/sfae061
25. Dunlap GS, DiToro D, Henderson J, Shah SI, Manos M, Severgnini M, et al. Clonal Dynamics of Alloreactive T Cells in Kidney Allograft Rejection After Anti-PD-1 Therapy. *Nat Commun* (2023) 14(1):1549. doi:10.1038/s41467-023-37230-4
26. Johnson DB, Balko JM, Compton ML, Chalkias S, Gorham J, Xu Y, et al. Fulminant Myocarditis With Combination Immune Checkpoint Blockade. *N Engl J Med* (2016) 375(18):1749–55. doi:10.1056/NEJMoa1609214
27. Owoyemi I, Vaughan LE, Costello CM, Thongprayoon C, Markovic SN, Herrmann J, et al. Clinical Outcomes of Solid Organ Transplant Recipients With Metastatic Cancers Who Are Treated with Immune Checkpoint Inhibitors: A Single-Center Analysis. *Cancer* (2020) 126(21):4780–7. doi:10.1002/cncr.33134
28. Van Meerhaeghe T, Baurain JF, Bechter O, Orte Cano C, Del Marmol V, Devresse A, et al. Cemiplimab for Advanced Cutaneous Squamous Cell Carcinoma in Kidney Transplant Recipients. *Front Nephrol* (2022) 2: 1041819. doi:10.3389/fneph.2022.1041819
29. Schenk KM, Deutsch JS, Chandra S, Davar D, Eroglu Z, Khushalani NI, et al. Nivolumab + Tacrolimus + Prednisone ± Ipilimumab for Kidney Transplant Recipients With Advanced Cutaneous Cancers. *J Clin Oncol* (2024) 42(9): 1011–20. doi:10.1200/JCO.23.01497
30. Barnett R, Barta VS, Jhaveri KD. Preserved Renal-Allograft Function and the PD-1 Pathway Inhibitor Nivolumab. *New Engl J Med* (2017) 376(2):191–2. doi:10.1056/NEJMc1614298
31. Danesh MJ, Mulvaney PM, Murakami N, Riella LV, Silk AW, Hanna GJ, et al. Impact of Corticosteroids on Allograft Protection in Renal Transplant Patients Receiving Anti-PD-1 Immunotherapy. *Cancer Immunol Immunother* (2020) 69(9):1937–41. doi:10.1007/s00262-020-02644-2
32. Manohar S, Thongprayoon C, Cheungpasitporn W, Markovic SN, Herrmann SM. Systematic Review of the Safety of Immune Checkpoint Inhibitors Among Kidney Transplant Patients. *Kidney Int Rep* (2020) 5(2):149–58. doi:10.1016/j.ekir.2019.11.015
33. Remon J, Auclin E, Zubiri L, Schneider S, Rodriguez-Abreu D, Minatta N, et al. Immune Checkpoint Blockers in Solid Organ Transplant Recipients and Cancer: The INNOVATED Cohort. *ESMO Open* (2024) 9(5):103004. doi:10.1016/j.esmoop.2024.103004
34. Abdel-Wahab N, Safa H, Abudayyeh A, Johnson DH, Trinh VA, Zobniw CM, et al. Checkpoint Inhibitor Therapy for Cancer in Solid Organ Transplantation Recipients: An Institutional Experience and a Systematic Review of the Literature. *J ImmunoTherapy Cancer* (2019) 7(1):106. doi:10.1186/s40425-019-0585-1
35. d'Izarny-Gargas T, Durrbach A, Zaidan M. Efficacy and Tolerance of Immune Checkpoint Inhibitors in Transplant Patients with Cancer: A Systematic Review. *Am J Transplant* (2020) 20(9):2457–65. doi:10.1111/ajt.15811
36. Kumar V, Shinagare AB, Rennke HG, Ghai S, Lorch JH, Ott PA, et al. The Safety and Efficacy of Checkpoint Inhibitors in Transplant Recipients: A Case Series and Systematic Review of Literature. *Oncologist* (2020) 25(6):505–14. doi:10.1634/theoncologist.2019-0659
37. Zhang H, Li X, Huang X, Ma H, Zeng R. Impact of Corticosteroid Use on Outcomes of Non-Small-Cell Lung Cancer Patients Treated With Immune Checkpoint Inhibitors: A Systematic Review and Meta-Analysis. *J Clin Pharm Ther* (2021) 46(4):927–35. doi:10.1111/jcpt.13469
38. Rünger A, Schadendorf D, Hauschild A, Gebhardt C. Immune Checkpoint Blockade for Organ-Transplant Recipients With Cancer: A Review. *Eur J Cancer* (2022) 175:326–35. doi:10.1016/j.ejca.2022.08.010
39. Abdel-Wahab N, Safa H, Abudayyeh A, Johnson DH, Trinh VA, Zobniw CM, et al. Checkpoint Inhibitor Therapy for Cancer in Solid Organ Transplantation Recipients: An Institutional Experience and a Systematic Review of the Literature. *J Immunother Cancer* (2019) 7(1):106. doi:10.1186/s40425-019-0585-1
40. Naik MG, Jürgensen JS, Arns W, Basic E, Budde K, Eitner F, et al. Determinants of Successful Use of Sirolimus in Renal Transplant Patients. *Transpl Proc* (2020) 52(10):3103–11. doi:10.1016/j.transproceed.2020.02.159
41. Cuadrado-Payán E, Diekmann F, Cucchiari D. Medical Aspects of mTOR Inhibition in Kidney Transplantation. *Int J Mol Sci* (2022) 23(14):7707. doi:10.3390/ijms23147707
42. Schena FP, Pascoe MD, Alberu J, del Carmen Rial M, Oberbauer R, Brennan DC, et al. Conversion From Calcineurin Inhibitors to Sirolimus Maintenance Therapy in Renal Allograft Recipients: 24-Month Efficacy and Safety Results From the CONVERT Trial. *Transplantation* (2009) 87(2):233–42. doi:10.1097/TP.0b013e3181927a41
43. Wahl AO, Small W, Jr., Dixler I, Strom S, Rademaker A, Leventhal J, et al. Radiotherapy for Rejection of Renal Transplant Allografts Refractory to Medical Immunosuppression. *Am J Clin Oncol* (2006) 29(6):551–4. doi:10.1097/01.coc.0000231452.47998.88
44. Haanen J, Obeid M, Spain L, Carbonnel F, Wang Y, Robert C, et al. Management of Toxicities From Immunotherapy: ESMO Clinical Practice Guideline for Diagnosis, Treatment and Follow-Up. *Ann Oncol* (2022) 33(12): 1217–38. doi:10.1016/j.annonc.2022.10.001
45. Larkin J, Hodi FS, Wolchok JD. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. *N Engl J Med* (2015) 373(13):1270–1. doi:10.1056/NEJMc1509660
46. Postow MA, Sidlow R, Hellmann MD. Immune-Related Adverse Events Associated With Immune Checkpoint Blockade. *N Engl J Med* (2018) 378(2):158–68. doi:10.1056/NEJMra1703481
47. Seethapathy H, Zhao S, Chute DF, Zubiri L, Oppong Y, Strohbehn I, et al. The Incidence, Causes, and Risk Factors of Acute Kidney Injury in Patients Receiving Immune Checkpoint Inhibitors. *Clin J Am Soc Nephrol* (2019) 14(12):1692–700. doi:10.2215/CJN.00990119
48. Cortazar FB, Marrone KA, Troxell ML, Ralto KM, Hoenig MP, Brahmer JR, et al. Clinicopathological Features of Acute Kidney Injury Associated With Immune Checkpoint Inhibitors. *Kidney Int* (2016) 90(3):638–47. doi:10.1016/j.kint.2016.04.008
49. Manohar S, Kompotiatis P, Thongprayoon C, Cheungpasitporn W, Herrmann J, Herrmann SM. Programmed Cell Death Protein 1 Inhibitor Treatment Is Associated With Acute Kidney Injury and Hypocalcemia: Meta-Analysis. *Nephrol Dial Transpl* (2019) 34(1):108–17. doi:10.1093/ndt/gfy105
50. Kitchlu A, Jhaveri KD, Wadhwani S, Deshpande P, Harel Z, Kishibe T, et al. A Systematic Review of Immune Checkpoint Inhibitor-Associated Glomerular Disease. *Kidney Int Rep* (2021) 6(1):66–77. doi:10.1016/j.ekir.2020.10.002
51. Barbir EB, Kitchlu A, Herrmann SM. Immune Checkpoint Inhibitor-Associated Nephritis - Treatment Standard. *Nephrol Dial Transpl* (2024): gfae184. doi:10.1093/ndt/gfae184
52. Loupy A, Haas M, Roufosse C, Naesens M, Adam B, Afrouzian M, et al. The Banff 2019 Kidney Meeting Report (I): Updates on and Clarification of Criteria for T Cell- and Antibody-Mediated Rejection. *Am J Transpl* (2020) 20(9): 2318–31. doi:10.1111/ajt.15898
53. Adam BA, Murakami N, Reid G, Du K, Jasim R, Boils CL, et al. Gene Expression Profiling in Kidney Transplants With Immune Checkpoint Inhibitor-Associated Adverse Events. *Clin J Am Soc Nephrol* (2021) 16(9): 1376–86. doi:10.2215/CJN.00920121
54. Isik B, Alexander MP, Manohar S, Vaughan L, Kottschade L, Markovic S, et al. Biomarkers, Clinical Features, and Rechallenge for Immune Checkpoint Inhibitor Renal Immune-Related Adverse Events. *Kidney Int Rep* (2021) 6(4):1022–31. doi:10.1016/j.ekir.2021.01.013
55. Gupta S, Short SAP, Sise ME, Prosek JM, Madhavan SM, Soler MJ, et al. Acute Kidney Injury in Patients Treated With Immune Checkpoint Inhibitors. *J Immunother Cancer* (2021) 9(10):e003467. doi:10.1136/jitc-2021-003467
56. Cortazar FB, Kibbelaar ZA, Glezerman IG, Abudayyeh A, Mamlouk O, Motwani SS, et al. Clinical Features and Outcomes of Immune Checkpoint Inhibitor-Associated AKI: A Multicenter Study. *J Am Soc Nephrol* (2020) 31(2):435–46. doi:10.1681/ASN.2019070676

57. Mohan A, Krisanapan P, Tangpanithandee S, Thongprayoon C, Kanduri SR, Cheungpasitporn W, et al. Association of Proton Pump Inhibitor Use and Immune Checkpoint Inhibitor Mediated Acute Kidney Injury: A Meta-Analysis and a Review of Related Outcomes. *Am J Nephrol* (2024) 55: 439–49. doi:10.1159/000538274
58. Yan H, Tang M, Zhu W, Yang Y. Immune Checkpoint Inhibitor-Associated Acute Kidney Injury in Patients With Cancer: A Systematic Review and Meta-Analysis of Risk Factors. *Clin Exp Nephrol* (2023) 27(7):603–12. doi:10.1007/s10157-023-02344-y
59. Chen B, Yang C, Dragomir MP, Chi D, Chen W, Horst D, et al. Association of Proton Pump Inhibitor Use With Survival Outcomes in Cancer Patients Treated With Immune Checkpoint Inhibitors: A Systematic Review and Meta-Analysis. *Ther Adv Med Oncol* (2022) 14:17588359221111703. doi:10.1177/17588359221111703
60. Chen JJ, Lee TH, Kuo G, Yen CL, Lee CC, Chang CH, et al. All-Cause and Immune Checkpoint Inhibitor-Associated Acute Kidney Injury in Immune Checkpoint Inhibitor Users: A Meta-Analysis of Occurrence Rate, Risk Factors and Mortality. *Clin Kidney J* (2024) 17(1):sfad292. doi:10.1093/ckj/sfad292
61. Barbir EB, Ghaffar A, Otley C, Dudek AZ, Kukla A Immune Checkpoint Inhibitor Therapy Use in Kidney Transplant Recipients: A Single Center Study [ASN Kidney Week Abstract]. *J Am Soc Nephrol* (2024) 35.
62. Cook S, Samuel V, Meyers DE, Stukalin I, Litt I, Sangha R, et al. Immune-Related Adverse Events and Survival Among Patients With Metastatic NSCLC Treated With Immune Checkpoint Inhibitors. *JAMA Netw Open* (2024) 7(1): e2352302. doi:10.1001/jamanetworkopen.2023.52302
63. Romão R, Mendes AS, Ranchor R, Ramos MJ, Coelho J, Pichel RC, et al. Impact of Immune-Related Adverse Events on Immune Checkpoint Inhibitors Treated Cancer Patients' Survival: Single Center Experience and Literature Review. *Cancers (Basel)* (2023) 15(3):888. doi:10.3390/cancers15030888
64. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. *New Engl J Med* (2015) 373(1):23–34. doi:10.1056/NEJMoa1504030
65. Lasek W. Cancer Immunoediting Hypothesis: History, Clinical Implications and Controversies. *Cent Eur J Immunol* (2022) 47(2):168–74. doi:10.5114/ceji.2022.117376
66. Acuna SA. Etiology of Increased Cancer Incidence After Solid Organ Transplantation. *Transpl Rev (Orlando)* (2018) 32(4):218–24. doi:10.1016/j.trre.2018.07.001
67. Rossi E, Schinzari G, Maiorano BA, Esposito I, Acampora A, Romagnoli J, et al. Immune-Checkpoint Inhibitors in Renal Transplanted Patients Affected by Melanoma: A Systematic Review. *Immunotherapy* (2022) 14(1):65–75. doi:10.2217/imt-2021-0195
68. Esfahani K, Al-Aubodah TA, Thebault P, Lapointe R, Hudson M, Johnson NA, et al. Targeting the mTOR Pathway Uncouples the Efficacy and Toxicity of PD-1 Blockade in Renal Transplantation. *Nat Commun* (2019) 10(1):4712. doi:10.1038/s41467-019-12628-1
69. Tanaka K, Albin MJ, Yuan X, Yamaura K, Habicht A, Murayama T, et al. PDL1 Is Required for Peripheral Transplantation Tolerance and Protection From Chronic Allograft Rejection1. *J Immunol* (2007) 179(8):5204–10. doi:10.4049/jimmunol.179.8.5204
70. Ho J, Schaub S, Jackson AM, Balshaw R, Carroll R, Cun S, et al. Multicenter Validation of a Urine CXCL10 Assay for Noninvasive Monitoring of Renal Transplants. *Transplantation* (2023) 107(7):1630–41. doi:10.1097/TP.0000000000004554
71. Ho J, Schaub S, Wiebe C, Gao A, Wehmeier C, Koller MT, et al. Urinary CXCL10 Chemokine Is Associated With Alloimmune and Virus Compartment-Specific Renal Allograft Inflammation. *Transplantation* (2018) 102(3):521–9. doi:10.1097/TP.0000000000001931
72. Ciftci HS, Tefik T, Savran MK, Demir E, Caliskan Y, Ogret YD, et al. Urinary CXCL9 and CXCL10 Levels and Acute Renal Graft Rejection. *Int J Organ Transpl Med* (2019) 10(2):53–63.
73. Hricik DE, Nickerson P, Formica RN, Poggio ED, Rush D, Newell KA, et al. Multicenter Validation of Urinary CXCL9 as a Risk-Stratifying Biomarker for Kidney Transplant Injury. *Am J Transpl* (2013) 13(10):2634–44. doi:10.1111/ajt.12426
74. Bloom RD, Bromberg JS, Poggio ED, Bunnapradist S, Langone AJ, Sood P, et al. Cell-Free DNA and Active Rejection in Kidney Allografts. *J Am Soc Nephrol* (2017) 28(7):2221–32. doi:10.1681/ASN.2016091034
75. Huang E, Sethi S, Peng A, Najjar R, Mirocha J, Haas M, et al. Early Clinical Experience Using Donor-Derived Cell-Free DNA to Detect Rejection in Kidney Transplant Recipients. *Am J Transpl* (2019) 19(6):1663–70. doi:10.1111/ajt.15289
76. Stites E, Kumar D, Olaitan O, John Swanson S, Leca N, Weir M, et al. High Levels of dd-cfDNA Identify Patients With TCMR 1A and Borderline Allograft Rejection at Elevated Risk of Graft Injury. *Am J Transpl* (2020) 20(9):2491–8. doi:10.1111/ajt.15822
77. Migden MR, Luke JJ, Chai-Ho W, Kheterpal M, Wise-Draper TM, Poklepovic AS, et al. An Open-Label, Multicenter, Phase 1b/2 Study of RP1, a First-In-Class, Enhanced Potency Oncolytic Virus in Solid Organ Transplant Recipients With Advanced Cutaneous Malignancies (ARTACUS). *J Clin Oncol* (2022) 40(16_Suppl. l):TPS9597. doi:10.1200/jco.2022.40.16_suppl.tps9597

ESOT | Transplant International

MINI REVIEW
published: 25 November 2024
doi: 10.3389/ti.2024.13204

Immunotherapy for Cancer in Kidney Transplant Patients: A Difficult Balance Between Risks and Benefits

Mónica Bolufer[1,2]*, *Jordi Soler*[1,2], *María Molina*[1,2], *Omar Taco*[1,2], *Anna Vila*[1,2] and *Manuel Macía*[3,4]

[1]Department of Nephrology, Hospital Universitario Germans Trias i Pujol, Barcelona, Spain, [2]Redes de Investigación Cooperativa Orientadas a Resultados en Salud (RICORS) 2024, Badalona, Spain, [3]Department of Nephrology, Hospital Nuestra Señora de Candelaria, Santa Cruz de Tenerife, Spain, [4]Redes de Investigación Cooperativa Orientadas a Resultados en Salud (RICORS) 2024, Santa Cruz de Tenerife, Spain

Cancer is a major cause of morbidity and mortality in kidney transplant patients. Unfortunately, the use of new anti-cancer therapies such as immune checkpoint inhibitors (ICPIs) in this population has been associated with rejection rates up to 40%, in retrospective studies. The main challenge is to maintain the patient in a delicate immunologic balance in which, while antitumor therapy defeats cancer the graft is safely protected from rejection. Recent clinical trials with ICPI have included kidney transplant recipients (KTRs) and the results advocate for a paradigm shift in the management of basal immunosuppression. This suggests that downward adjustments should be avoided or, even better, that this adjustment should be "dynamic." This review summarizes the latest scientific evidence available in renal transplantation under ICPI treatment: case series, prospective studies, histopathologic diagnosis, immunosuppression regimens and new biomarkers. This article will provide the latest information in on this specific field, allowing nephrologists to gain valuable knowledge and to be aware of new approaches to immunosuppression management in oncological kidney transplant patients.

Keywords: kidney transplant, cancer, checkpoint inhibitors, immunotherapy, immunosuppresion

OPEN ACCESS

***Correspondence**
Mónica Bolufer,
mboluferc.germanstrias@gencat.cat

Received: *29 April 2024*
Accepted: *06 November 2024*
Published: *25 November 2024*

Citation:
Bolufer M, Soler J, Molina M, Taco O, Vila A and Macía M (2024) Immunotherapy for Cancer in Kidney Transplant Patients: A Difficult Balance Between Risks and Benefits. Transpl Int 37:13204. doi: 10.3389/ti.2024.13204

INTRODUCTION

Kidney transplant recipients (KTRs) have a significantly higher risk of developing cancer than the general population. This is a major cause of their associated morbidity and mortality [1]. The increased risk of *de novo* and recurrent cancer is multifactorial and has been attributed to immunosuppression, oncogenic viruses and altered T-cell immunity [2, 3]. Chronic kidney disease and cancer are bidirectionally related, as there are some risk factors that promote both pathologies, such as oxidative stress, chronic inflammation, alcohol and tobacco use, viral infections and aging. Impaired renal excretory function could prolong the plasma half-life of some proinflammatory cytokines such as IL-1 beta (interleukin 1 beta), IL-6, and TNF-alpha, and this could be associated with a persistent proinflammatory state in the body [4]. For example, in a Danish study with 5,594 patients who underwent renal biopsy, a higher rate of cancer rate was observed in those who had a specific type of glomerulonephritis, such as minimal change and membranoproliferative [5].

The introduction of new anti-cancer therapies in the treatment of cancer has transformed the field of oncology. These therapies, also known as immunotherapy, are immune checkpoint inhibitor

monoclonal antibodies (ICPI): anti-programmed cell death 1 inhibitors (PD1); anti-programmed cell death ligand 1 inhibitors (PDL1) and anti-cytotoxic T-lymphocyte-associated antigen 4 inhibitors (CTLA4). Malignancies are divided into "solid tumors" and "hematologic malignancies," with ICPIs being largely reserved for solid tumors (invasive and cutaneous). Recently, it has been estimated that 10.5% of all incident malignancies could benefit from receiving ICI treatment, with 49.7% benefiting from this in terms of oncologic response [6]. Unfortunately, these monoclonal antibodies are not commonly used in the KTR population due to a lack of robust evidence regarding their efficacy and safety. Until 2017, KTR were systematically excluded from ICPI clinical trials. The results of some available retrospective clinical trials were disappointing, with an incidence of 42% of kidney rejection among those KTR treated with ICPI [7]. Before expanding the use of ICPI in KTRs, it is essential to identify the factors that predict the risk of rejection and the presumed response rate of the disease.

In this review, we will present the most important published data on the use of ICPI in the renal transplant population and the new immunomodulatory strategies proposed to preserve the effect of cytotoxic T lymphocytes against the tumor while preventing their deleterious effect on the graft.

IMMUNOPHYSIOPATHOLOGY AND BIOMARKERS

The immunophysiopathology of immune checkpoint inhibitors (ICPIs) in kidney transplant patients is a complex interaction between the recipient's immune system, the kidney graft, and the effect of these monoclonal antibodies on the regulation of the immune response. The balance between avoiding potential rejection and the progression of oncologic disease is poorly understood.

Checkpoint regulatory proteins are responsible for imprinting an activating or inhibitory response phenotype on the T cell. CD80/86 (B7-1/B7-2) expressed by the antigen presenting cell (APC) interacts with the CTLA-4 expressed by the T lymphocyte to induce an inhibitory response. Conversely, CD80/86 (APC) interacts with CD28 (T cell) to elicit an activating response. It is not yet known with which receptor on the T cell the PD-L1 receptor of the tumor cell interacts with to exert an activating function. However, we do know that when PD-L1 interacts with PD-1, the effect is suppressive [8]. ICPI monoclonal antibodies block the inhibitory response, thereby favouring T-cell activation.

One of the key issues in both cancer and kidney transplant recipients is the role of exhausted effector T cells. $CD8^+$ exhaustion is a consequence of two events: prolonged and persistent exposure to non-self antigens, such as the tumor cell neoantigens or the antigens of a non-identical kidney allograft [9, 10], and lack of $CD4^+$ help [11]. Recent studies in kidney transplant patients have shown that long-term immunosuppressive treatment increases the expression of PD-1 but decreases that of PDL-1 and CTLA-4 [12]. Notably, the modulation differs between patients treated with calcineurin inhibitors (CNI) and those treated with mammalian target of rapamycin inhibitors (mTORi), who express more PD-1 and CTLA-4 [13]. The combination of all these factors explains some of the major mechanisms of allograft rejection associated with the use of ICPI. Here are the main factors that may contribute to the rejection process: 1) reactivation of primed alloreactive T cells by PD-1/PD-L1 blockade at the allograft site; 2) activation of the systemic inflammatory response by reactivation of quiescent T cells; 3) the possible development of new T lymphocytes that recognize antigenic specificities on the tumor that are shared by allogeneic peptides of the graft (cross-reaction); and 4) loss of function of T regs [14].

The use of non-invasive biomarkers to predict each patient's risk of developing graft rejection after initiation of ICPI is of great interest. Plasma donor-derived cell-free DNA (ddcfDNA) levels increase prior to rejection episodes in patients receiving anti-PD-1 treatment [15, 16]. Elevated ddcfDNA during ICPI treatment identified graft rejection 10–15 days earlier than creatinine elevation in two patients in the Schenk-led clinical trial. It is not currently recommended for clinical decision making, but an increase in ddcfDNA may help to monitor these patients more closely. Another biomarker studied in this clinical scenario is the increase in urinary CXCL-10 levels [17]; although the data are very limited, the authors suggest that elevated urinary levels of CXCL-10 prior to nivolumab treatment could predict early allograft rejection. Recently single cell RNA transcriptomics and T cell receptor sequencing have provided important results to understand the role of different CD8-positive T cell subtypes contributing to acute cellular rejection in this scenario [18]. Using pharmacovigilance and multi-omic data, a bivariate regression model of lymphocyte cytosolic protein 1 (LCP1) and adenosine diphosphate-dependent glucokinase (ADPGK) was developed to predict immune-mediated reactions in patients treated with ICPI, including nephritis [19].

OBSERVATIONAL DATA

A number of retrospective studies have been conducted to evaluate the use of ICPI in renal transplant recipients [20]. In this multicentre study of 69 patients, 29 experienced rejection and 66% of them (n = 19) required dialysis. In a series of six patients, Venkatachalam et al. reported poor outcomes for renal transplant recipients with metastatic cancer receiving ICPI, describing a high risk of rejection (50%) and poor remission rates (only one patient with melanoma had remission, but after experiencing mixed rejection and a return to dialysis) [21]. Murakami et al. conducted a large multicentre study (n = 69) to evaluate the safety and efficacy of ICPI in kidney transplant recipients with cancer. They found improved cancer outcomes, but a high risk of acute graft rejection (n = 29; 42%). Of these, 14 cases were confirmed by renal biopsy: 7 mixed rejection mediated by T cells and antibodies and 7 pure cellular rejection mediated by T cells. Most of them, 80%, occurred in the first 2 months after the start of ICPI treatment. After targeted treatment based mainly on high-dose corticosteroids and immunoglobulins, 19 patients (65.5%) lost the graft and returned to dialysis [7]. These high rejection rates are similar to data reported in subsequent literature reviews [22–25]. Tsung et al. demonstrated that

ICPI, when used with minimized CNI and steroids, is safe and effective for selected patients with advanced cutaneous squamous cell carcinoma [26]. These studies emphasize the complexity and challenges associated with the use of ICPIs in kidney transplant recipients, underscoring the importance of further research to optimize outcomes in this population.

INTERVENTIONAL STUDIES

As mentioned above, KTRs have been consistently excluded from clinical trials involving of ICPI due to lack of efficacy concerns and fear of inducing allograft rejection. Recently, this situation has changed with the publication of three prospective, single-arm, phase 1/2 studies in the past 2 years. Currently, another study on the use of ICPI in kidney transplant recipients is registered on clinicaltrials.gov [27].

In 2022, Carroll et al. published the first study on ICPI in KTR. The study population consisted of high immunologic risk patients with stable renal function. The immunosuppressive regimen was not modified prior to the initiation of the ICPI treatment. Only seventeen patients, with either skin or solid tumors, were enrolled (intended to treat) before the early stop of the trial due to the COVID-19 pandemic. The study demonstrated a response to anti-PD1 (nivolumab) comparable to that observed in the general population with a low rate of rejection (11.8%). One rejection episode was successfully treated with anti-rejection therapy.

Secondly, Hanna et al. conducted a phase 1 clinical trial involving 12 kidney transplant recipients (four of whom were second kidney transplant recipients). All participants had cutaneous squamous cell carcinoma [26]. All patients received anti-PD1 treatment (cemiplimab) and an immunosuppressive regimen based on mTOR inhibitors (sirolimus or everolimus, at trough blood levels of 4–6 ng/dL) combined with corticosteroids (40 mg/day gradually tapered to 10 mg/day on day +7). The antiproliferative agent was discontinued at the time of screening. No patient in the study experienced graft rejection or loss during treatment with cemiplimab.

The third study, published in 2024 by Schenk et al., analysed data from eight low-immunologic risk kidney transplant recipients (KTRs) with skin cancer (melanoma, cutaneous squamous cell carcinoma (SCC), or Merkel cell carcinoma) [28]. All received nivolumab and, in case of disease progression, four additional doses of Ipilimumab followed by another course of nivolumab. Immunosuppression was changed to dual therapy with minimized tacrolimus (2–5 ng/mL) and prednisone 5 mg/day. Two patients experienced mixed cellular and humoral rejection and one patient developed cellular rejection. The authors conclude that dual therapy with tacrolimus and prednisone does not protect against graft rejection and may decrease the antitumor response.

All three studies had significant limitations, including small sample sizes, heterogeneity in terms of inclusion criteria, population characteristics, immunosuppression management, tumor types (different types of cutaneous malignancies and solid tumors), ICPI monoclonal antibodies received, previous lines of treatment, outcomes, and in addition, none of them were controlled. A key from these studies is that the ICPI monoclonal antibodies treatment is feasible in kidney transplant recipients, but patients must be carefully selected to achieve good outcomes.

MANAGEMENT OF IMMUNE CHECKPOINT INHIBITION IN TRANSPLANT RECIPIENTS

Currently, there are no clinical guidelines with robust scientific evidence recommending modification of the immunosuppression regimen in KTR prior to treatment with immune checkpoint inhibitors. It is challenging to find the optimal balance between ensuring that the cancer immunotherapy does not counteract the patient's immunosuppressive therapy and cause graft rejection, while at the same time ensuring that the immunosuppression given does not make the cancer immunotherapy less effective.

Histopathologic Diagnosis and Rejection Risk Factors

In published cases with biopsy-proven kidney allograft rejection, the typical diagnosis is T-cell mediated rejection, with less frequent mixed T-cell and antibody-mediated rejection [7, 20, 23, 28–30]. In contrast to acute interstitial nephritis, which occurs 14 weeks after initiation of ICPI, the latency in kidney transplantation is much shorter, usually between 22 and 24 days after initiation of anti-cancer treatment [29, 31–34]. There are overlapping histopathological features between related to ICPI T-cell rejection and acute interstitial nephritis. Adam et al. performed an analysis of 725 immune-related genes and found a high degree of similarity between the two entities. They also identified biopsy-based measurement of IFI27 (IFN-alpha inducible protein 27) gene expression as a potential differentiating marker [35]. IFI27 is an immune response gene involved in interferon (IFN) signaling. Its expression is increased in ICPI-TCMR (T cell mediated rejection) and non-immune checkpoint inhibitor-associated TCMR. No differences were observed in the other groups studied (normal, interstitial nephritis secondary to ICPI, interstitial nephritis secondary to other drugs, BK polyomavirus nephropathy and ICPI-associated glomerulonephritis). In consequence, IFI27 could be a potential biomarker to differentiate ICPI-interstitial nephritis from rejection. When ICPI-induced kidney allograft rejection occurs, the response rate to standard treatment is low, with up to 66% graft loss and return to dialysis [7].

A review of the literature shows that the rejection rates are higher in patients treated with anti-PD1/anti-PDL1 than in those treated with anti-CTLA4 [23, 36, 37], in patients receiving low-dose corticosteroids, and in patients with history of previous graft rejection [14]. One explanatory hypothesis is that CTLA-4 acts primarily in secondary lymphoid organs, modulating early T cell activation in lymph nodes. Since the kidney relies more directly on the PD-1/PD-L1 interaction to maintain peripheral tolerance, PD-1/PD-L1 blockade has a more direct impact on breaking this tolerance. On the other hand, PD-1/PD-L1 signaling affects

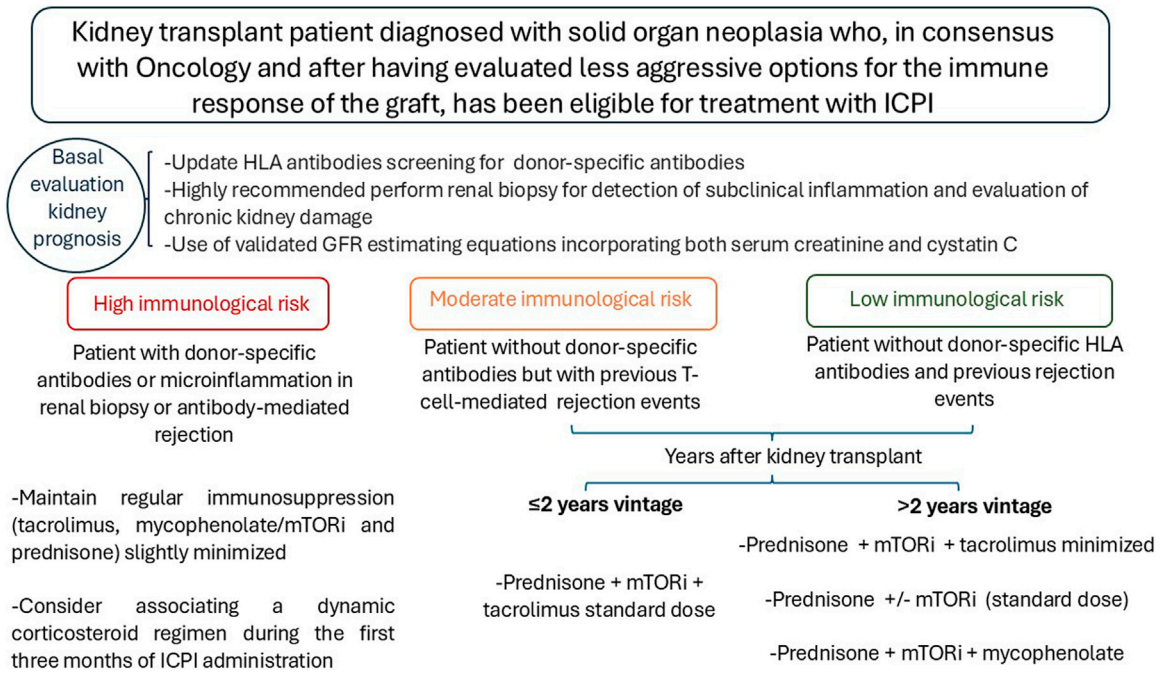


FIGURE 1 | Algorithm for adjusting immunosuppression in kidney transplant patients who will receive ICPI.

Treg activity in the renal graft microenvironment more than the CTLA4 axis. Conversely, factors associated with lower rejection rates include a longer time between transplantation and cancer diagnosis [23], the use of mTOR inhibitors, the maintenance of at least two immunosuppressive drugs at the time of ICPI initiation [32, 38], and deceased donor kidney transplantation [7]. Longer latency from transplantation to initiation of a new immunomodulatory therapy against cancer may reduce the risk of rejection due to: increased immunologic tolerance of the graft, greater stabilization of the immune microenvironment (increased T-reg and decreased effector T cells), greater potential for some effector T cells to convert to less active memory T cells or even T-reg, and, in general, less dependence on immunosuppression to maintain the graft.

Adjustment of Maintenance Immunosuppression to Prevent Allograft Rejection in Patients Treated With ICPI

There is no evidence or clinical guidelines recommending adjustment of immunosuppression prior to the initiation of ICPI. As a result, there is considerable variability in the therapeutic approach to these cases, as evidenced by both retrospective studies and clinical trials.

The majority of authors tend to reduce or discontinue maintenance immunosuppression to manage the patient's immunologic risk, with the aim of improving tumor response [2]. However, there is currently insufficient evidence to support either of the critical decisions they face; which immunosuppressive drug, if any, can be safely discontinued, or what are the target drug levels to be maintained. In one of the largest published multicenter case series of 65 renal transplant patients, only 34.8% were maintained on the same immunosuppressive regimen prior to initiating ICPI. The most common strategy was the combination of two immunosuppressive agents (46% of the patients), such as steroids with CNI or steroids with mTORi. A triple immunosuppressive regimen was used in only 14 cases [7].

In conclusion, some authors propose two different immunosuppressive treatment strategies in this complex scenario:

a) Dynamic steroid regimen; in this approach, the dose of corticosteroids is increased at the beginning of each immunotherapy cycle and then gradually tapered to the usual maintenance dose [39–41].
b) mTORi conversion; is a classic strategy in the management of immunosuppression in solid organ transplantation to prevent tumor growth due to its antitumor effects [42–44]. Despite the published experience, it is difficult to define the specific isolated effect of mTORi conversion because other treatment strategies are used concurrently at the time of cancer diagnosis.

As a summary of the available evidence, and always in consensus with the oncology team, the patient and the renal transplant unit, the follow-up algorithm is proposed based on the immunologic risk and time since transplantation. This is a very complex scenario in which multidisciplinary consensus and individualization of each case are essential **Figure 1**. Recommendations during treatment with ICPI: 1. Check

creatinine, urine sediment and proteinuria before each cycle. 2. Avoid the use of proton pump inhibitors, antibiotics, and nonsteroidal anti-inflammatory drugs. 3. Assess for extrarenal immune-mediated manifestations and, if present, monitor renal function more closely. 4. Evaluate monitoring of dd-cf-DNA and/or urinary CXCL-10 levels. 5. Biopsy indicated if rejection is suspected. 6. Balance patient prognosis and renal function prognosis in decision making.

DISCUSSION

Despite the revolutionary impact of immune checkpoint inhibitors in cancer treatment, there are still significant concerns about their use in kidney transplant patients, given the apparent high risk of organ rejection and the uncertainty about their efficacy in the context of immunosuppression.

However, there is evidence of improved survival in patients receiving triple immunosuppressive therapy. This is particularly true in patients with skin cancer, who actually showed improved outcomes prior to the era of immune checkpoint inhibitors. However, while the results of ICPI therapy appear to be improving in kidney transplant patients, it is important to note that these results remain disappointing in non-skin cancers. Therefore, while we await the results of ongoing clinical trials, the management of cancer treatment in these patients will continue to be highly individualized, particularly in the case of non-skin cancers. The significant risk of graft loss with immune checkpoint inhibitors must be considered. This will be particularly important in patients with a short life expectancy. In such cases, it is important to prioritize the patient's short-to medium-term outlook and wishes together with the patient's oncologist. We need to discuss with oncologists the risk of disease progression and death due to the neoplasia if the best available treatment is not received, and carefully weigh this against the options of returning to dialysis in the event of graft rejection. We must not overlook the fact that the loss of a kidney graft can be managed with dialysis by keeping the patient alive.

Cancer is an ongoing challenge in the transplant population. One of the biggest challenges physicians' faces is the limited opportunity for patients with kidney disease or renal transplant to participate in prospective clinical trials. The establishment of collaborative teams that include both oncologists and nephrologists is a critical step in gradually improving this scarce evidence base. Some hospitals have already established dedicated onco-nephrology units to facilitate the day-to-day management of these patients [45].

Recent data from the first phase I and II clinical trials in transplant patients suggest lower rejection rates than previously published in retrospective studies. However, these results should be interpreted with caution, as the sample size is still very small and cannot be extrapolated to patients with non-cutaneous cancers. Future results from ongoing trials will help to clarify this challenging issue and offer hope to our patients.

CONCLUSION

A complex therapeutic strategy is mandatory after the diagnosis of cancer in renal transplant patients and requires a multidisciplinary approach. The risk-benefit ratio of the ICPI in KTRs must be strictly evaluated. Before starting ICPI, it is advisable to maintain at least two immunosuppressive drugs with modulation of the corticosteroid dose and to switch the drug maintenance treatment from CNI to mTORi. Further prospective studies are needed to analyse the risk of rejection in order to predict it with the most accurate and individualized adjustments of immunosuppression.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

FUNDING

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This research was funded by Instituto de Salud Carlos III (ISCIII) RICORS program to RICORS2040 funded by European Union – NextGenerationEU, Mecanismo para la Recuperación y la Resiliencia (MRR).

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

ACKNOWLEDGMENTS

Instituto de Salud Carlos III (ISCIII) RICORS program and REMAR group (from Catalan, REcerca en Malalties d'Afectació Renal, or Kidney Related Diseases Research Group).

REFERENCES

1. Blosser CD, Haber G, Engels EA. Changes in Cancer Incidence and Outcomes Among Kidney Transplant Recipients in the United States Over a Thirty-Year Period. *Kidney Int* (2021) 99(6):1430–8. doi:10.1016/j.kint.2020.10.018
2. Au E, Wong G, Chapman JR. Cancer in Kidney Transplant Recipients. *Nat Rev Nephrol* (2018) 14(8):508–20. doi:10.1038/s41581-018-0022-6
3. Guba M, Graeb C, Jauch KW, Geissler EK. Pro- and Anti-Cancer Effects of Immunosuppressive Agents Used in Organ Transplantation. *Transplantation* (2004) 77(12):1777–82. doi:10.1097/01.tp.0000120181.89206.54
4. Gupta J, Mitra N, Kanetsky PA, Devaney J, Wing MR, Reilly M, et al. Association Between Albuminuria, Kidney Function, and Inflammatory

Biomarker Profile in CKD in CRIC. *Clin J Am Soc Nephrol* (2012) 7(12): 1938–46. doi:10.2215/CJN.03500412
5. Heaf JG, Hansen A, Laier GH. Quantification of Cancer Risk in Glomerulonephritis. *BMC Nephrol* (2018) 19(1):27. doi:10.1186/s12882-018-0828-2
6. Crocetti E, Ravaioli A, Falcini F, Vattiato R, Mancini S, Baldacchini F, et al. How Many Italian Cancer Patients Are Eligible for, and May Respond to, Italian Medicines Agency-Approved Immune Checkpoint Inhibitors? *Tumori* (2024) 110(2):109–15. doi:10.1177/03008916241229649
7. Murakami N, Mulvaney P, Danesh M, Abudayyeh A, Diab A, Abdel-Wahab N, et al. A Multi-Center Study on Safety and Efficacy of Immune Checkpoint Inhibitors in Cancer Patients with Kidney Transplant. *Kidney Int* (2020) 100: 196–205. doi:10.1016/j.kint.2020.12.015
8. Gravbrot N, Gilbert-Gard K, Mehta P, Ghotmi Y, Banerjee M, Mazis C, et al. Therapeutic Monoclonal Antibodies Targeting Immune Checkpoints for the Treatment of Solid Tumors. *Antibodies (Basel)* (2019) 8(4):E51. doi:10.3390/antib8040051
9. Studstill CJ, Hahm B. Chronic LCMV Infection Is Fortified With Versatile Tactics to Suppress Host T Cell Immunity and Establish Viral Persistence. *Viruses* (2021) 13(10):1951. doi:10.3390/v13101951
10. Matloubian M, Concepcion RJ, Ahmed R. CD4+ T Cells Are Required to Sustain CD8+ Cytotoxic T-Cell Responses During Chronic Viral Infection. *J Virol* (1994) 68(12):8056–63. doi:10.1128/JVI.68.12.8056-8063.1994
11. Lu YJ, Barreira-Silva P, Boyce S, Powers J, Cavallo K, Behar SM. CD4 T Cell Help Prevents CD8 T Cell Exhaustion and Promotes Control of *Mycobacterium tuberculosis* Infection. *Cell Rep* (2021) 36(11):109696. doi:10.1016/j.celrep.2021.109696
12. Li Y, An H, Shen C, Wang B, Zhang T, Hong Y, et al. Deep Phenotyping of T Cell Populations Under Long-Term Treatment of Tacrolimus and Rapamycin in Patients Receiving Renal Transplantations by Mass Cytometry. *Clin Transl Med* (2021) 11(11):e629. doi:10.1002/ctm2.629
13. Shaw BI, Espinosa JR, Stempora L, Miller A, Adams B, Kirk AD. Functional Characteristics and Phenotypic Plasticity of CD57+PD1- CD4 T Cells and Their Relationship With Transplant Immunosuppression. *J Immunol* (2021) 206(7):1668–76. doi:10.4049/jimmunol.2000736
14. Van Meerhaeghe T, Murakami N, Le Moine A, Brouard S, Sprangers B, Degauque N. Fine-Tuning Tumor- and Allo-Immunity: Advances in the Use of Immune Checkpoint Inhibitors in Kidney Transplant Recipients. *Clin Kidney J* (2024) 17(4):sfae061. doi:10.1093/ckj/sfae061
15. Hurkmans DP, Verhoeven JGHP, de Leur K, Boer K, Joosse A, Baan CC, et al. Donor-Derived Cell-free DNA Detects Kidney Transplant Rejection During Nivolumab Treatment. *J Immunother Cancer* (2019) 7(1):182. doi:10.1186/s40425-019-0653-6
16. Schenk KM, Stein JE, Chandra S, Davar D, Eroglu Z, Khushalani NI, et al. Nivolumab (NIVO) + Tacrolimus (TACRO) + Prednisone (PRED) +/- Ipilimumab (IPI) for Kidney Transplant Recipients (KTR) With Advanced Cutaneous Cancers. *J Clin Oncol* (2022) 40:9507. doi:10.1200/JCO.2022.40.16_suppl.9507
17. Carroll RP, Boyer M, Gebski V, Hockley B, Johnston JK, Kireta S, et al. Immune Checkpoint Inhibitors in Kidney Transplant Recipients: A Multicentre, Single-Arm, Phase 1 Study. *Lancet Oncol* (2022)(22) S1470–2045. doi:10.1016/S1470-2045(22)00368-0
18. Shi T, Burg AR, Caldwell JT, Roskin KM, Castro-Rojas CM, Chukwuma PC, et al. Single-cell Transcriptomic Analysis of Renal Allograft Rejection Reveals Insights into Intragraft TCR Clonality. *J Clin Invest* (2023) 133(14):e170191. doi:10.1172/JCI170191
19. Jing Y, Liu J, Ye Y, Pan L, Deng H, Wang Y, et al. Multi-omics Prediction of Immune-Related Adverse Events during Checkpoint Immunotherapy. *Nat Commun* (2020) 11(1):4946. doi:10.1038/s41467-020-18742-9
20. Kawashima S, Joachim K, Abdelrahim M, Abudayyeh A, Jhaveri KD, Murakami N. Immune Checkpoint Inhibitors for Solid Organ Transplant Recipients: Clinical Updates - PubMed. *Korean J Transpl* (2022) 36(2):82–98. doi:10.4285/kjt.22.0013
21. Venkatachalam K, Malone AF, Heady B, Santos RD, Alhamad T. Poor Outcomes with the Use of Checkpoint Inhibitors in Kidney Transplant Recipients. *Transplantation* (2020) 104(5):1041–7. doi:10.1097/TP.0000000000002914
22. Fisher J, Zeitouni N, Fan W, Samie FH. Immune Checkpoint Inhibitor Therapy in Solid Organ Transplant Recipients: A Patient-Centered Systematic Review. *J Am Acad Dermatol* (2020) 82(6):1490–500. doi:10.1016/j.jaad.2019.07.005
23. Nguyen LS, Ortuno S, Lebrun-Vignes B, Johnson DB, Moslehi JJ, Hertig A, et al. Transplant Rejections Associated With Immune Checkpoint Inhibitors: A Pharmacovigilance Study and Systematic Literature Review. *Eur J Cancer* (2021) 148:36–47. doi:10.1016/j.ejca.2021.01.038
24. Perazella MA, Shirali AC. Immune Checkpoint Inhibitor Nephrotoxicity: What Do We Know and What Should We Do? *Kidney Int* (2020) 97(1): 62–74. doi:10.1016/j.kint.2019.07.022
25. Mroue A, Moujaess E, Kourie HR, Azar H, Finianos S, Chelala D. Exploring the Knowledge Gap of Immune Checkpoint Inhibitors in Chronic Renal Failure: A Systematic Review of the Literature. *Crit Rev Oncol Hematol* (2021) 157:103169. doi:10.1016/j.critrevonc.2020.103169
26. Tsung I, Worden FP, Fontana RJ. A Pilot Study of Checkpoint Inhibitors in Solid Organ Transplant Recipients With Metastatic Cutaneous Squamous Cell Carcinoma. *The Oncologist* (2021) 26(2):133–8. doi:10.1002/onco.13539
27. National Cancer Institute (NCI). *A Phase 1/2 Study of Nivolumab and Ipilimumab in Combination with Sirolimus and Prednisone in Kidney Transplant Recipients with Selected Unresectable or Metastatic Cutaneous Cancers* (2024). Available from: https://clinicaltrials.gov/study/NCT05896839 (Accessed May 22, 2024).
28. Schenk KM, Deutsch JS, Chandra S, Davar D, Eroglu Z, Khushalani NI, et al. Nivolumab + Tacrolimus + Prednisone ± Ipilimumab for Kidney Transplant Recipients with Advanced Cutaneous Cancers. *J Clin Oncol* (2024) 42(9): 1011–20. doi:10.1200/JCO.23.01497
29. Kumar V, Shinagare AB, Rennke HG, Ghai S, Lorch JH, Ott PA, et al. The Safety and Efficacy of Checkpoint Inhibitors in Transplant Recipients: A Case Series and Systematic Review of Literature. *Oncologist* (2020) 25(6):505–14. doi:10.1634/theoncologist.2019-0659
30. Saberianfar S, Nguyen LS, Manouchehri A, Lebrun-Vignes B, Moslehi JJ, Johnson DB, et al. Solid Organ Transplant Rejection Associated with Immune-Checkpoint Inhibitors. *Ann Oncol* (2020) 31(4):543–4. doi:10.1016/j.annonc.2020.01.012
31. Alonso F, Martín de Francisco ÁLM, Auñón P, García-Carro C, García P, Gutiérrez E, et al. Adverse Renal Effects of Check-Point Inhibitors (ICI) in Cancer Patients: Recommendations of the Onco-Nephrology Working Group of the Spanish Society of Nephrology. *Nefrología* (2023) 43(5):622–35. doi:10.1016/j.nefroe.2023.11.001
32. Abdel-Wahab N, Safa H, Abudayyeh A, Johnson DH, Trinh VA, Zobniw CM, et al. Checkpoint Inhibitor Therapy for Cancer in Solid Organ Transplantation Recipients: An Institutional Experience and a Systematic Review of the Literature. *J Immunother Cancer* (2019) 7(1):106. doi:10.1186/s40425-019-0585-1
33. Rossi E, Schinzari G, Maiorano BA, Esposito I, Acampora A, Romagnoli J, et al. Immune-Checkpoint Inhibitors in Renal Transplanted Patients Affected by Melanoma: A Systematic Review. *Immunotherapy* (2022) 14(1):65–75. doi:10.2217/imt-2021-0195
34. Portuguese AJ, Tykodi SS, Blosser CD, Gooley TA, Thompson JA, Hall ET. Immune Checkpoint Inhibitor Use in Solid Organ Transplant Recipients: A Systematic Review. *J Natl Compr Canc Netw* (2022) 20(4):406–16.e11. doi:10.6004/jnccn.2022.7009
35. Adam BA, Murakami N, Reid G, Du K, Jasim R, Boils CL, et al. Gene Expression Profiling in Kidney Transplants with Immune Checkpoint Inhibitor-Associated Adverse Events. *Clin J Am Soc Nephrol* (2021) 16(9): 1376–86. doi:10.2215/CJN.00920121
36. Rünger A, Schadendorf D, Hauschild A, Gebhardt C. Immune Checkpoint Blockade for Organ-Transplant Recipients With Cancer: A Review. *Eur J Cancer* (2022) 175:326–35. doi:10.1016/j.ejca.2022.08.010
37. Manohar S, Thongprayoon C, Cheungpasitporn W, Markovic SN, Herrmann SM. Systematic Review of the Safety of Immune Checkpoint Inhibitors Among Kidney Transplant Patients. *Kidney Int Rep* (2020) 5(2):149–58. doi:10.1016/j.ekir.2019.11.015
38. d'Izarny-Gargas T, Durrbach A, Zaidan M. Efficacy and Tolerance of Immune Checkpoint Inhibitors in Transplant Patients with Cancer: A Systematic Review. *Am J Transpl* (2020) 20(9):2457–65. doi:10.1111/ajt.15811
39. Danesh MJ, Mulvaney PM, Murakami N, Riella LV, Silk AW, Hanna GJ, et al. Impact of Corticosteroids on Allograft Protection in Renal Transplant Patients

Receiving Anti-PD-1 Immunotherapy. *Cancer Immunol Immunother* (2020) 69(9):1937–41. doi:10.1007/s00262-020-02644-2

40. Barnett R, Barta VS, Jhaveri KD. Preserved Renal-Allograft Function and the PD-1 Pathway Inhibitor Nivolumab. *N Engl J Med* (2017) 376(2):191–2. doi:10.1056/NEJMc1614298
41. Hanna GJ. Safety and Efficacy of Cemiplimab (PD-1 Blockade) in Selected Organ Transplant Recipients with Advanced Cutaneous Squamous Cell Carcinoma (CONTRAC). *clinicaltrials.gov* (2024). Available from: https://clinicaltrials.gov/study/NCT04339062 (Accessed May 22, 2024). doi:10.1200/JCO.23.01498
42. Holdaas H, De Simone P, Zuckermann A. Everolimus and Malignancy after Solid Organ Transplantation: A Clinical Update. *J Transpl* (2016) 2016: 4369574. doi:10.1155/2016/4369574
43. Schreiber B, Abdelrahim M, Abudayyeh A, Murakami N. Emerging Concepts in Managing Malignancy in Kidney Transplant Patients. *Semin Nephrol* (2022) 42(1):63–75. doi:10.1016/j.semnephrol.2022.01.003
44. Euvrard S, Morelon E, Rostaing L, Goffin E, Brocard A, Tromme I, et al. Sirolimus and Secondary Skin-Cancer Prevention in Kidney Transplantation. *N Engl J Med* (2012) 367(4):329–39. doi:10.1056/NEJMoa1204166
45. Małyszko J, Bamias A, Danesh FR, Dębska-Ślizień A, Gallieni M, Gertz MA, et al. KDIGO Controversies Conference on Onco-Nephrology: Kidney Disease in Hematological Malignancies and the Burden of Cancer after Kidney Transplantation. *Kidney Int* (2020) 98(6):1407–18. doi:10.1016/j.kint.2020.07.012

ESOT | Transplant International

REVIEW
published: 24 January 2025
doi: 10.3389/ti.2025.13716

Donors With Previous Malignancy: When Is It Safe to Proceed With Organ Transplantation?

*Vitor Turra[1], Joao Manzi[1], Sarah Rombach[1], Simone Zaragoza[1], Raphaella Ferreira[2], Giselle Guerra[1], Kendra Conzen[3], Trevor Nydam[3], Alan Livingstone[4], Rodrigo Vianna[1] and Phillipe Abreu[3]**

[1]Miami Transplant Institute, Jackson Memorial Hospital, University of Miami, Miami, FL, United States, [2]HCA Healthcare–HealthOne Internal Medicine Residency Program, Sky Ridge Medical Center, Denver, CO, United States, [3]Department of Surgery, University of Colorado Anschutz Medical Campus, Aurora, CO, United States, [4]Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL, United States

The growing number of organ donors in the United States, from 14,011 in 2012 to 21,374 in 2022, highlights progress in addressing the critical issue of organ shortages. However, the demand remains high, with 17 patients dying daily while on the waiting list. As of August 2023, over 103,544 individuals are awaiting transplants, predominantly for kidneys (85.7%). To expand the donor pool, the inclusion of elderly donors, including those with a history of malignancies, is increasingly considered. In 2022, 7% of all donors were aged 65 and above, despite the complexities their medical histories may introduce, particularly the risk of donor-transmitted cancer (DTC). This review examines the challenges and potential benefits of using donors with known malignancy histories, balancing the risks of DTC against the urgency for transplants. A critical analysis is presented on current knowledge and the decision-making processes that consider cancer types, stages, and patient survival outcomes. The goal is to identify missed opportunities and improve strategies for safe and effective organ transplantation from this donor demographic.

Keywords: risk, cancer, donor, malignancy, transplant surgery

OPEN ACCESS

***Correspondence**
Phillipe Abreu,
phillipe.abreu@cuanschutz.edu

Received: *29 August 2024*
Accepted: *07 January 2025*
Published: *24 January 2025*

Citation:
Turra V, Manzi J, Rombach S, Zaragoza S, Ferreira R, Guerra G, Conzen K, Nydam T, Livingstone A, Vianna R and Abreu P (2025) Donors With Previous Malignancy: When Is It Safe to Proceed With Organ Transplantation? Transpl Int 38:13716. doi: 10.3389/ti.2025.13716

INTRODUCTION

Over the past few years there has been consistent growth in the number of organ donors with numbers rising from 14,011 donors in 2012 to 21,374 in 2022 in the United States [1, 2]. However, the problem of organ shortage remains a significant challenge with 17 patients on the waiting list losing their lives daily due to the unavailability of suitable organs [1, 2].

As of August 2023, the number of patients on the organ transplant waiting list reached 103,544 individuals [2]. Among the organ types, the kidney is the most prevalent, accounting for 85.7% of the patients, followed by those in need of a liver (9.8%), heart (3.2%), lung (0.9%), and other organs (0.4%) [2]. To address this critical need, there were 6,466 living donors and 14,903 deceased donors, totaling 21,369 individuals who donated organs. In 2022 alone, a total of 42,880 successful organ transplants were performed [1, 2].

As life expectancy continues to rise, a growing number of elderly patients appear as potential organ donors due to the necessity to increase the organ donor pool, even with marginal donors [3]. In 2022, 7% of all donors had 65+ years, the highest percentage ever [4]. However, this demographic

TABLE 1 | Risk assessment of major cancer types.

Risk classification categories	
Minimal risk of transmission (<0.1%) – Likely to be acceptable for all organ types and recipients	
Low risk of transmission (0.1% to <2%) – Likely to be acceptable for many organ types and recipients	
High risk of transmission (≥10%) – May be acceptable in exceptional circumstances	
Unacceptable risk – Use of organs is not recommended in any circumstance	
Breast cancer	
Ductal carcinoma *in situ*	
Stage Ia hormone-negative breast cancer, >5 years cancer free	
Stage Ib or higher hormone receptor-positive breast cancer	
Breast cancer diagnosed at retrieval	
Central nervous system Tumors (see **Table 2** for more information)	
Primary brain tumors	
Secondary brain tumors	
Cerebral lymphoma	
Colorectal Carcinoma	
Carcinoma *in situ* of the colon or rectum	
Treated Stage I colorectal cancer (N0/M0), >5 years cancer free (except familial adenomatous polyposis)	
Stage I colorectal cancer diagnosed during retrieval	
Stage IIa colorectal cancer, >10 years cancer free	
Stage II or higher colorectal cancer with ≤10 years cancer free	
Renal Cell Carcinoma	
Renal cell carcinoma <1 cm, Fuhrman Grade I-II	
Renal cell carcinoma >1 and ≤4 cm, Fuhrman Grade I-II	
Renal cell carcinoma >4–7 cm, Fuhrman Grade I-II	
Renal cell carcinoma with extra-renal extension or Fuhrman Grade III-IV	
Lung Cancer	
In situ lung cancer	
Any history of metastatic lung cancer	
Prostate Adenocarcinoma	
Prostate cancer with Gleason score ≤6 or treated with Gleason score 7	
Recently diagnosed prostate cancer with Gleason score 7	
Prostate cancer with distant metastasis	
Skin Cancers	
In situ cutaneous melanoma	
In situ squamous cell carcinoma	
Basal cell carcinoma	
Cutaneous melanoma ≤0.8 mm (T1/N0/M0) completely resected or >0.8 mm (T2-T4/N0/M0) with >10 years cancer free	
Invasive cutaneous squamous cell carcinoma with nodal involvement or metastasis	
Cutaneous melanoma T2-T4 with ≤10 years cancer free with nodal involvement or metastasis	
Uveal or mucosal melanoma	
Thyroid Cancers	
Papillary thyroid microcarcinoma	
Differentiated thyroid tumors ≤4 cm limited to the thyroid (T1/T2)	
Newly diagnosed differentiated thyroid cancer >4 cm (T3, M0) or with extensive spread (T4), treated and ≥2 years cancer free	
Thyroid lymphomas, thyroid sarcomas, and other rare tumors of the thyroid	
Treated thyroid cancer with incomplete macroscopic tumor resection	
Others	
Choriocarcinoma	

Table 1 *was built using the most recent guidelines around the world, including from the European Committee on Organ Transplantation, the Transplantation Society of Australia and New Zealand (TSANZ), the Advisory Committee on the Safety of Blood, Tissues, and Organs (SaBTO) of the UK Government. Guidelines from the USA, spain, and Italy were also included [9–15, 19].*

often carries a history of comorbidities, including malignancies, which adds complexity to an already risk full procedure [5, 6]. One of the significant concerns is the possibility of transmitting diseases or malignancies from the donor to the recipient [7].

Donors with a history of cancer, the main focus of this review, are individuals who have been previously diagnosed and treated for malignancy, but whose cancer is considered cured or in remission at the time of organ donation. In contrast, donors with a known tumor prior to organ procurement or detected during procurement are individuals where the malignancy, such as renal cell carcinoma (RCC) or certain brain tumors, is actively identified either in pre-donation evaluations or during the

retrieval process, raising immediate considerations for recipient safety and donor eligibility. Finally, donors with unknown or undetected tumors at the time of transplantation represent a distinct category, as these malignancies, such as malignant melanoma, are discovered only post-transplantation, often in the recipient, posing significant challenges in terms of retrospective diagnosis and management of transmitted cancer. These categories highlight the varying levels of risk and clinical decision-making required in the evaluation and use of organs from donors with malignancy-related considerations.

Even among donors with previous malignancy history, there are substantial differences in the risks [8–14]. Weighing the risks associated with donor-transmitted cancer (DTC) against the probability of a patient dying while waiting for a donation is a delicate and complex decision [15]. Clinical assessment, considering various factors such as the type and stage of cancer, as well as patient survival on the waiting list, is essential in determining the feasibility and safety of organ transplantation in such cases [8–14]. Even with optimal donor evaluation, there remains an inherent risk of tumor transmission, particularly as donor age increases, due to the higher likelihood of undetected or subclinical malignancies in older individuals.

This review will focus on known malignancy history to gather and present the most up-to-date knowledge about donor-transmitted cancer and critically analyze potential missed opportunities.

ASSESSMENT OF TRANSMISSION RISK

Reported rates of donor-derived cancer transmission to organ recipients vary significantly, ranging from 0 to 42 percent, depending on the data source [8, 9, 13, 16–18]. These high variations could be explained by older data relying on voluntary reporting of index cases and may, therefore, be prone to overestimation [11, 13, 14].

While the exact risk of transmitting any specific cancer from the donor to the recipient is often uncertain, it is possible to broadly assess the likelihood of transmission based on available knowledge regarding the cancer type, its stage, metastatic potential, and recurrence patterns in both transplant and non-transplant settings. **Table 1** summarizes the main cancer types and stages and was prepared based on the most recent guidelines [8–14, 20].

PRIMARY BRAIN TUMORS

Primary solid central nervous system (CNS) tumors may occasionally lead to death in circumstances where organ donation is possible [19]. Extracranial spread of brain tumors is rare, though there are reports of malignancy transmission to the recipients of organs from such donors [21–31].

Primary brain tumors are graded by the World Health Organization (WHO) from grade I to grade IV based on their biological behavior and prognosis [32]. Grade IV tumors are considered cytologically malignant and generally fatal, leading to the perception that they pose the highest risk of transmitting malignancy from donor to recipient [32]. However, several cases of organ transplants from donors with grade IV tumors have been reported without the transmission of malignancy to the recipients [19, 33].

For instance, a UK review of 448 recipients who received organs from 177 donors with primary CNS tumors, including 23 donors with grade IV gliomas and 9 with medulloblastoma, found no evidence of tumor transmission over a minimum follow-up period of 5 years [34]. Similarly, an Australian and New Zealand registry review of 46 donors (9 with high-grade tumors) who provided organs to 153 recipients did not identify any transmission events [35].

Another report from the United Network for Organ Sharing (UNOS) database, which included 642 recipients of organs from donors with CNS tumors, including 175 recipients from donors with high-grade tumors, documented a single case of disease transmission from a donor with glioblastoma multiforme to three recipients [25, 36]. Finally, in a Czech report of 42 donors (11 with high-grade tumors), no transmission was observed among 88 recipients monitored for 2–14 years [37].

A more recent study also from the UK had a 10-year survival of transplants from donors with brain tumors of 65% (95% CI, 59%–71%) for single kidney transplants, 69% (95% CI, 60%–76%) for liver transplants, 73% (95% CI, 59%–83%) for heart transplants, and 46% (95% CI, 29%–61%) for lung transplants [19] which stays in proximity with UNOS national average without malignancy [38–41] (**Figure 1**). For example, kidney had a 78.15% (95%CI, 73.5%–82.7%) 10-year survival, liver had a 64.1%, heart had a 5-year survival of 80% and lung transplants had a 32.8% survival in 10 years [38–41].

Overall, The UK's Advisory Committee on the Safety of Blood, Tissues, and Organs (SaBTO) [11] estimates the risk of tumor transmission from WHO grade I and II tumors to be minimal (<0.1%), the risk from grade III tumors to be low (0.1 to <2%) and the risk of transmission from grade IV tumors as 2.2% [10].

Subsequent reports, where WHO grading was adopted, have suggested that the risk of transmission is much lower [33–37, 42]. Of >77 donors with grade 4 CNS tumors donating to >338 recipients (>34 liver recipients), there was only one that transmitted cancer, with three recipients affected [25, 36]. Despite these favorable registry reports, there have been cases of CNS tumor transmission, including 6 in LT recipients [22, 23, 25, 27, 29, 31, 43–45].

In addition to the reported risks, other factors show clinical significance pertaining to CNS malignancy transmission. Interventions such as brain irradiation, chemotherapy, previous craniotomy, and ventriculoperitoneal shunt procedures may increase the risk of transmitting CNS malignancy from donors to recipients [11, 43, 46]. These interventions potentially breach the blood-brain barrier, facilitating tumor spread. However, it is challenging to differentiate between causality and coincidence. It is possible that certain interventions are more commonly employed in tumors that are more prone to spreading.

One important factor is that the presence of brain metastases can sometimes be incorrectly diagnosed as primary CNS tumors or intracranial hemorrhage, and organ transplantation from these donors has been associated with a poor prognosis for the recipients [46]. A study involving 42 recipients of organs from

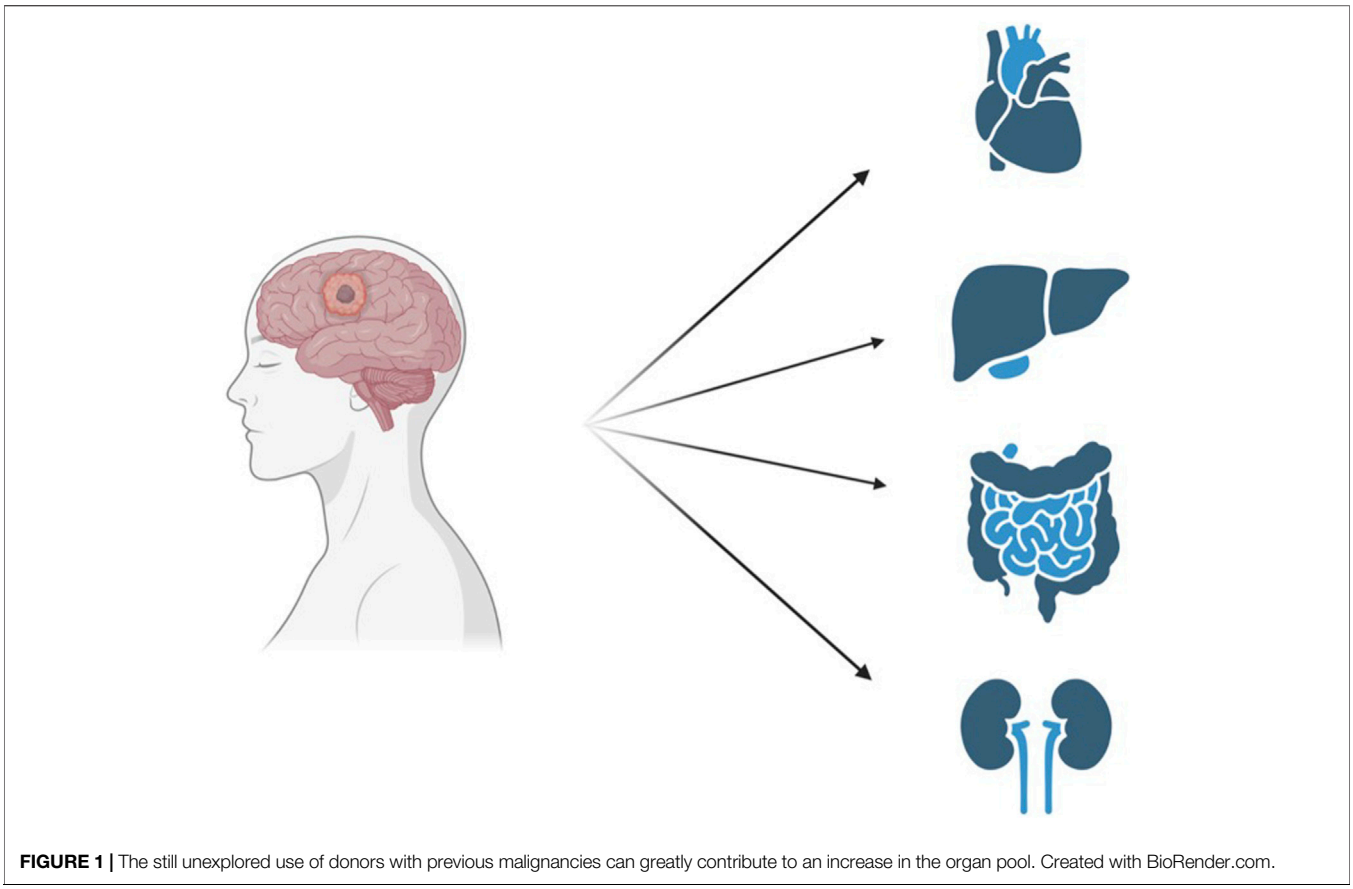


FIGURE 1 | The still unexplored use of donors with previous malignancies can greatly contribute to an increase in the organ pool. Created with BioRender.com.

patients with misdiagnosed primary CNS tumors revealed that 74% of the recipients developed a malignancy derived from the donor, and 64% developed metastatic disease [46]. The 5-year survival rate for these recipients was only 32% [46]. Therefore, in cases where donors present with unexplained intracranial hemorrhage or suspected primary CNS neoplasm without a biopsy, it is crucial to consider conducting an evaluation specifically for metastatic disease [46].

The risk assessment of CNS cancers, specifically pertaining to organ transplantation shown in **Table 2** has been conducted by utilizing the recommendations provided by the Advisory Committee on the Safety of Blood, Tissues, and Organs (SaBTO) [10] and the UNOS recommendations [11]. These assessments have incorporated findings from the SaBTO report, and the outcomes of more recent studies conducted, including those within the United Kingdom [19, 34, 47]. This led to a revised understanding of the risks associated with CNS tumors, but still deficient in quantity and quality of evidence.

BREAST CANCER

Breast cancer is the most frequent cancer in females and is associated with the highest mortality [48]. Organs from donors with a history of invasive breast cancer should only be considered when a low risk of transmission criteria is observed because of the potential for metastasis and late recurrence [49, 50]. A history of Stage I, T1A, node-negative, hormone receptor-negative breast cancer may still be viable in a donor that has had full treatment and complete remission with follow-up >5 years [51]. Any other type of invasive breast cancer is considered a high risk (>10%) of malignancy transmission, regardless of the disease-free interval [13].

Hormone-positive breast cancer poses a high cumulative risk of recurrence at 20 years post-treatment [49, 50]. Given this fact, donors with this type of cancer have a high transmission risk [9]. Lobular breast cancer and ductal carcinoma provide a similar risk of recurrence [52], so it is possible to group them together under Stage I breast cancer with >5 years of recurrence-free survival for risk assessment. In the event of a known history of invasive breast cancer but insufficient data, either pathologic or clinical, donation should only be considered for recipients facing an imminent threat to life [9]. Invasive breast cancer diagnosed during retrieval poses an unacceptable risk to potential transplant recipients [13].

RENAL CARCINOMA

Literature shows documentation of successful kidney transplantation after renal cell carcinoma resection for tumors <4 cm detected at organ retrieval [53–55]. In one study following 21 kidneys with tumors from 0.1 to 2.1 cm, as

TABLE 2 | Risk assessment of CNS tumors.

Absolute contraindications
• Primary cerebral lymphoma
• All secondary intracranial tumors
• Any cancer with metastatic spread
Intracranial tumors with Intermediate risk of cancer transmission (2.2%) include WHO Grade 4 tumors
• Atypical teratoid/rhabdoid tumor
• Choriocarcinoma
• Diffuse midline glioma, H3K27 M-mutant
• Embryonal tumor (all subtypes)
• Giant cell glioblastoma (old classification)
• Glioblastoma (IDH wild type and IDH mutant)
• Gliosarcoma
• Malignant peripheral nerve sheath tumor (MPNST) – grade 4
• Medulloblastoma
• Medulloepithelioma
• Pineoblastoma
Intracranial tumors with a lower risk of cancer transmission (<2%) include WHO Grade 3 tumors
• Anaplastic CNS tumors
• Choroid plexus carcinoma
• Ependymoma: RELA fusion-positive
• Haemangiopericytoma/solitary fibrous tumor
• Papillary tumor of the pineal region
• Pineal parenchymal tumor of intermediate differentiation
• Malignant peripheral sheath tumor grade 3
Intracranial tumors with minimal risk of cancer transmission (<0.1%)
• Low-grade CNS tumor (WHO grade I or II)
• Primary CNS mature teratoma

*The risk assessment of CNS cancers, specifically pertaining to organ transplantation shown in **Table 2** has been conducted by utilizing the recommendations provided by the Advisory Committee on the Safety of Blood, Tissues, and Organs (SaBTO) [10] and the UNOS recommendations [11]. These assessments have incorporated findings from the SaBTO report, and the outcomes of more recent studies conducted [19, 34, 47].*

well as 47 contralateral kidneys and 198 non-renal organs, no cases of malignancy transmission were identified [53]. Another study showed no cases of transmission in 97 kidney transplantations after RCC resection <4 cm, although there was one case in the transplant of 22 contralateral kidneys [54]. In the case of well-differentiated RCC, the risk of transmission was assessed as minimal (<0.1%) in tumors ≤1.0 cm in size, or low (<2%) for tumors >1.0 cm to ≤4 cm in size [10]. Therefore, all organs are considered for transplantation, including the affected kidney, after resection on as RCC <4 cm with Fuhrman grade I-II, when satisfactory margins are achieved [10, 11, 56]. Outside of organ retrieval, if RCC diagnosis was less than 5 years before organ donation, the same risks for RCC diagnosed during organ retrieval apply. For patients with RCC >5 years with appropriate follow-up, theoretical risks may be even lower [9]. Donors with RCC 4–7 cm with Fuhrman I-II, with higher than 5 years cancer-free interval may be considered for non-renal organs [57] Any history of invasive RCC or Fuhrman grade III-IV represents an unacceptable risk [13].

PRIMARY LIVER TUMORS

Liver, biliary, or pancreatic cancers that are diagnosed during organ retrieval provide an unacceptable risk of malignancy transmission in organ transplantation [9]. Even if identified in treated history, they are usually also considered unacceptable risks given the aggressive nature and high recurrence of these cancers [9].

However, benign liver tumors are relatively common, occurring in up to 20% of the general population [58] the most frequent lesions being hepatic hemangioma (HH), focal nodular hyperplasia (FNH), and hepatocellular adenoma (HCA and are safe to transplant, so it's essential to differentiate between a tumor is malignant before ruling out donation [58, 59]. Some studies exist showing cancer transmission in liver, biliary, or pancreatic cancer [42, 60–63].

MALIGNANT MELANOMA

Melanoma of the skin represents 5% of all new cancer cases in the US [64]. Melanoma is known for its potential transmission from donor to recipient during transplantation [36, 65–68] particularly pronounced when the diagnosis is overlooked in the donor, leading to significant implications [36, 57, 69–73]. The prevalence of melanoma as a tumor type is high, marked by early micro metastasis and the inherent challenge of detection [74, 75]. Invasive melanoma constitutes around 30% of reported cases of donor-related cancers [18, 76] with fatal consequences, as it correlates with a high recipient mortality rate, estimated at approximately 60% [7]. The level of risk associated with the transmission of cutaneous melanoma hinges on factors like Breslow thickness and the stage of melanoma at the time of diagnosis and treatment [77]. Notably, *in situ* cutaneous melanoma, being non-invasive, presents minimal chances of donor-derived transmission due to the absence of metastatic risk associated [65, 78, 79].

Invasive cutaneous melanoma is considered a high to unacceptable risk of transmission as it may recur regardless of many years of disease-free interval and poses a theoretically higher threat on immunosuppressed patients, given that on non-immunosuppressed individuals, the lifetime risk of recurrence is greater than 2% for T1a (<0.8 mm thickness) and greater than 10% in T1b (0.9–1.0 mm) [80–82]. Another hazard of melanoma is its spread to distant sites, even during the early stages of the disease, with cells that may stay dormant and undetectable for many years after primary resection [83]. If transplanted, these cells may lead to metastatic growth in an immunosuppressed patient [66, 84–86], with high mortality rates [87, 88]. Similarly, uveal and mucosal melanoma pose an unacceptable risk to donation, given a high risk of undetected micro metastases, regardless of the length of disease-free survival, as does cutaneous melanoma with a history of nodal involvement or distant metastases [89–91].

Considering all these factors, there are instances where organs from donors with melanoma, other than *in situ*, may be used under exceptional life-or-death circumstances [13]. As always, this decision must be based on a thorough assessment of risk status, with ample information available, and always accompanied by the informed consent of the recipient.

PROSTATE CANCER

Prostate cancer provides a minimal-to-low risk of malignancy transmission given, as with many other types of cancer, its confinement to the original organ [92]. It is one of the most prevalent cancers accounting for 14.7% of all new cancer cases in the U.S. In 2023, there were an estimated 4,956,901 men living with prostate cancer in the World [48, 93]. A study conducted on organ donors showed that 23% of those aged 50–59 years, 35% of those aged 60–69, and 46% of those aged 70–81 years had undiagnosed prostate cancer [94]. However, there was no evidence of higher prevalence of prostate cancer among transplant recipients relative to the general male population [95, 96].

The Gleason score is a valuable tool when deciding to proceed with the donation [97, 98]. A Gleason score of 6 provides an almost-zero risk of transmission [99]. A donor with a history of a Gleason 7 prostate cancer may also be considered minimal risk, provided the tumor was organ-confined and the donor has been cancer-free for more than 3 years [92, 100]. Analyzing 120 reports of transplants coming from donors with confirmed prostate cancer, only one case was identified [101], and that came from a donor later found to have metastatic disease [102]. A meta-analysis concluded that the risk of remaining on the waiting list was higher than the risk of transmission in transplants with a donor with prostate cancer [92].

PRIMARY LUNG CARCINOMA

There are registry and case reports of occult donor transmission with kidney transplantation, highly fatal outcomes, and very aggressive behavior from donor-transmitted lung cancer [57, 103–105]. Benign pulmonary nodules – such as hamartomas and papillomas – are relatively common, especially after 45 years of age and account for more than 95% of all pulmonary nodules [106]; hence it is important to distinguish between benign tumors in the lung and lung cancer in the donor.

Transmission of lung cancer to liver transplant recipients has been reported with fatal consequences in 2 cases, including 1 undergoing urgent transplantation when the adenocarcinoma was found on donor autopsy [107, 108]. There are also reports of transmission in several registry studies [17, 18, 20, 60, 69, 109]. In contrast, there are a few reports of donor lung cancer not being transmitted to liver transplant recipients [17, 20, 110]. Still, lung cancer at any stage (excluding *in situ* – high risk) [13] is considered an unacceptable risk [9, 13].

COLORECTAL CANCER

Colorectal cancer is common in the population and a common cause of mortality [48]. The liver is the most frequent site of metastasis [111]. A 2003 US consensus agreed on the use of Stage I – T1, node-negative – colorectal cancer individuals as organ donors given the low risk of nodal or metastatic disease associated [112]. For individuals with Stage I familial adenomatous polyposis who are potential donors, caution should be exercised when considering pancreas transplantation due to an elevated risk of duodenal cancers [13]. However, under specific circumstances and clinical assessment, transplantation of certain other organs might still be viable [9]. In cases where Stage II or higher colorectal cancer is detected either during retrieval or in the donor's medical history, with a cancer-free period of up to 10 years, the potential for transmitting cancer to recipients is deemed unacceptable [11, 13].

However some more recent studies suggest the risk might be lower [110, 113]. As new forms of cancer targeting appear [114] and recently showed that patients with this type of cancer may have a good prognosis [115, 116] with effective surveillance [117], new data on colorectal cancer and its safety should appear in the following years. It is important that pathology reports are made available to accurately determine the stage of cancer before proceeding with transplantation. During retrieval procedures, surgeons should meticulously inspect all intra-abdominal and intra-thoracic structures for any suspicious lesions [15, 109].

THYROID TUMORS

Approximately 90% of thyroid cancers are either papillary (80%) or follicular (10%) [118], usually with only localized spread [48]. The relative survival rate is 97% in a 5-year interval, if not in advanced stages [48, 119]. Distant metastases develop in 5%–23% of differentiated thyroid cancers, typically in the lungs and bones [120]. Post-operative risk of recurrence after tumor resection is low when the tumor does not have aggressive histology [121].

The risk of malignancy transmission in differentiated thyroid cancer varies depending on the size of the tumor and the spread, with cancers up to 4 cm providing a minimal risk of transmission if confined to the thyroid, even if only detected at organ retrieval [9, 11, 13]. On an important note, thyroid cancers are not affected by immunosuppression, which means that pre-existing thyroid cancers do not show increased rates of progression, and the incidence of thyroid cancer is not elevated in recipients [96, 122]. Additionally, even in the event of donor-derived transmission, metastatic differentiated thyroid cancer can still be treated with curative therapy, depending on histology [120].

OTHER CANCERS

While the main cancers associated with organ donation are well-documented, consideration should also be given to other less commonly reported malignancies, such as ovarian, cervical, and pancreatic cancers. These malignancies pose unique challenges due to their aggressive nature and potential for microscopic metastases. However, the current literature lacks sufficient data to assess the transmission risks or to establish evidence-based recommendations for the utilization of organs from donors with these types of cancers. As such, further studies and case reports are needed to better understand the risks and outcomes

associated with these malignancies in the context of organ transplantation.

DISCUSSION

History of malignancy or, in some cases, an active malignant disease in the potential donor should not automatically be a veto to organ donation. The estimated risk of tumor transmission should be balanced against the benefit of the transplant for recipients. Donor-transmitted cancer is still an area to be better understood, with few quality studies showing varied results that could either underestimate or overestimate the probability of developing DTC [123–125].

As the donor waiting lists continue to rise and general life expectancy tends to get older, reevaluating the risk of DTC could provide a powerful ally in increasing the donor pool, with many more donors becoming available. Currently, there is still a feeling of missed opportunities in perceived high-risk transplants that retrospectively have not shown the same risk, especially regarding CNS tumors [126], that's have historically been put in a >10% risk category [11] and are now reduced to a 2.2% risk [8–10, 13]. There is expectation concerning what other risk reductions are viable, but more detailed data, including reliable reporting of transmission events, is necessary to include, as of now, high-risk malignancies in a potential donor list and to allow a more evidence-based decision process.

The frequently urgent nature of organ transplantation often precludes the possibility of obtaining all of the desired information, and the physician must weigh available clinical data and published experience along with the medical condition and desires of the patient in arriving at the best possible decision. Although a certain transmission risk will remain in many cases, selected patients will benefit from these organs more than if they stayed on the waiting list.

It is important to notice, however, that even without a prior history of neoplasm, there is still a chance of donor-origin cancer (DOC) of 0.06%, as it was concluded by a study with 30,765 transplants conducted in the UK [17]. In this study of the 18 recipients who developed DOC from 16 donors (0.06%): 3 were DDC (donor-derived cancer - posterior growth of malignancy after transplantation, derived from donor cells), and 15 were DTC (donor-transmitted cancer). Of the 15 DTCs, 6 were renal cell cancer; 5 lung cancer; 2 lymphoma; 1 neuroendocrine cancer; and 1 colon cancer. This represented an unavoidable, but low risk of DOC in every transplant made [17], which should be taken into consideration when weighing the risks.

Noticeably, no guidelines exist on retransplantation in DTC events. Decisions should be made on a case-by-case basis with a multidisciplinary approach and after discussion with the patient or relatives. Retransplantation may be reasonably considered when the tumor identified in the donor is deemed of intermediate or high risk of transmission.

CONCLUSION

An individualized clinical judgment for using organs from donors with malignancy should be made and presented to the recipients, including the risk of not proceeding with transplantation, with fully informed consent being mandatory where the risks are higher than standard expectations.

This review stands to bring back the focus on DTC, urging for a more extensive evidence base providing more accurate and clinically relevant recommendations to aid the patient's physician in a more secure clinical decision, as well as providing an answer to an ever-higher donor waiting list.

AUTHOR CONTRIBUTIONS

Conceptualization of the study was done by JM, PA, and RV; VT, JM, SR, SZ, and RF participated in writing the original draft; GG, KC, TN, AL, PA, and RV participated in reviewing and editing the manuscript. PA supervised the project, which was administered by VT. All authors contributed to the article and approved the submitted version.

FUNDING

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

REFERENCES

1. OPTN. *Organ Procurement and Transplantation Network (OPTN) Metrics* (2023). Available from: https://insights.unos.org/OPTN-metrics/ (Accessed October 10, 2023).
2. Health Resources and Services Administration (HRSA). *Organ Donation Statistics | Organonor.Gov* (2024). Available from: https://www.organdonor.gov/learn/organ-donation-statistics (Accessed February 04, 2024).
3. Goldaracena N, Cullen JM, Kim DS, Ekser B, Halazun KJ. Expanding the Donor Pool for Liver Transplantation With Marginal Donors. *Int J Surg* (2020) 82:30–5. doi:10.1016/j.ijsu.2020.05.024
4. OPTN. *National Data* (2023). Available from: https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/ (Accessed October 11, 2023).
5. Kovac D, Choe J, Liu E, Scheffert J, Hedvat J, Anamisis A, et al. Immunosuppression Considerations in Simultaneous Organ Transplant. *Pharmacotherapy* (2021) 41(1):59–76. doi:10.1002/phar.2495
6. Scheuher C. A Review of Organ Transplantation: Heart, Lung, Kidney, Liver, and Simultaneous Liver-Kidney. *Crit Care Nurs Q* (2016) 39:199–206. doi:10.1097/CNQ.0000000000000115
7. Buell JF, Beebe TM, Trofe J, Gross TG, Alloway RR, Hanaway MJ, et al. Donor Transmitted Malignancies. *Ann Transpl* (2004) 9(1):53–6.
8. European Committee on Organ Transplantation. European Directorate for the Quality of Medicines and HealthCare. Guide to the Quality and Safety of

Organs for Transplantation. In: *European Committee on Organ Transplantation*. European Directorate for the Quality of Medicines and HealthCare. 8th ed (2022).
9. *Clinical Guidelines for Organ Transplantations From Deceased Donors*. The Transplantation Society of Australia and New Zealand TSANZ (2023). https://tsanz.com.au/storage/documents/TSANZ_Clinical_Guidelines_Version-111_13062023Final-Version.pdf.
10. *Transplantation of Organs From Deceased Donors With Cancer or a History of Cancer. Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO)*. UK Government Department of Healthx: London, UK (2014).
11. Nalesnik MA, Woodle ES, Dimaio JM, Vasudev B, Teperman LW, Covington S, et al. Donor-transmitted Malignancies in Organ Transplantation: Assessment of Clinical Risk. *Am J Transplant* (2011) 11:1140–7. doi:10.1111/j.1600-6143.2011.03565.x
12. Mahíllo B, Martín S, Molano E, Navarro A, Castro P, Pont T, et al. Malignancies in Deceased Organ Donors: The Spanish Experience. *Transplantation* (2022) 106(9):1814–23. doi:10.1097/TP.0000000000004117
13. Domínguez-Gil B, Moench K, Watson C, Serrano MT, Hibi T, Asencio JM, et al. Prevention and Management of Donor-Transmitted Cancer After Liver Transplantation: Guidelines From the ILTS-SETH Consensus Conference. *Transplantation* (2022) 106(1):e12–e29. doi:10.1097/TP.0000000000003995
14. Eccher A, Lombardini L, Girolami I, Puoti F, Zaza G, Gambaro G, et al. How Safe Are Organs from Deceased Donors With Neoplasia? The Results of the Italian Transplantation Network. *J Nephrol* (2019) 32:323–30. doi:10.1007/s40620-018-00573-z
15. Buell JF, Alloway RR, Steve Woodle E. How Can Donors With a Previous Malignancy Be Evaluated? *J Hepatol* (2006) 45:503–7. doi:10.1016/j.jhep.2006.07.019
16. Zhang S, Yuan J, Li W, Ye Q. Organ Transplantation From Donors (Cadaveric or Living) With a History of Malignancy: Review of the Literature. *Transplant Rev* (2014) 28:169–75. doi:10.1016/j.trre.2014.06.002
17. Desai R, Collett D, Watson CJ, Johnson P, Evans T, Neuberger J. Cancer Transmission From Organ Donors-Unavoidable but Low Risk. *Transplantation* (2012) 94(12):1200–7. doi:10.1097/TP.0b013e318272df41
18. Penn I. Transmission of Cancer From Organ Donors. *Ann Transplant : Q Polish Transplant Soc* (1997) 2(4):7–12.
19. Greenhall GHB, Rous BA, Robb ML, Brown C, Hardman G, Hilton RM, et al. Organ Transplants From Deceased Donors With Primary Brain Tumors and Risk of Cancer Transmission. *JAMA Surg* (2023) 158(5):504–13. doi:10.1001/jamasurg.2022.8419
20. Kaul DR, Vece G, Blumberg E, La Hoz RM, Ison MG, Green M, et al. Ten Years of Donor-Derived Disease: A Report of the Disease Transmission Advisory Committee. *Am J Transplant* (2021) 21(2):689–702. doi:10.1111/ajt.16178
21. Lefrancois N, Touraine JL, Cantarovich D, Cantarovich F, Faure JL, Dubernard JM, et al. Transmission of Medulloblastoma from Cadaver Donor to Three Organ Transplant Recipients. *Transpl Proc* (1987) 19(1 Pt 3):2242.
22. Frank S, Müller J, Bonk C, Haroske G, Schackert HK, Schackert G. Transmission of Glioblastoma Multiforme Through Liver Transplantation. *Lancet.* (1998) 352(9121):31. doi:10.1016/S0140-6736(98)24027-X
23. Chen H, Shah AS, Girgis RE, Grossman SA. Transmission of Glioblastoma Multiforme After Bilateral Lung Transplantation. *J Clin Oncol* (2008) 26(19):3284–5. doi:10.1200/JCO.2008.16.3543
24. Val-Bernal F, Ruiz JC, Cotorruelo JG, Arias M. Glioblastoma Multiforme of Donor Origin After Renal Transplantation: Report of a Case. *Hum Pathol* (1993) 24(11):1256–9. doi:10.1016/0046-8177(93)90224-5
25. Armanios MY, Grossman SA, Yang SC, White B, Perry A, Burger PC, et al. Transmission of Glioblastoma Multiforme Following Bilateral Lung Transplantation from an Affected Donor: Case Study and Review of the Literature. *Neuro Oncol* (2004) 6(3):259–63. doi:10.1215/S1152851703000474
26. Ruiz JC, Cotorruelo JG, Tudela V, Ullate PG, Val-Bernal F, De Francisco ALM, et al. Transmission of Glioblastoma Multiforme to Two Kidney Transplant Recipients From the Same Donor in the Absence of Ventricular Shunt. *Transplantation* (1993) 55(3):682–3.
27. Jonas S, Bechstein WO, Lemmens HP, Neuhaus R, Thalmann U, Neuhaus P. Liver Graft-Transmitted Glioblastoma Multiforme. A Case Report and Experience With 13 Multiorgan Donors Suffering From Primary Cerebral Neoplasia. *Transpl Int* (1996) 9(4):426–9. doi:10.1007/BF00335707
28. Zhao P, Strohl A, Gonzalez C, Fishbein T, Rosen-Bronson S, Kallakury B, et al. Donor Transmission of Pineoblastoma in a Two-Yr-Old Male Recipient of a Multivisceral Transplant: A Case Report. *Pediatr Transpl* (2012) 16(4):E110–4. doi:10.1111/j.1399-3046.2010.01463.x
29. Morse JH, Turcotte JG, Merion RM, Campbell DA, Burtch GD, Lucey MR. Development of a Malignant Tumor in a Liver Transplant Graft Procured From a Donor With a Cerebral Neoplasm. *Transplantation* (1990) 50(5):875–7. doi:10.1097/00007890-199011000-00026
30. Hynes CF, Ramakrishnan K, Alfares FA, Endicott KM, Hammond-Jack K, Zurakowski D, et al. Risk of Tumor Transmission after Thoracic Allograft Transplantation From Adult Donors With Central Nervous System Neoplasm—A UNOS Database Study. *Clin Transpl* (2017) 31(4). doi:10.1111/ctr.12919
31. Colquhoun SD, Robert ME, Shared A, Rosenthal JT, Millis JM, Farmer DG, et al. Transmission of Cns Malignancy by Organ Transplantation. *Transplantation* (1994) 57(6):970–4.
32. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: A Summary. *Acta Neuropathologica* (2016) 131:803–20. doi:10.1007/s00401-016-1545-1
33. Lee MS, Cho WH, Ha J, Yu ES, Jeong YS, Oh JS, et al. Safety of Donation From Brain-Dead Organ Donors With Central Nervous System Tumors: Analysis of Transplantation Outcomes in Korea. *Transplantation* (2020) 104:460–6. doi:10.1097/TP.0000000000002994
34. Watson CJE, Roberts R, Wright KA, Greenberg DC, Rous BA, Brown CH, et al. How Safe Is It to Transplant Organs From Deceased Donors With Primary Intracranial Malignancy? An Analysis of UK Registry Data. *Am J Transplant* (2010) 10(6):1437–44. doi:10.1111/j.1600-6143.2010.03130.x
35. Chui AKK, Herbertt K, Wang LS, Kyd G, Hodgeman G, Verran DJ, et al. Risk of Tumor Transmission in Transplantation From Donors With Primary Brain Tumors: An Australian and New Zealand Registry Report. In: *Transplantation Proceedings* (1999).
36. Kauffman HM, Cherikh WS, McBride MA, Cheng Y, Hanto DW. Deceased Donors With a Past History of Malignancy: An Organ Procurement and Transplantation Network/United Network for Organ Sharing Update. *Transplantation* (2007) 84(2):272–4. doi:10.1097/01.tp.0000267919.93425.fb
37. Pokorna E, Vítko Š. The Fate of Recipients of Organs From Donors With Diagnosis of Primary Brain Tumor. *Transpl Int* (2001) 14:346–7. doi:10.1007/s001470100334
38. Ghelichi-Ghojogh M, Ghaem H, Mohammadizadeh F, Vali M, Ahmed F, Hassanipour S, et al. Graft and Patient Survival Rates in Kidney Transplantation, and Their Associated Factors: A Systematic Review and Meta-Analysis. *Iranian J Public Health* (2021) 50:1555–63. doi:10.18502/ijph.v50i8.6801
39. *Lung Annual Data Report* (2023). Available from: https://srtr.transplant.hrsa.gov/annual_reports/2021/Lung.aspx#fig:LUtx-adult-Dth-all-C. (Accessed: October 11, 2023).
40. *Heart Annual Data Report* (2023). Available from: https://srtr.transplant.hrsa.gov/annual_reports/2021/Heart.aspx#fig:HRtx-adult-Dth-all-C. (Accessed: October 11, 2023).
41. *Liver Annual Data Report* (2023). Available from: https://srtr.transplant.hrsa.gov/annual_reports/2021/Liver.aspx. (Accessed: October 11, 2023).
42. Kauffman HM, McBride MA, Cherikh WS, Spain PC, Marks WH, Roza AM. Transplant Tumor Registry: Donor Related Malignancies. *Transplantation* (2002) 74(3):358–62. doi:10.1097/00007890-200208150-00011
43. Buell JF, Trofe J, Sethuraman G, Hanaway MJ, Beebe TM, Gross TG, et al. Donors With Central Nervous System Malignancies: Are They Truly Safe? *Transplantation* (2003) 76(2):340–3. doi:10.1097/01.TP.0000076094.64973.D8
44. NHS Blood and Transplant. *Events Investigated for Possible Donor-Derived Transmission of Infections, Malignancies and Other Cases of Interest* (2019). Available from: https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/24453/30-june-2021-report-events-investigated-for-possible-donor-derived-transmission-of-infections-malignancies-march-2018-march-202.pdf (Accessed on December 30, 2024).

45. Fatt MA, Horton KM, Fishman EK. Transmission of Metastatic Glioblastoma Multiforme From Donor to Lung Transplant Recipient. *J Comput Assist Tomogr* (2008) 32(3):407–9. doi:10.1097/RCT.0b013e318076b472
46. Buell JF, Gross T, Alloway RR, Trofe J, Woodle ES. Central Nervous System Tumors in Donors: Misdiagnosis Carries a High Morbidity and Mortality. *Transplant Proc* (2005) 37:583–4. doi:10.1016/j.transproceed.2004.12.125
47. Warrens AN, Birch R, Collett D, Daraktchiev M, Dark JH, Galea G, et al. Advising Potential Recipients on the Use of Organs From Donors With Primary Central Nervous System Tumors. *Transplantation* (2012) 93: 348–53. doi:10.1097/TP.0b013e31823f7f47
48. WHO. *WHO Global Cancer Observatory*. Cancer today (2023). Available from: https://gco.iarc.fr/today/home (Accessed August, 2023).
49. Pan H, Gray R, Braybrooke J, Davies C, Taylor C, McGale P, et al. 20-Year Risks of Breast-Cancer Recurrence After Stopping Endocrine Therapy at 5 Years. *New Engl J Med* (2017) 377(19):1836–46. doi:10.1056/NEJMoa1701830
50. Gonzalez-Angulo AM, Litton JK, Broglio KR, Meric-Bernstam F, Rakkhit R, Cardoso F, et al. High Risk of Recurrence for Patients With Breast Cancer Who Have Human Epidermal Growth Factor Receptor 2-Positive, Node-Negative Tumors 1 Cm or Smaller. *J Clin Oncol* (2009) 27(34):5700–6. doi:10.1200/JCO.2009.23.2025
51. Balkenhol MCA, Vreuls W, Wauters CAP, Mol SJJ, van der Laak JAWM, Bult P. Histological Subtypes in Triple Negative Breast Cancer Are Associated With Specific Information on Survival. *Ann Diagn Pathol* (2020) 46:151490. doi:10.1016/j.anndiagpath.2020.151490
52. Wang K, Zhu GQ, Shi Y, Li ZY, Zhang X, Li HY. Long-Term Survival Differences Between T1-2 Invasive Lobular Breast Cancer and Corresponding Ductal Carcinoma After Breast-Conserving Surgery: A Propensity-Scored Matched Longitudinal Cohort Study. *Clin Breast Cancer* (2019) 19(1):e101–15. doi:10.1016/j.clbc.2018.10.010
53. Pavlakis M, Michaels MG, Tlusty S, Turgeon N, Vece G, Wolfe C, et al. Renal Cell Carcinoma Suspected at Time of Organ Donation 2008-2016: A Report of the OPTN Ad Hoc Disease Transmission Advisory Committee Registry. *Clin Transpl* (2019) 33(7):e13597. doi:10.1111/ctr.13597
54. Yu N, Fu S, Fu Z, Meng J, Xu Z, Wang B, et al. Allotransplanting Donor Kidneys After Resection of a Small Renal Cancer or Contralateral Healthy Kidneys From Cadaveric Donors With Unilateral Renal Cancer: A Systematic Review. *Clin Transplant* (2014) 28:8–15. doi:10.1111/ctr.12262
55. Hevia V, Hassan ZR, Fraser Taylor C, Bruins HM, Boissier R, Lledo E, et al. Effectiveness and Harms of Using Kidneys With Small Renal Tumors From Deceased or Living Donors as a Source of Renal Transplantation: A Systematic Review. *Eur Urol Focus* (2019) 5:508–17. doi:10.1016/j.euf.2018.01.018
56. Nicol DL, Preston JM, Wall DR, Griffin AD, Campbell SB, Isbel NM, et al. Kidneys From Patients With Small Renal Tumours: A Novel Source of Kidneys for Transplantation. *BJU Int* (2008) 102(2):188–92. doi:10.1111/j.1464-410X.2008.07562.x
57. Eccher A, Girolami I, Motter JD, Marletta S, Gambaro G, Momo REN, et al. Donor-transmitted Cancer in Kidney Transplant Recipients: A Systematic Review. *J Nephrol* (2020) 33(6):1321–32. doi:10.1007/s40620-020-00775-4
58. Ostojic A, Mrzljak A, Mikulic D. Liver Transplantation for Benign Liver Tumors. *World J Hepatol* (2021) 13(9):1098–106. doi:10.4254/wjh.v13.i9.1098
59. Oldhafer KJ, Habbel V, Horling K, Makridis G, Wagner KC. Benign Liver Tumors. *Visc Med* (2020) 36:292–303. doi:10.1159/000509145
60. Ison MG, Nalesnik MA. An Update on Donor-Derived Disease Transmission in Organ Transplantation. *Am J Transplant* (2011) 11:1123–30. doi:10.1111/j.1600-6143.2011.03493.x
61. Gerstenkorn C, Thomusch O. Transmission of a Pancreatic Adenocarcinoma to a Renal Transplant Recipient. *Clin Transpl* (2003) 17(5):473–6. doi:10.1034/j.1399-0012.2003.00072.x
62. Georgieva LA, Gielis EM, Hellemans R, Van Craenenbroeck AH, Couttenye MM, Abramowicz D, et al. Single-Center Case Series of Donor-Related Malignancies: Rare Cases With Tremendous Impact. *Transpl Proc* (2016) 48(8):2669–77. doi:10.1016/j.transproceed.2016.07.014
63. Kim B, Woreta T, Chen PH, Limketkai B, Singer A, Dagher N, et al. Donor-Transmitted Malignancy in a Liver Transplant Recipient: A Case Report and Review of Literature. *Dig Dis Sci* (2013) 58:1185–90. doi:10.1007/s10620-012-2501-0
64. *Melanoma of the Skin — Cancer Stat Facts* (2023). Available from: https://seer.cancer.gov/statfacts/html/melan.html (Accessed: October 11, 2023).
65. Abdullayeva L. Donor-Transmitted Melanoma: Is It Still Bothering Us? *Curr Treat Options Oncol* (2020) 21:38. doi:10.1007/s11864-020-00740-0
66. Strauss DC, Thomas JM. Transmission of Donor Melanoma by Organ Transplantation. *The Lancet Oncol* (2010) 11:790–6. doi:10.1016/S1470-2045(10)70024-3
67. Bilal M, Eason JD, Das K, Sylvestre PB, Dean AG, Vanatta JM. Donor-Derived Metastatic Melanoma in a Liver Transplant Recipient Established by DNA Fingerprinting. *Exp Clin Transplant* (2013) 11(5):458–63. doi:10.6002/ect.2012.0243
68. Park CK, Dahlke EJ, Fung K, Kitchen J, Austin PC, Rochon PA, et al. Melanoma Incidence, Stage, and Survival After Solid Organ Transplant: A Population-Based Cohort Study in Ontario, Canada. *J Am Acad Dermatol* (2020) 83(3):754–61. doi:10.1016/j.jaad.2019.09.072
69. Green M, Covington S, Taranto S, Wolfe C, Bell W, Biggins SW, et al. Donor-Derived Transmission Events in 2013: A Report of the Organ Procurement Transplant Network Ad Hoc Disease Transmission Advisory Committee. *Transplantation* (2015) 99(2):282–7. doi:10.1097/TP.0000000000000584
70. Birkeland SA, Storm HH. Risk for Tumor and Other Disease Transmission by Transplantation: A Population-Based Study of Unrecognized Malignancies and Other Diseases in Organ Donors. *Transplantation* (2002) 74(10): 1409–13. doi:10.1097/00007890-200211270-00012
71. Chen KT, Olszanski A, Farma JM. Donor Transmission of Melanoma Following Renal Transplant. *Case Rep Transplant* (2012) 2012:764019. doi:10.1155/2012/764019
72. Cankovic M, Linden MD, Zarbo RJ. Use of Microsatellite Analysis in Detection of Tumor Lineage as a Cause of Death in a Liver Transplant Patient. *Arch Pathol Lab Med* (2006) 130(4):529–32. doi:10.1043/1543-2165(2006)130[529:UOMAID]2.0.CO;2
73. Morris-Stiff G, Steel A, Savage P, Devlin J, Griffiths D, Portman B, et al. Transmission of Donor Melanoma to Multiple Organ Transplant Recipients. *Am J Transplant* (2004) 4(3):444–6. doi:10.1111/j.1600-6143.2004.00335.x
74. Izraely S, Sagi-Assif O, Klein A, Meshel T, Tsarfaty G, Pasmanik-Chor M, et al. The Metastatic Microenvironment: Brain-Residing Melanoma Metastasis and Dormant Micrometastasis. *Int J Cancer* (2012) 131(5): 1071–82. doi:10.1002/ijc.27324
75. Cabrera R, Recule F. Unusual Clinical Presentations of Malignant Melanoma: A Review of Clinical and Histologic Features With Special Emphasis on Dermatoscopic Findings. *Am J Clin Dermatol* (2018) 19:15–23. doi:10.1007/s40257-018-0373-6
76. González-Cruz C, Ferrándiz-Pulido C, García-Patos BV. Melanoma in Solid Organ Transplant Recipients. *Actas Dermo-Sifiliograficas* (2021) 112:216–24. doi:10.1016/j.ad.2020.11.005
77. Dicker TJ, Kavanagh GM, Herd RM, Ahmad T, McLaren KM, Chetty U, et al. A Rational Approach to Melanoma Follow-Up in Patients With Primary Cutaneous Melanoma. Scottish Melanoma Group. *Br J Dermatol* (1999) 140(2):249–54. doi:10.1046/j.1365-2133.1999.02657.x
78. Toren KL, Parlette EC. Managing Melanoma *In Situ*. *Semin Cutan Med Surg* (2010) 29(4):258–63. doi:10.1016/j.sder.2010.10.002
79. Wright FC, Souter LH, Kellett S, Easson A, Murray C, Toye J, et al. Primary Excision Margins, Sentinel Lymph Node Biopsy, and Completion Lymph Node Dissection in Cutaneous Melanoma: A Clinical Practice Guideline. *Curr Oncol* (2019) 26(4):e541–e550. doi:10.3747/co.26.4885
80. Hollestein LM, Nijsten T. Survival Is Excellent For Most Patients With Thin Melanoma, But Patients May Die From Thin Melanoma. *Br J Dermatol* (2021) 184:4. doi:10.1111/bjd.19208
81. Lo SN, Scolyer RA, Thompson JF. Long-Term Survival of Patients With Thin (T1) Cutaneous Melanomas: A Breslow Thickness Cut Point of 0.8 Mm Separates Higher-Risk and Lower-Risk Tumors. *Ann Surg Oncol* (2018) 25(4):894–902. doi:10.1245/s10434-017-6325-1
82. Isaksson K, Mikiver R, Eriksson H, Lapins J, Nielsen K, Ingvar C, et al. Survival in 31 670 Patients With Thin Melanomas: A Swedish Population-Based Study. *Br J Dermatol* (2021) 184(1):60–7. doi:10.1111/bjd.19015
83. Crowley NJ, Seigler HF. Late Recurrence of Malignant Melanoma: Analysis of 168 Patients. *Ann Surg* (1990) 212(2):173–7. doi:10.1097/00000658-199008000-00010
84. Piérard-Franchimont C, Hermanns-Lê T, Delvenne P, Piérard GE. Dormancy of Growth-Stunted Malignant Melanoma: Sustainable and Smoldering Patterns. *Oncol Rev* (2014) 8:252. doi:10.4081/oncol.2014.252

85. Tseng WW, Fadaki N, Leong SP. Metastatic Tumor Dormancy in Cutaneous Melanoma: Does Surgery Induce Escape?. *Cancers* (2011) 3:730–46. doi:10.3390/cancers3010730
86. Linde N, Fluegen G, Aguirre-Ghiso JA. The Relationship between Dormant Cancer Cells and Their Microenvironment. *Adv Cancer Res* (2016) 132:45–71. doi:10.1016/bs.acr.2016.07.002
87. Benoni H, Eloranta S, Ekbom A, Wilczek H, Smedby KE. Survival Among Solid Organ Transplant Recipients Diagnosed With Cancer Compared to Nontransplanted Cancer Patients—A Nationwide Study. *Int J Cancer* (2020) 146(3):682–91. doi:10.1002/ijc.32299
88. Robbins HA, Clarke CA, Arron ST, Tatalovich Z, Kahn AR, Hernandez BY, et al. Melanoma Risk and Survival Among Organ Transplant Recipients. *J Invest Dermatol* (2015) 135(11):2657–65. doi:10.1038/jid.2015.312
89. Kaliki S, Shields CL. Uveal Melanoma: Relatively Rare but Deadly Cancer. *Eye (Basingstoke)* (2017) 31:241–57. doi:10.1038/eye.2016.275
90. Carvajal RD, Schwartz GK, Tezel T, Marr B, Francis JH, Nathan PD. Metastatic Disease From Uveal Melanoma: Treatment Options and Future Prospects. *Br J Ophthalmol* (2017) 101:38–44. doi:10.1136/bjophthalmol-2016-309034
91. Altieri L, Eguchi M, Peng DH, Cockburn M. Predictors of Mucosal Melanoma Survival in a Population-Based Setting. *J Am Acad Dermatol* (2019) 81(1):136–42. doi:10.1016/j.jaad.2018.09.054
92. Dholakia S, Johns R, Muirhead L, Papalois V, Crane J. Renal Donors With Prostate Cancer, No Longer a Reason to Decline. *Transplant Rev* (2016) 30:48–50. doi:10.1016/j.trre.2015.06.001
93. *Prostate Cancer — Cancer Stat Facts* (2023). Available from: https://seer.cancer.gov/statfacts/html/prost.html (Accessed: October 11, 2023).
94. Yin M, Bastacky S, Chandran U, Becich MJ, Dhir R. Prevalence of Incidental Prostate Cancer in the General Population: A Study of Healthy Organ Donors. *J Urol* (2008) 179(3):892–5. doi:10.1016/j.juro.2007.10.057
95. Rosales BM, De La Mata N, Vajdic CM, Kelly PJ, Wyburn K, Webster AC. Cancer Mortality in Kidney Transplant Recipients: An Australian and New Zealand Population-Based Cohort Study, 1980–2013. *Int J Cancer* (2020) 146(10):2703–11. doi:10.1002/ijc.32585
96. Na R, Grulich AE, Meagher NS, McCaughan GW, Keogh AM, Vajdic CM. Comparison of De Novo Cancer Incidence in Australian Liver, Heart and Lung Transplant Recipients. *Am J Transplant* (2013) 13(1):174–83. doi:10.1111/j.1600-6143.2012.04302.x
97. Short E, Warren AY, Varma M. Gleason Grading of Prostate Cancer: A Pragmatic Approach. *Diagn Histopathology* (2019) 25:371–8. doi:10.1016/j.mpdhp.2019.07.001
98. Gleason DF. Histologic Grading of Prostate Cancer: A Perspective. *Hum Pathol* (1992) 23(3):273–9. doi:10.1016/0046-8177(92)90108-f
99. Ross HM, Kryvenko ON, Cowan JE, Simko JP, Wheeler TM, Epstein JI. Do Adenocarcinomas of the Prostate With Gleason Score (GS)≤6 Have the Potential to Metastasize to Lymph Nodes? *Am J Surg Pathol* (2012) 36:1346–52. doi:10.1097/PAS.0b013e3182556dcd
100. Skalski M, Gierej B, Nazarewski Ł, Ziarkiewicz-Wróblewska B, Zieniewicz K. Prostate Cancer in Deceased Organ Donors: Loss of Organ or Transplantation with Active Surveillance. *Transpl Proc* (2018) 50(7):1982–4. doi:10.1016/j.transproceed.2018.02.129
101. Doerfler A, Tillou X, Le Gal S, Desmonts A, Orczyk C, Bensadoun H. Prostate Cancer in Deceased Organ Donors: A Review. *Transplant Rev* (2014) 28:1–5. doi:10.1016/j.trre.2013.10.003
102. Loh E, Couch FJ, Hendricksen C, Farid L, Kelly PF, Acker MA, et al. Development of Donor-Derived Prostate Cancer in a Recipient Following Orthotopic Heart Transplantation. *JAMA* (1997) 277(2):133–7. doi:10.1001/jama.1997.03540260047034
103. Desai R, Collett D, Watson CJE, Johnson P, Evans T, Neuberger J. Estimated Risk of Cancer Transmission from Organ Donor to Graft Recipient in a National Transplantation Registry. *Br J Surg* (2014) 101(7):768–74. doi:10.1002/bjs.9460
104. Forbes GB, Goggin MJ, Dische FE, Saeed IT, Parsons V, Harding MJ, et al. Accidental Transplantation of Bronchial Carcinoma From a Cadaver Donor to Two Recipients of Renal Allografts. *J Clin Pathol* (1981) 34(2):109–15. doi:10.1136/jcp.34.2.109
105. Göbel H, Gloy J, Neumann J, Wiech T, Pisarski P, Böhm J. Donor-Derived Small Cell Lung Carcinoma in a Transplanted Kidney. *Transplantation* (2007) 84:800–2. doi:10.1097/01.tp.0000281402.55745.e6
106. Mazzone PJ, Lam L. Evaluating the Patient With a Pulmonary Nodule: A Review. *JAMA* (2022) 327:264–73. doi:10.1001/jama.2021.24287
107. Sonbol MB, Halling KC, Douglas DD, Ross HJ. A Case of Donor-Transmitted Non-Small Cell Lung Cancer After Liver Transplantation: An Unwelcome Guest. *Oncologist* (2019) 24(6):e391–3. doi:10.1634/theoncologist.2018-0517
108. Lipshutz GS, Baxter-Lowe LA, Nguyen T, Jones KD, Ascher NL, Feng S. Death From Donor-Transmitted Malignancy Despite Emergency Liver Retransplantation. *Liver Transplant* (2003) 9(10):1102–7. doi:10.1053/jlts.2003.50174
109. Penn I. Evaluation of the Candidate With a Previous Malignancy. *Liver Transpl Surg.* (1996) 2(5 Suppl 1):109–13.
110. Benkö T, Hoyer DP, Saner FH, Treckmann JW, Paul A, Radunz S. Liver Transplantation from Donors With a History of Malignancy: A Single-Center Experience. *Transpl Direct* (2017) 3(11):e224. doi:10.1097/TXD.0000000000000738
111. Riihimaki M, Hemminki A, Sundquist J, Hemminki K. Patterns of Metastasis in Colon and Rectal Cancer. *Sci Rep* (2016) 6:29765. doi:10.1038/srep29765
112. Feng S, Buell JF, Chari RS, DiMaio JM, Hanto DW. Tumors and Transplantation: The 2003 Third Annual ASTS State-Of-The-Art Winter Symposium. *Am J Transplant* (2003) 3:1481–7. doi:10.1046/j.1600-6143.2003.00245.x
113. Eccher A, Girolami I, Marletta S, Brunelli M, Carraro A, Montin U, et al. Donor-Transmitted Cancers in Transplanted Livers: Analysis of Clinical Outcomes. *Liver Transplant* (2021) 27(1):55–66. doi:10.1002/lt.25858
114. Manzi J, Hoff CO, Ferreira R, Pimentel A, Datta J, Livingstone AS, et al. Targeted Therapies in Colorectal Cancer: Recent Advances in Biomarkers, Landmark Trials, and Future Perspectives. *Cancers* (2023) 15:3023. doi:10.3390/cancers15113023
115. Hernandez-Alejandro R, Ruffolo LI, Sasaki K, Tomiyama K, Orloff MS, Pineda-Solis K, et al. Recipient and Donor Outcomes After Living-Donor Liver Transplant for Unresectable Colorectal Liver Metastases. *JAMA Surg* (2022) 157(6):524–30. doi:10.1001/jamasurg.2022.0300
116. Dueland S, Smedman TM, Syversveen T, Grut H, Hagness M, Line PD. Long-Term Survival, Prognostic Factors, and Selection of Patients with Colorectal Cancer for Liver Transplant: A Nonrandomized Controlled Trial. *JAMA Surg* (2023) 158:e232932. doi:10.1001/jamasurg.2023.2932
117. Manzi J, Hoff CO, Ferreira R, Glehn-Ponsirenas R, Selvaggi G, Tekin A, et al. Cell-Free DNA as a Surveillance Tool for Hepatocellular Carcinoma Patients After Liver Transplant. *Cancers (Basel)* (2023) 15(12):3165. doi:10.3390/cancers15123165
118. *Types of Thyroid Cancer*. American Cancer Society (2023). Available from: https://www.cancer.org/cancer/types/thyroid-cancer/about/what-is-thyroid-cancer.html (Accessed: October 11, 2023).
119. Verburg FA, Mäder U, Tanase K, Thies ED, Diessl S, Buck AK, et al. Life Expectancy Is Reduced in Differentiated Thyroid Cancer Patients ≥ 45 Years Old With Extensive Local Tumor Invasion, Lateral Lymph Node, or Distant Metastases at Diagnosis and Normal in All Other DTC Patients. *J Clin Endocrinol Metab* (2013) 98(1):172–80. doi:10.1210/jc.2012-2458
120. Perros P, Colley S, Boelaert K, Evans C, Evans R, Gerrard G, et al. Guidelines for the Management of Thyroid Cancer. *Clin Endocrinol (Oxf)* (2014) 81:1–122. doi:10.1111/cen.12515
121. Cooper DS, Doherty GM, Haugen BR, Kloos RT, Lee SL, Mandel SJ, et al. Consensus Statement on the Terminology and Classification of Central Neck Dissection for Thyroid Cancer. *Thyroid* (2009) 19:1153–8. doi:10.1089/thy.2009.0159
122. Van Leeuwen MT, Webster AC, McCredie MRE, Stewart JH, McDonald SP, Amin J, et al. Effect of Reduced Immunosuppression After Kidney Transplant Failure on Risk of Cancer: Population Based Retrospective Cohort Study. *BMJ (Online)* (2010) 340(7744):c570. doi:10.1136/bmj.c570
123. Greenhall GHB, Ibrahim M, Dutta U, Doree C, Brunskill SJ, Johnson RJ, et al. Donor-Transmitted Cancer in Orthotopic Solid Organ Transplant Recipients: A Systematic Review. *Transpl Int* (2022) 35:10092. doi:10.3389/ti.2021.10092
124. Malvi D, Vasuri F, Albertini E, Carbone M, Novelli L, Mescoli C, et al. Donors Risk Assessment in Transplantation: From the Guidelines to Their Real-World Application. *Pathol Res Pract* (2024) 255:155210. doi:10.1016/j.prp.2024.155210

125. Lim WH, Au E, Teixeira-Pinto A, Ooi E, Opdam H, Chapman J, et al. Donors With a Prior History of Cancer: Factors of Non-Utilization of Kidneys for Transplantation. *Transpl Int* (2023) 36:11883. doi:10.3389/ti.2023.11883
126. Greenhall GHB, Rous BA, Robb ML, Brown C, Hardman G, Hilton RM, et al. Organ Transplants From Deceased Donors With Primary Brain Tumors and Risk of Cancer Transmission. *JAMA Surg* (2023) 158(5):504–13. doi:10.1001/jamasurg.2022.8419

ESOT | Transplant International

ORIGINAL RESEARCH
published: 16 June 2025
doi: 10.3389/ti.2025.14487

Renal Cell Carcinoma in Native Kidney After Kidney Transplantation: A Multicenter Case Control Study With a Focus on Screening Strategy

Pierre Pommerolle[1,2]*, *Maryam Assem*[1,2,3], *Marine Uhl*[4], *Philippe De Sousa*[4], *Dominique Guerrot*[5], *Marc Hazzan*[6], *Thierry Lobbedez*[7], *Ophélie Fourdinier*[1] and *Gabriel Choukroun*[1,2]

[1]Department of Nephrology, Dialysis, and Transplantation, Amiens University Hospital, Amiens, France, [2]MP3CV Research Unit, University of Picardie Jules Verne, Amiens, France, [3]Department of Nephrology, Tanger University Hospital, Tanger, Morocco, [4]Department of Urology and Transplantation, Amiens University Hospital, Amiens, France, [5]Department of Nephrology, Dialysis, and Transplantation, Rouen University Hospital, Rouen, France, [6]Department of Nephrology, Dialysis, and Transplantation, Lille University Hospital, Lille, France, [7]Department of Nephrology, Dialysis, and Transplantation, Caen University Hospital, Caen, France

Renal cell carcinoma (RCC) of native kidney is more prevalent after kidney transplantation than in the general population. Risk factors and the value of screening remain unclear. We conducted a multicenter case-control study in kidney transplant recipients transplanted between 1989 and 2017. All patients with RCC were included, and two controls were matched to each case. Two centers performed annual screening (AnS group) and the other two had other strategies (OS group). A total of 125 cancers were found in 113 patients. The majority of cancers were stage T1-T2 (92.0%), 1.6% had metastasis at diagnosis and ten (9.0%) had recurrence after nephrectomy. Men [OR 2.2; IC 95% (1.2–4.4); p = 0.02] and acquired cystic kidney disease [OR 3.2; IC 95% (1.8–5.9); p < 0.01] were associated with cancer in multivariate analysis. The 10-year survival was poorer in cases (65.6% vs. 79.1%, p < 0.001). The AnS group had fewer relapses (5.0% vs. 18.2%, p = 0.02) and a lower rate of cancer-related deaths (16.0% vs. 46.1%, p = 0.04). Survival of patients with RCC is lower than in control patients. Annual screening could improve cancer prognosis, its benefit needs to be evaluated in larger studies.

Keywords: renal cell carcinoma, native kidney, kidney transplantation, screening, survival

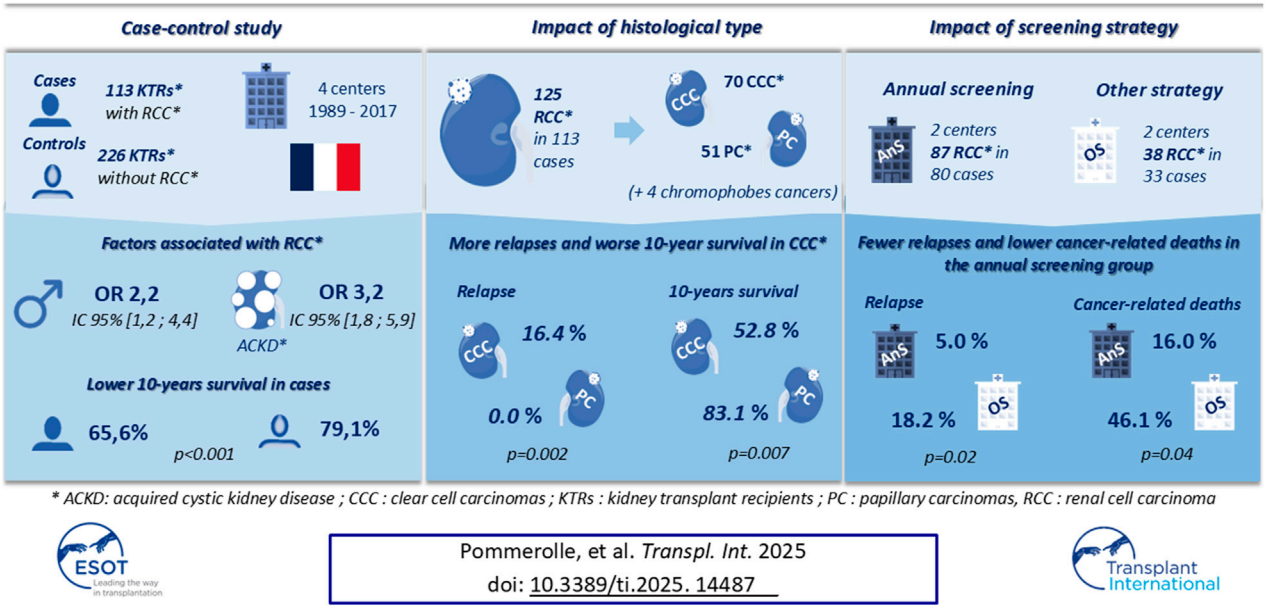
OPEN ACCESS

***Correspondence**
Pierre Pommerolle,
pommerolle.pierre@chu-amiens.fr

Received: *12 February 2025*
Accepted: *03 June 2025*
Published: *16 June 2025*

Citation:
Pommerolle P, Assem M, Uhl M, De Sousa P, Guerrot D, Hazzan M, Lobbedez T, Fourdinier O and Choukroun G (2025) Renal Cell Carcinoma in Native Kidney After Kidney Transplantation: A Multicenter Case Control Study With a Focus on Screening Strategy. Transpl. Int. 38:14487. doi: 10.3389/ti.2025.14487

Abbreviations: ACKD, acquired cystic kidney disease; Ans, annual screening group; ADPKD, autosomal dominant polycystic kidney disease; CVD, cardiovascular disease; Ch, chromophobe; CCC, clear cell carcinoma; CKD, chronic kidney disease; DSA, donor specific antibody; ESRD, end-stage renal disease; eGFR, estimated glomerular filtration rate; KT, kidney transplantation; KTRs, kidney transplant recipients; Os, other strategy group; PC, papillary carcinoma; RCC, renal cell carcinoma.



GRAPHICAL ABSTRACT |

INTRODUCTION

Kidney transplantation (KT) is the treatment of choice for chronic kidney disease (CKD), offering, in comparison to dialysis, a better quality of life and survival. However, the use of immunosuppressive treatments increases the risk of post-transplantation complications, mostly infections and cancers. Thus, the risk of cancer is 2 to 5-fold higher in kidney transplant recipients (KTRs) than in the general population [1, 2], and 20% of KTRs will develop cancer within 10 years after KT [3]. A higher risk is observed, compared to the general population, for skin cancer, Kaposi's sarcoma, post-transplantation lymphomas, and urological malignancies particularly the renal cell carcinoma (RCC) of native kidney [1, 2].

Every year, RCC affects 350,000 new patients worldwide and 30,000 patients die from their cancer [4]. The main risk factors for RCC are age older than 60 [5], male gender [5], smoking [6], high blood pressure [7–9], obesity [10, 11], and CKD [12]. Acquired cystic kidney disease (ACKD) is a multi-cystic differentiation of native kidneys, mainly affecting patients with end-stage of CKD. ACKD is suspected to be a risk factor for RCC, due to the strong association between ACKD and CKD-patients with RCC (70%–90%) [13]. Treatment for RCC is usually surgical but medical treatment (in particular the use of immunotherapies and tyrosine kinase inhibitors) has clearly improved prognosis of patients with metastatic disease [14, 15].

Several studies, generally retrospective, monocentric, and with small numbers of patients, have studied the risk of RCC in KTRs [16–27]. RCC is 15-fold higher in KT than in the general population [28, 29], and occurred in 0.7% of KTRs [30]. Interestingly, several studies have suggested that the frequency of RCC may be higher when systematic screening is performed (2.7%–4.6%) [18, 21, 23]. The explanations for this higher frequency in KT have not been optimally studied, due to a lack of studies comparing the characteristics of KTRs with RCC to those of KTRs without cancer. The impact of immunosuppressive regimen notably, remains unclear [31]. Finally, there is no consensus on systematic screening of RCC in KTRs. Indeed, the American Society of Transplantation and the Kidney Disease Improving Global Outcomes do not recommend systematic screening [2, 32], while the European Association of Urology recommends performing an annual ultrasound of the native kidneys [33]. The aim of this study is to determine the characteristics of KTRs with RCC in a large population of transplant patients. To evaluate the risk factors of RCC in KT, we compared characteristics of this population to a healthy and matched population of KTRs. Finally, we evaluated the outcome of KTRs with RCC according to the screening strategy of their center.

PATIENTS AND METHODS

Study Design

We conducted a multicentric, retrospective, case-control study in four University Hospitals in France (Amiens, Caen, Lille and Rouen). The study included KTRs transplanted between April 1989 and December 2017. The end of the follow-up was 31 January 2019.

Selection of Cases and Controls

All patients with a diagnosis of RCC during graft follow-up were included, while patients with a diagnosis of benign tumor of native kidney, graft cancer, or urinary tract malignancy were not. Cases were selected in all centers by the search for "Cancer of native kidney" or "Kidney carcinoma" in the CRISTAL database (Agence de la Biomedecine, Paris, France) and supplemented by questioning the Pathology Department of each center. Finally, the analysis of medical records ensured the diagnosis of RCC. Controls were selected from KTRs transplanted over the same period. All patients underwent pre-transplant evaluation, including abdominal imaging, to rule out active malignancy and RCC. We assigned two controls per case, matching by center, year of transplantation (±2 years), and age at transplantation (±2 years). Cases had to be alive with a functioning graft at the time of the case's cancer onset and anephric controls were excluded. These criteria was verified in the patient's medical records.

Patients' Medical Records

All data were collected retrospectively from the patients' medical records. The variables collected included sex, age at transplantation, age at cancer diagnosis (for cases), the number of transplants received, the type and duration of dialysis treatment before KT, cancer history, the presence of a single native kidney, smoking (current or former), obesity, diabetes mellitus, presence of ACKD, cause of end-stage renal disease (ESRD), estimated glomerular filtration rate (eGFR), immune complications (biopsy-proven graft rejection, rejection type and *de novo* donor-specific antibodies [DSA]), immunosuppression characteristics (regimen, drugs, blood calcineurin inhibitor level, and the dose of mycophenolate mofetil received), the histologic characteristics of cancers, cancer treatments (including initial treatment, treatment of recurrence and changes in immunosuppressive therapy). Single native kidney was defined as a single anatomical kidney (acquired or congenital) before KT; obesity was defined as a body mass index >30 kg/m^2; eGFR was calculated using the Modification of Diet in Renal Disease equation [34]; ACKD was defined as the presence of at least three single cysts in each native kidney on imaging tests (ultrasound, CT scan or magnetic resonance imaging), patients with autosomal dominant polycystic kidney disease (ADPKD) and those without available imaging examinations were excluded from this analysis. Tumors were classified by histological type according to current classifications the year of the discovery of the cancer, and according to the classifications of Fuhrman or International Society of Urological Pathology (based on date of diagnosis) for the tumor grade [35, 36]. The stage of the disease was evaluated according to the Union for International Cancer Control TNM 2017 classification [37, 38].

RCC Screening

We defined two groups of patients according to the screening strategy of each center: the "annual screening group" (AnS, including patients from Amiens and Rouen) and the "other strategy group" (OS, including patients from Caen and Lille). The annual screening strategy involved alternating CT scans and ultrasounds in Amiens center (alternately) and only an ultrasound screening in Rouen center. The use of iodinated contrast agent for CT scans was permitted but left to the discretion of the nephrologist. In the OS group, Caen center carried out ultrasound at 1 year of KT then every 3 years, while Lille center did not perform systematic screening. Patients in both groups (Ans and OS) could undergo additional imaging, after screening or incidental diagnosis.

Statistical Analysis

The normality tests used were the Shapiro-Wilk test and the Kolmogorov Smirnov test. In case of normal distribution, means and standard deviations were used to describe continuous variables. Otherwise, we described the results with the median and the interquartile range (IQR). For unpaired subjects, the means were compared by Student's t-test or the Mann-Whitney (depending on whether the variables were normally distributed or not), and frequencies by the chi-square test or the Fisher test. For matched subjects, frequencies were compared by the Cochran-Mantel-Haenszel test. Survival data (patient survival and graft survival) were evaluated at 10 years from baseline. Baseline corresponded to the date of cancer diagnosis in the cases, and the date of cancer of the matched case for the controls. For patients who had contralateral RCC, only the date of the first cancer was used in the analyses. Graft survival data were censored at the time of recipient death. Survival was analyzed by the Kaplan Meier method. Survival curves were compared by the Logrank test. The odds ratios, described with a 95% confidence interval, were calculated in a bivariate analysis, then included in a multivariate model if p was less than 0.1 using a logistic regression model. The results were considered significant for a p-value less than 0.05. Statistical analyses were performed using SPSS® software (version 21 SPSS Inc., Chicago, IL, United States) and Graphpad Prism (Graphpad Software San Diego, California, United States).

Ethics

The study followed the 1964 Declaration of Helsinki and its later amendments. In line with the French legislation on retrospective, non-interventional studies, this study was reviewed and approved by an ethic committee (Comité de Protection des Personnes Nord Ouest II, n°2011/17), all patients were informed about the collection of their data and were free to decline participation in the study. The study was registered with the French National Data Protection Commission (Commission Nationale de l'Informatique et des Libertés, Paris, France; registration number: CNIL MR001: n°1449904).

RESULTS

Comparison of Cases and Controls

Seven thousand and eighty-four patients were transplanted in the four centers between April 1989 and December 2017 (1511 in Amiens, 1377 in Caen, 2887 in Lille, 1449 in Rouen). One hundred and thirteen patients had a RCC during the study

TABLE 1 | Cases and controls characteristics.

Variables	Patients		
	Cases n = 113	Controls n = 226	p
Male	87 (77.0)	143 (63.3)	0.03
Age at transplantation	51.3 (10.9)	51.2 (10.9)	ns
Age at baseline	56.1 (10.6)	56.1 (10.7)	ns
Smoke	39 (33.6)	75 (33.2)	ns
Body mass index, kg/m^2	26.1 (23.4–28.9)	25.9 (22.8–28.5)	ns
Obesity	23 (20.4)	43 (19.0)	ns
Diabetes mellitus	21 (18.6)	40 (17.7)	ns
Acquired cystic kidney disease[a]	52 (50.0)	39 (24.1)	0.01
Single native kidney	12 (10.6)	23 (10.2)	ns
Dialysis before transplantation	106 (93.8)	211 (93.4)	ns
Hemodialysis	94 (88.7)	185 (87.7)	ns
Time to dialysis, months	27.2 (16.6–45.6)	23.7 (14.8–38.5)	ns
Time to dialysis >3 years	40 (35.4)	58 (25.7)	ns
eGFR at baseline, mL/min/1.73 m^2	47.0 (36.5–60.0)	46.0 (35.0–57.0)	ns
Prior cancer history	11 (9.7)	14 (6.2)	ns
History of pre-transplant RCC	2 (1.8)	0 (0.0)	ns
Prior transplantation	16 (14.2)	20 (8.8)	ns
Cause of ESRD			
Glomerulonephritis	55 (48.7)	84 (37.2)	0.04
Nephroangiosclerosis	14 (12.4)	10 (4.4)	0.02
Diabetes mellitus	8 (7.1)	10 (4.4)	ns
ADPKD	7 (6.2)	52 (23.0)	0.01
Chronic Interstitial Disease	7 (6.2)	14 (6.2)	ns
Urologic malformation	4 (3.5)	25 (11.1)	0.04
Other	8 (7.1)	8 (3.5)	ns
Unknown	10 (8.8)	23 (10.2)	ns

Data are expressed as mean (standard deviation) or median (interquartile range) for continuous variables (depending on the normal distribution or not) and number (percentage) for categorial variables. eGFR, estimated glomerular filtrate rate; RCC, renal cell carcinoma; ESRD, end stage renal disease; ADPKD, autosomal dominant polycystic kidney disease; ns, non-significant.

[a]*Patients with autosomal dominant polycystic kidney disease and those for whom imaging examinations were not available were excluded from the analysis of this variable.*

period, i.e., a prevalence of 1.6% in the entire population. The characteristics of the patients are summarized in **Table 1**.

Cases and controls mostly received a graft from a deceased donor (98.2% in cases and 97.8% in controls). Cases were more likely to be men (77.0% vs. 63.3%; p = 0.03) and to have an ACKD (50.0% vs. 24.1%; p = 0.01). The cause of ESRD was more frequently a glomerulonephritis (48.7% vs. 37.2%; p = 0.04) or a nephroangiosclerosis (12.4% vs. 4.4%; p = 0.02) in the cases, while ADPKD (6.2% vs. 23.0%; p = 0.01) and uropathies (3.5% vs. 11.1%; p = 0.04) were more frequent in controls (**Table 1**). There was no difference in the immunosuppressive treatment and immunological complications before baseline (**Table 2**).

In the univariate analysis, male gender [OR 1.9; CI 95% (1.1–3.1); p = 0.01], ACKD [OR 3.4; CI 95% (2.0–5.7); p < 0.01], glomerulonephritis [OR 1.7; CI 95% (1.0–2.7); p = 0.01] and nephroangiosclerosis [OR 2.8; CI 95% (1.2–6.5); p = 0.02] as a cause of ESRD were associated with RCC, while ADPKD [OR 0.2; CI 95% (0.1–0.5); p < 0.01] and uropathies [OR 0.4; CI 95% (0.1–0.9); p = 0.04] were protective factors. Only male gender [OR 2.2; CI 95% (1.2–4.4); p = 0.02] and ACKD [OR 3.2; IC 95% (1.8–5.9); p < 0.001] remained associated with the risk of RCC in the multivariate analysis (see the **Supplementary Table** for comprehensive results).

With respective median follow-up times of 62.5 months (IQR 29.9–120.1) and 82.1 months (IQR 39.9–134.4), the mortality rate (33.6% vs. 18.6%, p = 0.02) and 10-year survival (65.6% vs. 79.1%, p < 0.001; **Figure 1**) were better in controls. Patients with metastatic disease at diagnosis had a median survival of 9.0 months (IQR 8.6–9.3). RCC was the second cause of death in cases (10/38, 26.3%) after cardiovascular disease (CVD; 12/38, 31.6%) while infections (13/42, 30.9%), malignancies (10/42, 23.8%) and CVD (9/42, 21.4%) were the most common causes of death in controls. There was no difference in the 10-year graft survival censored on patient death (82.7% in cases vs. 86.7% in controls, p = 0.38; **Figure 2**), and chronic allograft nephropathy was the most common cause of graft loss in the two groups (60.0% in cases and 65.2% in controls). Finally, the risks after baseline of allograft nephropathy (9.7% in cases vs 6.2% in controls), humoral rejection (7.1% in cases vs. 5.6% in controls), cellular rejection (4.4% in cases and 1.3% in controls) and appearance of DSA (14.2% in cases and 13.5% in controls) were similar between the two groups.

RCC Characteristics

One hundred and twenty-five cancers were diagnosed in the 113 cases (**Figure 3**). Clear cell carcinoma (CCC) was the most common type of cancer (56.0%), followed by papillary (PC; 40.8%) and chromophobe subtypes (Ch; 3.2%). Due to the low number of Ch cancers, only CCC and PC were included in the following analysis. The median time between cancer diagnosis and transplantation was 38.4 months (17.3–84.3) for CCC and 42.1 months (15.2–102.2) for PC. There was no difference in the clinical characteristics according to the histological subtypes, except for ciclosporin use which was more frequent in patients with CCC (61.9% vs 36.6%; p = 0.01). Most cancers were low stage (stage T1-T2, 94.2%) and low grade (grade 1 or 2, 63.0%) at

TABLE 2 | Immunosuppressive treatments and immunological complications of cases and controls before baseline.

Variables	Patients	
	Cases n = 113	**Controls n = 226**
Induction therapy		
None	2 (1.8)	5 (2.2)
Thymoglobulin	69 (61.1)	134 (59.3)
Anti-IL2-R	42 (37.2)	87 (38.5)
Maintenance IS therapy		
Tacrolimus	50 (44.2)	95 (42.0)
Ciclosporin	58 (51.3)	116 (51.3)
Corticoids	86 (76.1)	166 (73.5)
Mycophenolic acid	85 (75.2)	171 (75.7)
Azathioprine	9 (8.0)	14 (6.2)
mTOR inhibitors	5 (4.4)	18 (8.0)
Belatacept	3 (2.7)	0 (0.0)
Dose/weight mycophenolate mofetil, mg/kg	17.3 (7.3)	16.1 (7.3)
Dose/weight mycophenolate sodium, mg/kg	10.6 (6.0)	13.2 (6.3)
Exposure time to CNI, months	40.8 (15.6–99.6)	44.6 (16.3–91.8)
Exposure time to TIT, months	18.0 (4.8–59.3)	14.6 (4.0–62.3)
Immunological complications		
Allograft nephropathy	10 (8.8)	22 (9.7)
Active-AMR	2 (1.8)	5 (2.2)
Chronic-AMR	1 (0.9)	1 (0.4)
Acute-TCMR	2 (1.8)	8 (3.6)
Acute rejection (type not specified)	6 (5.3)	9 (4.0)
De novo DSA	2 (1.8)	7 (3.1)

Data are expressed as mean (standard deviation) or median (interquartile range) for continuous variables (depending on the normal distribution or not) and number (percentage) for categorial variables. Baseline correspond to date of cancer diagnosis for cases and for controls on the date of cancer of the matched case; IL2R: interleukin-2, receptor; mTOR: mechanistic target of rapamycin; CNI: calcineurin inhibitor; TIT: triple immunosuppressive therapy; AMR: antibody-mediated rejection; TCMR: T cell-mediated rejection; DSA: donor specific antibody. There was no significant difference between cases and controls (p-value >0.05 for all variables).

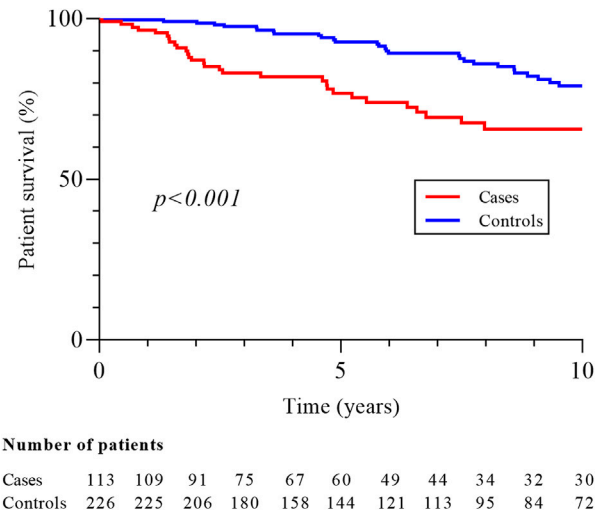


FIGURE 1 | Patient survival in cases and controls groups. Patient survival was measured from baseline, corresponding date of cancer diagnosis for cases and for controls on the date of cancer of the matched case.

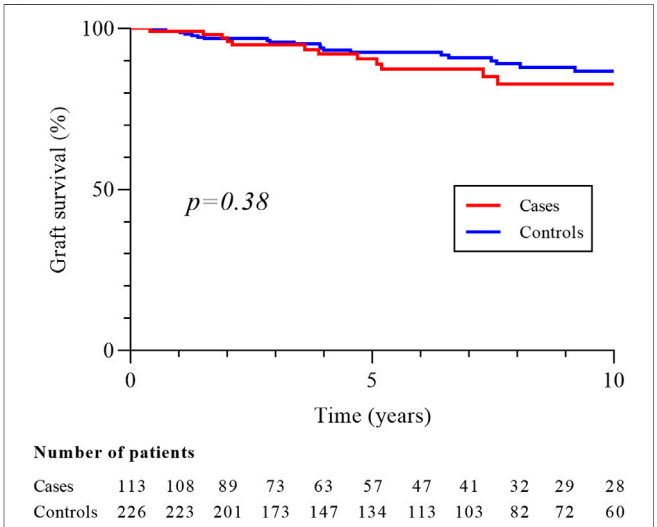


FIGURE 2 | Graft survival in cases and controls groups. Graft survival is censored on patient death and measured from baseline, corresponding date of cancer diagnosis for cases and for controls on the date of cancer of the matched case.

diagnosis in both types of cancer and there was no difference between CCC and PC for tumor size, stage, grade and focality (**Table 3**). Despite this, 10-year survival was worse in patients with CCC (52.8% vs 83.1%, p = 0.007; **Figure 4**), and the rate of cancer-related deaths had a clear tendency to be higher (33.3% vs. 0.0%, p = 0.07).

Treatment and Relapse

All cancers were treated by nephrectomy. A contralateral preventive nephrectomy was performed in 19 patients resulting in the diagnosis of 6 cancers. The immunosuppressive treatment was mostly unmodified after the surgery (68.0%) and 24 patients (19.2%)

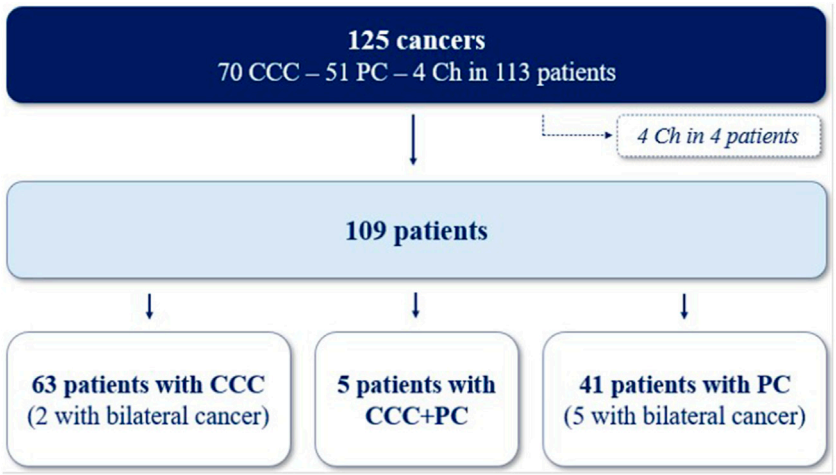


FIGURE 3 | Repartition of 125 cancers in 113 patients. CCC, clear-cell carcinomas; PC, papillary carcinomas; Ch, chromophobes cancers.

TABLE 3 | Histological characteristics of clear-cells and papillary carcinomas.

Variables	Cancers	
	Clear cells n = 70	Papillary n = 51
Tumor size, mm	23.5 (15.5–37.5)	22.0 (15.0–33.0)
TNM stage		
T1-T2	64 (91.4)	50 (98.0)
T3-T4	6 (8.6)	1 (2.0)
N+	1 (1.4)	0 (0.0)
M+	2 (2.9)	0 (0.0)
Grade[a]		
G1-G2	38 (62.3)	25 (64.1)
G3-G4	23 (37.7)	14 (35.9)
Multifocal	12 (17.1)	16 (31.4)

Data are expressed as median (interquartile range) for continuous variables and number (percentage) for categorial variables. Ns: non-significant.
[a]21 patients with unknown histological grade (9 in Clear cells group and 12 in Papillary group) were excluded from the analysis. There was no significant difference between two groups (p-value >0.05 for all variables).

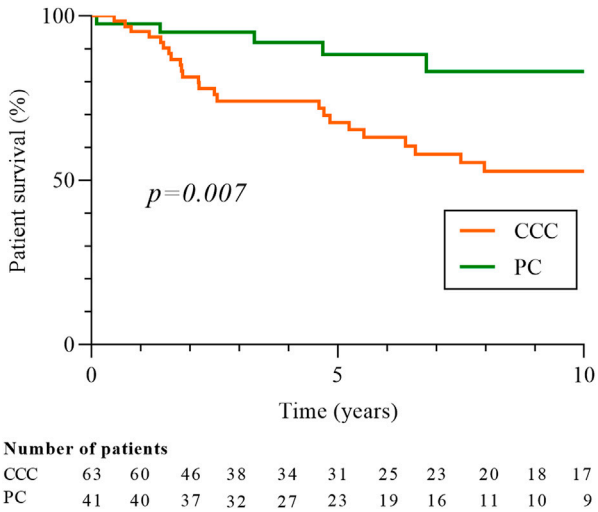


FIGURE 4 | Patients' survival according to histologic type of RCC, clear-cell or papillary carcinomas. Patient survival is measured from date of cancer diagnosis. Five patients with CCC and PC were excluded from the analysis. CCC: clear-cells carcinomas; PC: papillary carcinomas.

were switched to an mTOR inhibitor. Only one patient (with metastatic disease at diagnosis) received anti-angiogenic therapy. Ten patients (9.0%) relapsed after surgery, among whom 9 had metastases (**Table 4**). The median delay of relapse was 9.5 months (4.5–47.7). Patients were mostly men (90.0%), aged over 60 at diagnosis (80.0%) and all these patients had CCC (relapse rate: 16.4% for CCC and 0.0% for PC, p = 0.002). Changes in immunosuppressive treatments after relapse were not different from those across the cohort. This recurrence was treated by antiangiogenic therapy in 4 patients (2 with Sunitinib and 2 unspecified, 40.0%), and by an mTOR inhibitor in 3 (30.0%). Eight patients (80.0%) died after this relapse, mainly due to the progression of RCC (75.0%). The median delay between death and relapse was 24 months (19.7–44.9) and 21.6 months (17.0–27.0) for patients who died from RCC.

Impact of Screening Strategy

Eighty-seven cancers were diagnosed in the 80 patients from the AnS-group and 38 in the 33 patients of the OS-group. The two patients with a history of pre-transplant RCC were in the AnS group, and their screening strategy did not differ from that of the rest of the group. The prevalence of RCC was 2.7% in the AnS-cohort and 0.8% in the OS-cohort (p < 0.0001). The median time between cancer diagnosis and transplantation was 40.5 months (15.3–90.8) in the AnS-group and 46.4 months (21.1–101.5) in the OS-group (p = 0.34). Patients in the AnS-group (compared to-OS group) were younger at baseline (54.7 ± 10.5 vs. 59.5 ± 10.4 years, p = 0.03), more frequently dialyzed before transplantation (97.5% vs. 84.8%, p = 0.01), had more ciclosporin (60.0% vs. 30.3%, p = 0.004), corticoids (81.2% vs. 63.6, p = 0.04), less tacrolimus (33.7% vs. 69.7%, p < 0.001), and a lower dose of mycophenolate mofetil [dose/weight ratio: 14.4

TABLE 4 | Characteristics of patients with relapse.

No	Sex	Age[a]	IT[a]	Histology	Stage	Grade	Relapse (delay)	Treatment	Death (cause)
1	M	63	Cs, MMF, CT	CCC	T1bN0	G2	M+, lung, bones (47 months)	Addition of imTOR	Yes (INF)
2	M	62	Tac, MMF, CT	CCC	T1aN0	G2	M+, pancreas (85 months)	Palliative care	No
3	M	61	Cs, MMF	CCC	T1aN0	G1	M+, lung, liver, bones (6 months)	Stop of Cs for imTOR	Yes (RCC)
4	M	68	Tac, MMF	CCC	T1aN0	G2	M+, lung, bones, brain (12 months)	Stop of MMF	Yes (RCC)
5	M	62	Tac, MS, CT	CCC	T3N0	G4	M+, lung (5 months)	Addition of imTOR	Yes (RCC)
6	M	65	Cs, CT	CCC	T3N0	G3	Local (7 months)	Surgical	Yes (CVD)
7	F	63	Tac, CT	CCC	T1aN0	G3	M+, lung, bones (22 months)	Sunitinib	Yes (RCC)
8	M	44	Cs, MMF, CT	CCC	T3N0	G3	M+, bones (3 months)	Sunitinib	Yes (RCC)
9	M	65	Tac, MMF, CT	CCC	T3N0	G3	M+, pleura (2 months)	AAG	Yes (RCC)
10	M	51	Tac, MMF	CCC	unknown	unknown	M+, bones (50 months)	AAG	No

IT: immunosuppressive treatments; M: male; F: female; Cs: ciclosporin; MMF: mycophenolate mofétil; CT: corticoids; Tac: tacrolimus; CCC: clear-cell carcinoma; M+: metastasis; imTOR: inhibitor of mechanistic target of rapamycin; AAG: anti-angiogenic therapy; INF: infection; RCC: renal cell carcinoma; CVD: cardiovascular disease.
[a]*Data at baseline.*

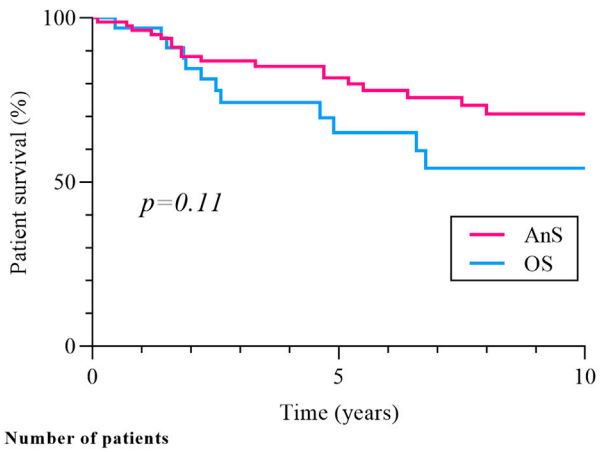


FIGURE 5 | Patients' survival according to screening strategy. Patient survival is measured from date of cancer diagnosis. Ans, annual screening, OS, other strategy.

(11.8–19.9) vs. 17.6 (14.3–25.3) mg/kg, p = 0.02]. Similar to the entire cohort, CCC remained the main histological subtype in each group (57.5% in AnS and 52.6% in OS, p = 0.61). Stage and grade were similar between the two cohorts, but cancers were significantly smaller in the AnS-group [median tumor size: 20.0 (15.5–32.5) vs. 30.0 (20.0–40.0) mm, p = 0.01]. Both patients with metastasis at diagnosis were in the AnS group, at the center alternating CT and ultrasound screening. Their last negative screening test was an ultrasound, performed respectively 3 and 12 months prior to the diagnosis of metastatic RCC. Relapses were less frequent in the AnS group (5.0% vs. 18.2%, p = 0.02) and the time between cancer diagnosis and relapse tended to be longer [29.5 (7.9–75.4) vs. 6.0 (2.7–29.0) months, p = 0.26). Finally, mortality rate (31.2% vs 39.4%, p = 0.40) and 10-year survival (70.3% vs 54.2%, p = 0.11, **Figure 5**] did not differ between the two groups, but the rate of cancer-related deaths was significantly lower in the AnS group (16.0% vs. 46.1%, p = 0.04).

DISCUSSION

This retrospective study reports the characteristics and outcome of 113 patients who presented RCC out of a population of just over 7,000 KTRs in four University Hospitals. One hundred and twenty-five cancers were diagnosed in this population during a 27-year period, mostly clear cell carcinomas at low grade and early stage. We identified two risk factors for the occurrence of native kidney cancer in KTRs: male gender and ACKD. RCC was associated with a reduction in patient survival but did not influence graft survival or immunological complications. Mortality was particularly high in patients with disseminated disease, whether at diagnosis or at relapse. Clear cell carcinoma was associated with a poorer prognosis, reduced survival and increased risk of recurrence compared to papillary carcinoma. We focused on the impact of screening and showed that patients in centers with annual screening had smaller cancers, a lower relapse rate, and a lower rate of cancer-related deaths.

Several studies have analyzed the risk of occurrence of RCC during KT, but most of them included only a small number of patients [16–27]. Moreover, these studies did not compare the characteristics of these patients to a control population, making it impossible to study the risk factors of RCC in KT. This work is, to our knowledge, the first study comparing patients with RCC to a control population of KTRs without RCC and is also one of the cohorts with the largest number of patients.

The recognized risk factors for RCC in the general population are age over 60, male gender, smoking, high blood pressure, obesity, and certain genetic disorders [5–12]. In the present study, only male gender and the presence of ACKD remain associated with an increase-risk of RCC in the multivariate analysis. Several potential RCC risk factors, including smoking quantification and family history, could not be assessed due to missing data inherent to the study design. Several studies have suggested an association between ACKD and RCC, due to the high prevalence of this anomaly in ESRD patients with RCC (70%–90%) [13, 17, 32]. ACKD and its potential link to RCC are not fully understood. Nephron reduction associated with renal failure could lead to the expression of growth factors (such as *Epidermal Growth Factor* and *Hepatocyte Growth Factor*) and proto-oncogenes (such as

c-jun), which can promote the hypertrophy and hyperplasia of tubular cells (contributing to the appearance of cysts), but also the development of RCC [13]. No difference in immunosuppression or immunological complications before baseline was observed between cases and controls. However, our analysis was mainly qualitative, as accurately quantifying immunosuppression remains challenging. Use of emerging biomarkers of immunosuppression levels, like Torque Teno Virus viremia, may offer a better assessment of the link between immunosuppression and RCC development [39, 40].

In line with previous studies RCC were mostly at low stage and low grade, and had a lower rate of relapse than in the general population (30.0%–40.0%) [35]. Despite these good outcomes we also showed that KTRs with RCC had a lower survival rate than controls. However, the higher frequency of males in RCC patients could partly explain this difference. Clear cell carcinomas were particularly associated with a poor prognosis, reflected by more recurrence and a higher mortality than papillary cancers. This poorer outcomes were already reported in the general population and could be related with worse stage and histological grade at diagnosis [41, 42], however we did not highlight any difference on these criteria in our analysis.

All cancers were managed by nephrectomy and no patient received alternative treatment such as radiofrequency ablation, cryotherapy, or active surveillance. Biopsy followed by active surveillance remains a possible option in transplant recipients, especially in frail patients or those with high surgical risk [29]. The management of immunosuppressive therapy after the diagnosis of cancer is an important concern for Transplant-nephrologists. We showed that the overall immunosuppression was modified in one-third of the patients, mainly for the use of a mTOR inhibitor. mTOR inhibitors indeed have immunosuppressive and anti-cancer effects, making them interesting in the treatment of post-transplant cancers [2]. However, the use of mTOR inhibitors in this indication has only been validated in the context of non-melanoma skin cancers and Kaposi sarcoma, moreover these treatments have lower immunosuppressive effects than CNI and can lead to the increase in proteinuria. Furthermore, mTOR inhibitors are used in the general population in the treatment of metastatic RCC, but they are not used as adjuvant treatment of localized cancers. Based on these elements and results of the present study, our opinion is that the use of an mTOR inhibitor in KTRs has a strong rational in the context of metastatic RCC and can be discussed in localized clear cell carcinomas (which have in the present study an increased risk of recurrence and mortality). Conversely, the best prognosis of papillary subtype that we report does not tend to offer these therapies in patients with localized papillary cancer.

The benefit of CRN screening in KTRs remains subject to debate. Although our study was not designed to evaluate the benefit of a screening procedure, we studied the association between the annual screening with abdominal imaging and the outcomes of KTRs with RCC. Our data suggest that annual screening is associated with earlier cancer diagnosis, leading to fewer relapses and fewer cancer-related deaths. However, we were not able to demonstrate a statistical link between annual screening and a better survival. From our point of view, there was a clear trend towards better survival in the AnS-group, and this result could be explained by a lack of statistical power linked to the low numbers in the OS-group. Despite these elements, systematic screening for RCC appears to have several limitations. Indeed, in our study, two patients undergoing annual screening presented with metastasis at diagnosis, and none in the OS-groups. Interestingly, both patients had a negative ultrasound as their last screening test, raising concerns about the sensitivity of this modality for RCC screening in transplant recipients. In addition, 19 preventive nephrectomies (therefore without visible anomaly on imaging) were performed in our study and almost a third of these allowed the incidental diagnosis of another cancer, which may suggest a lack of sensitivity of imaging tests. More of that, Tillou *et al,* presented a series of 21 RCCs from 31 patients in whom an imaging examination (ultrasound or scanner) had detected a suspicious lesion [23]. Here, almost a third of the operated patients (10/31, 32.3%) ultimately did not have cancer, also suggesting a risk of low specificity of imaging tests. Thus, our encouraging results regarding annual screening need to be confirmed in future work and on a larger cohort. Given the existing doubt about the benefit of RCC screening in KTRs, it seems appropriate to target this screening in patients at risk (notably in males and patients with ACKD).

This study has limitations and biases. Due to the retrospective design of the work, there are probably missing or incomplete data, particularly for older ones. We analyzed RCCs occurring after transplantation; however, despite thorough screening before transplantation, some tumors—especially those diagnosed soon after transplantation—may have preexisted. In addition, the high prevalence of native kidney cancer in one of the four centers may cause a "center-effect." More, we had a long study period, which could have led to heterogeneity in the definitions, classifications and patient care. Finally, we presented the outcome of patients with RCC as well as the centers' screening policy but did not collect the type of follow-up after the cancer diagnosis. A difference in monitoring that could interfere with the outcome of patients.

CONCLUSION

This work made it possible to better clarify the characteristics and outcome of kidney transplant recipients who developed native kidney cancer. Most cancers were localized at the time of diagnosis and recurrence after nephrectomy was rare. However, the prognosis of patients with disseminated disease was poor and survival of cases was lower than that of controls. Clear cell carcinomas had a particularly poor prognosis than papillary carcinomas and a modification of immunosuppressive treatment should be discussed. Finally, patients benefiting from annual screening tended to have cancers with better characteristics. The benefit of screening requires studies with larger numbers. As male sex and acquired cystic kidney disease are associated with native kidney cancer, these populations could constitute an interesting target for the screening.

DATA AVAILABILITY STATEMENT

The data analyzed in this study is subject to the following licenses/restrictions: All data are available on request from the corresponding author. Requests to access these datasets should be directed to pommerolle.pierre@chu-amiens.fr.

ETHICS STATEMENT

The studies involving humans were approved by the French Comité de Protection des Personnes Nord Ouest II, n°2011/17. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because, in line with the French legislation on retrospective, non-interventional studies, written consent was not mandatory, all patients were informed about the collection of their data and were free to decline participation in the study.

AUTHOR CONTRIBUTIONS

PP performed data collection. PP and MA performed statistical analysis. All authors contributed to the article and approved the submitted version.

FUNDING

The author(s) declare that no financial support was received for the research and/or publication of this article.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

GENERATIVE AI STATEMENT

The author(s) declare that no Generative AI was used in the creation of this manuscript.

ACKNOWLEDGMENTS

We thank the four centers and the study patients for agreeing to participate.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2025.14487/full#supplementary-material

REFERENCES

1. Piselli P, Serraino D, Segoloni GP, Sandrini S, Piredda GB, Scolari MP, et al. Risk of De Novo Cancers after Transplantation: Results from a Cohort of 7217 Kidney Transplant Recipients, Italy 1997-2009. *Eur J Cancer Oxf Engl* (2013) 49(2):336–44. doi:10.1016/j.ejca.2012.09.013
2. Małyszko J, Bamias A, Danesh FR, Dębska-Ślizień A, Gallieni M, Gertz MA, et al. KDIGO Controversies Conference on Onco-Nephrology: Kidney Disease in Hematological Malignancies and the Burden of Cancer after Kidney Transplantation. *Kidney Int* (2020) 98(6):1407–18. doi:10.1016/j.kint.2020.07.012
3. Vajdic CM, McDonald SP, McCredie MRE, van Leeuwen MT, Stewart JH, Law M, et al. Cancer Incidence before and after Kidney Transplantation. *JAMA* (2006) 296(23):2823–31. doi:10.1001/jama.296.23.2823
4. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer Incidence and Mortality Worldwide: Sources, Methods and Major Patterns in GLOBOCAN 2012. *Int J Cancer* (2015) 136(5):E359–386. doi:10.1002/ijc.29210
5. Levi F, Ferlay J, Galeone C, Lucchini F, Negri E, Boyle P, et al. The Changing Pattern of Kidney Cancer Incidence and Mortality in Europe. *BJU Int* (2008) 101(8):949–58. doi:10.1111/j.1464-410X.2008.07451.x
6. Theis RP, Dolwick Grieb SM, Burr D, Siddiqui T, Asal NR. Smoking, Environmental Tobacco Smoke, and Risk of Renal Cell Cancer: A Population-Based Case-Control Study. *BMC Cancer* (2008) 8:387. doi:10.1186/1471-2407-8-387
7. Zucchetto A, Dal Maso L, Tavani A, Montella M, Ramazzotti V, Talamini R, et al. History of Treated Hypertension and Diabetes Mellitus and Risk of Renal Cell Cancer. *Ann Oncol Off J Eur Soc Med Oncol* (2007) 18(3):596–600. doi:10.1093/annonc/mdl438
8. Deckers IA, van den Brandt PA, van Engeland M, van Schooten FJ, Godschalk RW, Keszei AP, et al. Polymorphisms in Genes of the Renin-Angiotensin-Aldosterone System and Renal Cell Cancer Risk: Interplay with Hypertension and Intakes of Sodium, Potassium and Fluid. *Int J Cancer* (2015) 136(5):1104–16. doi:10.1002/ijc.29060
9. Corrao G, Scotti L, Bagnardi V, Sega R. Hypertension, Antihypertensive Therapy and Renal-Cell Cancer: A Meta-Analysis. *Curr Drug Saf* (2007) 2(2):125–33. doi:10.2174/157488607780598296
10. Gati A, Kouidhi S, Marrakchi R, El Gaaied A, Kourda N, Derouiche A, et al. Obesity and Renal Cancer: Role of Adipokines in the Tumor-Immune System Conflict. *Oncoimmunology* (2014) 3(1):e27810. doi:10.4161/onci.27810
11. Bergström A, Hsieh CC, Lindblad P, Lu CM, Cook NR, Wolk A. Obesity and Renal Cell Cancer--a Quantitative Review. *Br J Cancer* (2001) 85(7):984–90. doi:10.1054/bjoc.2001.2040
12. Ljungberg B, Campbell SC, Choi HY, Jacqmin D, Lee JE, Weikert S, et al. The Epidemiology of Renal Cell Carcinoma. *Eur Urol* (2011) 60(4):615–21. doi:10.1016/j.eururo.2011.06.049
13. Rahbari-Oskoui F, O'Neill WC. Diagnosis and Management of Acquired Cystic Kidney Disease and Renal Tumors in ESRD Patients. *Semin Dial* (2017) 30(4):373–9. doi:10.1111/sdi.12605
14. Barata PC, Rini BI. Treatment of Renal Cell Carcinoma: Current Status and Future Directions. *CA Cancer J Clin* (2017) 67(6):507–24. doi:10.3322/caac.21411
15. Jonasch E, Gao J, Rathmell WK. Renal Cell Carcinoma. *BMJ* (2014) 349:g4797. doi:10.1136/bmj.g4797
16. Neuzillet Y, Lay F, Luccioni A, Daniel L, Berland Y, Coulange C, et al. De Novo Renal Cell Carcinoma of Native Kidney in Renal Transplant Recipients. *Cancer* (2005) 103(2):251–7. doi:10.1002/cncr.20745
17. Filocamo MT, Zanazzi M, Li MV, Guidoni L, Villari D, Dattolo E, et al. Renal Cell Carcinoma of Native Kidney after Renal Transplantation: Clinical

Relevance of Early Detection. *Transpl Proc* (2009) 41(10):4197–201. doi:10.1016/j.transproceed.2009.08.082
18. Moudouni SM, Lakmichi A, Tligui M, Rafii A, Tchala K, Haab F, et al. Renal Cell Carcinoma of Native Kidney in Renal Transplant Recipients. *BJU Int* (2006) 98(2):298–302. doi:10.1111/j.1464-410X.2006.06267.x
19. Leveridge M, Musquera M, Evans A, Cardella C, Pei Y, Jewett M, et al. Renal Cell Carcinoma in the Native and Allograft Kidneys of Renal Transplant Recipients. *J Urol* (2011) 186(1):219–23. doi:10.1016/j.juro.2011.03.032
20. Lee HH, Choi KH, Yang SC, Han WK. Renal Cell Carcinoma in Kidney Transplant Recipients and Dialysis Patients. *Korean J Urol* (2012) 53(4):229–33. doi:10.4111/kju.2012.53.4.229
21. Schwarz A, Vatandaslar S, Merkel S, Haller H. Renal Cell Carcinoma in Transplant Recipients with Acquired Cystic Kidney Disease. *Clin J Am Soc Nephrol CJASN* (2007) 2(4):750–6. doi:10.2215/CJN.03661106
22. Karczewski M, Rzymski P, Karczewski J. De Novo Renal Cell Carcinoma of Native Kidneys in Renal Transplant Recipients: A Single-Center Experience. *Exp Clin Transpl Off J Middle East Soc Organ Transpl* (2012) 10(4):310–3. doi:10.6002/ect.2011.0194
23. Tillou X, Demailly M, Hakami F, Westeel PF, Saint F, Petit J. De Novo Renal Carcinoma in Renal Transplant Recipients: Effect of Early Treatment. *Transpl Proc* (2009) 41(8):3314–6. doi:10.1016/j.transproceed.2009.08.036
24. Klatte T, Seitz C, Waldert M, de Martino M, Kikic Z, Böhmig GA, et al. Features and Outcomes of Renal Cell Carcinoma of Native Kidneys in Renal Transplant Recipients. *BJU Int* (2010) 105(9):1260–5. doi:10.1111/j.1464-410X.2009.08941.x
25. Moris D, Kakavia K, Argyrou C, Garmpis N, Bokos J, Vernadakis S, et al. De Novo Renal Cell Carcinoma of Native Kidneys in Renal Transplant Recipients: A Single-Center Experience. *Anticancer Res* (2017) 37(2):773–9. doi:10.21873/anticanres.11376
26. Gigante M, Neuzillet Y, Patard JJ, Tillou X, Thuret R, Branchereau J, et al. Renal Cell Carcinoma (RCC) Arising in Native Kidneys of Dialyzed and Transplant Patients: Are They Different Entities? *BJU Int* (2012) 110(11 Pt B):E570–573. doi:10.1111/j.1464-410X.2012.11273.x
27. Végsö G, Toronyi E, Hajdu M, Piros L, Görög D, Deák PA, et al. Renal Cell Carcinoma of the Native Kidney: A Frequent Tumor after Kidney Transplantation with Favorable Prognosis in Case of Early Diagnosis. *Transpl Proc* (2011) 43(4):1261–3. doi:10.1016/j.transproceed.2011.03.068
28. Kasiske BL, Snyder JJ, Gilbertson DT, Wang C. Cancer after Kidney Transplantation in the United States. *Am J Transpl Off J Am Soc Transpl Am Soc Transpl Surg* (2004) 4(6):905–13. doi:10.1111/j.1600-6143.2004.00450.x
29. Goujon A, Verhoest G, Sallusto F, Branchereau J, Boutin JM, Bessede T, et al. Renal Cell Carcinoma in Candidates for Renal Transplantation and Recipients of a Kidney Transplant: The French Guidelines from CTAFU. *Progres En Urol J Assoc Francaise Urol Soc Francaise Urol* (2021) 31(1):18–23. doi:10.1016/j.purol.2020.04.030
30. Chewcharat A, Thongprayoon C, Bathini T, Aeddula NR, Boonpheng B, Kaewput W, et al. Incidence and Mortality of Renal Cell Carcinoma after Kidney Transplantation: A Meta-Analysis. *J Clin Med* (2019) 8(4):E530. doi:10.3390/jcm8040530
31. Yanik EL, Clarke CA, Snyder JJ, Pfeiffer RM, Engels EA. Variation in Cancer Incidence Among Patients with ESRD during Kidney Function and Nonfunction Intervals. *J Am Soc Nephrol JASN* (2016) 27(5):1495–504. doi:10.1681/ASN.2015040373
32. Frascà GM, Sandrini S, Cosmai L, Porta C, Asch W, Santoni M, et al. Renal Cancer in Kidney Transplanted Patients. *J Nephrol* (2015) 28(6):659–68. doi:10.1007/s40620-015-0219-8
33. Rodríguez Faba O, Boissier R, Budde K, Figueiredo A, Taylor CF, Hevia V, et al. European Association of Urology Guidelines on Renal Transplantation: Update 2018. *Eur Urol Focus* (2018) 4(2):208–15. doi:10.1016/j.euf.2018.07.014
34. Musso CG, Álvarez-Gregori J, Jauregui J, Macías-Núñez JF. Glomerular Filtration Rate Equations: A Comprehensive Review. *Int Urol Nephrol* (2016) 48(7):1105–10. doi:10.1007/s11255-016-1276-1
35. Bensalah K, Bigot P, Albiges L, Bernhard JC, Bodin T, Boissier R, et al. French ccAFU Guidelines - Update 2020-2022: Management of Kidney Cancer. *Progres En Urol J Assoc Francaise Urol Soc Francaise Urol* (2020) 30(12S):S2–S51. doi:10.1016/S1166-7087(20)30749-1
36. Delahunt B, Eble JN, Egevad L, Samaratunga H. Grading of Renal Cell Carcinoma. *Histopathology* (2019) 74(1):4–17. doi:10.1111/his.13735
37. Paner GP, Stadler WM, Hansel DE, Montironi R, Lin DW, Amin MB. Updates in the Eighth Edition of the Tumor-Node-Metastasis Staging Classification for Urologic Cancers. *Eur Urol* (2018) 73(4):560–9. doi:10.1016/j.eururo.2017.12.018
38. Gray RE, Harris GT. Renal Cell Carcinoma: Diagnosis and Management. *Am Fam Physician* (2019) 99(3):179–84.
39. van Rijn AL, Wunderink HF, Sidorov IA, de Brouwer CS, Kroes AC, Putter H, et al. Torque Teno Virus Loads after Kidney Transplantation Predict Allograft Rejection but Not Viral Infection. *J Clin Virol Off Publ Pan Am Soc Clin Virol* (2021) 140:104871. doi:10.1016/j.jcv.2021.104871
40. Chauvelot L, Barba T, Saison C, Siska E, Kulifaj D, Bakker SJL, et al. Longitudinal Monitoring of Torque Teno Virus DNAemia in Kidney Transplant Recipients Correlates with Long-Term Complications of Inadequate Immunosuppression. *J Med Virol* (2024) 96(7):e29806. doi:10.1002/jmv.29806
41. Bensalah K, Albiges L, Bernhard JC, Bigot P, Bodin T, Boissier R, et al. French ccAFU Guidelines - Update 2018-2020: Management of Kidney Cancer. *Progres En Urol J Assoc Francaise Urol Soc Francaise Urol* (2018) 28(Suppl. 1):R5–R33. doi:10.1016/j.purol.2019.01.004
42. Patard JJ, Verhoest G, Culine S. Prognostic Factors in Localized and in Metastatic Renal Cell Carcinomas. *Progres En Urol J Assoc Francaise Urol Soc Francaise Urol* (2007) 17(5):912–6. doi:10.1016/s1166-7087(07)92387-8

ESOT | Transplant International

ORIGINAL RESEARCH
published: 02 July 2025
doi: 10.3389/ti.2025.14606

A 20-Year Single Center Experience of Right Lateral Sector Graft in Adult Living Donor Liver Transplantation With Special Reference to Biliary Complication

*Tomoaki Hayakawa, Nobuhisa Akamatsu, Takashi Kokudo, Kyoji Ito, Yujiro Nishioka, Yujiro Mihara, Akihiko Ichida, Takeshi Takamoto, Yoshikuni Kawaguchi and Kiyoshi Hasegawa**

Artificial Organ and Transplantation Surgery Division, Department of Surgery, Graduate School of Medicine, University of Tokyo, Tokyo, Japan

Right lateral sector grafts (RLSGs) in living donor liver transplantation (LDLT) expand donor options, however, their long-term outcomes and complication rates remain unclear. We analyzed 661 LDLTs (42 RLSGs, 363 right liver grafts, 243 left liver grafts, and 13 left lateral section grafts) performed between 2000 and 2021 at the University of Tokyo Hospital. RLSG donors experienced a 4.8% major complication (Clavien-Dindo grade ≥3b) rate with no mortality. RLSG recipients had a 38.1% major complication rate and a 9.5% 90-day mortality rate. Compared with other graft types, RLSG recipients had higher rates of hepatic artery thrombosis (9.5% vs. 3.1%), portal vein stenosis (14.3% vs. 1.9%), and biliary stricture (42.9% vs. 16.3%). The 5-year survival rate for RLSG recipients (79.2%) did not differ significantly from other graft types (84.7%). Graft bile ducts measuring >4 mm were associated with increased anastomotic biliary stricture. RLSG, the only option for 33 recipients, expanded the donor pool by 5%. Although RLSG is associated with higher vascular and biliary complication rates, it demonstrates favorable long-term survival and significantly expands the donor pool. For patients without suitable conventional graft options, RLSG represents a viable choice that provides life-saving transplantation opportunities.

Keywords: biliary stricture, living donor liver transplantation (LDLT), right lateral sector graft, donor pool expansion, vascular complication

***Correspondence**
Kiyoshi Hasegawa,
hasegawa-2su@h.u-tokyo.ac.jp

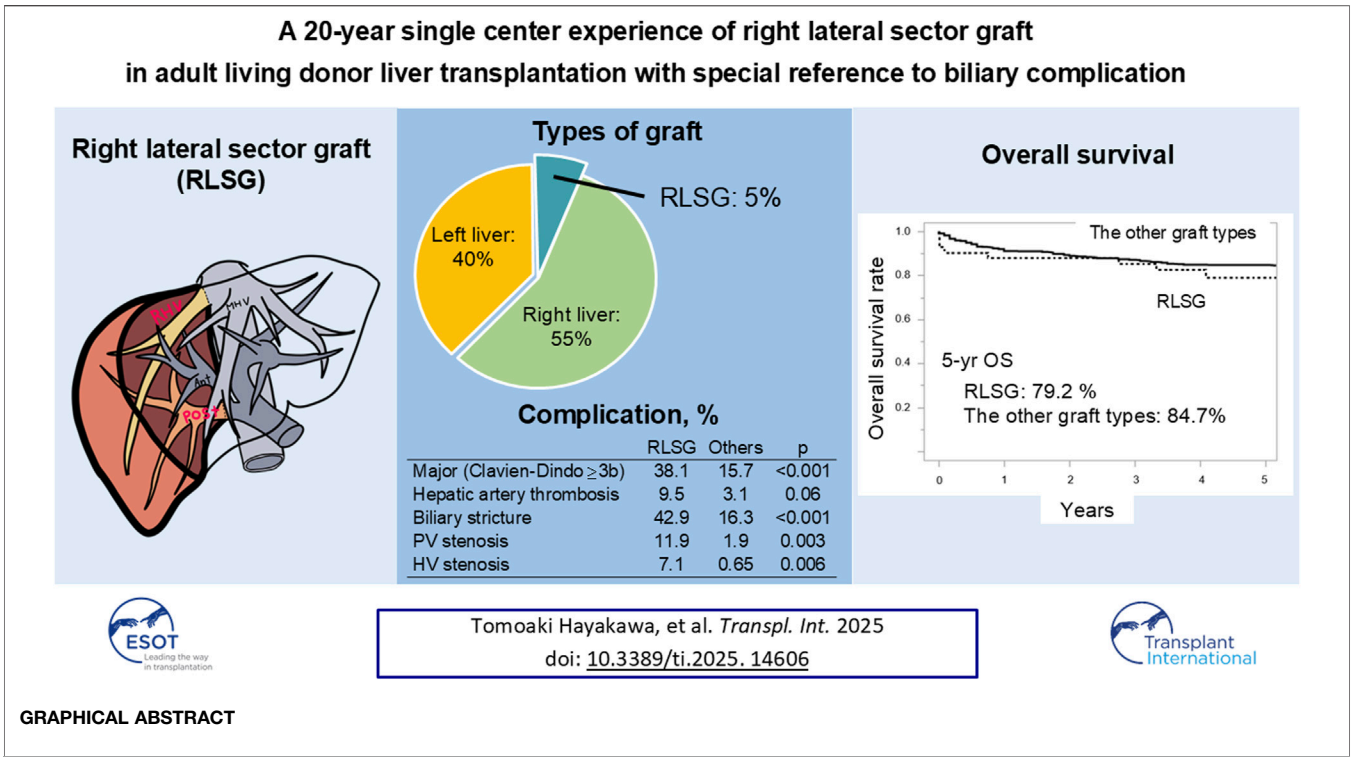
Received: *11 March 2025*
Accepted: *10 June 2025*
Published: *02 July 2025*

Citation:
Hayakawa T, Akamatsu N, Kokudo T, Ito K, Nishioka Y, Mihara Y, Ichida A, Takamoto T, Kawaguchi Y and Hasegawa K (2025) A 20-Year Single Center Experience of Right Lateral Sector Graft in Adult Living Donor Liver Transplantation With Special Reference to Biliary Complication. Transpl. Int. 38:14606. doi: 10.3389/ti.2025.14606

INTRODUCTION

Living donor liver transplantation (LDLT) is often performed in countries with a scarcity of deceased donors [1–4]. The use of left liver grafts in adult LDLT was first reported in the 1990s, considering donor safety [5]. Subsequently, the procurement of right liver grafts began because of the graft volume advantage it comes with [3, 6]. Due to their volume advantage, right liver grafts have become

Abbreviations: HAT, hepatic artery thrombosis; HV, hepatic vein; LDLT, living donor liver transplantation; PV, portal vein; RLSG, right lateral sector graft; SLV, standard liver volume.



GRAPHICAL ABSTRACT

a standard choice for transplantation [7]. However, since the right liver accounts for 60%–75% of the total liver volume, a relatively high incidence of mortality and postoperative liver failure has been reported among right liver graft donors [8], making this option inappropriate for donors whose right liver accounts for more than 70% of the organ's total volume [9].

To address this limitation, our group has previously reported using right lateral sector grafts (RLSGs) for cases where a hemiliver transplant (i.e., right liver grafts or left liver grafts) is inappropriate [10]. Following our initial report, some institutions began to procure RLSGs for LDLT. While we have previously demonstrated the feasibility of RLSGs [11], there is still inadequate data on the long-term outcomes and the extent of donor candidate expansion because of the relatively rare indication and the technical difficulty associated with RLSG procurement. In this study, we aimed to report the feasibility and recipients' long-term outcomes using RLSGs.

PATIENTS AND METHODS

Data Source

In this study, we included 661 LDLTs performed from 2000 to 2021 at the University of Tokyo Hospital. During this study period, the selected graft types were 363 right liver grafts, 243 left liver grafts, 13 left lateral section grafts, and 42 RLSGs. The demographic and clinical data of patients were recorded prospectively and analyzed retrospectively. The detailed eligibility criteria for donors have been described previously [9]. These criteria were [1] age 20–65 years [2], donor-recipient relationship within 3 degrees of consanguinity or spousal, and [3] the absence of significant comorbidities. The study was conducted per the principles outlined in the Declaration of Helsinki and the Declaration of Istanbul. Demographic and clinicopathological characteristics were entered into a computerized database and retrospectively reviewed with the approval of the Graduate School of Medicine and Faculty of Medicine, The University of Tokyo Research Ethics Committee/Institutional Review Board (Approval number: 2140). Patients' informed consent was obtained via opt-out on the website (http://plaza.umin.ac.jp/htokyotransplant/results/index.html).

Graft Type Selection Criteria

All donor candidates underwent abdominal ultrasonography to exclude fatty liver. A needle biopsy was performed if fatty liver was suspected, and regarding the degree of macrovascular steatosis, 10% was the criterion for donors. All donors had normal indocyanine green retention rates at 15 min. Graft types were selected based on the recipient's standard liver volume (SLV) and the donor's remnant liver volume. The graft selection algorithm is shown in **Figure 1** [9]. First, left liver procurement was considered if the graft volume exceeded 35% of the recipient's SLV. Second, right liver procurement was indicated if the donor's remnant liver volume exceeded 30% of the total liver volume. Finally, we considered using an RLSG, provided the RLSG volume was more than 35% of the recipient's SLV. Apart from the selection criteria, there were cases where RLSG was chosen due to anatomical factors, such as the unique branching of the portal vein (PV) in the right posterior section,

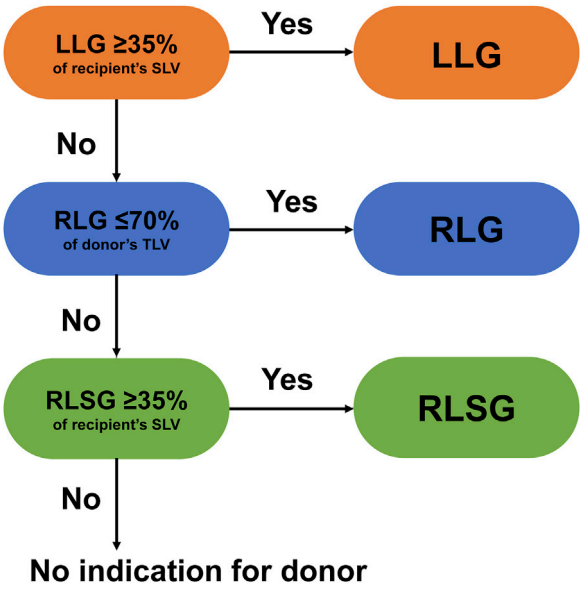


FIGURE 1 | Algorithm for liver graft type selection at the University of Tokyo Hospital [9].

even if the remnant liver volume met our eligibility criteria for right liver graft. While all donors underwent magnetic resonance cholangiopancreatography, when considering an RLSG, additional drip infusion cholecystocholangiography computed tomography was performed to rule out anomalies in the posterior bile duct that could make for unsuccessful transplantations. In nine out of the 42 RLSG cases, left liver graft or right liver graft could be selected; however, they used RLSG for favorable anatomical reasons.

Donor Hepatectomy

The surgical procedure for living donor liver procurement has previously been described in detail [7]. A J-shaped incision was made to procure RLSGs. After cholecystectomy, we performed extrahepatic hilar dissection to isolate the right posterior hepatic artery and the PV (**Supplementary Figure S1**). The root of the right hepatic vein is exposed, and the short hepatic veins are ligated and divided. The middle and inferior right hepatic veins were preserved and divided before graft procurement. Next, the right posterior PV and artery were isolated and taped. The bile duct's anatomy was confirmed using intraoperative cholangiography (**Supplementary Figure S2**). A demarcation line was identified after clamping the right posterior hepatic artery and PV. Finally, under Pringle's maneuvers, liver resection was performed under ultrasound guidance.

Recipient Surgery

The surgical procedure for recipients has previously been described in detail [10, 12, 13]. After total hepatectomy, the graft's hepatic vein (HV) with patch plasty was anastomosed to the recipient's inferior vena cava. When the graft contained a thick inferior right hepatic vein or middle right hepatic vein, we used the double inferior vena cava method to reconstruct these veins [14]. Subsequently, the right posterior PV was anastomosed to the recipient's right or main PV with 6-0 polypropylene continuous sutures, and the plastic surgeons anastomosed the hepatic artery under a microscope with 7-0 nylon interrupted sutures. Then, duct-to-duct or hepaticojejunostomy anastomosis was performed for the bile duct [15, 16]. For the duct-to-duct anastomosis, the posterior wall was anastomosed with continuous sutures using 6-0 polydioxanone, while the anterior wall was anastomosed with interrupted sutures using 5-0 polydioxanone. Hepaticojejunostomy was performed using interrupted sutures with 5-0 polydioxanone for both walls. Stents were placed inside all anastomoses.

TABLE 1 | Baseline characteristics and perioperative outcomes of right lateral sector graft donors and recipients.

Characteristics of donor	RLSG donor (n = 42)	Characteristics of recipient	RLSG recipient (n = 42)
Characteristics		Characteristics	
Age, yr	42 (30–49)	Age, yr	47 (32–56)
Sex (male/female)	25/17 (60.0/40.0)	Sex (male/female)	17/25
BMI, kg/m^2	23.3 (21.2–25.4)	Adult/Child	37/5
Operative data		BMI, kg/m^2	21.8 (19.2–24.6)
Operation time, min	525 (449–567)	MELD score	15.6 (12.6–20.9)
Blood loss, mL	543 (378–763)	Operative data	
Graft volume, g	458 (402–516)	Operation time, min	857 (745–968)
Hospital stay, days	14 (11–18)	Blood loss, ml	4,133 (2848–7,378)
Complication		Graft volume, g	458 (402–516)
Minor[a]	14 (33.3)	Graft-to-recipient SLV ratio, %	40.9 (36.6–46.1)
bile leakage	6 (14.3)		
Major[a]	2 (4.8)		
re-operation for postoperative bleeding	1 (2.4)		
Heart failure	1 (2.4)		
Death within 90 days	0 (0)		
Postoperative bile leakage	10 (23.8)		

Values are median (inter quartile range) or n (%).

[a]*minor complication was defined as Clavien-Dindo classification ≤3a, major complication was defined as ≥3b.*

Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase; PT-INR, prothrombin time-international normalized ratio; BMI, body mass index; MELD, model for end-stage liver disease; BMI, body mass index; MELD, model for end-stage liver disease.

TABLE 2 | Comparison of recipient characteristics and outcomes between right lateral sector and other grafts.

Characteristics	RLSG (n = 42)	Other graft types (n = 619)	OR	95% CI	p
Characteristics and graft data					
Age, yr	47 (32–56)	52 (43–58)	-	-	0.03
Sex, male/female (%)	17/25 (40.5/59.5)	336/283 (54.3/45.7)	-	-	0.08
BMI, kg/m^2	21.8 (19.6–23.9)	22.7 (20.2–25.2)	-	-	0.12
MELD score	15.6 (12.7–20.5)	16.6 (13.0–21.0)	-	-	0.60
Operation time, min	857 (745–968)	833 (744–925)	-	-	0.69
Blood loss, ml	4,133 (2848–7,378)	4,830 (3,000–7,220)	-	-	0.45
Graft volume, g	458 (402–516)	518 (439–614)	-	-	<0.001
Graft volume/SLV ratio, %	41.1 (37.0–46.5)	44.0 (39.0–51.8)	-	-	0.02
GRWR, %	0.81 (0.69–0.93)	0.86 (0.73–1.02)	-	-	0.10
Postoperative complication					
Major[a]	16 (38.1)	97 (15.7)	3.31	1.71–6.40	<0.001
HAT	4 (9.5)	19 (3.1)	3.32	0.93–9.38	0.06
Biliary leakage	10 (23.8)	71 (11.5)	2.41	1.09–4.98	0.03
Biliary stricture	18 (42.9)	101 (16.3)	3.85	1.99–7.32	<0.001
PV stenosis	5 (11.9)	12 (1.9)	6.84	2.29–20.4	0.003
HV stenosis	3 (7.1)	4 (0.65)	11.8	2.27–55.5	0.006
90 days survival rate, %	90.5	96.6	3.00	0.84–8.37	0.08
Re-transplantation	1 (2.4)	4 (0.6)	3.89	0.20–27.0	0.30
Survival rates					
1-year survival rate, %	88.1	91.0	-	-	0.23
5-year survival rate, %	79.2	84.7	-	-	0.17

Values are median (interquartile range) or n (%).

[a]*Major complication was defined as Clavien-Dindo classification ≥3b.*

Abbreviations: RLSG, right lateral sector graft; GRWR, graft-to-recipient body weight ratio; MELD, model for end-stage liver disease; HAT, hepatic artery thrombosis; HV, hepatic vein; PV, portal vein.

Definition of Postoperative Complications and Posttransplant Management

According to the Clavien–Dindo classification, postoperative abdominal complications were recorded and graded [17]. In this study, complications graded as ≤3a were minor, while those graded as ≥3b were major. Because minor complications were frequent among LDLT recipients, we concentrated on the major complication rate and the mortality rate. The diagnosis of biliary leakage was based on the definition of the International Study Group of Liver Surgery [18]. Anastomotic biliary stricture was suspected based on a laboratory test or US/computed tomography images and confirmed by direct cholangiography via endoscopic retrograde cholangiography. We first diagnosed and treated the anastomotic biliary stricture via endoscopic retrograde cholangiography, followed by percutaneous transhepatic biliary drainage if necessary. We performed Doppler US twice daily for 2 weeks postoperatively to confirm adequate hepatic circulation and to detect hepatic artery thrombosis (HAT), PV stenosis, and HV stenosis. Protocol multidetector computed tomography was performed 1, 3, and 12 months after LDLT, and additional imaging studies were conducted based on clinical and laboratory findings. Biliary stents were removed 2–3 months after LDLT.

Era Classification for the Technical Assessment

To assess the learning curve and technical evolution of this challenging procedure over time, we divided our 20-year experience with RLSG transplantation (2000–2021) into two equal periods: Era 1 (2000–2011) and Era 2 (2012–2021). This division enabled us to evaluate improvements in surgical times, complication rates, and postoperative outcomes as our surgical team accumulated experience with the technique.

Statistical Analysis

All statistical analyses were performed using JMP 18.0.1 (SAS Institute Inc., Cary, NC) software. Continuous variables were presented as median values with interquartile ranges. Categorical variables were presented as frequencies and percentages and analyzed using the chi-square or the likelihood ratio test, as appropriate. Continuous variables were analyzed with the Mann–Whitney U test. Survival curves were drawn using the Kaplan–Meier method and compared with the log-rank test. All statistical analyses were two-tailed, and p-values of <0.05 were considered statistically significant.

RESULTS

Among 661 LDLTs performed between 2000 and 2021, 42 (6.4%) utilized RLSGs, with RLSG being the only viable option for 33 recipients (5%) according to our institutional criteria. The median follow-up period was 88 months (range: 0–272).

Donor and Recipient Characteristics

RLSG donors (n = 42) had a median age of 42 years, with operation times of 525 min and blood loss of 543 mL (**Table 1**). The major complication (Clavien-Dindo grade ≥3b) rate was 4.8% (n = 2), with no mortality. Minor complications (Clavien-Dindo grade ≤3a) occurred in 33.3% (n = 14), with bile

TABLE 3 | Detailed summary of vascular and biliary stricture after right lateral sector grafts: onset, treatment, and outcomes.

Complication	Patient no.	Era	Postoperative day	Detail of treatment	Death within 90 days
Vascular complication					
HAT	1	1	3	Observation	Yes
	2		0	Re-operation	No
	3		19		No
	4		5		No
PV stenosis	1	1	1008	PTA	No
	2 (same as patient No.1 of HAT)		3	Observation	Yes
	3		1618	PTA	No
	4	2	6	Stent placement	Yes
	5		277		No
HV stenosis	1	2	776	Stent placement	No
	2		292		No
	3		119		No
Biliary stricture					
duct-to-duct	1	1	1535	External biliary drainage	No
	2		3	Re-operation	No
	3		816	Re-operation	No
	4		625	Inside stent placement	No
	5		216	Inside stent placement	No
	6		48	External biliary drainage	No
	7	2	107	External biliary drainage	No
	8		108	Inside stent placement	No
	9		84	Inside stent placement	No
	10		118	External biliary drainage	No
	11		72	Inside stent placement	No
	12		26	Inside stent placement	No
	13		95	Re-operation	No
	14		179	Inside stent placement	No
Hepaticojejunostomy	1	1	566	External biliary drainage	No
	2		790	Re-operation	No
	3		178	Re-operation	No
	4	2	139	Inside stent placement	No

Abbreviations: HAT, hepatic artery thrombosis; PV, portal vein; HV, hepatic vein; PTA, percutaneous transluminal angioplasty.

leakage being the most common (14.3%, n = 6). All donors recovered completely with no long-term sequelae. Recipients had a median age of 47 years and MELD score of 15.6. The median graft volume was 458g, representing 40.9% of the recipient's standard liver volume (**Table 1**).

Comparative Outcomes

Compared to other graft types, RLSG recipients experienced significantly higher rates of major complications (38.1% vs. 15.7%, OR = 3.31, p < 0.001) and vascular complications (**Table 2**). These included portal vein stenosis (11.9% vs. 1.9%, OR = 6.84, p = 0.003), hepatic vein stenosis (7.1% vs. 0.65%, OR = 11.8, p = 0.006), and a trend toward higher hepatic artery thrombosis (9.5% vs. 3.1%, OR = 3.32, p = 0.06).

Vascular Complications in RLSG

HAT occurred in 4 patients (9.5%), all in Era 1, with two cases resulting in early mortality. PV stenosis was observed in 5 patients (11.9%), occurring between postoperative day 3 and 1,618, with two cases resulting in mortality. Three cases (7.1%) of HV stenosis were reported, all in Era 2, occurring between postoperative day 119 and 776, with one case requiring stent placement (**Table 3**).

Biliary Complications

Biliary complications were notably higher in RLSG recipients, with stricture rates of 42.9% versus 16.3% in other grafts (OR = 3.85, p < 0.001) and leakage rates of 23.8% versus 11.5% (OR = 2.41, p = 0.03). Univariate analysis identified graft bile duct length >4 mm as a significant risk factor for anastomotic biliary stricture (OR = 8.85, p = 0.03; **Table 4**).

Anatomical analysis revealed that low right lateral sectoral duct-common hepatic duct junction variants (n = 10) had the highest rates of biliary complications, with 60% developing strictures and 20% experiencing severe leakage. This variant was also associated with a higher proportion of grafts with bile duct length >4 mm (40%) compared to standard right hepatic duct formation (4.2%; **Table 5**).

Long-Term Outcomes

Despite higher complication rates, RLSG recipients showed comparable long-term outcomes to other graft types (**Figure 2**). The 90-day mortality rate was 9.5% (n = 4), with causes detailed in **Supplementary Table S2**. Re-transplantation was required in one RLSG recipient (2.4%) and in four recipients (0.6%) with other graft types (p = 0.30). The 5-year survival rate

TABLE 4 | Univariate analysis of risk factors for biliary stricture in right lateral sector graft recipients.

Factor	No. of patients	No. of events	Univariate analysis		
			OR	95% CI	p
Patient factors					
Recipient age, yr	-	-	1.02	0.98–1.07	0.29
Sex	-	-			
Male	17	8	1.33	0.38–4.62	0.65
Female	25	10		reference	
BMI, kg/m^2	-	-	1.06	0.90–1.25	0.50
MELD score	-	-	0.95	0.87–1.04	0.26
Operation time, min	-	-	1.00	0.99–1.00	0.17
Blood loss, ml	-	-	1.00	1.00–1.00	0.09
Graft volume, g	-	-	1.00	0.99–1.01	0.77
Graft volume/SLV ratio, %	-	-	0.97	0.91–1.05	0.47
GRWR, %	-	-	0.30	0.02–3.97	0.32
CIT	-	-	0.99	0.97–1.00	0.16
WIT	-	-	0.98	0.95–1.00	0.12
incompatible ABO	2	2	-	-	-
ACR	17	9	2.00	0.57–7.01	0.276
Biliary anastomosis					
Graft bile duct length, mm					
>4	6	5	8.85	1.25–179	0.03
≤4	36	13		reference	
Graft bile duct diameter, mm	-	-	1.23	0.78–1.95	0.31
Number of anastomoses	-	-	0.63	0.08–3.67	0.61
Duct-to-duct anastomosis	30	14	1.75	0.45–7.74	0.43
Hepaticojejunostomy	12	4		reference	

Abbreviations: OR, odds ratio; CI, confidence intervals; BMI, body mass index; MELD, model for end-stage liver disease; SLV, standard liver volume; GRWR, graft-to-recipient body weight ratio; CIT, cold ischemia time; WIT, warm ischemia time; ACR, acute cellular rejection; SLV, standard liver volume; GRWR, graft-to-recipient body weight ratio; CIT, cold ischemia time; WIT, warm ischemia time; ACR, acute cellular rejection.

TABLE 5 | Comparison of biliary complications according to bile duct anatomical variants.

Anatomy	N	Biliary stricture, n (%)	Biliary leakage C-D ≥3a n (%)	Graft bile duct length >4 mm, n (%)
Standard RHD formation	24	9 (37.5)	2 (8.3)	1 (4.2)
RLSD–LHD junction	5	2 (40.0)	1 (20.0)	1 (20.0)
RLSD–LHD–RASD trifurcation	3	1 (33.3)	0 (0.0)	0 (0.0)
Low RLSD–CHD junction	10	6 (60.0)	2 (20.0)	4 (40.0)

Abbreviations: RHD, right hepatic duct; RLSD, right lateral sectoral duct; LHD, left hepatic duct; RASD, right anterior sectoral duct; CHD, common hepatic duct.

was 79.2% for RLSG recipients versus 84.7% for other graft types (p = 0.17).

Era Analysis

Comparing Era 1 (2000–2011) to Era 2 (2012–2021), we observed significant improvements in operative times for both donors (563 vs. 440 min, p < 0.001) and recipients (933 vs. 724 min, p < 0.001). Notably, hepatic artery thrombosis occurred exclusively in Era 1 (15.4% vs. 0%, p = 0.04), while hepatic vein stenosis was only observed in Era 2 (0% vs. 18.8%, p = 0.01; **Supplementary Table S1**).

DISCUSSION

This study represents the largest single-center experience of RLSG in LDLT, comprising 42 cases over 20 years. Through this extensive experience, we identified that RLSG recipients had significantly higher rates of vascular and biliary complications compared with other graft types, despite successfully expanding the donor pool by 5%.

Biliary Complications

Our analysis identified that graft bile ducts measuring >4 mm were significantly associated with anastomotic biliary stricture, particularly in cases with low right lateral sectoral duct-common hepatic duct junction. While surgeons traditionally consider this anatomical variant advantageous for RLSG procurement due to the ease of preserving a longer bile duct, our findings demonstrate that these longer ducts paradoxically increase the risk of stricture formation. This may be attributed to potentially compromised blood supply to the distal bile duct and/or increased risk of bile duct kinking at the anastomosis site. Based on these findings, we propose shortening the bile duct to maintain the anastomosis within the hilar plate, which may provide better blood supply to the

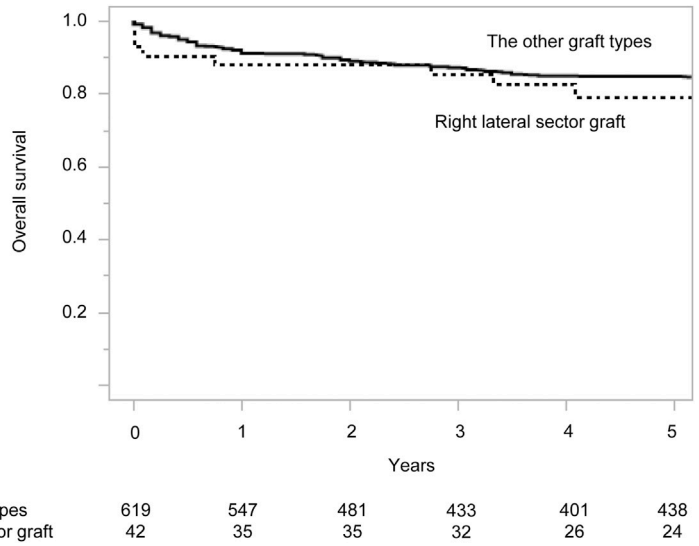


FIGURE 2 | Overall survival of living donor liver transplantation recipients according to graft type. Numbers below the x-axis indicate the number of at-risk patients.

anastomosis and potentially reduce the risk of bile duct kinking. However, we have not yet implemented this modified approach; therefore, its effectiveness remains to be evaluated in future studies.

Vascular Complications

Our cohort demonstrated significantly higher rates of vascular complications, including HAT (9.5% vs. 3.1%), PV stenosis (14.3% vs. 1.9%), and HV stenosis (7.1% vs. 0.65%) compared to other graft types. The increased risk of HV stenosis might be attributable to unique anatomical features: the RHV runs beneath the graft's raw surface, making it vulnerable to inflammatory changes, and the venous anastomosis alignment can be distorted during graft regeneration. Notably, while HAT occurred exclusively in Era 1, suggesting improvements in surgical technique over time, PV stenosis—not previously reported in RLSG studies—emerged as a significant complication requiring careful attention during reconstruction.

Era Analysis and Technical Evolution

The comparison between Era 1 (2000–2011) and Era 2 (2012–2021) revealed significant improvements in surgical efficiency: operative times decreased substantially for both donors (563 vs. 440 min, $p < 0.001$) and recipients (933 vs. 724 min, $p < 0.001$). Additionally, donors' hospital stays were significantly shorter in Era 2 (15 vs. 11 days, $p = 0.006$). Most notably, HAT, which occurred in 15.4% of cases in Era 1, was completely eliminated in Era 2 ($p = 0.04$), demonstrating the successful refinement of our surgical technique. However, the overall major complication rates remained comparable between eras (43.8% vs. 34.6%, $p = 0.56$), suggesting that while certain technical aspects improved over time, the intrinsic challenges of RLSG transplantation persist.

Long-Term Outcomes and Donor Pool Expansion

Despite these technical challenges, our 1-year survival rate for RLSG recipients was 88.1%, consistent with previous reports (57.1%–100%) [19–21]. The 1-year survival rate for recipients of other graft types in our cohort was 91.0%, which did not differ significantly from RLSG recipients. Our 5-year survival rate of 79.2% for RLSG recipients was also comparable to previously reported RLSG survival rates (50%–100%) [20–22]. Among 661 LDLTs performed at our institution, RLSG was the only viable option in 33 cases, effectively expanding our donor pool by 5%.

This study has several limitations that are worth mentioning. Being a single-center retrospective study, its results still need to be validated in a multicenter prospective cohort study. The study period spans over 20 years, during which surgical techniques and perioperative management have evolved significantly, potentially affecting the outcomes and complication rates reported herein. These improvements include refinements in vascular reconstruction techniques, advancements in postoperative monitoring protocols, and developments in immunosuppressive regimens—all of which may have contributed to the differences observed between Era 1 and Era 2. In addition, there may have been selection bias in the decision-making process for RLSG, although we followed our institutional algorithm for graft type selection.

Thus, while RLSG transplantation successfully expanded our donor pool by 5%, our analyses revealed two critical findings that impact surgical strategy: first, preservation of longer bile ducts (>4 mm) significantly increases the risk of biliary complications, particularly in cases with low right lateral sectoral duct-common hepatic duct junction; second, RLSG recipients face a notably higher risk of portal vein stenosis than previously reported. These findings suggest that surgical success with RLSG could be

improved by minimizing bile duct length and paying particular attention to portal vein reconstruction.

CONCLUSION

RLSG transplantation represents a viable option for expanding the donor pool in living LDLT, demonstrating comparable long-term survival outcomes despite higher complication rates. While technical refinements over two decades have improved surgical efficiency and reduced certain complications, careful attention to anatomical factors - particularly biliary and vascular reconstruction - remains crucial for optimal outcomes. This procedure offers a valuable alternative for patients who would otherwise lack suitable donors, but its successful implementation requires surgical technique and careful patient selection.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving humans were approved by Graduate School of Medicine and Faculty of Medicine, The University of Tokyo Research Ethics Committee/Institutional Review Board. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required from the participants or the participants' legal guardians/next of kin because This was a retrospective study using existing clinical data, and informed consent was obtained via opt-out method on the institutional website as approved by the ethics committee (approval number: 2140). The opt-out approach was deemed appropriate for this type of retrospective data analysis in accordance with institutional guidelines.

AUTHOR CONTRIBUTIONS

Concept and design: TH, TK, NA. Acquisition of data: TH, NA, TK, KI, YN, YM, AI, TT, YK, and KH. Analysis and interpretation of data: TH, TK, NA. Drafting the article: TH, TK, NA. Critical revision of the article for important intellectual content: TH, NA, TK, KI, YN, YM, AI, TT, YK, and KH. All authors contributed to the article and approved the submitted version

FUNDING

The author(s) declare that financial support was received for the research and/or publication of this article. This work was supported by JSPS KAKENHI Grant Number JP 23K08149.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

GENERATIVE AI STATEMENT

The author(s) declare that no Generative AI was used in the creation of this manuscript.

ACKNOWLEDGMENTS

Meeting presentation: A preliminary version of this work was presented at the Asian Transplantation Week, November 2022, Seoul, Korea.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2025.14606/full#supplementary-material

SUPPLEMENTARY FIGURE S1 | Intraoperative view of extrahepatic hilar dissection and isolation of the posterior branch of the right hepatic artery and right portal vein.

SUPPLEMENTARY FIGURE S2 | Intraoperative cholangiography images showing the right hepatic duct's anterior and posterior branches.

SUPPLEMENTARY FIGURE S3 | Various patterns of bile duct branching: **(a)** Standard right hepatic duct formation, **(b)** right lateral sectoral duct-left hepatic duct junction, **(c)** right lateral sectoral duct-left hepatic duct-right anterior sectoral duct trifurcation, and **(d)** low right lateral sectoral duct-common hepatic duct junction.

REFERENCES

1. Chen C-L, Fan S-T, Lee S-G, Makuuchi M, Tanaka K. Living-Donor Liver Transplantation: 12 Years of Experience in Asia. *Transplantation* (2003) 75(3 Suppl. l):S6–11. doi:10.1097/01.TP.0000046533.93621.C7
2. Akamatsu N, Sugawara Y, Kokudo N. Living Donor Liver Transplantation for Patients with Hepatocellular Carcinoma. *Liver Cancer* (2014) 3(2):108–18. doi:10.1159/000343866
3. Strong RW, Lynch SV, Ong TH, Matsunami H, Koido Y, Balderson GA. Successful Liver Transplantation from a Living Donor to Her Son. *N Engl J Med* (1990) 322(21):1505–7. doi:10.1056/NEJM199005243222106
4. Middleton PF, Duffield M, Lynch SV, Padbury RTA, House T, Stanton P, et al. Living Donor Liver Transplantation--Adult Donor Outcomes: A Systematic Review. *Liver Transpl* (2006) 12(1):24–30. doi:10.1002/lt.20663
5. Hashikura Y, Makuuchi M, Kawasaki S, Matsunami H, Ikegami T, Nakazawa Y, et al. Successful Living-Related Partial Liver Transplantation to an Adult Patient. *Lancet* (1994) 343(8907):1233–4. doi:10.1016/s0140-6736(94)92450-3

6. Yamaoka Y, Washida M, Honda K, Tanaka K, Mori K, Shimahara Y, et al. Liver Transplantation Using a Right Lobe Graft from a Living Related Donor. *Transplantation* (1994) 57(7):1127–9. doi:10.1097/00007890-199404150-00024
7. Kokudo N, Sugawara Y, Imamura H, Sano K, Makuuchi M. Tailoring the Type of Donor Hepatectomy for Adult Living Donor Liver Transplantation. *Am J Transpl* (2005) 5(7):1694–703. doi:10.1111/j.1600-6143.2005.00917.x
8. Muzaale AD, Dagher NN, Montgomery RA, Taranto SE, McBride MA, Segev DL. Estimates of Early Death, Acute Liver Failure, and Long-Term Mortality Among Live Liver Donors. *Gastroenterology* (2012) 142(2):273–80. doi:10.1053/j.gastro.2011.11.015
9. Akamatsu N, Kokudo N. Living Liver Donor Selection and Resection at the University of Tokyo Hospital. *Transpl Proc.* (2016) 48(4):998–1002. doi:10.1016/j.transproceed.2016.01.019
10. Sugawara Y, Makuuchi M, Takayama T, Imamura H, Kaneko J. Right Lateral Sector Graft in Adult Living-Related Liver Transplantation. *Transplantation* (2002) 73(1):111–4. doi:10.1097/00007890-200201150-00021
11. Kokudo T, Hasegawa K, Arita J, Yamamoto S, Kaneko J, Akamatsu N, et al. Use of a Right Lateral Sector Graft in Living Donor Liver Transplantation Is Feasible, but Special Caution Is Needed with Respect to Liver Anatomy. *Am J Transpl* (2016) 16(4):1258–65. doi:10.1111/ajt.13604
12. Kaneko J, Sugawara Y, Akamatsu N, Kishi Y, Niiya T, Kokudo N, et al. Prediction of Hepatic Artery Thrombosis by Protocol Doppler Ultrasonography in Pediatric Living Donor Liver Transplantation. *Abdom Imaging* (2004) 29(5):603–5. doi:10.1007/s00261-003-0156-1
13. Kyoden Y, Tamura S, Sugawara Y, Akamatsu N, Matsui Y, Togashi J, et al. Biliary Complications in Right Lateral Sector Graft Live Donor Liver Transplantation. *Transpl Int* (2008) 21(4):332–9. doi:10.1111/j.1432-2277.2007.00613.x
14. Sugawara Y, Makuuchi M, Imamura H, Kaneko J, Kokudo N. Outflow Reconstruction in Extended Right Liver Grafts from Living Donors. *Liver Transpl* (2003) 9(3):306–9. doi:10.1053/jlts.2003.50021
15. Sugawara Y, Matsui Y, Noritomi T, Kaneko J, Makuuchi M. Safe Bile Duct Division in Right Lateral Sector Graft. *Hepatogastroenterology* (2005) 52(61):170–2.
16. Dulundu E, Sugawara Y, Sano K, Kishi Y, Akamatsu N, Kaneko J, et al. Duct-to-Duct Biliary Reconstruction in Adult Living-Donor Liver Transplantation. *Transplantation* (2004) 78(4):574–9. doi:10.1097/01.tp.0000128912.09581.46
17. Dindo D, Demartines N, Clavien P-A. Classification of Surgical Complications: A New Proposal with Evaluation in a Cohort of 6336 Patients and Results of a Survey. *Ann Surg* (2004) 240(2):205–13. doi:10.1097/01.sla.0000133083.54934.ae
18. Koch M, Garden OJ, Padbury R, Rahbari NN, Adam R, Capussotti L, et al. Bile Leakage after Hepatobiliary and Pancreatic Surgery: A Definition and Grading of Severity by the International Study Group of Liver Surgery. *Surgery* (2011) 149(5):680–8. doi:10.1016/j.surg.2010.12.002
19. Hwang S, Lee S-G, Lee Y-J, Park K-M, Kim K-H, Ahn C-S, et al. Donor Selection for Procurement of Right Posterior Segment Graft in Living Donor Liver Transplantation. *Liver Transpl* (2004) 10(9):1150–5. doi:10.1002/lt.20225
20. Kim B-W, Xu W, Wang H-J, Park Y-K, Lee K, Kim M-W. Volumetry-Based Selection of Right Posterior Sector Grafts for Adult Living Donor Liver Transplantation. *Liver Transpl* (2011) 17(9):1046–58. doi:10.1002/lt.22338
21. Hori T, Kirino I, Uemoto S. Right Posterior Segment Graft in Living Donor Liver Transplantation. *Hepatol Res* (2015) 45(11):1076–82. doi:10.1111/hepr.12469
22. Yoshizumi T, Ikegami T, Kimura K, Uchiyama H, Ikeda T, Shirabe K, et al. Selection of a Right Posterior Sector Graft for Living Donor Liver Transplantation. *Liver Transpl* (2014) 20(9):1089–96. doi:10.1002/lt.23924

ESOT | Transplant International

LETTER TO THE EDITOR
published: 31 July 2025
doi: 10.3389/ti.2025.14664

BK Virus: Beyond Nephropathy Metastatic BK Virus-Induced, Donor-Derived Bellini's Carcinoma in a Kidney Allograft Recipient: Boosting Rejection to Treat the Cancer

*Flora Lefevre[1], Mélanie Benoit-Janin[2], Emilien Seizilles-de-Mazancourt[3], Xavier Matillon[3], Fanny Buron[4], Alice Koenig[4], Valérie Dubois[5], Matthieu Dietz[6], Olivier Rouvière[7], Emmanuel Morelon[4], Olivier Thaunat[4] and Xavier Charmetant[4]**

[1]Centre of Nephrology and Renal Transplantation, Centre Hospitalo-Universitaire (CHU) Conception, Marseille, France, [2]Department of Pathology, Groupement Hospitalier Est, Hospices Civils de Lyon, Bron, France, [3]Department of Urology and Transplantation Surgery, Edouard Herriot Hospital, Hospices Civils de Lyon, Lyon, France, [4]Department of Transplantation, Nephrology and Clinical Immunology, Edouard Herriot Hospital, Hospices Civils de Lyon, Lyon, France, [5]French National Blood Service (EFS), Human Leukocyte Antigen (HLA) Laboratory, Decines, France, [6]Department of Nuclear Medicine, Groupement Hospitalier Est, Hospices Civils de Lyon, Bron, France, [7]Department of Urinary and Vascular Radiology, Edouard Herriot Hospital, Hospices Civils de Lyon, Lyon, France

Keywords: donor-derived carcinoma, BK virus BKPyV, BK virus derived carcinoma, alloimmune response, collecting duct carcinoma

Dear Editors,

BK virus (BKV), present in 80%–90% of the population, establishes a lifelong persistent infection in the kidney and urinary tract after a subclinical primary infection. It can reactivate and cause *de novo* infection in immunocompromised kidney transplant recipients (KTRs) lacking neutralizing antibodies against the donor strain [1], causing nephropathy (BKVAN) in 4%–8% of cases. Persistent BKV infection increases the risk of urothelial carcinoma and collecting duct carcinoma (CDC) [2].

A 73-year-old KTR was admitted for asthenia, acute kidney injury (creatinine 320 μmol/L), inflammatory syndrome (CRP 130 mg/L), and anaemia (Hb 75 g/L). He was followed for a KT performed 9 years earlier, complicated by biopsy-proven BKVAN at month 10. Mycophenolate mofetil was switched to everolimus (3–8 ng/mL), then to leflunomide, and tacrolimus to ciclosporin (80–120 ng/mL). The viral load decreased over 5 months and BKV was never detected again in the blood. At admission, MRI revealed a hypovascular mass in the graft with central necrosis and retroperitoneal inflammation. Biopsy confirmed a tumour composed of irregular tubular structures, trabeculae and single cells (**Figure 1**). The nuclei had a high mitotic index. Necrotic changes were observed. This tumour proliferation infiltrated between non-tumour and dysplastic premalignant tubules (**Figure 1A**). Immunohistochemistry showed diffuse positivity of tumour cells for PAX8, CK7, INI1, fumarate hydratase, and SDHB, and focal positivity for GATA3 (**Figure 1B**), but negativity for CK20, p504S, p63, or ALK. Only tumour cells showed strong nuclear staining with anti-SV40 large T-antigen (**Figure 1C**), leading to the diagnosis of BKV-associated CDC. No metastases were initially found, and transplantectomy was performed. On pathological examination, the tumour invaded the surgical margins of the transplantectomy. Immunosuppressive therapy was tapered by withdrawing leflunomide and reducing tacrolimus trough levels, but not entirely discontinued in order to minimize the risk of donor-specific alloimmunization. Two months later, PET/CT showed iliac, retroperitoneal, pelvic lymph node metastases, and a right ischiopubic bone metastasis. Bulk HLA genotyping of the biopsy revealed that the tumour was

***Correspondence**
Xavier Charmetant,
xavier.charmetant01@chu-lyon.fr

Received: 23 March 2025
Accepted: 21 July 2025
Published: 31 July 2025

Citation:
Lefevre F, Benoit-Janin M, Seizilles-de-Mazancourt E, Matillon X, Buron F, Koenig A, Dubois V, Dietz M, Rouvière O, Morelon E, Thaunat O and Charmetant X (2025) BK Virus: Beyond Nephropathy Metastatic BK Virus-Induced, Donor-Derived Bellini's Carcinoma in a Kidney Allograft Recipient: Boosting Rejection to Treat the Cancer. Transpl. Int. 38:14664. doi: 10.3389/ti.2025.14664

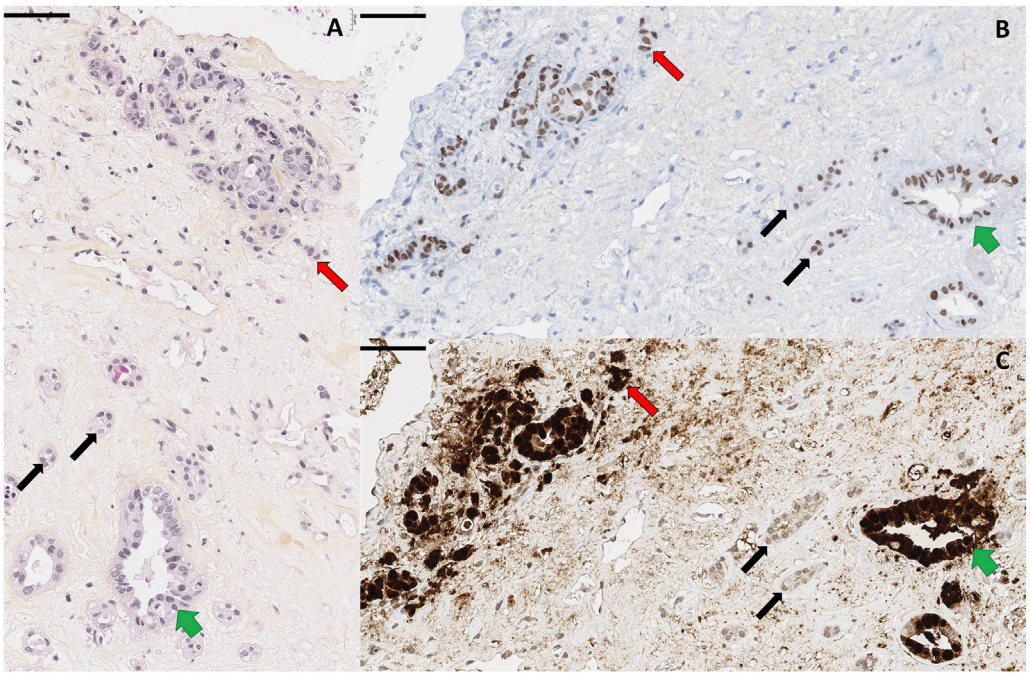


FIGURE 1 | Pathological findings. **(A)** Haematoxylin-Eosin-Safran staining showing infiltrative carcinomatous cells (red arrows), dysplastic premalignant (green arrows) and normal (black arrows) renal tubules. **(B,C)** Immunohistochemical examinations showing PAX8 [renal origin, **(B)**] and Sv40 [viral antigen, **(C)**] labelling of the tumour. Scale bars 60 µm.

not of recipient origin. Immunosuppression was completely withdrawn to stimulate the allo-immune anti-tumoral response, and the patient achieved complete metastatic regression within 3 months. At 2 years, he remained recurrence-free.

This is a very rare case of metastatic donor-derived BKV-induced CDC in a KTR, successfully managed without chemotherapy nor immunotherapy. Bellini's CDC is a rare (<1%) and aggressive variant of renal cell carcinoma [2]. It has been hypothesized that CDC could be linked to BKV in transplanted patients [3]. No other specific risk factor have been identified. The tumorigenesis induced by BKV is known. Polyomaviruses encode 2 viral oncogenes, the small and the large T-antigen [4, 5]. They can inactivate tumour suppressor genes p53 and pRb. Deletion of p53 and pRB leads to gene instability and replication errors that contribute to oncogenesis. Dysregulation of large T-antigen, with persistent over-expression in non-lytic cells, promotes cell growth, genetic instability and neoplasic transformation [6, 7]. The high levels of large T-antigen expression in tumour nuclei is visualized by SV40 staining in immunohistochemistry. Microdissected samples of neoplasic cells usually contain DNA sequences specific for segments of BK-polyomavirus large T-antigen and VP1 genes. On the contrary, no BKV DNA sequences are detected in microdissected normal renal parenchyma [8]. Donor-derived tumours in KTRs are rare (<0.1%) and may arise from donor cells predisposed to oncogenesis. Key oncogenic drivers occur as early as late childhood and early adolescence. Then, late events during transplantation and under immunosuppression, such as BKV infection and genomic integration, may promote further oncogenesis in donor renal cells [9]. These donor-derived tumours offer a unique treatment opportunity: withdrawal of immunosuppression led to spontaneous alloimmune tumour rejection by enabling the immune system to target the graft through alloimmune and antitumour responses. Ortega *et al* reported remission of a metastatic donor-derived urothelial tumour after transplantectomy and immunosuppression withdrawal [10]. Meier *et al* achieved similar success in a metastatic Bellini carcinoma by boosting the anti-tumour immune response with IL-2 immunotherapy [3] (**Supplementary Table S1**).

This case highlights the specificity of urological tumours in KTRs. Identifying donor-derived malignancies may refine treatment strategies, reducing reliance on aggressive therapies. The clinical history reported in this case suggests pragmatic management, although this is by no means a recommendation. Firstly, given the very unfavourable prognosis of these tumours, it seems legitimate to perform surgery and completely stop immunosuppression. The two expected benefits of surgery are the removal of the largest possible tumour mass, and the avoidance of symptomatic toxic graft rejection. The addition of immunotherapy or chemotherapy should be discussed on a case-by-case basis, after evaluating the efficacy of the initial treatment. Given BKV's oncogenic potential, long-term monitoring should

extend beyond the risk of nephropathy to include surveillance for malignancy. Options could include annual urinary cytology screening, early invasive urological evaluation in the event of haematuria and potentially biannual imaging of the graft.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

FL and XC were responsible for data collection and interpretation and drafting the article. FL and XC generated the figure. All authors contributed to the article and approved the submitted version.

FUNDING

The author(s) declare that no financial support was received for the research and/or publication of this article.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

GENERATIVE AI STATEMENT

The author(s) declare that no Generative AI was used in the creation of this manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2025.14664/full#supplementary-material

SUPPLEMENTARY TABLE S1 | table summarizing post-transplant CDC cases linked to BK virus.

REFERENCES

1. Solis M, Velay A, Porcher R, Domingo-Calap P, Soulier E, Joly M, et al. Neutralizing Antibody-Mediated Response and Risk of BK Virus-Associated Nephropathy. *J Am Soc Nephrol Janv* (2018) 29(1):326–34. doi:10.1681/ASN.2017050532
2. Dao M, Pécriaux A, Bessede T, Dürrbach A, Mussini C, Guettier C, et al. BK virus-associated Collecting Duct Carcinoma of the Renal Allograft in a kidney-pancreas Allograft Recipient. *Oncotarget. 13 mars* (2018) 9(19):15157–63. doi:10.18632/oncotarget.24552
3. Meier RPH, Muller YD, Dietrich PY, Tille JC, Nikolaev S, Sartori A, et al. Immunologic Clearance of a BK virus-associated Metastatic Renal Allograft Carcinoma. *Transplant 1 févr* (2021) 105(2):423–9. doi:10.1097/TP.0000000000003193
4. Wang Y, Liu Y, Deng W, Fu F, Yan S, Yang H, et al. Viral Integration in BK polyomavirus-associated Urothelial Carcinoma in Renal Transplant Recipients: Multistage Carcinogenesis Revealed by next-generation Virome Capture Sequencing. *Oncogene. 27 août* (2020) 39(35):5734–42. doi:10.1038/s41388-020-01398-6
5. Starrett GJ, Yu K, Golubeva Y, Lenz P, Piaskowski ML, Petersen D, et al. Evidence for virus-mediated Oncogenesis in Bladder Cancers Arising in Solid Organ Transplant Recipients. *Éditeur Elife 24 Mars* (2023) 12:e82690. doi:10.7554/eLife.82690
6. Kenan DJ, Mieczkowski PA, Burger-Calderon R, Singh HK, Nickeleit V. The Oncogenic Potential of Bk-Polyomavirus Is Linked to Viral Integration into the Human Genome. *J Pathol* (2015) 237(3):379–89. doi:10.1002/path.4584
7. Tognon M, Corallini A, Martini F, Negrini M, Barbanti-Brodano G. Oncogenic Transformation by BK Virus and Association with Human Tumors. *Oncogene. 11 août* (2003) 22(33):5192–200. doi:10.1038/sj.onc.1206550
8. Papadimitriou JC, Randhawa P, Rinaldo CH, Drachenberg CB, Alexiev B, Hirsch HH. BK Polyomavirus Infection and Renourinary Tumorigenesis. *Am J Transpl févr* (2016) 16(2):398–406. doi:10.1111/ajt.13550
9. Mitchell TJ, Turajlic S, Rowan A, Nicol D, Farmery JHR, O'Brien T, et al. Timing the Landmark Events in the Evolution of Clear Cell Renal Cell Cancer: Tracerx Renal. *Cell. 19 avr* (2018) 173(3):611–23.e17. doi:10.1016/j.cell.2018.02.020
10. Michel Ortega RM, Wolff DJ, Schandl CA, Drabkin HA. Urothelial Carcinoma of Donor Origin in a Kidney Transplant Patient. *J Immunother Cancer* (2016) 4:63. doi:10.1186/s40425-016-0167-4

ESOT | Transplant International

CONSENSUS REPORT
published: 11 September 2025
doi: 10.3389/ti.2025.14711

Dermatology Scheduling Triage of Transplant Patients and Transplant Candidates to Improve Early Diagnosis and Prevention of Skin Cancer: International Immunosuppression and Transplant Skin Cancer Collaborative Expert Consensus Recommendations

Kelsey E. Hirotsu[1], Lauren Crowe[2], Basia Michalski-McNeely[3], Sarah T. Arron[4], Kristin Bibee[5], Matthew J. Bottomley[6,7], David R. Carr[8], Joi B. Carter[9], Sean R. Christensen[10], Christina Chung[11], Anokhi Jambusaria[12], Kimberly M. Ken[13], Manisha J. Loss[14], Gyorgy Paragh[15], Elsemieke I. Plasmeijer[16,17], Charlotte Proby[18], Melissa Pugliano-Mauro[19], Kathryn T. Shahwan[8], Melodi Javid Whitley[20] and Bryan T. Carroll[21]*

[1]Department of Dermatology, Stanford University School of Medicine, Redwood City, CA, United States, [2]Dermatology Associates of Tallahassee, Tallahassee, FL, United States, [3]Division of Dermatology, Washington University in St. Louis, St. Louis, MO, United States, [4]Palo Alto Foundation Medical Group, Palo Alto, CA, United States, [5]Department of Dermatology, University of Virginia, Charlottesville, VA, United States, [6]CAMS Oxford Institute, University of Oxford, Oxford, United Kingdom, [7]Oxford Kidney and Transplant Unit, Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom, [8]Division of Dermatology, The Ohio State University, Columbus, OH, United States, [9]Department of Dermatology, Dartmouth Hitchcock Medical Center, Lebanon, NH, United States, [10]Department of Dermatology, Yale School of Medicine, New Haven, CT, United States, [11]Schweiger Dermatology Group, New York, NY, United States, [12]Division of Dermatology, Department of Internal Medicine, Dell Medical School, University of Texas, Austin, TX, United States, [13]Department of Dermatology, Penn State Health, Penn State Milton S. Hershey Medical Center, Hershey, PA, United States, [14]Department of Dermatology, Johns Hopkins University School of Medicine, Baltimore, MD, United States, [15]Department of Dermatology, Roswell Park Comprehensive Cancer Center, Buffalo, NY, United States, [16]Department of Dermatology, The Netherlands Cancer Institute, Amsterdam, Netherlands, [17]Department of Dermatology, Leiden University Medical Centre, Leiden, Netherlands, [18]Molecular and Clinical Medicine, School of Medicine, University of Dundee, Dundee, United Kingdom, [19]Department of Dermatology, University of Pittsburgh, Pittsburgh, PA, United States, [20]Department of Dermatology, Duke University School of Medicine, Durham, NC, United States, [21]Department of Dermatology, University Hospitals Cleveland Medical Center, Case Western Reserve University School of Medicine, Cleveland, OH, United States

OPEN ACCESS

***Correspondence**
Kelsey E. Hirotsu,
Kelsey.hirotsu@gmail.com

Received: 01 April 2025
Accepted: 18 August 2025
Published: 11 September 2025

Citation:
Hirotsu KE, Crowe L, Michalski-McNeely B, Arron ST, Bibee K, Bottomley MJ, Carr DR, Carter JB, Christensen SR, Chung C, Jambusaria A, Ken KM, Loss MJ, Paragh G, Plasmeijer EI, Proby C, Pugliano-Mauro M, Shahwan KT, Whitley MJ and Carroll BT (2025) Dermatology Scheduling Triage of Transplant Patients and Transplant Candidates to Improve Early Diagnosis and Prevention of Skin Cancer: International Immunosuppression and Transplant Skin Cancer Collaborative Expert Consensus Recommendations. Transpl. Int. 38:14711. doi: 10.3389/ti.2025.14711

Solid organ transplant recipients (SOTRs) have a high risk of developing aggressive skin cancers. However, there are no standardized triage guidelines to assist dermatology clinics with scheduling new patients pre- or post-transplant. Dermatologic care of SOTRs requires multidisciplinary coordination, extensive assessment, tailored counseling, and longitudinal care. Specialized high-risk transplant clinics are designed to address this clinical need but are a limited resource. This triage algorithm aims to provide a practical framework for tertiary care centers or community practice clinics receiving pre- or post-transplant referrals for active concerning growths or routine skin cancer screening exams. In summary, our expert panel recommends SOTRs are seen within 1–2 weeks for evaluation of an active growth and triaged according to their risk factors for the initial post-transplant screening visit (6 months–2+ years post-transplant). Transplant candidates should be seen for pre-transplant evaluation within 1 month of the referral for a skin cancer screening exam, depending on the transplant team's timeline and

dermatologist availability. Overall, dermatologists face numerous challenges in caring for transplant patients, and scheduling these patients in a timely manner according to the acuity of their needs will facilitate prevention and early diagnosis of skin cancer, thus improving transplant patient outcomes.

Keywords: skin cancer, squamous cell carcinoma, transplant assessment, melanoma, dermatology, triage, scheduling, SUNTRAC

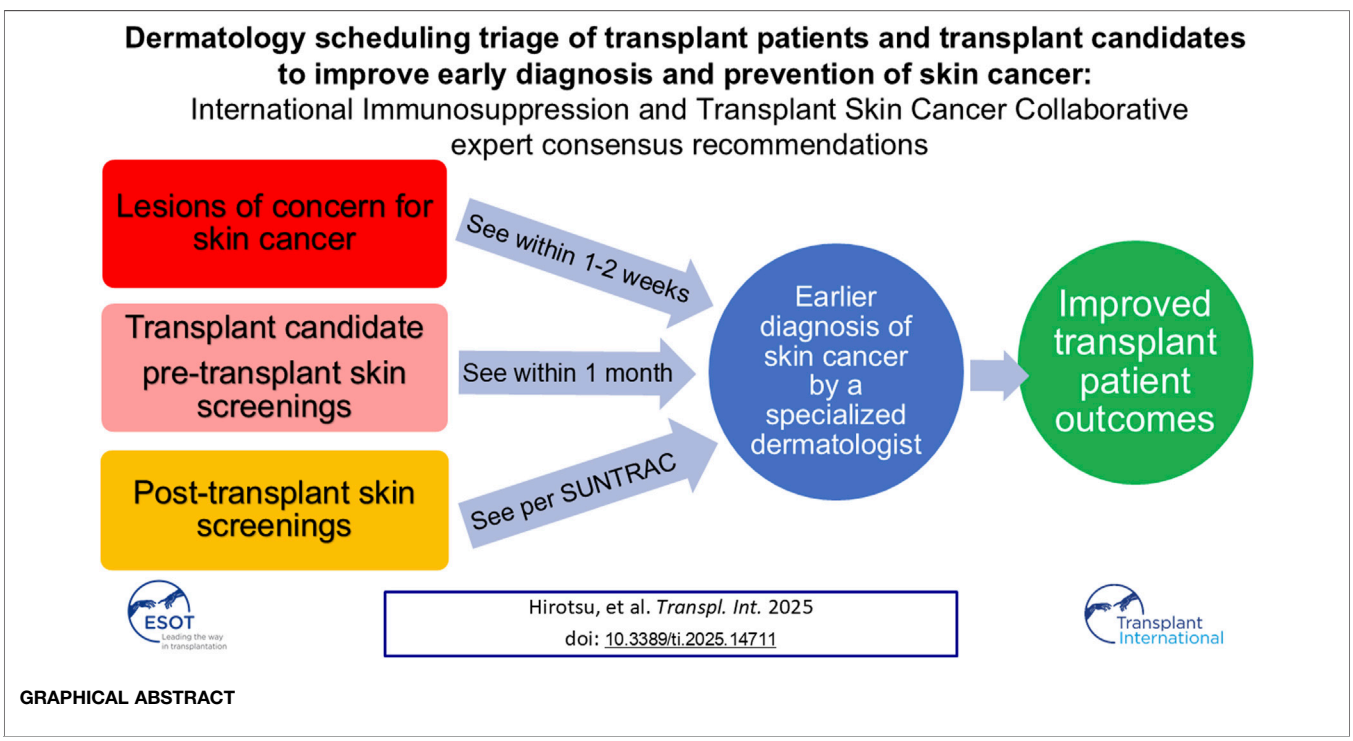
INTRODUCTION

Solid organ transplant recipients (SOTRs) have a much greater risk of developing aggressive skin cancers due to chronic immunosuppression including a 65 to 250-fold increased risk of developing squamous cell carcinoma compared to the general population [1, 2]. Additionally, patients who are transplant candidates awaiting an organ or undergoing evaluation for an organ should be seen in a timely manner to screen for skin cancers that can affect transplant candidacy [3, 4]. The Skin and Ultraviolet Neoplasia Transplant Risk Assessment Calculator (SUNTRAC) was developed to stratify SOTRs by skin cancer risk for post-transplant screening guidelines. SUNTRAC and a published Delphi consensus for initial skin cancer screenings have together established guidelines for screenings post-transplant, but do not provide a recommended timeline for scheduling transplant patients with active concerning growths, or for those needing pre-transplant skin screening [5, 6].

Comprehensive dermatologic management of transplant patients to reduce their risk of cutaneous malignancy requires a complex level of care including multidisciplinary coordination and communication, longitudinal care from a pre-transplant risk assessment to long-term follow-up screenings, and management of topical and oral chemoprophylaxis. This level of care can be provided in the community or at tertiary care dermatology clinics in the form of high-risk transplant clinics (HRTCs). HRTCs are specifically designed to address this clinical need; however, patient access can be challenging as these specialist resources are limited. The goal of this triage algorithm is to provide a practical framework for dermatology clinic schedulers and non-specialized providers when receiving new patient referrals for transplant recipients and transplant candidates with an active concerning growth or for routine skin cancer screening.

METHODS

To frame expert recommendations, we formed an expert panel comprised of 17 physicians: 14 from the United States, two from the United Kingdom, and one from the Netherlands (**Table 1**). 15 experts currently practice at academic centers. Experts were defined as board-certified dermatologists or transplant physicians with at least 5 years of experience caring for SOTRs with skin cancer. A literature review was conducted to identify relevant prior research studies through a comprehensive key word search of PubMed, Embase, and MEDLINE for the following terms:



GRAPHICAL ABSTRACT

TABLE 1 | Demographics of the expert panel.

Characteristics	Number (%)
Country	
United States	14 (82%)
Northeast	6 (35%)
Southeast	2 (12%)
Southwest	1 (6%)
Midwest	3 (18%)
West	2 (12%)
United Kingdom	2 (12%)
Netherlands	1 (6%)
Academic Center	
Yes	15 (88%)
No	2 (12%)
Specialty	
Dermatologic Surgery	9 (53%)
Medical Dermatology	7 (41%)
Transplant Nephrology	1 (6%)

triage; scheduling; transplant; immunosuppression; skin cancer; screening; guidelines. The panel determined that the low levels of evidence available would be augmented by this expert consensus study design to define best practice.

To address this clinical practice gap in our transplant patient population, this agenda item was presented to and discussed by attendees at the 2024 International Immunosuppression and Transplant Skin Cancer Collaborative (ITSCC) symposium, which included ITSCC and Skin Care in Organ Transplant Patients- Europe (SCOPE) members. ITSCC and SCOPE are physician organizations that perform integrative collaborative research focused on transplant recipients and their risk of cutaneous malignancy. Attendees of the symposium included Mohs micrographic and dermatologic oncology surgeons, medical dermatologists, medical oncologists and nephrologists. **Table 2** was presented to the attendees and feedback was collected and incorporated into our triage algorithm, which was distributed to the expert panel and underwent two iterations before a finalized version was approved by all authors. In the first iteration, the revised consensus recommendations in **Table 2** were provided to the panelists for open-ended feedback, which was subsequently integrated by authors KEH and BTC. In the second iteration, the manuscript and all tables and figures were presented to the panelists. After obtaining an expert consensus, the recommendations were approved by the ITSCC Board of Directors.

RESULTS

Suggested Scheduling Timeline for Solid Organ Transplant Recipients and Transplant Candidates

Real-world experience from the expert panel determined that the most critical transplant-related new patient referrals were for transplant recipients with active concerning growths. Other time-sensitive scheduling matters included pre- and post-transplant skin screening exams (**Table 2**). We defined three clinical settings that receive these new patient referrals: tertiary dermatology clinics with a high-risk transplant clinic (HRTC), tertiary dermatology clinics without a HRTC, and community dermatology clinics. The panel determined that both the timelines for scheduling new patients and the appropriate type of physician can vary based on the reason for referral and the clinical setting. While ideally all patients would have access to a tertiary dermatology center with a HRTC, the triage algorithm

TABLE 2 | Recommended dermatology scheduling triage of solid organ transplant recipient and transplant candidate new patient referrals.

Urgency: Acute → Less acute	Tertiary dermatology clinic with a HRTC	Tertiary dermatology clinic without a HRTC	Community dermatology clinic
SOTR with an active growth (rapidly growing, tender or painful, or easily bleeding)	See within 1–2 weeks with HRTC, MMS or general dermatology	See within 1–2 weeks with MMS or general dermatology	See within 1–2 weeks for biopsy with MMS or general dermatology, or urgently route directly to the nearest tertiary dermatology clinic to be seen within 2 weeks Consider referral to the nearest tertiary dermatology clinic (ideally with a HRTC) for co-management
Transplant candidate pre-transplant screen	See within 1 month[a] for screening with HRTC if available, or general dermatology	See within 1 month[a] for screening with general dermatology, or consider referral to the nearest HRTC	See within 1 month[a] for screening with general dermatology Consider referral to the nearest tertiary dermatology clinic (ideally with a HRTC) for co-management
SOTR with a history of skin cancer	See within 6 months-2+ years post-transplant[b] with HRTC.	See within 6 months-2+ years post-transplant[b] Consider long-term co-management with the nearest HRTC if available	See within 6 months-2+ years post-transplant[b] Consider referral to the nearest tertiary dermatology clinic (ideally with a HRTC) for co-management
SOTR with no history of skin cancer	See within 1–5 years post-transplant[b] with HRTC.	See within 1–5 years post-transplant[b] with general dermatology	See within 1–5 years post-transplant[b] with general dermatology

SOTR, solid organ transplant recipient; HRTC, high-risk transplant clinic; MMS, Mohs micrographic surgery/surgeon.

[a]*This recommendation can be tailored to each individual patient case, depending on the transplant team's timeline and dermatologist availability.*

[b]*Refer to SUNTRAC for the recommended timeline for the initial skin cancer screening visit [5].*

reflects recommendations but not guidelines given the limitation of this resource and potential barriers to patient access. The HRTC model, components of the pre-transplant screening visit, and a suggested approach to follow-up after the initial visit are outlined in subsequent sections of the results.

Based on the identified clinical need and resource availability challenges defined above:

1. We recommend that SOTRs with an active concerning growth (lesion that is rapidly growing, tender or painful, or easily bleeds) are seen by a dermatologist, preferably in a HRTC if available, within 1–2 weeks of receiving the referral. All referrals for concerning growths should include high-quality photographs of the growth, ideally one from close-up to demonstrate lesion morphology and one from further away to demonstrate relevant anatomic landmarks. These referrals may be triaged via teledermatology prior to an in-person visit, and lesions concerning for invasive squamous cell carcinoma or other aggressive cutaneous malignancies on teledermatology should be seen within 1–2 weeks.
2. We recommend that transplant candidates are seen within 1 month of receiving a referral for a pre-transplant skin cancer screening exam (see "*the pre-transplant screening visit*" section below). If a pre-transplant screening is not feasible or is not performed, the patient can be seen within the first year after transplant for this visit. If the patient is admitted to the hospital and expected to be hospitalized until the transplant takes place, the skin cancer screening exam can take place in the inpatient setting if possible.
3. We recommend that SOTRs referred for routine skin screenings without active concerning growths should be seen according to the SUNTRAC and/or Delphi consensus guidelines [5, 6]. All referrals to dermatology should include patient race, sex assigned at birth, history of skin cancer (yes/no), age at time of transplant, and organ transplant type, to fulfill the criteria for the SUNTRAC tool.
4. For SOTRs seen by a community dermatologist, consider referral to a HRTC for co-management of patients with a history of skin cancer, a growth that is concerning for skin cancer, or if the actinic burden is high to discuss chemoprevention and non-surgical management.

High-Risk Transplant Center Clinical Model

HRTCs provide comprehensive dermatologic care for transplant patients in an ideal model that is highly dependent on resource availability and not feasible in every practice setting [7–9]. In general, transplant dermatologists offer screening exams, field treatments, oral chemoprevention, surgical and non-surgical treatments for skin cancer, access to multispecialty care for management of high-risk skin cancers, and coordination with the primary transplant team to manage systemic immunosuppression to mitigate skin cancer risk. Counseling for all patients includes patient-specific skin cancer risk assessment and prevention. Additionally, these clinics should have the capacity for urgent add-on visits for lesions concerning for invasive squamous cell carcinoma or other aggressive cutaneous malignancies ideally within 1–2 weeks. Although most dermatologists who provide this comprehensive transplant care are at dedicated HRTCs, community or academic dermatologists who specialize in transplant dermatology can also meet this ideal clinic model and serve as a valuable resource for transplant patients.

The Pre-Transplant Screening Visit

The pre-transplant screening visit should include a comprehensive review of the patient's pertinent medical history, thorough physical exam, and appropriate counseling, either within a HRTC (if available) or general dermatology clinic depending on the patient's history of skin cancer (**Table 3**). If the pre-transplant screening visit has not been conducted or is not feasible with the transplant team's timeline, the components of this visit should be included with the first post-transplant visit. Regarding the medical history review, this should include the patient's history of melanoma and non-melanoma skin cancer, reviewing relevant previous pathology records and confirming all skin cancers were appropriately treated, any history of risk factors for skin cancer (i.e., history of extensive UV exposure including tanning bed use, actinic keratoses and prior field treatments, HPV-associated lesions, radiation therapy, relevant family history), and history of immunosuppression.

For patients with a history of melanoma, Merkel cell carcinoma, and high-risk squamous cell carcinoma, a consensus opinion from ITSCC has been published for recommended waiting periods prior to transplant in 2016 [4]. More recently in 2021, the delay time for patients with a pre-transplant diagnosis of melanoma has been revised by the American Society of Transplantation [10]. The physical exam should ideally be in-person, including mucosal regions (oral and genital) and an overall photodamage assessment. Counseling can be introductory and tailored to the patient to include a preventative therapy plan and education regarding skin cancer risk and prevention. Following the pre-transplant visit screening, referring transplant teams should receive documentation from the visit including any necessary delay time, the treatment status and risk profile of any known skin cancers, actinic burden and any plans for field therapy and/or chemoprevention, and surveillance recommendations (**Figure 1**).

To determine transplant candidacy for each individual patient, the primary transplant team has numerous tasks to complete. Dermatologists play a critical role in the pre-transplant screen as the most qualified providers to fully assess a patient's eligibility based on their history of skin cancer and their current skin exam. Therefore, providing a pre-transplant screening visit in a timely manner is a valuable contribution to the transplant team and establishes a patient-provider relationship that will continue post-transplant. While we recommend seeing these patients within 1 month of receiving the referral from the primary transplant team as a professional courtesy, the timeline can be tailored to each patient's case depending on the transplant team's timeline and dermatologist availability. Furthermore, follow-up dermatology visits may be indicated if the patient is waiting for an organ for an extended period.

TABLE 3 | A comprehensive pre-transplant screening visit checklist for transplant dermatologists.

Components of the visit	Patient questions
Medical History	1. Does the patient have an extensive history of UV exposure including sunburns or tanning bed use? 2. Does the patient have a history of melanoma and/or non-melanoma skin cancer? 3. When and how were all skin cancers treated? (Assess the trend of new skin cancers diagnosed per year and obtain/review relevant previous pathology records.) 4. Does the patient have a history of risk factors for skin cancer (i.e., actinic keratoses and prior field treatments, HPV-associated lesions, history of radiation therapy, relevant family history)? 5. Does the patient have a history of immunosuppression (i.e., hematologic malignancy, HIV, or long-term immunosuppression medication exposure for autoimmune or inflammatory diseases)?
Physical Exam	1. In-person head-to-toe mucocutaneous examination for lesions concerning for malignancy, pre-malignancy, or infection. Biopsy as needed 2. Overall photodamage assessment 3. Consider palpation of relevant lymph node basins based on patient history
Counseling	1. Discuss a preventative therapy plan including sun protective measures 2. Based on the patient history and physical exam, discuss potential future therapies including topical and/or oral treatment to mitigate skin cancer risk

- This is a transplant candidate with a {low/moderate/high risk} for an aggressive cancer of the skin.
  - Skin Cancer Risk Post-Transplant/Cumulative Incidence of Skin Cancer (SUNTRAC): average 5-year risk (%), average 10-year risk (%)
- The actinic burden on the scalp, face, arms, trunk, legs is currently {low/high}
  - Justifying field treatment with {topical 5% 5-fluorouracil/PDT/other}
- The patient {has/does not have} a known metastatic cancer and {is/is not} undergoing therapy, or completed definitive treatment and has no evidence of recurrence for (#) years
- Return to clinic in (#) months and as needed for any new, changing or rapidly growing skin lesions
- Skin surveillance exams: q (#) months
- Patient education: The patient was educated on sun protection, monthly self skin examinations and to call for evaluation of new or changing lesions.
- **This patient currently {does/does not} have any dermatologic contraindications to transplant at this time. {If the patient has contraindications to transplant, this has been communicated directly to the transplant physician and/or coordinator.}**

FIGURE 1 | Example of a pre-transplant dermatologic assessment communication back to the referring transplant team.

Follow-Up After High-Risk Transplant Clinic Evaluation

After a transplant patient or transplant candidate has undergone an in-person evaluation by a dermatologist at a HRTC, subsequent follow-up appointments may be performed either at the HRTC or by their local dermatologist. The frequency of follow-up visits and the recommendation for an appropriate physician is based on the high-risk transplant dermatologist's discretion. These will be patient-specific and will depend on the patient's skin cancer risk factors and practical considerations, including travel, patient preference, and out-of-pocket costs. For patients deemed at low risk for skin cancer or with barriers to frequent HRTC visits, follow-up visits can be scheduled alternating between HRTC and their local community dermatologist or with their local community dermatologist only and HRTC as needed.

DISCUSSION

Dermatologic management of transplant patients requires multidisciplinary coordination, extensive assessment and tailored counseling, and longitudinal care from pre-transplant screening visits to routine follow-up skin exams. The spectrum of care required will vary, often significantly, from patient to patient. Dedicated HRTCs are a specialized, valuable resource intended to provide optimal dermatologic management for our transplant patients and triage patients for lower acuity follow-up after initial evaluations. Access to care remains a concern for many patients. Therefore, coordination between local dermatologists and HRTCs serves an indispensable role for patients with a low risk of skin cancer and those who live far from HRTCs. Although limitations of our recommendations include the lack of diversity of global representation of the expert panel and a restricted thematic analysis, overall dermatologists face numerous challenges in caring for SOTRs, and scheduling these patients in a timely manner according to patient needs will aim to improve prevention and early diagnosis of skin cancer.

Given the increased risk of skin cancer in SOTRs, these triage recommendations aim to ensure prompt access to dermatologic services in order to reduce the skin cancer burden and progression of high-risk skin cancers in SOTRs with the ultimate goal of improving patient morbidity and mortality. Additionally, the benefits of screening and appropriate triage may include reduction of overall healthcare costs, as transplant recipients have a higher cost of skin cancer-related care relative to nonimmunosuppressed patients [11, 12]. Early assessment and

intervention with the pre-transplant screening visit will serve as primary prevention to alter the trajectory of skin cancer risk in future transplant patients. Furthermore, timely appointments with the appropriate physician for SOTRs with lesions concerning for aggressive skin cancer will mitigate risks of complications such as metastatic spread (secondary prevention) through early diagnosis of potentially high-risk skin cancers. Lastly, these recommendations address post-transplant initial skin cancer screening surveillance timelines based on the evidence-based SUNTRAC guidelines. Together, these preventative aims of the scheduling triage algorithm present multiple stepwise opportunities to mitigate the impact of skin cancer in SOTRs, thus improving transplant patient outcomes.

AUTHOR CONTRIBUTIONS

KEH and BTC wrote the manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

The author(s) declare that financial support was received for the research and/or publication of this article. This work was supported by ITSCC academic mentorship program fund.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

GENERATIVE AI STATEMENT

The author(s) declare that no Generative AI was used in the creation of this manuscript.

REFERENCES

1. Lindelöf B, Sigurgeirsson B, Gäbel H, Stern RS. Incidence of Skin Cancer in 5356 Patients Following Organ Transplantation. *Br J Dermatol* (2000). doi:10.1111/j.1365-2133.2000.03703.x
2. Euvrard S, Kanitakis J, Pouteil-Noble C, Dureau G, Touraine JL, Faure M, et al. Comparative Epidemiologic Study of Premalignant and Malignant Epithelial Cutaneous Lesions Developing After Kidney and Heart Transplantation. *J Am Acad Dermatol* (1995) 33:222–9. doi:10.1016/0190-9622(95)90239-2
3. Kang W, Sampaio MS, Huang E, Bunnapradist S. Association of Pretransplant Skin Cancer with Posttransplant Malignancy, Graft Failure and Death in Kidney Transplant Recipients. *Transplantation* (2017) 101(6):1303–9. doi:10.1097/TP.0000000000001286
4. Zwald F, Leitenberger J, Zeitouni N, Soon S, Brewer J, Arron S, et al. Recommendations for Solid Organ Transplantation for Transplant Candidates with a Pretransplant Diagnosis of Cutaneous Squamous Cell Carcinoma, Merkel Cell Carcinoma and Melanoma: A Consensus Opinion from the International Transplant Skin Cancer Collaborative (ITSCC). *Am J Transpl* (2016) 16(2):407–13. doi:10.1111/ajt.13593
5. Jambusaria-Pahlajani A, Crow LD, Lowenstein S, Garrett GL, Melcher ML, Chan AW, et al. Predicting Skin Cancer in Organ Transplant Recipients: Development of the SUNTRAC Screening Tool Using Data from a Multicenter Cohort Study. *Transpl Int* (2019) 32:1259–67. doi:10.1111/tri.13493
6. Crow LD, Jambusaria-Pahlajani A, Chung CL, Baran DA, Lowenstein SE, Abdelmalek M, et al. Initial Skin Cancer Screening for Solid Organ Transplant Recipients in the United States: Delphi Method Development of Expert Consensus Guidelines. *Transpl Int* (2019) 32:1268–76. doi:10.1111/tri.13520
7. Christenson LJ, Geusau A, Ferrandiz C, Brown CD, Ulrich C, Stockfleth E, et al. Specialty Clinics for the Dermatologic Care of solid-organ Transplant Recipients. *Dermatol Surg* (2004) 30(4 Pt 2):598–603. doi:10.1111/j.1524-4725.2004.00143.x
8. Papier K, Gordon LG, Khosrotehrani K, Isbel N, Campbell S, Griffin A, et al. Management of Organ Transplant Recipients Attending a High-Throughput Skin Cancer Surgery and Surveillance Clinic in Queensland. *Br J Dermatol* (2019) 180(3):631–6. doi:10.1111/bjd.17001
9. Gordon LG, Rodriguez-Acevedo AJ, Papier K, Khosrotehrani K, Isbel N, Campbell S, et al. The Effects of a Multidisciplinary high-throughput Skin Clinic on Healthcare Costs of Organ Transplant Recipients. *J Eur Acad Dermatol Venereol* (2019) 33(7):1290–6. doi:10.1111/jdv.15458
10. Al-Adra DP, Hammel L, Roberts J, Woodle ES, Levine D, Mandelbrot D, et al. Pretransplant Solid Organ Malignancy and Organ Transplant Candidacy: A Consensus Expert Opinion Statement. *Am J Transpl* (2021) 21(2):460–74. doi:10.1111/ajt.16318
11. O'Connell KA, Groover MK, Lim S, Kus K, Gupta N, Murad F, et al. Cost of Skin Cancer-Related Dermatological Care Is Higher in Transplant Recipients Compared with Nonimmunosuppressed Patients. *JAAD* (2024) 90(1):150–2. doi:10.1016/j.jaad.2023.08.077
12. Jäckel D, Schlothauer NI, Zeeb H, Wagner G, Sachse MM. Hautkrebsscreening und Behandlungskosten: Inanspruchnahme des Hautkrebsscreenings und Kosten der Hautkrebsbehandlung bei organtransplantierten Patienten [Skin cancer screening and treatment costs: Utilisation of the skin cancer screening and skin cancer treatment costs in organ transplant recipients]. *Hautarzt* (2018) 69(7):570–5. doi:10.1007/s00105-018-4159-9

Transplant International

Official journal of the European Society for Organ Transplantation

Editorial Office

Avenue du Tribunal Fédéral 34
CH – 1005 Lausanne
Switzerland

Tel +41 (0)21 510 17 40
Fax +41 (0)21 510 17 01

tieditorialoffice@frontierspartnerships.org
frontierspartnerships.org/journals/transplant-international

frontiers | Publishing Partnerships