Yemen Journal of Medicine

https://yemenjmed.com

Article information

DOI: 10.63475/yjm.v5i2.0459

Article history:
Received: 05 July 2026
Accepted: 17 July 2026
Published: 22 July 2026

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How to cite this article
Habas E, Rayani A, Habas A, Habas A, Hamad A, Habas E, et al. Post-kidney transplantation malignancy: Risk, pathogenesis, and management. Yemen J Med. 2026;5(2):274-286.

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Review Article

Post-Kidney Transplantation Malignancy: Risk, Pathogenesis, and Management

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ABSTRACT

The rising incidence of cancer in kidney transplant patients poses a significant barrier to long-term patient and graft survival. Immunosuppression is a primary component in cancer risk, although the interaction of recipient characteristics, viral oncogenesis, and donor-related factors complicates risk assessment. Current research highlights the increased prevalence and mortality linked to some malignancies, including lymphomas, skin cancers, and virus-associated tumors, as well as the limited effectiveness of some existing preventative and treatment approaches. Despite progress, significant challenges persist, particularly in balancing immunosuppression and cancer control, defining the role of prophylactic vaccinations, and validating customized screening techniques. This review examines the pathophysiological mechanisms, evaluates guidelines, and presents contemporary data on the incidence and management of post-kidney transplantation malignancies, highlighting both recent advances and unresolved issues. The current evidence, largely constrained by observational and registry-based studies, underscores the urgent need for prospective research. There is an urgent requirement for prospective research to enhance personalized care, facilitate early detection, and provide safer immunosuppressive protocols. Collaboration among nephrology, oncology, and infectious disease specialists is crucial to improve care and increase survival in this at-risk group.

Key words: Post-renal transplant, malignancy after renal transplant, immunosuppression and malignancy, solid organ transplantation and cancer, mTOR inhibitors, CNI

INTRODUCTION

Kidney transplantation is the most effective long-term renal replacement therapy. However, kidney transplant recipients (KTRs) face a significantly elevated cancer risk compared to the general population, which translates into markedly higher cancer-related mortality. As a major obstacle to long-term survival, cancer accounts for up to 56% of fatalities in patients with functioning grafts, making it the second or third highest cause of death in KTRs. [1,2] Variation in mortality rates of malignancy following kidney transplantation suggests variations in the biology and severity of the cancer. [2]

Numerous factors, including the patient's medical history, the duration after the kidney transplant, and post-kidney transplant medication duration, affect the risk of post-

transplant malignancy. [3] Additionally, cumulative pre-kidney transplant immunosuppressive therapy, advanced age, duration of dialysis before kidney transplantation, and decreased immunocompetence are significant risk factors. [4,5] To reduce the risks associated with kidney transplantation, a thorough assessment of the kind and length of immunosuppressive treatment is necessary, as is regimen tailoring depending on personal risk factors. [6] A recent study by Chukwu et al. highlighted the necessity for personalized screening, prevention, and management strategies to effectively address de novo post-transplant malignancies in an aging and immunosuppressed kidney transplant demographic. [7]

Besides the recipient-related risk factors, which include age, sun exposure, and a history of malignancy, donor-transmitted cancers occur infrequently. The prevalent cancer types observed following kidney transplantation are nonmelanoma skin cancers, lymphoma, and colorectal cancer. However, optimal management strategies following a cancer diagnosis remain poorly defined, with a lack of high-quality evidence to guide practice. [8]

Clinicians must implement preventive screening strategies and treatment plans for organ-transplant populations in response to the increasing incidence of cancer in KTRs. Cancer screening programs for the general population are well established; however, the frequency and preferred methods for screening solid organ recipients remain unclear. [9,10] Early diagnosis and effective treatment, including surgery, chemotherapy, or radiotherapy, are essential for tumor therapy in KTRs. Drug modification following a cancer diagnosis presents a significant challenge in these patients' follow-up strategies. Given the available data, it is evident that a continued focus on post-transplant malignancies remains essential in clinical practice. This article examines pathophysiological mechanisms, evaluates guidelines, and presents data on the incidence and management strategies of various cancers from a contemporary viewpoint.

A literature search was conducted using Scopus, Google Scholar, EMBASE, and PubMed for original and review articles published in the last 5 years ("post-transplant malignancy," "kidney transplant recipient cancer," "immunosuppression and malignancy," "post-transplant lymphoproliferative disorder," "calcineurin inhibitor cancer risk," "mTOR inhibitor and cancer," "donor-transmitted malignancy," and "cancer screening in solid organ transplant recipients"). The search focused on identifying studies relevant to epidemiology, pathogenesis, risk factors, and management of malignancies in KTRs.

EPIDEMIOLOGY

KTRs have a 3 to 4-fold malignancy risk compared to the general population. [11] Reported incidence rates vary across studies. One study reported that 19% of KTRs experienced the development of at least one cancer. [1,12] An Italian multicenter study with a 25-year follow-up reported an incidence rate of approximately 13%. [13] Other studies reported a cancer incidence of 7.2% in a single-center study with a follow-up period of 7.8 years [14] and 6.2% in another single-center study. [15]

Malignancy peaks in incidence typically 3 to 5 years post-transplantation. [16,17] A study analyzed the outcomes of 293 KTRs, and the findings indicated that the malignancy incidence following a Kidney transplant was 4.4% at 10 years and 14.6% at 20 years. The prevalence of nonmelanoma skin cancer was 10.3% and 33.5%, respectively. [18] A long-term retrospective study revealed an annual incidence of newly developing cancer at 1%, excluding nonmelanoma cutaneous cancers. [19] The standardized incidence ratio (SIR) quantifies the increased risk of malignancies in KTRs relative to a comparable cohort in the general population based on age and gender. Kaposi sarcoma is coupled with the highest severity of the SIR. Lymphoma, nonmelanoma skin, anogenital, and lip cancers exhibit the highest SIRs. [20] Certain cancers, including breast, ovarian, and prostate cancers, exhibit stable SIRs post-transplantation, aligning with those of the general population. Other common malignancies associated with a slightly elevated risk are colorectal and lung cancers. [21]

The recipient's age significantly influences the heightened incidence of post-transplant malignancy in kidney transplant patients. Younger recipients have lower malignancy rates than elderly kidney transplant patients. [22] The increased cancer risk in the elderly can be due to genetic changes and environmental exposures like smoking and UV radiation. Older recipients may have greater cancer rates because their immune systems are less efficient at recognizing and eradicating cancer cells. While immunosuppressive medication reduces immune surveillance, older individuals may have had more lifetime exposure to carcinogens or oncogenic viruses and be at a higher risk of post-kidney transplant malignancy development. Non-melanoma skin and head/neck malignancies are more common in elderly transplant recipients, probably due to cumulative risk exposures. [23,24] It is important to distinguish absolute incidence from relative risk in this context: while older recipients accumulate a higher absolute burden of cancer, SIRs—which compare observed cancer rates to an age-matched general population—can paradoxically be highest in the youngest recipients. A Taiwanese nationwide cohort found that recipients transplanted before age 20 years had the highest SIR of any age group, reflecting the very low baseline cancer incidence in young people rather than a higher absolute cancer burden. [25] **Table 1** summarizes the epidemiology of malignancies associated with kidney transplantation.

IMPACT OF MALIGNANCY ON PATIENT AND GRAFT OUTCOMES

The development of malignancy post-kidney transplantation is a pivotal event that profoundly impacts patient survival, graft function, and overall quality of life. Understanding these outcomes is essential for risk-benefit analysis and clinical decision-making.

Impact on Patient and Graft Survival

KTR patients with a PTM face a 2.4-fold increased risk of all-cause mortality and a significantly elevated risk of cancer-specific death. [10,26] The key prognostic factors that affect the outcome include cancer type, graft survival and function, and tumor management.

Table 1: Epidemiology of common malignancies after kidney transplantation.

Malignancy type	Key subtypes/ associations	Standardized incidence ratio (SIR)*	Typical peak onset post-transplant	Key risk factors (non-exhaustive)
Virus-associated				
Post-Transplant Lymphoproliferative Disorder (PTLD)	EBV (especially in EBV seronegative recipients)	Very high (e.g., ~10–20)	Early (<1–2 years) for EBV+; Later for EBV-	T-cell depleting induction, EBV seromismatch, high immunosuppression burden
Kaposi Sarcoma	Human herpesvirus-8 (HHV-8)	Highest of all cancers (e.g., >50)	1–3 years	Geographic origin (Mediterranean, Middle East, Africa), HHV-8 seropositivity
Cervical/anogenital cancers	Human papillomavirus (HPV)	Significantly elevated (e.g., 5–15)	Variable, often >3–5 years	HPV infection, number of sexual partners, and lack of vaccination
Skin cancers				
Non-melanoma skin cancer (NMSC)	Squamous cell carcinoma (SCC), basal cell carcinoma (BCC)	Very high (e.g., 20–65)	3–5 years, risk accumulates over time	Caucasian race, high sun exposure, age, and azathioprine use
Melanoma		Moderately elevated (e.g., 2–5)	Variable	Personal/family history, sun exposure, T-cell depleting agents
Other common cancers				
Kidney cancer	In native kidneys (not a transplant kidney)	Elevated (e.g., 5–10)	Variable, risk increases with dialysis vintage	Acquired cystic kidney disease, long dialysis duration
Lip cancer		Very high (e.g., 20–30)	>3–5 years	Sun exposure, Caucasian race
Lung cancer		Moderately elevated (e.g., 1.5–2)	Variable, similar to the general population	Smoking history, age
Colorectal cancer		Slightly elevated (e.g., 1.5–2.5)	Variable, similar to the general population	Age, family history, lifestyle factors
Cancers with minimally changed/no increased SIR	Breast cancer, prostate cancer	~1 (not significantly elevated)	N/A	Risk factors similar to those in the general population

*SIR is a measure of relative risk compared to the general population, adjusted for age and sex. An SIR of 2 indicates a two-fold increased risk. The values provided are representative ranges from the literature cited in this review; exact figures vary between studies and populations.

- **Cancer Type and Stage:** Prognosis varies dramatically by malignancy. PTLD carries the poorest 5-year survival (approximately 40%), followed by lung cancer and melanoma (2-year survival <50%). In contrast, non-melanoma skin cancers and localized renal cell carcinoma have 5-year survival rates exceeding 80% with prompt treatment. [27,28] Early-stage (T1/T2) disease has a significantly better prognosis than metastatic cancer. Malignancies diagnosed within the first year post-transplant often have a more aggressive course and worse outcomes than those developing later. [29]
- **Immunosuppression Regimen:** The type and intensity of immunosuppression influence outcomes. Induction therapy with T-cell depleting antibodies and high-dose Calcineurin Inhibitors (CNIs) is associated with a poorer prognosis for certain cancers. However, conversion to mTOR inhibitors may improve cancer-specific survival in some cases, such as Kaposi's sarcoma and non-melanoma skin cancer. [1,30]
- **Mortality and Graft Loss Data:** Registry data underscore the significant mortality burden. The US Renal Data System reports a 2.3-fold increased mortality risk in KTRs diagnosed with cancer. [21] In an Italian cohort, over half (51.7%) of the deaths in patients who developed cancer were directly attributable to malignancy, with a median survival of only 23 months from diagnosis. [1] The ANZDATA registry noted that cancer is responsible for 30% of deaths in recipients with a functioning graft. [31] Cancer-specific mortality is elevated in KTRs compared to non-transplant cancer patients, even after adjusting for stage and treatment, particularly for melanoma, colorectal, and breast cancers. [10] This is partly because cancers in KTRs often present at a more advanced stage; one study found lymph node or metastatic spread in 20% of breast cancers, 45% of lung cancers, and 40% of colorectal cancers at diagnosis. [32]

A cancer diagnosis also jeopardizes the renal allograft. PTM is associated with a significantly increased risk of graft loss (adjusted HR, 2.56). [10,33] This risk is most pronounced with aggressive malignancies like PTLD, which nearly sextuples the risk of allograft loss. [18] The primary driver of graft

injury is the necessary modification of immunosuppression, which increases the risk of acute rejection (15%–30%) and subsequent chronic graft damage. [30]

GENERAL MANAGEMENT PRINCIPLES AND THEIR IMPACT

The management of cancer in post-kidney transplant patients presents a distinctive challenge, requiring a balance between oncologic control and the preservation of allograft function. The chosen strategy directly influences both patient and graft outcomes.

- **Immunosuppression Reduction:** A cornerstone of management across all cancer types is the reduction of the number and doses of immunosuppression, which aims to replenish the immune system's ability to survey and eliminate malignant cells. [6]
- The effect is most pronounced for virus-associated cancers (e.g., PTLD, Kaposi's sarcoma). However, the benefit must be balanced against a quantifiable increase in the risk of acute rejection and graft loss. [30]
- **Conversion to mTOR Inhibitors:** Randomized trials, such as the TUMORAPA trial, have demonstrated that switching KTRs with a history of squamous cell carcinoma from a CNI-based regimen to sirolimus can reduce the risk of skin cancer recurrence by almost 50%. [34,35] This strategy has shown benefit for Kaposi's sarcoma and other cancers. However, its impact on overall survival remains unclear and must be weighed against its potential for worsening proteinuria and graft function. [36]
- **Complete Immunosuppression Withdrawal:** Withdrawal of immunosuppressants completely is a last-resort strategy reserved for the most aggressive, life-threatening cancers. While it may offer a chance at prolonged life, it almost universally leads to acute rejection and graft loss, rendering the patient dialysis-dependent. [37] While this risk is acceptable for life-threatening cancers like metastatic melanoma, it poses a significant dilemma for less aggressive malignancies. [37]
- Cancer-Specific Management
    A. For non-melanoma skin cancer, the commonest malignancy after kidney transplantation, management involves attentive surveillance and often complex management involving topical therapies, procedural destruction, and systemic chemoprevention such as nicotinamide [38] or immunosuppression modification with mTOR inhibitors. [39]For a detailed discussion of the clinical management of field cancerization and advanced nonmelanoma skin cancer in transplant recipients, see references. [38,40]
    B. For PTLPD, which is often driven by Epstein-Barr virus, the initial management involves a significant reduction of immunosuppression. This first-line intervention can be curative in a subset of patients. For those who do not respond, treatment typically advances to include the anti-CD20 monoclonal antibody, rituximab, often in combination with chemotherapy. [27,41]
    C. The management of other solid tumors (e.g., lung, colorectal, and breast cancer) generally follows standard oncologic protocols, involving surgery, radiation, or chemotherapy. However, critical considerations must be made for potential interactions between chemotherapeutic agents and immunosuppressive drugs (e.g., calcineurin inhibitors), as well as the need for dose adjustments in the context of reduced renal function. [2,22]
    D. A modern and high-risk therapeutic option is the use of immune checkpoint inhibitors (e.g., PD-1/PD-L1 inhibitors). While these drugs can be highly effective against advanced cancers, they carry a profoundly high risk of inducing allograft rejection, necessitating extensive patient counseling and close collaboration between transplant and oncology teams. [26]

In summary, malignancy poses a dual threat to the KTR, significantly increasing mortality and the risk of graft failure. Outcomes are highly dependent on the type and stage of cancer, and management requires a delicate, often individualized, balance between controlling malignancy and preserving graft function through strategic modification of immunosuppression. Multidisciplinary care involving transplant nephrologists, oncologists, and dermatologists is essential for navigating these complex decisions and optimizing outcomes.

PATHOPHYSIOLOGY OF MALIGNANCY POST-KIDNEY TRANSPLANTATION

The loss of T-cell-mediated immunosurveillance, a cornerstone of immunosuppressive therapy, provides a permissive environment for the reactivation and proliferation of oncogenic viruses, underpinning the high incidence of malignancies like PTLD (Epstein-Barr virus) and Kaposi sarcoma (human herpesvirus-8). This impaired immune control is a primary mechanism of pathogenesis, as the prolonged immunosuppression required to prevent graft rejection disrupts the normal immune surveillance that eliminates cancerous cells and suppresses viral replication, ultimately leading to unchecked cellular proliferation.

Pathogenic Mechanisms of Drug-Induced Cancer Post-Kidney Transplantation

The development of malignancy after kidney transplantation is a multifactorial process driven principally by the essential iatrogenic impairment of the immune system. The pathophysiological mechanisms are categorized into three interconnected pathways: (1) Loss of Immunosurveillance, (2) Direct Oncogenic Effects of Immunosuppressive Drugs, and (3) Viral Oncogenesis.

1. Loss of Immunosurveillance

The primary effect of immunosuppressive therapy is the suppression of T-cell-mediated immunity to prevent graft rejection. Unfortunately, this effect impairs the critical immune surveillance functions that normally identify, prevent, and eliminate malignant or virally infected cells.

***Innate Immunity**:* Natural killer (NK) cells and dendritic cells, integral to the innate immune system, are essential for early

tumor cell detection and clearance. Immunosuppressive agents reduce NK cell activity and dendritic cell function, resulting in a significant loss of this first-line anticancer defense. [21,22,34]

Adaptive Immunity: CD4+ and CD8+ T-lymphocytes are the primary effectors of adaptive antitumor immunity. Suppressing these cell functions allows pre-malignant cells to proliferate. Furthermore, certain regimens affect regulatory T-cells (Tregs), particularly CD4+, FOXP3+, CD127-low subsets, which may further inhibit effector T-cell proliferation and facilitate tumor immune evasion. [22,34]

2. Direct Oncogenic Effects of Immunosuppressive Drugs

Beyond general immunosuppression, several agents have direct, drug-specific pro-carcinogenic properties.

Calcineurin Inhibitors (Cyclosporine, Tacrolimus): CNIs do not just cause cancer via immunosuppression. Experimental evidence indicates they can encourage tumor progression and metastasis by increasing levels of transforming growth factor-beta (TGF-β). [42,43]

Furthermore, cyclosporine can directly inhibit DNA repair mechanisms, specifically by downregulating xeroderma pigmentosum complementation groups A and G, causing the accumulation of UV-induced mutations. [44,45]

***Azathioprine*:** This agent acts as a direct photosensitizer. It incorporates into DNA as 6-thioguanine. The 6-thioguanine is a strong UV-A radiation absorbent, generating reactive oxygen species that lead to severe oxidative DNA injuries and significantly elevate the risk of non-melanoma skin cancers. [46]

mTOR Inhibitors (Sirolimus, Everolimus)*:* mTOR inhibitors exhibit potential antitumor effects. They inhibit the principal signaling pathway involved in cell proliferation, angiogenesis, and metabolism. By inducing cell-cycle arrest and apoptosis in certain cancer cell lines, they can inhibit tumor growth. [47]

3. Viral Oncogenesis

A compromised immune system is permissive for the reactivation and uncontrolled proliferation of oncogenic viruses, which is a primary driver of specific post-transplant malignancies.

This pathway promotes the high incidence of Post-Transplant Lymphoproliferative Disorder (PTLD), which is associated with Epstein-Barr virus (EBV) reactivation. Kaposi Sarcoma is driven by Human Herpesvirus-8 (HHV-8). Anogenital Cancers (cervical, vulvar, anal) are linked to persistent infection with high-risk strains of Human Papillomavirus (HPV). The loss of viral-specific T-cell control is the central mechanism for these cancers.

In summary, the interplay of these pathways (diminished immune surveillance, direct drug-induced carcinogenesis, and unchecked viral replication) creates a perfect storm for carcinogenesis in the transplant recipient. The specific mechanisms associated with major drug classes are summarized in **Table 2**.

IMMUNOSUPPRESSIVE REGIMENS AND MALIGNANCY RISK

The cumulative load of immunosuppression is a recognized, dose-dependent risk factor for cancer following transplantation. This risk stems from a combination of impaired immune surveillance, decreased regulation of oncogenic viruses, and the direct pro-carcinogenic effects of some drugs. The cumulative burden of immunosuppression is crucial, although the risk profile is substantially influenced by the selection of certain medications, as outlined below.

Induction Therapy and Malignancy Risk

Induction drugs, especially those that induce significant lymphocyte depletion, are linked to an increased risk of some malignancies, notably PTLD.

A. *T-Cell Depleting Antibodies*: Anti-thymocyte globulin (ATG) and alemtuzumab induce significant immunosuppression by depleting T-cells (including CD4+ and CD8+ subsets) and natural killer (NK) cells, essential for antiviral and anticancer immunity. This extensive depletion increases vulnerability to virus-related illnesses and malignancies. [48–50] The SIR of lymphoma is markedly elevated with T-cell depleting antibody induction in comparison to IL-2 receptor antagonists (IL-2Ra) or the absence of induction. [51] The risk is contingent upon the particular drug and dosage; for example, OKT3 and high-dose rabbit ATG (rATG) are associated with

Table 2: Mechanisms of immunosuppression-induced malignancy.

Pathway/ component	Normal function	Disrupted effect post-transplant	Major immunosuppressive agent(s) involved
NK cells	Eliminate tumor/virus-infected cells	Reduced immune surveillance	CNIs, T-cell depletion agents
Dendritic cells	Antigen presentation, priming T cells	Impaired tumor and virus detection	CNIs, corticosteroids
CD4+/CD8+ T lymphocytes	Eliminate pro-oncogenic cells	Reduced cytotoxicity/antitumor responses	All types (esp. T-cell depleting antibodies)
Treg cells (CD4+, FOXP3+)	Modulate/suppress immune response	Enhanced suppression of antitumor immunity	Increased with many immunosuppressants
DNA repair pathways	Repair UV/other carcinogen-induced DNA damage	Increased mutation accumulation	Azathioprine, cyclosporine
Antiviral surveillance	Suppress oncogenic virus replication	Increased viral-mediated malignancies	Most (especially with high dosage)

an elevated risk of PTLD. [52–54] Registry analyses indicate that T-cell depleting antibodies, utilized for either induction or rejection therapy, correlate with a greater than two-fold elevation in the incidence of early-onset non-Hodgkin lymphoma. [55]

B. *Interleukin-2 Receptor Antagonists (IL-2Ra):* In contrast to T-cell depleting drugs, induction therapy with IL-2Ra (e.g., basiliximab) does not seem to correlate with a markedly increased cancer risk relative to the absence of induction therapy. [28,56]

Maintenance Immunosuppression and Malignancy Risk

A. *Calcineurin Inhibitors (CNIs):* Cyclosporine and tacrolimus are associated with an increased risk of malignancy, which seems to be dose-dependent. [57] In addition to its general immunosuppressive properties, cyclosporine exhibits direct pro-carcinogenic effects, such as the upregulation of transforming growth factor-beta (TGF-β) and the inhibition of DNA repair mechanisms. [42,44] Initial evidence indicated an increased risk associated with tacrolimus; however, this has since been linked to early and excessive dosing practices. Reduced tacrolimus trough levels correlate with a significantly lower risk of malignancy. [40,58,59]

B. *Azathioprine*: This agent is a recognized etiological factor in the development of neoplasms, especially in NMSC, particularly squamous cell carcinoma. It functions as a direct photosensitizer; its metabolite, 6-thioguanine, integrates into DNA and produces reactive oxygen species upon UV-A exposure, leading to oxidative DNA damage. [46,60,61]

C. *Mycophenolate Mofetil (MMF):* Research demonstrates that the use of MMF correlates with a decreased risk of PTLD. [56,62] This effect may result from a decreased incidence of acute rejection, consequently diminishing the necessity for intensive immunosuppression. The evidence for a protective effect of MMF in other cancer types is less definitive. [40,62]

D. *mTOR Inhibitors (Sirolimus, Everolimus):* Compared to other immunosuppressants, mTOR inhibitors exhibit a lower risk of certain malignancies. The mTOR pathway, which plays a role in cell proliferation, angiogenesis, and metabolism, is inhibited by these agents. [47] Meta-analyses indicate that sirolimus is linked to a 40% reduction in overall cancer risk and a 56% decrease in non-melanoma skin cancer risk. However, this benefit is predominantly observed in patients transitioning to sirolimus from a calcineurin inhibitor-based regimen, rather than in those using it de novo. [39,63] The TUMORAPA trial indicated that transitioning KTRs with a history of squamous cell carcinoma to sirolimus significantly reduced the risk of skin cancer recurrence by nearly 50%. [35] The application of mTOR inhibitors is frequently constrained by adverse effects such as proteinuria, delayed wound healing, and dyslipidemia, with their influence on overall survival remaining ambiguous. [39]

E. *Belatacept:* The co-stimulation blocker presents an increased risk profile for PTLD comparable to that of CNIs and is not advised for recipients who are EBV-seronegative. [64] Initial reports of central nervous system PTLD raised concerns; however, subsequent data from clinical trials indicate only a minor increase in malignancies following transplantation. [65,66]

Other Risk Factors And Adjunctive Strategies

A. *Sun Exposure:* KTRs exhibit a heightened risk for skin cancer, with sun exposure identified as a significant modifiable risk factor. [27,67] Research indicates that sunscreen application decreases the risk of melanoma. [68] Oral nicotinamide chemoprevention reduces keratinocyte cancer incidence in high-risk immunocompetent populations, [38] but a dedicated phase 3 trial in solid-organ transplant recipients found no significant reduction in keratinocyte cancers or actinic keratoses, indicating that efficacy does not extend to the immunosuppressed transplant population. [69]

B. *Rejection Episodes:* The management of rejection episodes, characterized by heightened immunosuppression (frequently utilizing T-cell depleting antibodies), is associated with a greater risk of overall malignancy. An analysis of the ANZDATA registry indicated that acute rejection managed with T-cell depleting antibodies correlated with a significantly increased risk of cancer, especially for genitourinary tract cancers. [70]

MALIGNANCY TRANSMISSION FROM THE DONORS TO THE RECIPIENTS

Numerous donor-transmitted malignancies have been reported, including breast cancer, lung cancer, melanoma, colorectal cancer, Kaposi sarcoma, kidney cancer, and glioblastoma multiforme. Donor transmission is an uncommon yet concerning etiology of malignancy after organ transplant, potentially causing metastatic pathology in the recipient. [71,72] Transmission rates are reported to be less than 0.03%; however, these figures are likely under-reported and underdiagnosed. [73,74] Malignancies such as lung and renal cancer, lymphoma, and melanoma are the most frequently transmitted cancers. [75–77] The likelihood of donor transmission is contingent upon the type and severity of the primary donor malignancy.

A history of lung carcinoma, melanoma, or choriocarcinoma in donors is correlated with a higher transmission and death risk; hence, donors who have these malignancies should be excluded from organ donation lists. Conversely, donors with renal cell cancer lacking capsular invasion and central nervous system tumors (excluding medulloblastoma); consideration and organ donation is deemed acceptable due to the low associated risk, which reflects the diminished metastatic potential of these tumors. [77,78]

Early donor-transmitted malignancy (diagnosed ≤6 weeks post-transplantation) correlated with improved outcomes relative to late donor-transmitted cancer. [76] The 5-year survival rate for KTRs with donor-transmitted cancer was 83%, compared to 93% for those without such cancer, without statistical significance ($P = 0.077$). [75,76] KTR with transmitted kidney cancers had superior outcomes, achieving over 70%

two-year survival following transplantation. In contrast, those with lung cancer and skin melanoma experienced less than 50% two-year survival post-transplantation. [27]

Living versus deceased donors have been connected with diverse malignancy risks. The overall cancer risks are 1080, 1444, and 2018/100,000 patient-years for living-donor KTRs, standard deceased donors, and expanded criteria deceased donor kidneys, respectively. [79] The heightened risk associated with various donor types was not influenced by age, sex, or duration of dialysis. [79] The KTRs of living-donor kidneys exhibited a reduced risk of malignancy, especially concerning genitourinary cancer and PTLD. [79]

Dialysis duration pre-kidney transplant is another recognized factor that increases malignancy risk in KTRs. A study revealed a linear correlation between dialysis duration and solid organ malignancy risk in KTRs, independent of recipient age. [80] Another study assessed the incidence of various cancer types concerning non-renal function intervals (time on dialysis, either while on the waiting list or following transplant failure) and kidney function intervals (time with a functioning graft and under immunosuppression). [30] The incidence of infection-linked and immune-linked malignancies, such as non-Hodgkin lymphoma, Kaposi sarcoma, non-epithelial skin cancer, and lip cancer, was elevated during kidney function intervals. Conversely, the incidence of ESRD-linked malignancies, specifically thyroid and kidney cancer, was reduced during these intervals. Status changes (non-renal function interval/kidney function interval) correlated with varying incidences of melanoma, pancreatic, lung, non-Hodgkin's lymphoma, and non-epithelial skin cancers, which were more prevalent during function intervals. On the contrary, thyroid and renal malignancies exhibited higher incidences during non-function intervals. This indicates significant short-term kidney dysfunction and the effects of immunosuppressive agents on cancer incidence. [30] **Table 3** summarizes the cancer risk, effects, and common immunosuppressive agents.

OTHER FACTORS AFFECTING POST-TRANSPLANT MALIGNANCY DEVELOPMENT

Different factors affect the risk of malignancy development after kidney transplantation, such as patient age, duration of dialysis, and others (**Table 4**).

Table 3: Cancer risk and effects of common immunosuppressive agents.

Agent/class	Mechanism	Effect on cancer risk	Evidence/notes
CNIs (Cyclosporine, Tacrolimus)	T-cell suppression, DNA repair impact	Increased (dose-dependent)	More with high/initial dosing
Azathioprine	DNA incorporation, repair inhibition	Increases skin/myelodysplasia risk	Especially squamous cell carcinoma
mTOR inhibitors (Sirolimus, etc.)	mTOR blockade, cell cycle arrest	Decreases risk (esp. skin cancer)	The benefit is seen mostly after switching
T-Cell depleting antibodies	Profound lymphocyte suppression	Increased PTLD, non-Hodgkin lymphoma	Dose/type dependent
MMF	Antimetabolite inhibits T- and B-lymphocyte proliferation	Reduced PTLD risk; neutral or unclear for other cancers	Often related to lower rejection
Belatacept	Co-stimulation blockade	Similar PTLD risk to CNI	Not for EBV-negative patients

Table 4: Characteristics, their correlation with malignancy incidence, and key notes.

Characteristic	Correlation with malignancy incidence	Key notes/study findings
Recipient age	Increased age → higher overall cancer risk	Older recipients have higher post-kidney transplant malignancy rates; age is an independent risk factor.
Dialysis duration pre-RTx	Longer duration → higher risk, especially for solid organ malignancies	Linear correlation with risk, even after adjustment for age, is specifically noted for kidney cancer.
Donor type	Living donor → lower cancer risk Standard deceased donor → moderate risk Expanded criteria deceased donor → highest risk	Cancer incidence per 100,000 patient-years: Living donor = 1080; Standard deceased donor = 1444; Expanded criteria deceased donor = 2018. Living donor kidneys especially reduce genitourinary cancer and PTLD risk.
Donor cancer history	Cancers with high metastatic potential (lung, melanoma, choriocarcinoma) → high recipient risk; RCC without capsular invasion/CNS tumors (not medulloblastoma) → low risk	Certain donor cancers contraindicate donation due to high transmission/mortality risk, while others with low metastatic potential may be acceptable.
Recipient sex	Females may have a higher overall risk than males in some populations	Notably higher rates of bladder, renal, and liver cancer in female recipients in some studies.
Age at transplant (young)	Younger recipients (<20 years) may have the highest incidence of post-kidney transplant malignancy in some populations.	Observed in a Chinese cohort, possibly due to longer immunosuppression

RCC, renal cell carcinoma; PTLD, post-transplant lymphoproliferative disorder.

Younger recipients (<20 years) may have the highest SIR for post-kidney transplant malignancy in some populations, reflecting low general-population baseline risk in this age group rather than higher absolute incidence.

POST-RENAL TRANSPLANT MALIGNANCY SCREENING

The significantly elevated cancer risk in KTRs necessitates a thorough screening approach to enable early detection and improve outcomes. The optimal approach is poorly defined, often relying on extrapolations from general population guidelines that may insufficiently account for the unique risks and divergent mortality factors in this cohort. A critical unmet need in transplant healthcare is the development of evidence-based, cost-effective screening protocols tailored for kidney transplant patients.

General Principles and Challenges

It is agreed that KTRs must, at the very least, comply with cancer screening protocols set for the general population. This baseline method neglects to include the modified risk profile of transplant recipients. Significant obstacles hinder the development of precise post-transplant screening techniques. The absence of extensive randomized controlled trials showing a mortality advantage for most cancer screening modalities in KTRs results in recommendations often relying on retrospective data, expert consensus, and modeling analyses. Moreover, the conflicting mortality risks from cardiovascular disease and infections may reduce the relative advantages of prolonged cancer screening for some individuals. Any screening program must be assessed for cost-effectiveness, since the financial burden of comprehensive screening for all KTRs might be considerable. Ultimately, patient adherence and systemic obstacles, including access to specialized care, profoundly influence the practical efficacy of any screening technique.

Evidence for Site-Specific Screening

The evidence supporting screening varies significantly by cancer type, reflecting their differing incidence and risk profiles post-transplant.

- *Skin Cancer (Non-Melanoma and Melanoma):* Screening for skin cancer is the most highly endorsed and widely recommended approach. The increased prevalence and severity of squamous cell carcinoma in KTRs need continuous, lifelong dermatological monitoring. Expert recommendations advocate for an annual comprehensive skin examination by a dermatologist, with increased frequency (e.g., every 3–6 months) for high-risk individuals (e.g., those with fair skin, significant sun exposure, or a history of skin cancer). [81,82] Educating patients on self-skin exams and sun protection is fundamental to prevention.
- *Renal Cell Carcinoma:* KTRs have a significantly heightened risk of cancer in their native kidneys, mostly attributable to acquired cystic kidney disease. The absolute risk is significant, although the cost-effectiveness of universal renal ultrasonography screening remains contentious. Modeling research indicated no benefit and substantial expense for screening all KTRs. [83] Thus, a focused strategy is often preferred, advocating for yearly renal ultrasound for high-risk people, including those with a prolonged dialysis history, acquired cystic kidney disease, or a history of renal cell carcinoma before transplantation. [83,84]
- *Cervical Cancer:* Due to the increased risk of HPV-related anogenital malignancies, cervical cancer screening is deemed essential. Guidelines generally advocate for more regular cervical cytology (Pap smears) than for the general population, commonly yearly, although particular intervals may differ by institution and guideline. [17,43] The function of HPV co-testing is changing, yet it remains broadly endorsed.
- *Colorectal Cancer:* The risk of colorectal cancer is considerably increased. Modeling studies have shown that screening in KTRs is cost-effective. [84] KTRs are advised to adhere to regular population standards for colorectal cancer screening, such as colonoscopy, commencing at age 50, or earlier if there is a familial history or other risk factors. The decision between colonoscopy and fecal immunochemical testing must be personalized.
- *Breast and Prostate Cancer:* For malignancies such as breast and prostate, where the post-transplant SIR is not markedly increased, screening guidelines often align with those for the general population. [31,85] This includes conventional mammography and deliberation on prostate-specific antigen (PSA) testing according to established age and risk variables. The emphasis is on ensuring that KTRs are not neglected in follow-up and have these standard-of-care examinations.

Gap in Screening Adherence

Notwithstanding the acknowledged elevated cancer risk, empirical evidence repeatedly indicates that KTRs are insufficiently checked. A substantial cohort study revealed concerningly low percentages of individuals who were "up-to-date" with screenings: just 22.5% for colorectal cancer, 30.2% for cervical cancer, and 8.6% for breast cancer. [85] This indicates a significant implementation deficiency. Barriers are multifaceted, including insufficient patient knowledge, ambiguous delineation of responsibilities between primary care doctors and transplant facilities, and restricted access to healthcare resources.

Limitations

This review has several limitations that should be considered when interpreting its findings. First, the literature search was restricted to studies published in English over the last five years, which may have introduced selection bias and excluded relevant older foundational studies or data from non-English-speaking regions. Second, the majority of the evidence presented is derived from observational studies, registry analyses, and retrospective cohort studies. While these provide valuable real-world insights, they are inherently susceptible to confounding factors, such as variations in

immunosuppressive protocols, patient selection criteria, and transplant center practices, which limit the generalizability of the conclusions and preclude the establishment of causality. Related to this, the potential for immortal time bias in some cited observational data, the inability to deeply explore center-specific effects due to the aggregate nature of registry data, and the lack of a systematic meta-analysis to quantitatively evaluate the effectiveness of interventions such as switching to mTOR inhibitors further constrain the strength of the conclusions that can be drawn. Furthermore, the narrative structure of this review presents its own constraints. Specifically, the "Outcome of Allograft and Recipient" section interweaves mortality statistics, cancer-specific prognoses, and management strategies. A more structured approach, separating this content into distinct subsections such as "Epidemiology and Mortality" and "Management Impact on Outcomes," would have enhanced clarity and flow. This reflects a broader challenge in synthesizing such a complex and multifaceted topic. Finally, the rapid evolution of immunosuppressive regimens and oncology treatments (e.g., immune checkpoint inhibitors) means that the landscape of post-transplant malignancy management is continually changing, and some recommendations may become outdated quickly.

PROSPECTIVE

The future of decreasing cancer-related mortality in KTRs depends on a systematic enhancement of individualized oncological monitoring systems. In the future, research should shift from retrospective observation to prospective intervention, emphasizing four critical priorities:

Initially, enhanced risk classification is essential for the individualized initiation of immunosuppression from the beginning. This necessitates the development and validation of integrated risk-prediction models that encompass recipient characteristics (age, genetics, pre-existing diseases), virus serostatus (EBV, HHV-8, HPV), and intended immunosuppressive regimens. Such models might facilitate a proactive, rather than a reactive, strategy for cancer prevention.

Secondly, it is imperative to build evidence-based prevention and screening strategies. This encompasses assessing the extensive application of pre-transplant HPV and HBV vaccination, conducting studies for additional viral carcinogenic targets, and evaluating the cost-effectiveness of targeted screening measures beyond general population standards. The objective is to transition from standardized screening to protocols customized to the recipient's individual risk profile for cancers such as PTLD, skin cancer, and anogenital malignancies.

Ultimately, overseeing the oncology-transplant interface necessitates immediate focus. The effectiveness and safety of new cancer treatments, especially immune checkpoint inhibitors, must be thoroughly assessed in transplant recipients using prospective registries and clinical studies. Moreover, investigation into the management of immunosuppression during and following standard cancer therapies (chemotherapy, radiation) is essential to enhance both oncological control and graft preservation.

CONCLUSIONS

Post-transplant malignancy is a preeminent challenge to the long-term survival of KTRs. Addressing this requires a fundamental shift from a one-size-fits-all immunosuppressive model to a strategy of personalized oncological vigilance. The interplay of chronic immunosuppression, viral oncogenesis, and recipient-specific factors creates a perfect storm for carcinogenesis, leading to a disproportionate burden of virus-associated and skin cancers. While mTOR inhibitors offer a promising tool for managing certain malignancies, their benefits must be balanced against potential adverse effects. The management of these patients is fraught with dilemmas, particularly in balancing the reduction of immunosuppression to combat cancer against the risk of precipitating allograft rejection. Current evidence, largely constrained to observational data, is insufficient to resolve these conflicts. Therefore, the path forward demands prospective, collaborative research to refine risk stratification, validate screening protocols, and develop evidence-based, individualized therapeutic strategies that simultaneously safeguard both the patient and the graft.

LEARNING POINTS

A. KTRs face a 3 to 4 times greater risk of cancer, making it a significant cause of mortality post-transplant. High rates of skin, lymphoma, and virus-associated malignancies characterize the cancer spectrum.
B. Chronic immunosuppression is the main cause, impairing immune surveillance. Some medications directly cause cancer and reactivate oncogenic viruses.
C. Type and level of immunosuppression affect cancer risk. T-cell depleting antibodies and high-dose calcineurin inhibitors increase risk; however, mTOR inhibitors can reduce skin cancer risk.
D. Post-transplant cancer management requires a delicate balance between lowering immunosuppression and preventing organ rejection. This decision greatly affects patient and graft survival.
E. Transplant recipients often fail to follow current cancer screening protocols. Prospective research to establish tailored risk assessment, validated screening techniques, and better treatment solutions through interdisciplinary collaboration is important.

AUTHORS' CONTRIBUTION

All authors have significantly contributed to the work, whether by conducting literature searches, drafting, revising, or critically reviewing the article. They have given their final approval of the version to be published, have agreed with the journal to which the article has been submitted, and agree to be accountable for all aspects of the work.

SOURCE OF FUNDING

None.

CONFLICT OF INTEREST

None.

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