10.5152/turkjnephrol.2024.23631

Review

Turkish Journal of Nephrology

Post-transplant Malignancies: Current Perspective on Risk Factors, Prevention, and Management

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ABSTRACT

Post-transplant malignancies arise from a complex interplay of factors, with immunosuppression playing a pivotal role. Chronic immunosuppressive treatment compromises the recipient's immune system, rendering it less efficient at recognizing and eliminating malignant cells. Additionally, viral infections, especially Epstein–Barr virus and Human papillomavirus, are major contributors to malignancy development. Lifestyle modifications, including smoking cessation and sun protection, are recommended for reducing certain cancer risks. Regular screening for malignancies may provide the early diagnosis as in the general population. After the diagnosis of cancer, tailoring immunosuppressive regimens to maintain graft function is crucial. Treatment options, such as chemotherapies, targeted therapies, and immunotherapies, should be selected with consideration of the patient's overall health and the potential impact on the transplanted organ. A multidisciplinary approach is required in order to provide optimal treatment to our kidney transplant recipients. With this review article, we aim to discuss pathophysiological mechanisms, review guidelines, and provide information on the incidence and management options for various cancers.

Keywords: Immune checkpoint inhibitors, malignancy, prevention, kidney transplantation, screening

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Received: August 22, 2023 **Revision Requested:** November 22, 2023
Last Revision Received: March 16, 2024 **Accepted:** April 4, 2024 **Publication Date:** August 26, 2024

Cite this article as: Velioglu A, Barutcu Atas D, Hellemans R. Post-transplant malignancies: current perspective on risk factors, prevention, and management. *Turk J Nephrol.* 2024;33(4):316-323.

INTRODUCTION

Kidney transplantation is the most effective treatment that provides a better quality of life and extends the expected lifespan in end-stage kidney disease patients. However, cancer risk is greater among kidney transplant (KT) recipients than in the general population.[1] Additionally, compared to non-transplant cancer patients, solid organ transplant recipients have higher cancer-related mortality rates.[2] Cancer is the third leading cause of mortality among KT recipients, after cardiovascular disease and infections.[3] The increased cancer risk can be multifactorial and is mostly attributed to the effects of immunosuppressive drugs. Age, sun exposure, and a history of cancer are recipient-related risk factors. Donor-transmitted cancers are rare. The most common types of cancer seen after kidney transplantation include non-melanoma skin cancers, lymphoma, and colorectal cancer.

Clinicians are compelled to address preventive, screening, and treatment strategies for this at-risk population due to the rising incidence of cancer. While cancer screening programs in the general population are well established, the frequency and preferred screening methods for solid organ transplant recipients are not clear.[4] Screening for skin, cervical, and colorectal cancers is part of post-transplant follow-up in many transplant centers. Early diagnosis and effective cancer treatment, including surgery, chemotherapy, or radiotherapy, are vital for KT recipients. Immunosuppressive

drug modification after cancer diagnosis is also another challenging step in the follow-up. In light of all this data, we can conclude that special emphasis on post-transplant malignancies is still needed in clinical practice. This article reviews guidelines, discusses pathophysiological mechanisms, and includes information on the incidence and management options of various cancers from a current perspective.

EPIDEMIOLOGY

Kidney transplant recipients have a higher risk of developing malignancy than the general population.[5] The peak incidence varies with age but is generally observed 3-5 years after transplantation.[6] A Swiss single-center study reported the outcomes of 293 KT recipients transplanted before 2000, and they found that the incidence of cancer after kidney transplantation was 4.4% at 10 years and 14.6% at 20 years. The incidence of non-melanoma skin cancer was 10.3% and 33.5%, respectively.[7] In a long-term retrospective study by Fröhlich et al,[8] the incidence of overall newly developing cancer was found to be 1% per year, excluding cutaneous cancers other than melanoma.

The standardized incidence ratio (SIR) quantifies the elevated risk of developing malignancies in KT recipients compared to those in the general population who have the same age and gender characteristics. The greatest SIR is seen with Kaposi sarcoma. Other cancers with the highest SIRs are lymphoma, non-melanoma skin cancers, anogenital, and lip cancers.[1] Some cancers' SIRs are not increasing following transplantation, such as prostate, breast, and ovarian cancer SIRs, which are comparable to the general population. Other prevalent malignancies with a modestly increased risk include colorectal and lung cancers (Figure 1).[9,10]

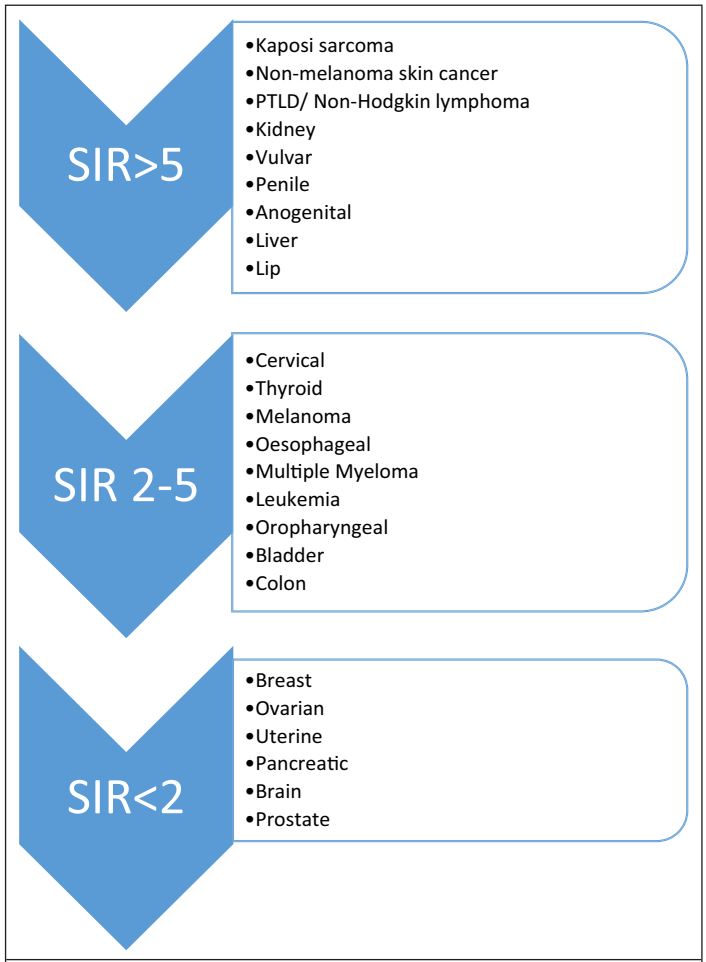

Figure 1. The standardized incidence ratio (SIR) quantifies the elevated risk of developing malignancies in KT recipients compared to those in the general population.

It is well known that a recipient's age plays a substantial role in the increased prevalence of post-transplant malignancy among KT patients. However, studies have shown a greater relative risk of developing malignancy in young organ transplant recipients compared to older recipients.[11,12] This can be explained by the relatively low incidence of malignancy found in the younger general population.

After the development of malignancy, the mortality risk is also significantly high. Indeed, in a recent analysis of registry reports from the United States, cancer-specific mortality was higher compared with non-transplanted cancer patients, particularly in the patients with melanoma, colorectal cancer, and breast cancer after adjustment for stage and treatment.[13] With advancements in transplant practice, transplant patients are experiencing longer lifespans and improved outcomes. Consequently, it is expected that the incidence of cancer will increase as a major contributor to morbidity and death in KT patients.

MAIN POINTS

- Recipients of kidney transplants have a higher incidence of cancer and cancer-related mortality than individuals of the same age and gender in the general population.
- Multiple factors, including viruses and altered T cell functions by immunosuppression, contribute to the elevated risk of cancer in kidney transplant recipients.
- To avoid early recurrence and cancer-related mortality, kidney transplant candidates with previous cancer should undergo a waiting period of 2-5 years after cancer treatment, depending on the cancer type and stage.
- Cancer screening should be individualized for each patient, taking into consideration their comorbidities and individual cancer risks.
- When a transplant recipient develops cancer, treatment plans include gradually reducing immunosuppression and utilizing standard cancer treatments, taking into consideration drug doses, drug interactions, and how chemotherapeutic agents may impact graft function.

PATHOPHYSIOLOGY AND SPECIFIC RISK FACTORS

Immunosuppressive therapy is considered a leading cause of post-transplant malignancies. The weakened immune

surveillance of neoplastic cells seems to be the most important mechanism for pathogenesis. In an immunocompetent condition, protective mechanisms of immune surveillance remove cancerous cells, suppress viral replication, and inhibit viral-induced cell replication. However, this immunosurveillance pathway may be compromised under long-term immunosuppression, and may result in uncontrolled cell proliferation and cancer in solid organ transplant recipients.[14]

Natural killer (NK) cells and dendritic cells, which are members of the innate immune system, play a crucial role in immune responses against viral infections and tumor cells by identifying and releasing cytotoxic granules that induce cell death in tumor or virally infected cells.[15,16] Reduction in NK cell activity and decreased dendritic cell by immunosuppressive agents can cause loss of cancer immunosurveillance.[15,16] Additionally, adaptive immune cells and molecules stop them from transforming into tumor cells. Adaptive immune cells ($CD4^+$ and $CD8^+$ T cells) are very important for immunosurveillance because they eliminate the cells exposed to the prooncogenic stimuli. In transplant recipients, T_{reg} cells (especially $CD4^+ FOXP3^+ CD127^{low}$ T cells) potentially inhibit the antitumor response through the inhibition of effector T cell proliferation, thereby allowing tumor cells to escape the immune system.[15,16]

Immunosuppressive Drugs

Besides impaired immunosurveillance, immunosuppressive agents can also increase the risk of cancer development through other mechanisms, including impaired DNA repair mechanisms and failure to inhibit oncogenic virus replication.[16]

In general, KT recipients receive antibody induction therapy and multidrug maintenance immunosuppressive treatment, and some also require treatment for rejection. Therefore, it is exceedingly challenging to distinguish the effect of a single immunosuppressive agent on cancer development.

Numerous agents have been used as induction therapy, including lymphocyte-depleting antibodies, anti-IL-2 receptor (CD25) antibodies, and alemtuzumab (anti-CD52). In an older analysis by the Collaborative Transplant Study (CTS) conducted on about 200 000 recipients over a 10-year period, the incidence ratio of lymphoma was greater with T-cell-depleting antibody induction compared to IL-2Ra or no induction therapy.[17] Furthermore, the ANZDATA registry provided data indicating that the T-cell-depleting agents were linked to a greater than 2-fold rise in the incidence of post-transplant lymphoproliferative disorder (PTLD).[18] These increased risks may be attributed to the use of ATG at larger doses in earlier years. Indeed, a more recent US registry analysis did not find an excess risk of PTLD with polyclonal T-cell-depleting (e.g., ATG) induction.[19] However, the same study found an increased incidence of melanoma with these drugs. Induction therapy with alemtuzumab, an anti-CD52 monoclonal antibody, was associated with a significant increase in PTLD, colorectal cancer, and thyroid cancer.[19] Non-depleting induction therapy with IL-2Ra, on the other hand, has not been associated with a significant increase in cancer or PTLD risk.[17,20] However, there is insufficient high-quality data to accurately assess the long-term adverse effects of induction therapy.

With regard to maintenance immunosuppressive treatments, there is compelling evidence that some are oncogenic. Calcineurin inhibitors (CNI) increase the synthesis of transforming growth factor (TGF) beta, vascular endothelial growth factor (VEGF), and IL-6, leading to a decrease in DNA repair capacity, which is particularly important in skin cancers.[3] This increased risk has been found to be associated with higher trough levels, and decreased cancer risks were achieved with reduced doses in a case–control study.[21]

Azathioprine use increases the risk of non-melanoma skin cancer with prolonged use, and possibly also the risk of other cancers.[22] Currently, it has been largely replaced by mycophenolate analogs. Studies from the United States and CTS registries found no increased risk of cancer in patients with mycophenolate mofetil.[23]

Regimens containing a mammalian target of rapamycin inhibitor (mTORi) have been associated with a lower risk of non-melanoma skin cancers. [24-26] Additionally, switching to an mTORi after the diagnosis of Kaposi's sarcoma may result in remission.[27] However, current evidence does not recommend the use of an mTORi purposefully to decrease cancer incidence. In the meta-analysis published by Knoll et al,[26] despite a lower risk of malignancy, patients taking sirolimus were found to have a higher mortality risk owing to cardiovascular and infection-related deaths.

The BENEFIT study raised concerns about a possible increase in the risk of PTLD with belatacept.[28] Nevertheless, a comprehensive meta-analysis of 5 trials conducted by Cochrane, comparing belatacept to calcineurin inhibitors (CNI), did not find substantial evidence indicating an elevated risk of PTLD.[29] However, the PTLD numbers are so low and the experience too limited that it is impossible to draw any definitive conclusions.

Sunlight Exposure

Sunlight exposure is an important risk factor for skin cancer. With the concomitant use of immunosuppressive drugs, particularly azathioprine, UV radiation can reduce the capacity for immune-mediated tumor surveillance and also increase the risk of pro-oncogenic mutations development.[30] A screening tool called Skin and Ultraviolet Neoplasia Transplant Risk Assessment Calculator (SUNTRAC) is designed to assess the risk of skin cancer in post-transplant patients. A comprehensive multicenter study involving 6340 transplanted patients demonstrated that the SUNTRAC tool predicts skin cancer in organ transplant recipients.[31]

Viral Infections

The leading oncogenic viruses are Epstein–Barr virus (EBV), human herpesvirus 8 (HHV-8), human papillomavirus (HPV), and Merkel cell polyomavirus. The viruses associated with post-transplant malignancies are shown in Figure 2.[32] Epstein–Barr virus is associated with PTLD, responsible for more than half of all PTLD cases. A 20-fold greater incidence of PTLD is reported in EBV-negative recipients who received kidneys from EBV-positive donors.[33] The primary EBV infection, especially in pediatric cases, can cause early onset PTLD, mostly seen in the first year after transplantation.[34] Human herpesvirus 8 can be associated with Kaposi's sarcoma. Patients with HPV are at increased risk of cervical, anogenital, and nasopharyngeal cancers. Merkel cell polyomavirus is a very rare virus, but it can be present in Merkel cell carcinoma of the skin. Besides these viruses, hepatitis B and C may cause hepatocellular carcinoma (HCC) in cirrhotic patients. The BK virus has been identified in some studies as having an association with uroepithelial cancers.[35] However, this association is primarily supported by case reports and series.

Acquired Cystic Kidney Disease

Although KT recipients with polycystic kidney disease do not seem to have a higher risk of kidney cell carcinoma, a cohort study consisting of 561 KT recipients showed that those with acquired cystic kidney disease have a higher risk of kidney cell carcinoma (19.4% vs. 0.5%).[36] Regarding the higher prevalence of acquired cystic disease in dialysis patients, current data clearly identify KT recipients with acquired cysts in their native kidneys as having a high risk for kidney cell carcinoma.

Previous History of Cancer

Kidney transplant recipients with a history of pre-transplant malignancy are at increased risk for cancer recurrence. In a meta-analysis published in 2017 that included 32 cohort studies, the presence of pre-transplant cancer history was found to be associated with an increased risk of all-cause mortality, cancer-related mortality, and de-novo cancer after transplantation, compared to transplant recipients without pre-transplant cancer.[37] Therefore, KT recipients with pre-transplant cancer should be considered high-risk patients requiring careful follow-up strategies. Also, for KT candidates with a history of cancer, waiting time periods are recommended by the Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline for the care of kidney transplant candidates.[38] According to this guideline, no waiting period is necessary for low-risk tumors, such as localized basal cell carcinoma, superficial bladder cancer, low-grade prostate cancer, and incidental T1 kidney cell carcinomas. At least a 2-year waiting period is recommended for most other tumors. However, for high-risk tumors, advanced-stage tumors, and invasive tumors, a 5-year waiting period is required after initial remission. All uncontrolled and untreated cancers are accepted as contraindications for kidney transplantation.

Despite this simplified and practical approach, the KDIGO guideline for KT candidates also proposes that the timing of KT following potentially curative treatment for cancer is dependent on the cancer type and stage at the initial diagnosis. Therefore, transplantation decisions for candidates in cancer remission should be individualized through collaborative efforts involving oncologists, transplant physicians, patients, and their healthcare providers.[38]

Recent KDIGO guidelines for KT candidates suggest that candidates with multiple myeloma (MM) or monoclonal gammopathy of kidney significance should be excluded unless they have received a potentially curative treatment regimen and are in stable remission with a grade 2D evidence level. In fact, the prognosis of patients with MM has improved in recent years due to the use of novel therapies, such as autologous stem cell transplantation. It is recommended that transplant units reconsider kidney transplantation as a feasible treatment option for patients with MM.

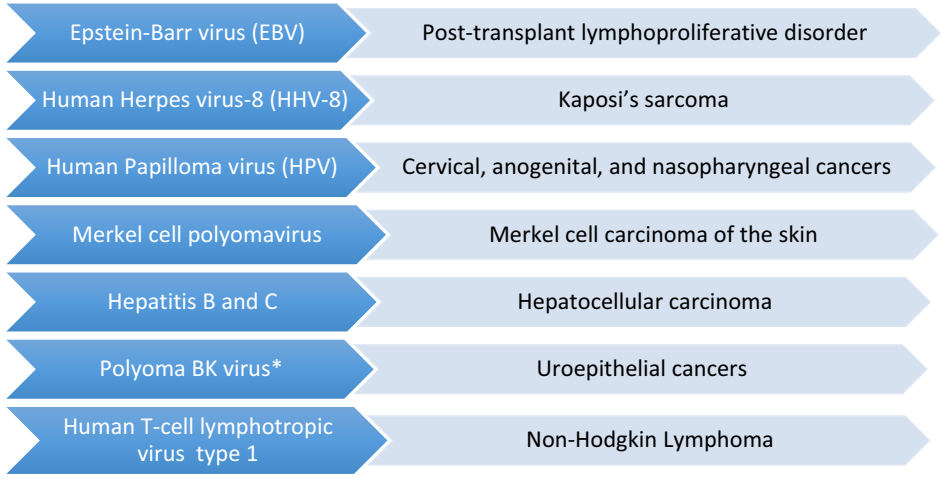

Figure 2. Oncogenic Viruses-Associated Post-transplant Malignancies[32] *The association between BK Virus and urogenital tumors is based on case reports and series.

PREVENTION AND SCREENING

It is well known that the risk of cancer development is increased in KT recipients and is associated with a poor prognosis. Therefore, prevention measures should be applied to all KT recipients. Avoiding excessive immunosuppression, sun protection, vaccinations, and smoking cessation are the most important preventative measures. Among vaccinations, aside from hepatitis B and C, which help prevent HCC resulting from chronic hepatitis and cirrhosis, in recent years HPV vaccines have prevented HPV-related cancers in transplant recipients, similar to the general population. Human papillomavirus vaccines, especially multivalent ones, are safe for transplant recipients and seem to be more effective when administered before transplantation.[1]

Screening is also one of the most effective methods for preventing cancer in the general population. It is important content because it aims to detect abnormal pre-cancerous lesions in a target population so that lesions can be recognized and treated in the earliest period, and we may prevent aggressive and advanced-stage malignancy. However, current evidence of cancer screening specific to the transplant population is limited only to observational data. The efficacy of screening tests in the KT population is mainly unknown, and there are no randomized controlled trials to inform decision-making. Given the limited evidence available for cancer screening in KT recipients, the majority of transplant-specific recommendations parallel those for the general population. Although screening for skin cancer is addressed uniformly in almost all guidelines, screening recommendations for other malignancies are variable.[4] Self-screening (monthly) may be advised for patients, and an annual clinical skin examination is recommended by all relevant nephrology guidelines.[39-43] In these guidelines, screening recommendations for breast, cervical, lung, colorectal, liver, and prostate cancers are mostly derived from general population guidelines. Even though routine screening for kidney cell carcinoma has not been recommended by the guidelines, a study published in 2011 showed that ultrasonographic screening (at least annually) of the native kidneys may be considered a cost-effective method for patients at risk of developing kidney cell carcinoma (presence of acquired cystic disease, family history, history of heavy smokers, or long-term analgesics use) to detect occult malignancy.[44] Routine monitoring of EBV viral load in high-risk patients (donor EBV seropositive/recipient seronegative) is recommended for early detection of possible PTLD as an expert opinion in the KDIGO clinical practice guideline for the care of KTrecipients.[41] The American Society of Transplantation (2009) guideline recommended some additional screening procedures. It recommends more frequent screening than yearly for high-risk skin cancer patients. Also, urologic examination is advised in all cases of new-onset microhematuria for individuals at an increased risk of urogenital malignancies (those with prior cyclophosphamide usage or a history of analgesic nephropathy). Cervical cancer screening is recommended by all guidelines. Yearly pelvic exams and Pap smears are recommended, even for patients who have undergone total hysterectomies. In addition, KDIGO, AST, and the Canadian Society of Transplantation (CST) guideline advise that patients with hepatitis B or hepatitis C undergo screening for hepatocellular carcinoma every 6 months using abdominal ultrasound and serum alpha-fetoprotein level.[45] The current screening strategies outlined in the guidelines are summarized in Table 1.

Despite these recommendations, a population-based cohort study investigating the cancer screening adherence of solid organ recipients in the United States showed that only 40%-50% of the recipients had received up-to-date screening for cervical, breast, and colorectal cancers.[46] This can be attributed to limited awareness, fear of cancer, prioritizing graft functions, and other comorbidities. Nevertheless, it should be known that the performance of screening tests on KT recipients remains unclear due to a lack of randomized controlled studies.

TREATMENT

Although specific cancer treatments, including chemotherapy and radiotherapy, are the cornerstone, adapting and/or reducing immunosuppression is also crucial in the follow-up after a cancer diagnosis. Unfortunately, prospective studies on this are lacking. Reducing or stopping of antimetabolites and reducing the dose of CNIs are often considered to reduce the risk of recurrence after curative treatment. Switching from CNI to an mTORi may provide some benefit in regard to remission or prevention of recurrence in non-melanoma skin cancers.[47] However, the benefit of mTORi(s) is less clear in other cancers. Of note, large registry studies and meta-analyses of RCTs did not show a reduction in overall cancer incidence (other than non-melanoma skin cancer) in KT recipients using mTORi(s).[26] Studies on cancer patients suggest that the anticancer effect of mTORi(s) is dose-dependent and that the anticancer dose of mTORi(s) is frequently poorly tolerated.[48] Switching to mTORi(s) plus low-dose CNIs might be tolerated better and reveal less rejection risk. Nevertheless, it is unknown if this combination can improve the prognosis once post-transplant cancer occurs. Therefore, understanding the balance between immunologic risk and the severity of the malignancy is required to optimize immunosuppressive dosages to avoid acute rejection and regression of cancer.

During cancer treatment, dosing of the chemotherapeutics and drug–drug interactions are the most important considerations. Most transplant patients with cancer face more toxicity than non-transplanted cancer patients, which may limit their ability to receive effective cancer treatment. Oncologists and nephrologists should also be aware of adverse events from chemotherapeutics. Regarding the evolution of novel anticancer therapies in recent years, clinicians should gain data on specific anticancer therapies, especially molecular targeted therapies. Anti-VEGF antibodies and tyrosine kinase inhibitors have been linked to hypertension and proteinuria.[49] Proteinuria results

Table 1. Current Cancer Screening Recommendations for Kidney Transplant Recipients Based on Guidelines and Expert Opinions[40-45]

Type of Organ	Screening Recommendations	Related Guidelines or Expert Opinions
Skin	Monthly self-skin examination and 6- to 12-monthly total body skin examination by expert physicians and dermatologists.	KDIGO 2009[40] AST 2000[45] CST 2010[42] KHA-CARI 2012[43]
Lung	For adults aged 55-79 years, annual low-dose computed tomography scans for those who have smoked 1 pack per day for 30 years or equivalent.	Extrapolation from general population guidelines.
Breast	For women aged 50-74 years, screening mammography once every 2 years.	AST 2000[45] ERPG 2002[41] KDIGO 2009[40] CST 2010[42]
Liver	Routine screening using US, with and without α-fetoprotein, every 6 months in patients with cirrhosis.	AST 2000[45] KDIGO 2009[40] CST 2010[42]
Kidney	Routine screening for kidney cell carcinoma using US is not recommended for all recipients of transplants, except for high-risk individuals.	Based on a study by Wong G et al.[44]
Colon–rectum	For adults aged 45-75 years, fecal immunochemical testing biennially, sigmoidoscopy every 5 years, or colonoscopy every 5-10 years.	AST 2000[45] ERPG 2002[41] KDIGO 2009[40] CST 2010[42]
Cervix	Annual Pap testing with HPV testing every 3-5 years starting at the age of 25 years until 74 years.	AST 2000[45] ERPG 2002[41] KDIGO 2009[40] CST 2010[42] KHA-CARI 2012[43]
Prostate	For men aged 55-69 years, screening decisions should be individualized. Men ≥70 years should not be routinely screened for prostate cancer.	AST 2000[45] ERPG 2002[41]

AST, American Society of Transplantation; CST, Canadian Society of Transplantation; ERBG, European Renal Best Practice Guideline; HPV, human papillomavirus; KDIGO, Kidney Disease: Improving Global Outcomes; KHA-CARI, Kidney Health Australia Caring for Australians with Renal Impairment; US, ultrasound.

from a combination of diminished nitric oxide production and endothelial injury and is commonly accompanied by hypertension. Additionally, transplant patients using these drugs have a higher risk of thrombotic microangiopathy. BRAF inhibitors have been associated with acute interstitial nephritis and acute tubular injury. Anaplastic lymphoma kinase inhibitors (crizotinib) and CDK4/CDK6 inhibitors (abemaciclib) can cause creatinine rise without kidney impairment due to the inhibition of tubular secretion of creatinine. Hypomagnesemia is an adverse event of using cetuximab, an EGF inhibitor.

Another special topic that should be considered is the use of immune checkpoint (ICP) inhibitors in transplant recipients. These drugs are effective in some cancer types, such as non-small cell lung cancer, melanoma, and kidney cell carcinoma. Nevertheless, it is possible that they might result in graft rejection as a result of enhanced T-cell responses specifically targeting the graft in KT recipients.

Previous studies showed that at least 40% of patients suffered rejection after the use of ICP inhibitors, and half of those patients lost grafts due to rejection.[49] In a recent study of 17 KT recipients with advanced cancer, the authors found no cases of irreversible allograft rejection after exposure to ICP inhibitors while maintaining baseline immunosuppression.[50] Prophylactic steroid use and/or maintaining baseline higher immunosuppression may be associated with a decreased risk of rejection, but possibly worse malignancy outcomes. Therefore, as part of a collaborative decision-making process with patients, the advantages of ICP inhibitors should be weighed against the risks of allograft rejection.[51]

More recently, cellular therapies involving EBV-directed cytotoxic T-cell therapy and chimeric antigen receptor-T therapy (CAR-T) have been introduced for conventional therapy-refractory PTLD cases.[49] However, again, clinicians should be aware that there is a risk of rejection, acute kidney injury, and cytokine release syndrome in these challenging therapy options.[52] More research is needed to determine future directions in PTLD.

CONCLUSION

Kidney transplant recipients are at a greater risk of developing cancer and cancer-related death compared to age- and gender-matched persons in the general population. Regular screening, early diagnosis, avoidance of risk factors, and effective cancer treatment can reduce morbidity and mortality in KT patients

with cancer. A multidisciplinary approach is required to provide optimal care for these patients.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – A.V., D.B.A., R.H.; Design – A.V., D.B.A., R.H.; Supervision – A.V., D.B.A., R.H.; Resource – A.V., D.B.A., R.H.; Materials – A.V., D.B.A., R.H.; Data Collection and/or Processing – A.V., R.H.; Analysis and/or Interpretation – A.V., D.B.A., R.H.; Literature Search – A.V., D.B.A.; Writing – A.V., D.B.A., R.H.; Critical Review – A.V., R.H.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: The authors declared that this study has received no financial support.

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