De Novo Malignancies after Kidney Transplantation

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Abstract
Cancer is an important outcome after kidney transplantation because it is the second leading cause of death in most Western countries. The excess risk of cancer after transplantation is approximately two to three times higher than the age- and sex-matched general population, driven largely by viral- and immune-related cancers. Once cancer develops, outcomes are generally poor, particularly for those with melanoma, renal cell carcinoma, and post-transplant lymphoproliferative disease. More importantly, effective screening and treatment strategies are limited in this high-risk population. In this review, we begin with a patient’s journey that maps the experience of living with a kidney transplant and understand the patient’s knowledge, education, and experience of cancer in the context of transplantation. The epidemiology and burden of cancer in recipients of kidney transplants, along with the up-to-date screening and treatment strategies, are discussed. We also focus on the current understanding of optimal care for recipients of kidney transplants who are living with cancer from the patients’ perspectives.

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Patient’s Voice
As someone living with a kidney transplant for >16 years, this article resonated with me. When my nephrologist identified me as a pre-emptive candidate for a kidney transplant, he educated me immediately on the cardiovascular risks post-transplant. In addition, he persuaded me to adopt routine exercise into my lifestyle as a proactive measure. That recommendation has served me well because I have maintained routine exercise post-kidney transplant.

I have a sense of control in mitigating my cardiovascular risk. Beyond routine exercise, I have ensured my BP is within the recommended range. I strive to maintain a heart-healthy diet, and my transplant nephrologist prescribed a cholesterol-lowering medication immediately after my transplant when my metabolic panel was out of range. Recently, I scheduled an appointment with a preventive cardiologist. That appointment resulted in the prescription of a sodium-glucose cotransporter-2 inhibitor to reduce the risk of prediabetes, and a follow-up appointment for a computed tomography scan.

In contrast, my experience with managing cancer risks has not been clear. Although the risks of skin cancer were communicated, I had to ensure the guidelines were followed closely. For example, from the very beginning, I scheduled quarterly surveillance appointments with my dermatologist. Initially, quarterly appointments were discouraged until skin biopsy specimens were positive. Mole mapping was initially discouraged until the dermatologists discovered irregular moles. Nonetheless, I feel confident now in managing the risk of skin cancers. For my other cancer risks, a proactive path remains elusive.

Because the United States is moving to 3-year outcomes for transplant metrics, this affords the US transplant community to assess the effectiveness of patient education. As a first step, I would like to see the American Society of Transplantation and the American Society of Nephrology survey recipients of kidney transplants regarding their awareness of their health risks, including cancer. Moreover, the survey could also gain insights into the recipients’ ability to self-manage their health risks. In turn, this information would guide the community in their patient education and activation efforts.

Introduction
Kidney transplantation is the best treatment option for acceptable candidates with kidney failure because it improves the quality (1) of life and overall survival for patients on maintenance dialysis (2). It is also the most cost-effective treatment strategy for those needing KRT (3). However, transplantation is not a cure. Patients require life-long immunosuppression to maintain optimal allograft function. One of the most feared complications associated with immunosuppression after kidney transplantation is cancer (4). Cancer is also considered as one of the core clinical outcomes by clinicians, patients, and caregivers, and there is now consensus among key stakeholders suggesting cancer should be included as an outcome in all interventional trials of kidney transplantation (5).

After cardiovascular disease, cancer is the second leading cause of death among recipients of transplants in most Western countries (6). The higher risks and poorer cancer outcomes have prompted clinicians and policy makers to adopt preventive policies, such as human papillomavirus (HPV) vaccination (7) and cancer-screening strategies, to detect cancers at their earliest possible stage before they progress into advanced-stage, incurable disease (8). It is also imperative to understand the mechanistic insights into cancer cell development under the influence of immunosuppression and devise innovative treatment strategies for recipients of transplants. This review focuses on the incidence, mechanisms, diagnosis, prevention, and treatment of cancer after kidney transplantation.
Incidence of All-Cause and Site-Specific Cancer after Transplantation

The cumulative incidence of solid organ cancer ranges between 10% and 15% (6,9–11) at around 15 years after transplantation. For skin cancers, the cumulative incidence reaches >60% in Europe, Australia, and New Zealand. The excess overall cancer risk in patients with kidney transplant exceeds that of the general population by approximately two- to three-fold after adjustment for age and sex. The magnitude of the higher risk is also dependent on cancer types, with the greatest risk in viral-related and immune-driven cancers such as post-transplant lymphoproliferative disease (PTLD), anogenital cancer, and Kaposi sarcoma (12,13). Interestingly, certain solid organ cancers such as breast and prostate cancers are not increased in recipients of transplants (Figure 1).

Cancer Mortality in Recipients of Kidney Transplants

Once cancers develop, the risk of death is high. Observational data in most Western countries have shown the standard mortality ratios for all cancer types are at least 1.8–1.9 times higher compared with the age- and sex-matched general population. The risk is greatest among those with melanoma, urogenital cancers, and non-Hodgkin lymphoma, with an overall risk of cancer-related death exceeding five to ten times that of those without kidney transplants (Figure 2) (14). The exact reasons for the higher risk of death are unclear, but may be due to potential differences in the cancer cell biology in recipients of transplants resulting from long-term immunosuppression, associated comorbidities, and low uptake of recommended prevention and screening strategies (15). Patients are primarily committed to and preoccupied with their kidney and graft health, and their present health needs. Cancer screening and prevention may impose multiple burdens on patients’ daily lives (16), hence, effective patient education and heightened awareness are key.

Risk Factors for Cancer Development

There are many reasons for the higher cancer risk after transplantation. Some of these factors, such as increasing age, male sex, smoking, and prolonged sun exposures, are shared by patients in the general population. Other risk factors, including immunosuppression use (T cell-depleting agents), acute rejection (17), sensitization status (18), and duration of dialysis before transplantation (19), are specific to those with kidney disease and transplant populations. Although long-term immunosuppression is a major contributor to cancer development after transplantation, there is now convincing observational evidence to suggest that having CKD (irrespective of the CKD stage) is associated with higher cancer risk and poor cancer outcomes (20,21). Many of these cancers, such as renal cell carcinoma and multiple myeloma, are over-represented in the CKD/kidney-failure populations. Cancer may also develop in recipients of kidney transplants because of impaired tumor surveillance and immunity to viral or other tumor antigens. The observed higher cancer risk is further compounded in patients who have had a previously treated pretransplant malignancy (22–24). Recent studies indicate a higher incidence of all-cause mortality in recipients of solid organ transplants who have a pretransplant malignancy than those without, but the cause of death may not necessarily be driven by cancer recurrence alone (24–26).

The specific types of cancer that develop after transplantation also vary by geographic areas. Observational and registry data from Europe, North America, Australia, and New Zealand indicate the most common cancer types are nonmelanoma skin cancers (NMSCs), PTLD, and lip cancer (10,27–29). In contrast, data from non-Western Asian and Middle Eastern transplant cohorts suggest higher incidences of urothelial transitional cell carcinoma, renal cell carcinoma, and gastrointestinal cancers in their populations (9). It is unclear why these regional variations exist, but it may be related to distinct regional dietary suplements, such as aristolochic acid, which have been associated with urothelial carcinoma (30). A nationwide population study of 4716 recipients of kidney transplants in Taiwan reported an excess risk of liver cancer of approximately five-fold compared with the sex- and age-matched general population (31). Taiwan is an endemic area for chronic hepatitis B virus (HBV) infection in Far East Asia. The estimated prevalence rate of HBV antigenemia in recipients of kidney transplants is estimated to be 9%–24%. HBV is also a major risk factor of liver cancer. This finding supports the hypothesis of a loss of control of oncogenic viral replication and control in the context of chronic immunosuppression. For cancer associated with kidney disease and kidney failure, such as kidney and bladder cancer, the overall standardized incidence ratios (SIRs) are 44 and 43, respectively. When stratified by sex, women have a much higher risk than men for kidney (SIR, 94.6; 95% confidence interval [95% CI], 75 to 120) and bladder cancers (SIR, 120; 95% CI, 77 to 134) (31).

Mechanisms of Cancer Development after Transplantation

Maintenance immunosuppression decreases acute and chronic rejection, and subsequent allograft loss. Although
the precise mechanisms are unclear, the effects of immunosuppression on dampening the immune system may create a variety of pathways for cancer development. One potential mechanism is through poor immune control of known oncogenic viruses in patients on immunosuppression. For example, increases in viral-associated cancers, such as Kaposi sarcoma (human herpesvirus 8), PTLD (Epstein–Barr virus [EBV]), and lip and anal cancers (HPV) are common in patients with suppressed immune systems (32). Another mechanism of immunosuppression-related cancer development is through accumulation of mutations that would otherwise be repaired or recognized by the immune system. This mechanism may be predominant in skin cancers, where immunosuppression impairs the cells’ ability to repair ultraviolet (UV) radiation–induced DNA damage. More specifically, immunosuppression can lead to a decrease of xeroderma pigmentosum complementation groups A and G, which are components of nucleotide excision repair (33).

Currently, there is no conclusive evidence to suggest one type of immunosuppression is more oncogenic than others (34). However, experimental studies in hepatocellular carcinoma, human lung adenocarcinoma cells, and renal cell carcinoma have shown that tacrolimus increases the level of TGF-β and thereby promotes tumor progression and metastasis. In addition, calcineurin inhibitors inhibit signaling via calcineurin and NF of activated T cells, which can activate p53, a hallmark of some NMSCs (35). Cyclosporine also has direct effects on tumor development and progression, through TGF-β or IL-6 overexpression pathways (36). Recent evidence has shown cyclosporine is capable of inhibiting DNA repair, thereby accumulating mutations, inducing apoptosis in activated T cells, and inhibiting apoptosis in other cells by opening the mitochondrial permeability transition pores (37). The potential oncogenic potential of azathioprine is well known and well recognized. Azathioprine sensitizes the skin to UVA radiation and causes the accumulation of 6-thioguanine in the DNA, leading to a higher risk of NMSCs (38).

Mammalian target of rapamycin (mTOR) inhibitors, on the contrary, may have potential antitumor effects by inhibiting cancer growth through cell-cycle arrest and initiation of apoptosis. Growth inhibition of tumor cells has been demonstrated in vitro for cells from tumors, such as small cell lung cancer, sarcoma, neuroblastoma, glioblastoma, osteosarcoma, pancreatic cancer, breast cancer, prostate cancer, leukemia, and B-cell lymphomas (39). On a molecular level, several mechanisms have been identified for mTOR inhibitor–mediated tumor inhibition. Specifically, mTOR inhibitors can induce apoptosis in a cell type–specific fashion. It can also induce cell death in B-cell lymphoma lines, phosphatase and tensin homolog–lacking human tumors, and dendritic cells, possibly through p53 activation and reduction in the cyclin and survivin levels (39).

Induction therapy with T cell–depleting agents (including polyclonal agents, such as anti-thymocyte globulin, and monoclonal agents, such as anti-CD52 and, historically, Ortho Kung T3 [muromonab-CD3]) increases the risks of cancers, such as PTLD and melanoma (40). In addition, T cell–depleting agents used in the treatment of acute rejection of the kidney allograft also heighten the risk of cancer development (17). The mechanisms behind the short-term use of these therapies and the development of cancer years later are uncertain. However, after T-cell depletion, there is often an incomplete T-cell recovery (41), which may have a long-term effect on immune homeostasis, leading to an impaired immune system (42,43) and subsequent cancer development.

Common Cancers after Transplantation

Although the risk of overall cancer development is high after transplantation, the risks of certain cancer types are much higher than others. Here, we discuss the three most common cancer types: renal cell carcinoma, skin cancer, and PTLD.

Renal Cell Carcinoma

Compared with the general population, recipients of kidney transplants have a higher risk (up to seven-fold) of renal cell carcinoma (44–48). Due to increased abdominal imaging, the majority of kidney masses detected in patients post-transplantation are typically early, low-grade, small kidney masses (8,49); of which, 75%–80% are renal cell carcinoma, with the risk of metastasis at presentation being <2% (50). Ninety percent of renal cell carcinomas develop in the native kidneys as opposed to the allograft. Risk factors for development of renal cell carcinomas post-transplantation include male sex (female hazard ratio [HR], 0.56; 95% CI, 0.47 to 0.66), increasing age (60+ years; HR, 6.59; 95% CI, 4.29 to 10.15), African descent (HR, 1.50; 95% CI, 1.24 to 1.80), and longer time on dialysis (3+ years; HR, 2.23; 95% CI, 1.58 to 3.13) (46). With regard to disease etiology, patients transplanted for kidney failure secondary
to glomerular diseases (HR, 1.24; 95% CI, 1.05 to 1.47), hypertensive nephrosclerosis (HR, 1.55; 95% CI, 1.29 to 1.86), and vascular disease (HR, 1.53; 95% CI, 1.15 to 2.03) appear to have the greatest associated risk; in contrast, patients with kidney failure secondary to diabetes (HR, 0.77; 95% CI, 0.62 to 0.94) or autosomal dominant polycystic kidney disease (HR, 0.81; 95% CI, 0.62 to 1.06) have a lower risk of renal cell carcinomas. De novo renal cell carcinomas should be definitively managed according to urologic guidelines on the basis of risk stratification and staging (51,52), in conjunction with patient factors (age, comorbidities, functional status) and kidney-mass characteristics (size, biopsy specimen findings, growth kinetics).

The outcome of renal cell carcinomas after radical treatment in the transplant population is comparable with that of the general population, with 5-year, disease-specific and overall patient survival rates of 88%–97% and 69%–88%, respectively (53–56). Negative prognostic factors include presence of symptoms at diagnosis, higher Fuhrman grade (≥2), absence of transplantation, and advanced-stage disease (53–56). Renal cell carcinoma in the kidney allograft is rare, and multicenter data have demonstrated an incidence of 0.1%. Most are low-grade T1 lesions, clear cell carcinomas, or papillary renal cell carcinomas, and occur more commonly in males. The majority of tumors were treated by partial nephrectomy (67%), radical nephrectomy (19%), and percutaneous ablation (12%); surveillance was rarely used. This experience suggests that nephron-sparing surgery was safe and an appropriate method of treatment, with cure rates of 95%–100% (59). In inoperable cases, primary radiation therapy may achieve local cure rates. Patients who develop multiple squamous cell carcinomas (more than five) every year, those who have aggressive squamous cell carcinomas, or those with early onset of squamous cell carcinomas can be considered for chemophrophylaxis. These may include retinoids (63) and nicotinamide (64). In patients with metastatic cutaneous squamous cell carcinoma, systemic chemotherapy and/or immunotherapy are recommended (59).

Patients treated with calcineurin inhibitors are at particularly high risk for Kaposi sarcoma. Decreasing the intensity or switching immunosuppressive agents to an mTOR inhibitor is the cornerstone of treatment. Regression of Kaposi sarcoma has been reported after switching from calcineurin inhibitors to sirolimus by restoring effector and memory T-cell immune activity against human herpesvirus 8 (65). The risk of developing malignant melanoma is elevated by approximately five- to eight-fold in recipients of transplants, and these patients have much poorer outcomes than the general population (59). Among all skin cancer types, melanoma has the highest mortality (66).

Skin Cancer
Skin cancer is the most common cancer type in recipients of kidney transplants and is more aggressive than skin cancers occurring in the general population. The most commonly reported skin cancers in recipients of kidney transplants include cutaneous squamous cell carcinoma, basal cell carcinoma, Kaposi sarcoma, and malignant melanoma, with keratinocyte carcinomas comprising 90%–95% of these skin cancers (59,60). The pathogenesis of skin carcinoma involves a complex interaction of risk factors, including exposure to UV radiation, HPV, pretransplant skin cancer, older age, race, and sex (males at greater risk than females). Additionally, immunosuppressive medications augment the carcinogenic effects (mainly cyclosporine and azathioprine) (61,62). Kaposi sarcoma is also more commonly seen in certain ethnic groups, including patients from the Mediterranean, Africa, and Central Europe. Although Kaposi sarcoma is a rare cancer, the incidence of Kaposi sarcoma in recipients of transplants exceeds 100 times that of the general population.

Compared with the general population, recipients of transplants experience an excess risk of squamous cell carcinoma by approximately 250 times (59). In patients with actinic keratoses and squamous cell carcinoma in situ, management options with good outcomes include topical fluorouracil and imiquimod cream, photodynamic therapy, and surgical excision or electrodesiccation and curettage. For biopsy sample–proven cutaneous squamous cell carcinoma in recipients of transplant, Mohs micrographic surgery, with histologic confirmation of negative margins, offers the most definitive method of treatment, with cure rates of 95%–100% (59). In inoperable cases, primary radiation therapy may achieve local cure rates. Patients who develop multiple squamous cell carcinomas (more than five) every year, those who have aggressive squamous cell carcinomas, or those with early onset of squamous cell carcinomas can be considered for chemophrophylaxis. These may include retinoids (63) and nicotinamide (64). In patients with metastatic cutaneous squamous cell carcinoma, systemic chemotherapy and/or immunotherapy are recommended (59).

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Post-Transplant Lymphoproliferative Disease
PTLD is a well-recognized complication after kidney transplantation. Although it is a rare disease, it is associated with poor outcomes. In most instances (approximately 90%), PTLD is associated with EBV. EBV is a common virus, and most people acquire the virus during childhood. Most present with mild or minimal symptoms, but the virus can infect the B cells and remain dormant in these cells during the latent phase. After transplantation, these viruses can reactivate because of depressed T-cell function, with a lack of T-cell control over B-cell proliferation, and contributes to the development of PTLD. Most PTLDs are of B-cell types, with approximately 5% of patients having the T-cell type.

The cumulative incidence of PTLD in the first 10 years after kidney transplantation is around 1%–2% in adult recipients and approximately 3% in pediatric recipients of transplants (67). There is evidence to suggest that the incidence of PTLD has been decreasing in recent years. A recent analysis from the Australian and New Zealand Dialysis and Transplant Registry reported the incidence of PTLD was higher in the period of 1995–2000 compared with the current era, with an 8% reduction in the risk of
developing PTLD from 2000 onward (67). There also appears to be a bimodal distribution in PTLD incidence, with the risk of PTLD being the highest in the 12 months post-transplant, and it then decreases until the fifth year after transplantation. Pretransplant EBV seronegativity and primary EBV infection are important risk factors for early EBV-positive PTLD, particularly in younger recipients of transplants, and may explain the higher risk of disease early post-transplant. In contrast, a significant proportion (approximately 40%–50%) of late B-cell PTLDs involves EBV-negative lesions (68).

Compared with adult recipients of transplants, the risk of developing lymphoproliferative disease in pediatric recipients of transplants is at least 30-times higher than the age- and sex-matched general population. Apart from younger age at transplantation, male sex, use of T cell–depleting agents, Ortho Kung T3 (muromonab-CD3), and high dose tacrolimus, negative recipient EBV serology (with positive donor EBV serology) incur a four-fold excess risk of PTLD, after accounting for potential confounding factors (67). The use of costimulatory blockade, such as belatacept, has also been found to be associated with a higher risk of PTLD, particularly cerebral PTLD in patients who are EBV negative, and when used in higher doses (69).

The treatment goal of PTLD is to cure the disease, and the mainstream of treatment is immunosuppression reduction. However, the response to immunosuppression reduction varies considerably between individuals. Prior work reported the use of rituximab and chemotherapy (doxorubicin, cyclophosphamide, vincristine, prednisone) have improved overall survival, with 5-year survival at around 60% (70). Rituximab is also generally well tolerated with minimal side effects, and factors that predicted response included positive EBV status and normal lactate dehydrogenase levels (70).

Once PTLD develops, the risk of death is high. Epidemiologic studies have shown that the risk of death among recipients of kidney transplants who have PTLD is >14-fold higher than recipients without PTLD. However, contemporary data have shown there is an improvement in overall survival in more recent times due to the use of chemotherapies, such as rituximab, and other novel therapies, such as immunotherapy. Registry analyses have indicated the overall survival after PTLD was around 62%–68% at 1 year and approximately 41%–48% at 10 years (71). The risk of death also appears to be dependent on site, with those having bone marrow, reticuloendothelial disease experiencing the greatest risk of death, followed by extranodal and nodal disease. The median time from diagnosis to death is 6 months. Apart from site, other predictive factors of death included male sex and increasing age of diagnosis.

Cancer Screening Strategies in Transplant Recipients

High-quality, randomized controlled trials have shown that cancer screening through early detection reduces cancer-specific mortality in the general population (72). In patients with kidney disease, some have questioned the benefits of routine screening (73). Although some cancers are more common in patients with kidney disease, the expected patient survival, particularly for those on dialysis, is shorter than the time to develop cancers, suggesting screening may not be as effective in terms of costs and survival benefits (74). Despite the lack of trial-based evidence to support routine screening in this high-risk group, routine population-based cancer screening for breast, colorectal, and cervical cancer is recommended and should be aligned to the guidelines as per the general population (75) (Table 1). Some guidelines also suggest routine skin checks by dermatologists in recipients of transplants who are at high risk, and abdominal ultrasounds and serum α-fetoprotein levels should be checked every 6 months for those with underlying liver disease and chronic HBV infections. For patients who are at risk of developing renal cell carcinoma (such as those with a history of acquired cystic disease, those with a family history, those who are heavy smokers, and those who use long-term analgesics), ultrasonographic screening (annually or biennially) of the native kidneys may be considered to detect occult malignancy (76).

Patients with kidney disease and kidney transplants undergo radical changes to their overall health and well-being, which could be overwhelming for the patients and their caregivers. Many patients are unprepared to undertake a multitude of tests on issues they may see as distant (83,84). From the patient’s perspective, decisions about cancer screening are becoming increasingly complex. Screening decisions must be made with clear considerations of patients’ preferences and values, incorporating the potential harms and benefits of the various options. A shared decision-making process, defined as an approach where clinicians and patients share the best available evidence when faced with the task of making decisions, and where patients are supported to consider options to achieve informed preferences, should be adopted to guide decision making (85,86).

Human Papillomavirus Vaccination in Recipients of Kidney Transplants

The incidence of HPV-related anogenital cancer is at least ten- to 15-fold higher in recipients of kidney transplants compared with the age- and sex-matched general population. Quadrivalent vaccines (against genotype 6, 11, 16, and 18) and, more recently, the HPV 9-valent vaccines (against five additional genotypes of 31, 33, 45, 52, and 58) are highly effective and have an overall efficacy of 99%–100% for the prevention of cervical intraepithelial neoplasia in randomized clinical trials. HPV vaccination is indicated in both males and females aged 9–25 years in the general population for the prevention of HPV-related malignancies. Some recent data have shown that it is also efficacious in women up to the age of 45 years. In the transplant population, HPV vaccines are generally safe. However, seropositivity was only detected in approximately 50%–60% of patients, depending on genotypes, and higher tacrolimus levels were also detected in nonresponders (87). Although HPV vaccination is recommended for women after transplantation, it may be more efficacious to vaccinate before transplantation.

Management of Recipients of Kidney Transplants Who Have Cancer

Immunosuppression Management and Treatment in Transplant Recipients with Cancer

Management of immunosuppression in recipients of transplants who are living with cancer is complex and
Therefore, there are insufficient data to consider mTOR inhibitors as protective against other cancer types apart from squamous cell carcinoma and Kaposi sarcoma (92).

**Immunotherapy**

The use of immune-checkpoint inhibitors targeting the programmed death-1/programmed death ligand-1 interaction and/or the CD28-CD80/86 axis with cytotoxic T lymphocyte–associated protein-4 Ig has revolutionized the treatment of a variety of malignancies through immune-system activation against the cancer (93–95). However, the use of checkpoint inhibitors is limited in recipients of transplants given the potential for rejection with nonspecific immune-system activation (96,97). Although checkpoint inhibitors are effective in treating melanoma, non–small cell lung cancer, and renal cell carcinoma in the general population, their use in the kidney transplant population requires further investigation and cannot be recommended at this time, outside of a study protocol.

**Putting Patients’ Perspectives at the Heart of Cancer Management**

Patients with cancer and transplant may experience multiple symptoms, and the burden of self-management in the context of multiple morbidities is immense. Understanding patients’ personal experiences in their journey for the fight of cancer is crucial because this will provide important insights to guide clinicians and health care professionals to deliver relevant and appropriate care. The use of multimodal interventions to alleviate concurrent, multiple symptoms is an example of where a multidisciplinary team could deliver the suitable measures for

<table>
<thead>
<tr>
<th>Cancers</th>
<th>Recommendations</th>
<th>Evidence</th>
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<tr>
<td>Breast</td>
<td>For women aged 50–74 years, screening mammography once every 2 years. For women &lt;50, the decision to start regular screening should be an individual one (77).</td>
<td>Extrapolation from general population</td>
</tr>
<tr>
<td>Prostate</td>
<td>For men aged 55–69 years, screening decisions should be individualized after a conversation with their clinician about the potential benefits and harms. For men ≥70 years, the potential benefits may not outweigh the expected harms, and these men should not be routinely screened for prostate cancer (78).</td>
<td>Extrapolation from general population</td>
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<tr>
<td>Cervical</td>
<td>Annual Pap testing or HPV testing every 3–5 years starting at the age of 25 years until 74 years (72).</td>
<td>In view of the higher risk of disease, some have suggested more frequent Pap testing. However, no evidence to suggest increased frequency of HPV testing.</td>
</tr>
<tr>
<td>Bowel</td>
<td>For adults aged 45–75 years, fecal immunochromic testing biennially, sigmoidoscopy every 5 years, or colonoscopy every 5–10 years (79).</td>
<td>Screening using fecal immunochromic testing is accurate in recipients of kidney transplants. However, it may be associated with higher risk of complications associated with diagnostic colonoscopies (80).</td>
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<td>Lung</td>
<td>For adults aged 55–79 years, annual low-dose computed tomography scans for those who have smoked one pack per day for 30 years or equivalent (two packs per day for 15 years) (81).</td>
<td>Extrapolation from general population</td>
</tr>
<tr>
<td>Skin</td>
<td>Monthly self-skin examination and 6- to 12-monthly total body skin examination by expert physicians and dermatologists (82).</td>
<td>Expert opinions</td>
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<tr>
<td>Liver</td>
<td>Routine screening using US, with and without α-fetoprotein, every 6 months in patients with cirrhosis.</td>
<td>Extrapolation from general population</td>
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<td>PTLD</td>
<td>Routine monitoring of patients at high risk (donor EBV seropositive/recipient seronegative) for EBV by NAT. Once in the first week after transplantation, monthly for the first 3–6 months, and every 3 months until the end of the first post-transplant year (82).</td>
<td>Expert opinions</td>
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Pap, Papanicolaou; HPV, human papillomavirus; US, ultrasonography; PTLD, post-transplant lymphoproliferative disease; EBV, Epstein–Barr virus; NAT, nucleic acid amplification techniques.
patients transitioning between many disciplines of care. Patients living with kidney transplants are often frustrated with the lack of innovative strategies to prevent the risk of acute rejection from under-immunosuppression, and cancer resulting from over-immunosuppression (98). Therefore, a personalized, rather than a one-size-fits-all approach is most preferred. Ongoing dialogues between clinicians and patients, and close attention to the patients’ overall personal needs, limited not only to health issues, are crucial to ensure our patients’ voices are heard. For patients who have progressed to advanced-stage malignancy, complete immunosuppression withdrawal is a difficult decision for both patients and clinicians. Patients may experience signs and symptoms of acute rejection, and, to some, it may also represent a loss of hope and complete medical abandonment. Some clinicians may consider stopping either or both the calcineurin inhibitors and antiproliferative agents gradually and rotate to higher-dose corticosteroids to prevent the anticipated symptoms. Therefore, a multidisciplinary, integrated approach that involves the transplant and palliative care team is crucial. The team should consist of a palliative care physician to assist with the medical aspects of managing the high symptom burden, together with a social worker, dietician, clinical psychologist, and other allied health workers to address the psychosocial, functional, and nutritional issues experienced by our patients.

Conclusions
Cancer is the leading cause of morbidity and mortality in patients with kidney transplants. Having cancer is a devastating event for patients and their families because the lifestyle changes and the complex feelings caused by the diagnoses are overwhelming. The priorities of optimizing allograft function with immunosuppression are often challenged and superseded by having a “cure” for the cancer, and may involve immunosuppression reduction or cessation to reduce the risk of cancer relapse and improve long-term cancer survival. Currently, the evidence to define the amount of immunosuppression by which a clinician could safely reduce is unknown. More importantly, evidence to support primary prevention and screening programs in recipients of transplants are largely extrapolated from the general population, and the findings may not necessarily be applicable to the transplant population. Collaborative efforts between health care professionals, policy makers, trialists, and patients are needed to ensure quality evidence—in the form of intervention trials, large-care observational studies, and qualitative and health service research—are generated to support the long-term care of our recipients of transplants.

Disclosures
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References
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