COMPREHENSIVE REVIEW

Urologic malignancies in kidney transplantation

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With advances in immunosuppression, graft and patient outcomes after kidney transplantation have improved considerably. As a result, long-term complications of transplantation, such as urologic malignancies, have become increasingly important. Kidney transplant recipients, for example, have a 7-fold risk of renal cell carcinoma (RCC) and 3-fold risk of urothelial carcinoma (UC) compared with the general population. While extrapolation of data from the general population suggest that routine cancer screening in transplant recipients would allow for earlier diagnosis and management of these potentially lethal malignancies, currently there is no consensus for posttransplantation RCC or UC screening as supporting data are limited. Further understanding of risk factors, presentation, optimal management of, and screening for urologic malignancies in kidney transplant patients is warranted, and as such, this review will focus on the incidence, surveillance, and treatment of urologic malignancies in kidney transplant recipients.

KEYWORDS


1 | INTRODUCTION

Kidney transplantation has been established as the optimal treatment for select patients with end-stage renal disease (ESRD) as transplantation offers a significant survival benefit with an associated 63-80% lower mortality risk than remaining on dialysis.1-3 Patients who receive a transplant compared with remaining on the waitlist on average double their life expectancy,4 and not surprisingly, kidney transplantation has become a lifesaving option for many patients.

With advances in immunosuppression, graft and patient outcomes after transplantation have improved considerably. As a result, long-term complications of transplant have become increasingly important. From large cohort analyses, malignancies have been identified as one of the 3 leading causes of death in kidney transplant recipients5 after cardiovascular disease and infection, and all solid organ transplant recipients have seen an increase in the incidence of malignancies in recent years.6 The cause for this is multifactorial, but longer life expectancy posttransplantation, older age at transplantation, more potent immunosuppression, and better diagnostic tools have all contributed to an increase in diagnosis. The most common malignancies encountered after solid organ transplantation are non-Hodgkin lymphoma, skin, and kidney cancers, with the greatest risk of kidney cancers observed in kidney transplant recipients (standard incidence ratio [SIR] 6.66, 95% confidence interval [CI] 6.12-7.23).7 This review will focus on urologic malignancies, including renal cell carcinoma (RCC) and urothelial carcinoma (UC), in kidney transplantation (Table 1).

2 | RENAL CELL CARCINOMA

2.1 | Epidemiology in general population

In the United States, the lifetime risk of renal cancers is 1.62%, with the annual incidence steadily increasing during the past several years.8 Renal cancers are more common in developed nations than

Abbreviations: ACKD, acquired cystic kidney disease; ADPKD, autosomal dominant polycystic kidney disease; AHR, adjusted hazard ratio; ANZDATA, Australia and New Zealand Dialysis and Transplant Registry; BCG, bacillus Calmette-Guerrin; BKV, BK virus; CI, confidence interval; CKD, chronic kidney disease; CNI, calcineurin inhibitor; EAU, European Association of Urology; EDTA, European Dialysis and Transplant Association; ERBP, European Renal Best Practice; ESRD, end-stage renal disease; HPV, human papillomavirus; HR, hazard ratio; IPITTR, Israel Penn International Transplant Tumor Registry; IRR, incidence rate ratio; mTOR, mechanistic target of rapamycin; RCC, renal cell carcinoma; SEER, Surveillance, Epidemiology, and End Results database; SIR, standardized incidence rate; TUR-BT, transurethral resection of bladder tumor; UC, urothelial carcinoma; USRDS, US Renal Data System.
TABLE 1 Summary of risk factors and treatment options for common urologic cancers in kidney transplantation

<table>
<thead>
<tr>
<th>Type of malignancy</th>
<th>Incidence (SIR compared with general population)</th>
<th>Risk factors</th>
<th>Common therapies</th>
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| Renal cancer       | 5.2-7.9 (7)                                   | ACKD, duration of dialysis | • Nephrectomy of native kidneys  
|                    |                                               |              | • Partial nephrectomy  
|                    |                                               |              | • Radiofrequency ablation for allograft tumors  
| Urothelial cancer  | 1.4-4.8 (19)                                  | BK virus, significant smoking history | • Intravesical bacillus Calmette-Guerin therapy for noninvasive tumors  
|                    |                                               |              | • Radical cystectomy with lymphadenectomy  
|                    |                                               |              | • Urinary diversion for invasive tumors  

SIR, standardized incidence rate; ACKD, acquired cystic kidney disease.

in developing nations (age-standardized incidence of 9.2 vs 2.6 per 100,000).9 More than 85% of kidney cancers are defined as RCCs, with 25% of patients presenting with advanced disease (locally invasive or metastatic disease). Roughly 10% to 30% of patients who undergo resection for local disease will have recurrence, and the median survival for patients with metastatic disease is 13 months.10, 11 The majority of RCCs are now identified incidentally on radiographic imaging performed for other diagnostic reasons as common presenting symptoms can be nonspecific (eg, fatigue, weight loss, anemia).10 Risk factors for RCC in the general population include male sex, African ancestry, obesity, tobacco use, chronic kidney disease (CKD), viral hepatitis, and hypertension.12 Prognosis is closely correlated with the stage of RCC: stage I: tumor less than 7 cm in greatest dimension and limited to the kidney, 5-year survival 95%; stage II: tumor greater than 7 cm in greatest dimension and limited to the kidney, 5-year survival 88%; stage III: tumor in major veins or adrenal gland, tumor within Gerota fascia, or 1 regional lymph node involved, 5-year survival 59%; and stage IV: tumor beyond Gerota fascia or more than 1 regional lymph node involved, 5-year survival 20%.10

There are 5 distinct types of RCC. Clear cell RCC accounts for nearly 75% of all RCCs.10 Clear cell RCC is seen in von Hippel–Lindau disease, in which RCCs arise from the inactivation of the remaining normal VHL allele. Defects in the VHL gene also account for approximately 60% of cases of sporadic clear cell RCC.13 Papillary RCC represents the second most common type of RCC (~12%). Genetic mutations in MET, TFE3, and FH have been associated with sporadic and inherited forms of papillary RCC. Localized papillary RCC metastasizes less frequently than clear cell RCC14; however, survival is significantly worse for metastatic papillary compared with metastatic clear cell RCC.15 Less common types of RCC include chromophobe (4%), collecting duct (<1%), and those that are of an unspecified type.10

2.2 Epidemiology in ESRD population

Data from the US Renal Data System (USRDS) linked to Medicare claims for patients receiving dialysis during 1997 through 2005 indicate the incidence of RCC among patients with ESRD to be 5.2/1000 person-years at risk.16 Male sex, increasing age, African ancestry, acquired cystic kidney disease (ACKD), and ESRD due to tuberous sclerosis, focal segmental glomerulosclerosis, or obstruction all increased the risk of RCC; interestingly, in this cohort, smoking was not associated with increased RCC risk, nor did dialysis modality influence risk.16 Longer dialysis duration also increases the risk of renal cancers,17 and some data suggest the risk may be bimodal, peaking in the first year after dialysis initiation and then again in years 4 through 15.7 The increased incidence of RCC observed in patients of African descent compared with other ethnicities is partly attributed to their greater burden of ESRD.18 Although patients receiving dialysis have a 3-fold increased risk of RCC compared with the general population,17 patients with earlier stages of CKD who are not dialysis dependent do not have an increased risk of RCC compared with the general population.19 Patient cohorts from the European Dialysis and Transplant Association (EDTA) and Australia and New Zealand Dialysis and Transplant Registry (ANZDATA) have also demonstrated elevated rates of RCC among dialysis patients, with an SIR of 3.3 (95% CI 3.1-3.6) and 9.9 (95% CI 7.7-12.3), respectively.20

Patients with ESRD who develop RCC are at increased risk for mortality, with an adjusted hazard ratio (AHR) of 1.97 (95% CI 1.90-2.04) in at least 1 study, and as such, there has been interest in use of routine ultrasound screening for detection of RCC in patients with ESRD.16 ACKD develops within 3 to 7 years of initiating dialysis, with an associated 1.6-7.0% incidence of RCC.16 Fortunately, RCCs tend to be smaller, lower stage, and lower grade among patients with ESRD compared with the general population, therefore early screening, detection, and treatment is associated with cure.21,22 Although surveillance remains a controversial topic, some have suggested that routine screening begin 3 years after initiation of dialysis to encourage early identification of these tumors.16

2.3 Epidemiology in transplant population

To assess the cancer risk of patients receiving renal replacement therapy, Shang et al performed a meta-analysis of multiple cohort studies and found a pooled SIR for RCC of 9.7 (95% CI 5.69-16.53) among transplant recipients compared with a pooled SIR of 4.87 (95% CI 4.14-5.72) among dialysis patients, suggesting that the risk of RCC is higher among transplant patients than among dialysis patients.23 In contrast to the findings of Shang et al, a recent retrospective analysis of the national transplant registry by Yanik and colleagues demonstrated that the SIR for RCC was lower among first-time transplant recipients (SIR 6.4, 95%-CI 5.9-6.8) compared with waitlist candidates (SIR 9, 95%-CI 8.4-9.6). While seemingly contradictory, it is likely that...
both findings have merit as it is important to highlight that Shang et al looked at pooled SIR for dialysis patients, which represent a very different group of patients than the highly selected waitlist candidates examined by Yanik et al. Both studies have limitations, and as such, further study is needed to fully elucidate the true SIR for renal cancer in these unique populations.  

Compared with the general population, kidney transplant recipients have a 5- to 7-fold increased risk of renal cancers, with RCC accounting for 4.6% of post–renal transplantation malignancies. Ninety percent of RCCs develop in the native kidneys as opposed to the allograft. The natural history of RCC seems to be more aggressive in kidney transplant recipients than in their counterparts remaining on dialysis. Compared with dialysis patients, post–kidney transplantation patients are diagnosed at a younger age with earlier-stage tumors likely related to surveillance bias. Miao et al compared the incidence, severity, and treatment of malignancies in transplant recipients (from Israel Penn International Transplant Tumor Registry [IPITTR]) to the general population (from Surveillance, Epidemiology, and End Results database [SEER]). In the transplant population with RCC, 73% (61/84) of patients were diagnosed at early stages (defined as 0, I, or II) compared with 58% (32,221/55,545) of controls. The finding of earlier stage at diagnosis in the transplant population may be secondary to increased abdominal imaging exposure over time. The median time from transplantation to diagnosis was 6.4 years. Compared with the general population, transplant recipients had similar stage-stratified, disease-specific survival for stage I/II RCCs but significantly worse survival for stage IV RCC (0% difference versus 20% difference at 3 years), and transplantation itself was a significant risk factor for disease-related mortality. A meta-analysis of cancer risk after transplantation found it to be highest in the first year after surgery with a subsequent decrease over time. Reasons for this high initial risk are likely multifactorial. Uremia is known to cause immune dysfunction and inflammation and decreased significantly after consistent allograft function. It has been postulated that patients with ESRD have impaired DNA repair mechanisms, reduced antioxidant defense, and accumulation of carcinogenic compounds that may improve after transplantation. Additional hypotheses for initial elevated risk are increased surveillance in the presence of preexisting tumors or more potent immunosuppression in the first posttransplantation year.

The etiology for risk of RCC among transplant recipients is likely multifactorial. Historically, investigators hypothesized life-long immunosuppression was responsible. However, the lack of association between increased risk for RCC and infection with HIV suggests the development of RCC is not a consequence of immunosuppression alone. In fact, a study comparing long-term outcomes among 8000 HIV-infected patients and more than 7000 transplant recipients, populations known to be immunosuppressed, found these vulnerable populations to be at increased risk for only advanced-stage melanoma and bladder cancer. Moreover, Yanik et al evaluated more than 200,000 kidney transplant candidates and recipients using linkage between the Scientific Registry of Transplant Recipients and 13 regional cancer registries. The study compared intervals with nonfunctional kidneys (time on waitlist or after allograft failure; requires dialysis) with intervals with functional kidneys (time immediately after transplantation; requires immunosuppression). The posttransplantation group had higher incidence of Kaposi sarcoma, lymphomas, and skin cancers but lower incidences of thyroid and renal cancers. In addition, the rarity of RCC in the allograft compared with native kidneys suggests that an intrinsic factor within the native kidneys may be contributing to the higher incidence. In fact, autosomal dominant polycystic kidney disease (ADPKD) has been described as a risk factor for RCC development, with these patients having a 2 to 3 times higher risk of RCC compared with the general ESRD population; in contrast, among patients transplanted for ESRD secondary to ADPKD, the risk of RCC is lower than that among patients transplanted for other disease etiologies. Taken together, these data suggest that posttransplantation immunosuppression may not increase the risk for RCC among transplant recipients.

Risk factors for development of RCC posttransplantation include male sex (hazard ratio [HR] 1.79), increasing age (60+ years; HR 6.59), African descent (HR 1.50), and longer time on dialysis (3+ years; HR 2.23). With regard to disease etiology, patients transplanted for ESRD secondary to glomerular diseases (HR 1.24), hypertensive nephrosclerosis (HR 1.55), and vascular disease (HR 1.53) appear to have the greatest associated risk; in contrast, patients with ESRD secondary to diabetes (HR 0.77) or ADPKD (HR 0.81) have a lower risk of RCC. Interestingly, patients undergoing repeat transplantation (unadjusted incidence rate ratio [IRR] 1.61) have an increased risk for RCC, as well as patients receiving kidney transplants from older, male donors (HR 1.16). The incidence of ACKD in both patients with ESRD and kidney transplant recipients who go on to develop RCC has been reported to be greater than 80%. However, the presence of native renal cysts secondary to ACKD remains a controversial risk factor for the development of posttransplantation RCC. Specifically, Lee et al found that among patients with ESRD diagnosed with RCC (0.3%), 82% had ACKD, whereas among kidney transplant recipients diagnosed with RCC (0.8%), only 5% had ACKD. In contrast, other studies have shown that transplant recipients with ACKD have a 1.7-fold increased risk of RCC compared with transplant recipients without ACKD.

RCC management pre–kidney transplantation

Approximately 5% of patients on the waitlist will have RCC at the time of transplantation. Denton et al examined specimens from native nephrectomy at the time of transplantation in asymptomatic patients with ESRD. In their sample of 260 kidneys, 33% had ACKD, 14% had renal adenomas, and 4.2% had RCC at the time of transplantation. Similarly, a series of 258 ipsilateral nephrectomies at the time of transplantation identified RCC in 12 (4.7%). There was no significant difference in graft function or patient survival posttransplantation; however, 2 (25%) patients developed contralateral RCC.

The high incidence of RCC diagnosed in the first 6 to 12 months after transplantation suggests that many recipients have preexisting
RCC that goes undetected before transplantation and implies a role for pretransplantation screening. Pretransplantation screening and management of RCC, however, is controversial. The European Renal Best Practice (ERBP) transplantation guidelines suggest screening transplant candidates with ultrasound for RCC. The ERBP recommends that patients with RCC who are appropriately treated are then immediately eligible to be placed on the waitlist, while the European Association of Urology (EAU) does not define a disease-free waiting period. Cimino et al used data from the Cincinnati Transplant Tumor Registry to examine risk of recurrence of cancers seen in waitlisted patients. Recurrence rates posttransplantation were low (<10%) for incidentally discovered, small renal tumors and high (>25%) for symptomatic or large renal carcinomas. Others have shown similar findings, with posttransplantation recurrence rates as high as 30% among patients with previous history of symptomatic RCC, 61% of whom had been treated for less than 2 years before transplantation, compared with a recurrence rate of less than 1% for incidentally discovered RCC. Death secondary to recurrent disease posttransplantation approaches 80% and, as such, the time from RCC treatment to transplantation varies based on likelihood of recurrence. Guidelines from the Canadian Society of Transplantation recommend that (1) patients with small (<5 cm) incidental tumors require no waiting period, (2) patients with a past history of symptomatic RCC wait at least 2 years from treatment to transplantation; and (3) patients with large (≥5 cm) or invasive RCC wait at least 5 years from treatment to transplantation.

2.5 Use of kidneys with RCC for transplantation

The demand for kidneys continues to far exceed the supply of donor organs and, as such, consideration for the use of kidneys from donors with cancer is warranted. The risk of contralateral RCC in the general population is estimated to be 0.4% at 10 years and 0.8% at 20 years, suggesting that contralateral kidneys from donors with solitary renal tumors may be an underused source of allografts.

Lugo-Baruqui et al recently published a systematic review of outcomes among recipients of kidney allografts with small, excised RCCs (<3 cm). The authors reviewed 7 studies with a total of 122 recipients and found that only 1 patient experienced a recurrence (follow-up varied from 15 to 69 months). In general, the kidneys were allocated to high-risk patients with ESRD who were older than 60 years and had significant comorbidities. Transplanted kidneys included living donors (kidneys from patients who required radical nephrectomy for RCC, underwent tumor resection ex vivo, and then are used for donation) and deceased donors (either contralateral kidney or affected kidney with tumor resection). It is important to note, however, that when potential living kidney donors are found to have a kidney mass, not all will require radical nephrectomy. In fact, for small tumors, a nephron-sparing tumor excision or ablation may be more appropriate. As highlighted by Fletcher et al, incidental small renal tumors identified during living kidney donor evaluation warrant careful analysis and discussion with regard to potential risks and benefits for the potential donor and his/her recipient.

Despite the potential risks of disease transmission, the use of such marginal organs is still preferable to maintenance dialysis; Brook et al reported a superior 5-year survival in recipients of allografts with small (<3 cm) tumors resected before transplantation compared with patients remaining on the waitlist (88% vs. 74%). While long-term follow-up is lacking and no consensus on optimal immunosuppression regimen or cancer surveillance posttransplantation exists, the available evidence supports the safe use of donor kidneys with small RCCs for transplantation.

2.6 RCC management post–kidney transplantation

Posttransplantation cancer diagnosis has a negative effect on patient mortality while escalating health care costs; the diagnosis of solid organ cancers within 3 years of transplantation triples 3-year mortality. Cancer diagnosis within a similar time frame was associated with a $14 500 to $18 000/year increase in inpatient billing and a $8000 to $9000/year increase in outpatient billing. Studies have found the risk of RCC over time posttransplantation to be biphasic: risk is high immediately posttransplantation, declines until 2.5 years posttransplantation, then steadily increases with second peak at 4 to 15 years. Understanding the variation in cancer risk after kidney transplantation may help guide screening and contain costs. The 5- and 10-year cancer-specific survival rates for RCC are 71% and 58%, respectively.

The management of posttransplantation RCCs is dependent on location and stage of the tumor: (1) native kidney RCC: radical nephrectomy is the standard of care; (2) transplanted kidney RCC: partial transplant nephrectomy is preferred but is dependent on tumor size and characteristics; and (3) metastatic RCC: currently no consensus exits, options include tyrosine kinase inhibitor target therapies and/or immunotherapy. For RCC in the native kidneys, radical nephrectomy can be performed safely with satisfactory oncologic outcomes. In a series of 22 nephrectomies, there were no episodes of rejection, dialysis, or injury to the allograft. In a separate study, Tillou et al reported a series of 33 patients with suspicious lesions on imaging (computed tomography or ultrasound) who underwent nephrectomy and found that 65% of the patients had malignant lesions (all RCC stage I) with 92% survival at 5 years. Even though RCC rarely occurs in the allograft (10% of the time), treatment of these tumors is important for long-term renal function. A large retrospective study from France examined management of de novo RCCs in transplanted kidneys. In 41 806 patients transplanted between 1998 and 2012, only 79 (0.2%) de novo allograft tumors were diagnosed, and mean time posttransplantation was 12 years. Ninety-five percent of tumors were pT1a, and the majority were papillary RCC (58%), with clear cell tumors being the second most common (35%). All patients underwent partial allograft nephrectomy, with no statistical difference between baseline and 1-month postoperative creatinine. After a mean follow-up of 35 months, 41 (52%) patients had a functional graft, and all patients were cured of their RCC. Several groups have reported success with percutaneous energy ablation (includes radiofrequency ablation and cryotherapy) of an allograft RCC with no changes in graft function or
tumor recurrence.\textsuperscript{64,65} Finally, while immunotherapy is used for the treatment of metastatic RCC, few data exist on the safety and efficacy of immunotherapy in the transplantation setting. Use of high-dose interleukin-2 and programmed cell death protein 1 inhibitors can potentiate allograft rejection in transplant recipients and should be used with caution in transplant patients.\textsuperscript{66} Moreover, programmed cell death protein 1 inhibitors and other checkpoint inhibitors have been associated with the development of immune complex–induced nephropathy. Discontinuation of therapy should be considered in the setting of significant proteinuria.\textsuperscript{67}

Management of maintenance immunosuppression in the setting of posttransplantation RCC remains a challenge, and equipoise exists in the transplant community with regard to need for dosage reduction and immunosuppression type. Previous studies have shown an association between T-cell–depleting antibody and hematologic malignancies.\textsuperscript{68} A large study by Lim et al followed 7153 renal transplant recipients to determine if the need for T-cell–depleting antibody for acute rejection episodes affected cancer risk.\textsuperscript{68} The most frequent cancers were genitourinary, and patients requiring T-cell–depleting antibodies for rejection had a higher cancer risk than those who did not have an acute rejection episode (AHR 2.20). In addition, this increased risk was not observed in patients with rejection who underwent treatment with other agents.\textsuperscript{68} In contrast, a more recent study of more than 111,000 patients in the Transplant Center Match Study examined the relationship between antibody induction therapies and common cancers posttransplantation. None of the induction agents evaluated (polyclonal anti–T cell, muromonab-CD3, alemtuzumab, or interleukin-2 receptor antagonists) were associated with renal cancer.\textsuperscript{69} Interestingly, in a series of 17 patients with posttransplantation RCC, Tollefson et al continued standard immunosuppression after RCC treatment and found a low rate of progression, suggesting reduction in dosage is not necessary for local RCC. However, the study does have several important limitations, including the heterogeneity of the study population (included patients with totally excised RCC before transplantation and patients who developed RCC posttransplantation) and, as such, equipoise remains with regard to appropriate maintenance immunosuppression dosing in the setting of RCC.\textsuperscript{70}

Target-of-rapamycin (mTOR; sirolimus and everolimus) inhibitors have been used therapeutically after a posttransplantation malignancy has been diagnosed. It is hypothesized that mTOR inhibitors may be useful in attenuating calcineurin inhibitor (CNI)-induced posttransplantation cancer progression by reducing expression of carcinogenic cytokines and chemokines (ie, vascular endothelial growth factor).\textsuperscript{71} Specifically, Yanik et al performed a meta-analysis examining the use of sirolimus in renal transplant recipients; sirolimus was associated with decreased risk of nonmelanoma skin cancers (IRR 0.49), as well as a reduction in renal cancer incidence (IRR 0.4) but increased prostate cancer incidence (IRR 1.85).\textsuperscript{72} Similarly, a retrospective study of the Organ Procurement and Transplantation Network database found that the incidence rates at 2.6 years for de novo malignancy were 0% for sirolimus/everolimus, 0.47% for sirolimus/everolimus plus a CNI, and 1.0% for a CNI alone.\textsuperscript{73} Multivariate analysis revealed that mTOR inhibitors were associated with a 60% reduction in all posttransplantation malignancies and a 55% reduction in solid posttransplantation malignancies.\textsuperscript{73} A prospective trial by the CONVERT study group randomized 830 renal transplant recipients to continue CNI-based therapy or switch to sirolimus-based therapy.\textsuperscript{74} After 2 years of therapy, the sirolimus group had a lower rate of malignancy compared with the CNI group (2.1 vs 6.0 malignancies per 100 person-years of exposure).\textsuperscript{74} The ZEUS study compared cyclosporine- and everolimus-based therapies and found a higher rate of malignancy in the cyclosporine group (6.4%) compared with everolimus (1.6%).\textsuperscript{75} However, several other studies with shorter follow-up have failed to show any difference.\textsuperscript{76} One meta-analysis of sirolimus use in post–renal transplantation patients found a 40% reduced risk of solid organ malignancy but an increased mortality (HR 1.43, 95% CI 1.21-1.71).\textsuperscript{77} Another meta-analysis found a significant cancer risk reduction for skin cancer and a modest reduction for renal cancers.\textsuperscript{72} While mTOR inhibitors may be associated with decreased risk of posttransplantation malignancy and have been used to treat advanced RCC in the nontransplantation setting, more data are needed as equipoise about the use of mTOR inhibitors in the setting of RCC remains.\textsuperscript{76,78-80}

### 2.7 | RCC screening post–renal transplantation

Renal ultrasound is an inexpensive, noninvasive test for the diagnosis of RCC in renal transplant recipients, with a positive predictive value of 100% and a negative predictive value of 94%.\textsuperscript{81} In a study by Lee et al comparing RCC diagnoses in patients with ESRD with diagnoses in renal transplant recipients, there was no difference in tumor stage at diagnosis.\textsuperscript{45} Kato et al reported results of a screening program in renal transplant recipients in which patients underwent yearly computed tomography and ultrasound for RCC and urine cytology every 3 to 6 months.\textsuperscript{82} Twelve patients were diagnosed with RCC in the native kidneys, of which 8 (66%) were diagnosed through screening.

There are no randomized clinical trials that have shown posttransplantation screening improves cancer-specific and overall mortality;\textsuperscript{82} however, several consensus groups have made recommendations. The Kidney Disease Improving Global Outcomes and American Society of Transplantation guidelines for posttransplantation care do not recommend screening for RCC;\textsuperscript{84,85} only the ERBP guidelines recommend native kidney ultrasound as RCC screening in kidney transplant recipients.\textsuperscript{86} The EAU recommends annual ultrasound of native kidneys and allograft for anyone with ACKD, previous RCC, or von Hippel–Lindau disease.\textsuperscript{50} Goh et al recommended screening ultrasound every 2 years for patients with ACKD and every 5 years for recipients without ACKD.\textsuperscript{46} Frasca et al proposed annual screening ultrasound for patients with ADPKD or ACKD and every 2 years for patients older than 60 years who had been receiving dialysis longer than 5 years before transplantation.\textsuperscript{87}

Screening in the posttransplantation population could be problematic secondary to overdetection and/or overtreatment of clinically insignificant disease.\textsuperscript{86} Standard RCC treatment (reduction in immunosuppression or surgical resection) can be potentially harmful to the allograft, and patient life expectancy must be taken into account. Other potential adverse effects of screening include discomfort, potential
radiation exposure, need for invasive follow-up tests, financial burden, inconvenience, and anxiety. There are no prospective data on RCC screening cost-effectiveness in the transplant or general populations. However, Markov decision modeling suggests that biennial ultrasound screening in the renal transplant population would cost $252 100/life-year saved; focusing on high-risk subpopulations could improve the incremental cost-effectiveness ratio. As there is no consensus, more research is needed to identify the ideal surveillance for different populations.

3 | UROTHELIAL CARCINOMA AND BLADDER CANCER

3.1 | Epidemiology in general population

The annual incidence of bladder cancer in the general population is 0.02%, and the incidence of UC (also known as transitional cell carcinoma) varies with geography. Eighty-five percent of patients present as early stage (defined as stage 0 or I), and the 5-year survival for localized bladder cancer is 70.1%. UC can be found in the renal collecting system or ureter but is most common in the bladder epithelium. The most important patient factors that are predictive of outcomes in a recent systematic review were male sex, advanced age, tobacco exposure, diabetes mellitus with poor glycemic control, and CKD.

3.2 | Epidemiology in transplant population

The risk of bladder cancer is increased in patients with ESRD, but the magnitude is not as great as for RCC; SIRs for bladder cancer from the USRDS, EDTA, and ANZDATA were 1.4 (1.3-1.5), 1.5 (1.4-1.7) and 4.8 (3.6-6.2), respectively. A pooled meta-analysis found the SIR of bladder cancer in dialysis patients to be 2.51 compared with 3.15 in transplant recipients. A meta-analysis comparing transplant recipients with other immunosuppressed populations, such as persons with HIV infection, found that bladder cancer rates were increased in transplant recipients but not in patients with HIV infection.

The overall SIR for bladder cancer among renal transplant patients compared with the general population ranges from 1.6 to 3.2, with the highest SIR among Asian renal transplant recipients (SIR 14,74). Risk factors for the development of bladder cancer from a multivariate analysis in the post–renal transplantation population included polyomavirus infection (ie, BK virus [BKV]) (RR 11.6) and smoking (RR 6.1). UC is by far the most common type of bladder cancer, although both squamous cell and small cell cancers have been reported in posttransplantation patients. The impact of immunosuppression on the development of UC has yet to be fully detailed in the literature.

BKV nephropathy is an important cause of graft dysfunction in kidney transplantation patients. In addition, BKV has been associated with the development of malignancy in immunosuppressed populations, although there are insufficient data to support causality. Primary infection occurs in early childhood, after which the virus is latent in renal tubular and transitional epithelial cells; iatrogenic or pathologic immunosuppression allows for reactivation of the virus with resultant clinical manifestations, such as nephropathy, hemorrhagic cystitis, ureteral stenosis, and malignancy. At the time of diagnosis, the virus is most commonly localized to the renal calyces, renal pelvis, ureters, and bladder. A review of population studies found viruria in 29% and viremia in 11% of renal transplant recipients. For virus-associated malignancies, such as BKV nephropathy, reduction in immunosuppression should be considered.

While there is an association between BKV and carcinogenesis in rodent models, the evidence of BKV as the etiology for human malignancies is limited. The presence of viruria in transplant recipients has been associated with a 5-fold increase in UC compared with patients without BKV. The role of BKV in tumorigenesis in the renal transplant population was recently reviewed by Papadimitriou et al, who identified 20 cases of BKV infection and resultant genitourinary carcinomas. These tumors occurred several years (range 2-12) after transplantation and were aggressive, high-grade tumors at diagnosis. Recently, Kenan et al published a case report of a kidney transplant recipient who developed RCC in the allograft 5 years after being diagnosed with BKV nephropathy; the tumor stained positive for large T antigen by SV40. The authors proposed that BKV infection can lead to viral integration into the human genome, where the large T antigen inhibits p53 and promotes oncogenesis; while intriguing, this hypothesis has not been prospectively validated. For virus-associated malignancies (ie, BKV), the most common treatment involves reduction in maintenance immunosuppression regimen. More research is needed to elucidate the link between BKV and carcinogenesis.

Similarly, human papillomavirus (HPV) has been associated with the development of UC in renal transplant patients. Husain et al demonstrated that among 5 cases of UC, 4 were positive for HPV. Of those positive for HPV, 3 contained a high-risk type (HPV 16). More research is needed to clarify the posttransplantation association between HPV and UC.

3.3 | Management post–renal transplantation

Data are lacking for the posttransplantation management of UC. In the series reported by Ardelt et al, 25 patients with UC diagnosed posttransplantation were identified. The majority of these lesions were located in the bladder (92%), with the remainder in the upper urinary tract. In this series, most patients presented with microscopic or gross hematuria and were treated with repeated transurethral bladder resection; few underwent cystectomy or nephroureterectomy. In general, however, treatment for UC is based on stage: (I) superficial bladder UC—transurethral resection of bladder tumor (TUR-BT) with post–TUR-BT cystoscopic surveillance and consideration for instillation of intravesical bacillus Calmette-Guerin (BCG) therapy or mitomycin; (II) muscle-invasive bladder UC—neoadjuvant chemotherapy and radical cystectomy with urinary diversion; (III) transplant ureter—total transplant nephroureterectomy (transplant preserving surgery has been reported with varying success). Importantly, UC may also arise in the native upper urinary tracts (renal and ureteral),
as well as the transplant renal pelvis and calyceal collecting system. In these cases, radical nephroureterectomy should be considered.

Unlike RCC, duration of dialysis was not a risk factor for the development of UC. Graft function was equivalent at the time of last follow-up for the UC group (72%) compared with controls (68%).

The risk of contralateral UC in posttransplantation patients who have previously undergone unilateral laparoscopic nephroureterectomy is high. In a small series, 5 of 12 patients had UC in the contralateral kidney after prophylactic nephroureterectomy. Two of the 5 patients with contralateral tumors had hydronephrosis on preoperative imaging. Moreover, in a similar series of 15 patients with confirmed upper tract UC (among 663 transplant recipients), Liao et al found that 8 of 15 patients had contralateral UC after simultaneous bilateral native nephroureterectomy.

Renal transplant patients with UC present at a later stage than the general population. The proportion of patients presenting with muscle-invasive disease is higher in both renal transplant recipients (37%) and patients with ESRD (33%) than in the general population (24%). From analysis of IPITTR and SEER, in the transplant population with bladder carcinoma, 66% (35/53) of patients were diagnosed at early stages (defined as 0, I, or II) compared with 85% (95 708/112 019) of nontransplant patients. Siani et al also demonstrated that transplant recipients were more likely to be diagnosed with regional (odds ratio 1.42) or distant disease (odds ratio 1.80) than was the general population. The median time from transplantation to diagnosis was 4.5 years. The relatively short interval from transplantation to cancer diagnosis may be related to the intensity of immunosuppression, suggesting that malignancy risk may decrease with time as immunosuppression is weaned.

Stage-stratified, disease-specific survival was equal for stage I/II tumors but significantly worse for stage III/IV bladder cancer compared with controls. The 5- and 10-year cancer-specific survival rates in transplant patients with UC were 50% and 0%, respectively.

UC is rarely found in the transplanted kidney, and the allograft can often be preserved during treatment. However, there are case reports of allograft malignancies requiring either local resection and reconstruction or nephroureterectomy and lymphadenectomy.

One of the largest series detailing treatment of bladder cancer after kidney transplantation followed standard therapy despite immunosuppression: intravesical BCG [live attenuated bacteria and works through immunomodulation and therefore has 2 implications in the transplant population: (i) may be less effective in someone receiving immunosuppression and (ii) immunosuppressed patients may be at higher risk for BCG complication including sepsis] for noninvasive tumors and radical cystoprostactectomy with lymphadenectomy and urinary diversion for invasive tumors. Reconstruction with an ileal neobladder is also an option, though avoided by some because of immunosuppression and abnormal pelvic anatomy. Small series have shown preservation of graft function after resection of invasive cancer.

No standard of care has been established for the management of immunosuppression after treatment of UC, although no change in regimen may be appropriate with localized UC.

The optimal adjuvant chemotherapeutic regimen in these patients is sparse; a small study of 22 renal transplant patients with locally advanced UC compared surgery alone to surgery followed by gemcitabine and cisplatin. The surgery-plus-chemotherapy group had a longer mean survival time compared with the surgery-alone group (31 vs 14 months) but a higher incidence of hematologic toxicities requiring dose reduction. Transplantation society guidelines do not specifically recommend screening transplant recipients for UC.

4 | CONCLUSIONS

Urologic cancers in kidney transplantation are an important cause of morbidity and mortality in this population. Routine screening in transplant recipients would allow for earlier diagnosis and management of these potentially lethal malignancies. However, there is no consensus for posttransplantation RCC screening, as data are limited. Prospective studies to determine the best cancer screening methods and intervals are urgently needed.

DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the American Journal of Transplantation.

REFERENCES


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