Cancer Medicine Journal

Research Article | Vol 3 Issue 1

De-Novo Genitourinary Neoplasms in Transplant Recipients: The Present and Future

Subodh K Regmi, Song Jiang and Christopher A. Warlick*

Department of Urology, University of Minnesota, Minneapolis, Minnesota, USA

***Corresponding author:** Christopher A. Warlick, Department of Urology, University of Minnesota, Minneapolis, Minnesota, USA, Tel: 6126257486; E-mail: cwarlick@umn.edu

Abstract

The risk of genitourinary cancers following transplantation is increased following majority of solid organ transplants but is best described following renal transplantation. Increasing average age of the transplant recipient as well as increases in post- transplant survival increases the risk of these malignancies. The risk of Kidney cancer is the highest following most solid organ transplants, whereas prostate cancer risk is lower than the general population in multiple large population-based studies. The etiology of increased risk of cancer following transplant is multifactorial with the predominant influence of immunosuppression and direct toxicity of immunosuppressants, however, the significance of end stage disease particularly in the causation of renal cancer in renal transplant recipients is undeniable. Modifications in immunosuppression regimens as well as changes in the standard treatment principles of some cancers may require changes in the management of some post-transplant malignancies. Standard screening guidelines have not been established but screening for renal tumors in renal transplant recipients is the only widely studied entity. Further work is needed to prepare the urologic oncological community with this once rare population group and standardized recommendations need to be established for screening and for the use of new age cancer therapeutics like immunotherapy.

Keywords: ***Genitourinary cancers; Transplant; Immunosuppression; Transplant recipient; Cancer screening***

Received Date: October 28, 2019; **Accepted Date:** November 08, 2019; **Published Date:** November 15, 2019

Introduction

The increased risk of de-novo malignancy following transplantation has been a keen area of interest since early descriptions by Starzl and Penn [1]. This increased risk has been quoted to be 3-5 folds and is not limited to skin or hematological malignancies alone [2-4]. The incidence of genitourinary malignancies are increased by up to 23% following most solid organ transplants [5]. This incidence can vary with the organ transplanted and, by far, is most common and best documented following renal transplant [6].

The importance of genitourinary malignancies in the transplanted population is further highlighted by another important fact associated with the modern era of transplantation. The average transplant recipient is now older and transplant related complications, including death, are much lower than previously reported [7]. Thus, current transplant patients are at increased

Citation: Christopher A. Warlick, De-Novo Genitourinary Neoplasms in Transplant Recipients: The Present and Future. Cancer Med J 3(1): 10-22.

risk of genitourinary malignancies not just because of the inherent risks of post-transplant immunosuppression but also because of their increasing age. Additionally, global trends of increasing incidence and death from urologic cancers as well as the inherently higher incidence of genitourinary cancers in populations older than 60-years [8] is likely to compound this problem. Renal transplant recipients diagnosed with renal cancers have also been associated with the need for further transplant or maintenance hemodialysis following cancer diagnosis and treatment [9]. Therefore, genitourinary malignancy related morbidity and survivorship are important issues that need to be addressed in this unique population.

Our review, aimed at genitourinary malignancies in solid organ transplant recipients (namely kidney, liver, lung and heart), will highlight existing knowledge on the epidemiology, etiology and management along with identification of gaps in knowledge and opportunities for further research.

Epidemiology

The cumulative incidence of cancer in the transplant population has been found to be increasing steadily over time due to decreases in complications like death, graft failure and re-transplantation [7]. Genitourinary cancers were reported to have the highest incidence of cancers among kidney and heart transplant patients in a study which used the US Organ Procurement Transplant Network/United Network for Organ Sharing (UNOS) database [10]. This study which evaluated the primary kidney, liver, lung and heart transplantation cohort between 1999 and 2008 studied the incidence in 1000 person years of various malignancies [10]. Older white males were found to be most at risk along with kidney and liver transplant patients who had documented use of induction therapy for immunosuppression. The combined incidence of genitourinary cancers (including genital cancers) was higher in the post-transplant population as compared to the 55-59-years-old US population in each of the four solid organs transplanted. When analyzed individually, kidney/renal pelvis cancer and bladder cancer incidence were uniformly high whereas testicular and prostate cancer incidence were higher only in the heart transplant population [10].

Engels et al. [6], performed a linkage study using the Scientific Registry of Transplant Registries (SRTR) and the population based cancer registries of 13 US states. They studied over 175,000 transplant patients between 1987-2008 calculating standardized incidence ratios (SIR) and excess absolute risk (EAR) to measure the relative risk of cancer in transplant recipients. Transplant recipients had an overall doubling of cancer (SIR = 2.10) and EAR of 719.3 person years. Overall, SIRs were significantly elevated for the cancers of the kidney (4.65), penis (4.13), renal pelvis (2.05), testis (1.96) and urinary bladder (1.52). SIR and EAR for prostate cancer, however was lower than expected (0.92 and -11.3, respectively) [6]. Kidney cancer was among the 4 most common malignancies in the transplanted population and with the highest SIR among kidney transplant recipients (SIR = 6.66) followed by liver and heart recipients (SIR = 2.90 and 1.80 respectively). Interestingly, there was a bimodal pattern of kidney cancer risk in these patients with the first peak within the first year of transplant and the second peak seen between 4-15-years after transplant. The reason for this second peak is not clearly evident but it may be due to the nephrotoxic or cytotoxic effects of immune-suppressants [6]. A similar study from the UK, found that the overall cancer risk was more than doubled in the transplant population. Kidney cancer SIRs were increased for all solid organ transplants with the highest risk among renal transplant recipients (SIR = 7.9) [11].

Our own data suggests a decreased risk of developing prostate cancer after renal transplant with a 30-years incidence risk of 3.9% compared to 10.8% in a group of age-matched patients from the SEER database [12]. This lower risk may be due to the

intensive screening patients undergo prior to being eligible to list for renal transplant. This is in contrast to multiple smaller series looking at the transplant population around the world that have not only noted similar trends with increased incidence [13,14] and higher proportion of genitourinary tumors (20%-23%) [15,16] but have also noted higher SIR for prostate cancer [14,17,18]. This may be a reflection of different study era as well as varying screening practices for prostate cancer. Although the risk of prostate cancer in the transplant population is generally lower than expected, it is still the predominant genitourinary cancer in renal, liver and heart transplant recipients [10] and therefore is of paramount importance to the practicing urologist. Table 1 summarizes relevant studies on the Incidence of genitourinary tumors following various solid organ transplantations.

Authors	Incidence Reported	Transplant organ	Genitourinary Malignancy				
			Renal	Prostate	Bladder/Urothelial	Testis	Penile
Sampio et al. [10]	Incidence per 1000 PY	Kidney	0.79†	0.82	0.29	0.02	NA
		Liver	0.21†	0.88	0.27	0.04	NA
		Heart	0.57†	3.07	0.57	0.12	NA
		Lung	0.37†	0.88	0.51	NA	NA
Engels et al. [6]	SIR	All SOT	4.65	0.92	1.52 & 2.05‡	1.96	4.13
Kaneko et al. [14]	SIR	Liver	6.4	2.2	NA	NA	NA
Maggi et al. [13]	SIR	Liver		1.6	3.3	NA	NA
Antunes et al. [16]	Incidence rate (%)	Kidney	0.8	1	0.2	NA	0.03%
Jiang et al. [12]	30 year CI	Kidney	6.00	3.93	2.31	0.53§	

Table 1: Genitourinary malignancy incidence following solid organ transplant (SOT).

Note: † Includes renal parenchymal and pelvic tumors; ‡ SIR of bladder and renal pelvic cancer respectively; § Combined penile and testicular cancer 30 year CI; PY: person years, NA: not available, SIR: standardized incidence ratio, SOT: solid organ transplant, CI: cumulative incidence estimate.

Racial and ethnic differences in the incidence of cancer in the transplant population is an important issue that has not been extensively researched. Hall et al. [19], looking at the Transplant Cancer Match Study data, found that racial differences in the incidence of cancer following renal transplant were comparable to the general population except in the case of renal and prostate cancer. SIRs for kidney cancers were increased across all races but were significantly higher for Blacks (8.96) and Hispanics (5.95) than whites (4.44). The risk for prostate cancer (SIR) was lower than the general population for Whites (0.75) and Hispanics (0.70) but was higher in Blacks (1.21).

Etiology

The genesis of de-novo tumors following solid organ transplantation is likely multifactorial [20]. Multiple immune related processes secondary to the induction of immunosuppression form the primary basis of oncogenesis in these patients. These include impaired immune-surveillance as well as oncogenesis induced by various pathogenic organisms. Direct cytotoxicity of immune-suppressants is also of considerable importance in this regard along with the role of end stage disease causative factors and other cancer-causing risk factors. Their precise role in the genesis of genitourinary tumors is difficult to define precisely but complex interactions of several of these factors perhaps exist and specific roles in genitourinary tumors need to be outlined.

Impaired Immuno-surveillance

The theory of immune-surveillance, conceived by Thomas and Burnet in 1957 [21], and its role in tumor genesis and growth was initially refuted due to the inability at that time to confirm these findings. The increased incidence of malignant tumors seen in immunodeficient mice was therefore attributed to the role of oncogenic viruses until further developments led to a better understanding of the complex process of immune-editing [22] comprising of elimination, equilibrium and escape phases. These processes require an intact immune system and involve CD8+ cytotoxic T cells, Natural Killer (NK) cells, dendritic cells and central memory T cells among others [20,23]. Elimination is the suppression of tumor growth brought about by destruction of cancer cells or inhibition of outgrowth. Equilibrium and Escape phases promote tumor progression by selecting fitter tumor cells for survival in an immunocompetent host and establishing a microenvironment facilitating tumor outgrowth [23]. Upon immunosuppression, Calcineurin inhibitors (CNIs) and inhibitors of mammalian target of Rapamycin (mTOR) decrease the elimination response against the cancer cells while CNIs also tip the balance in favor of tumor cells by promoting the Escape phase [20,24,25]. Azathioprine and mycophenolate mofetil (MMF) also favor tumor growth by influencing the equilibrium and escape phases [26,27]. These resultant tumors are more immunogenic in comparison to an immunocompetent host and therefore also respond better to immunotherapy with immune check point inhibitors or to immune reconstitution upon decreasing immunosuppression. However, rejection related complications are also more common following decrease in immunosuppression or initiation of PD-1 and CTLA-4 checkpoint inhibitors [20].

Role of Oncogenic Pathogens

The impairment of anti-viral T cell mediated defense mechanisms are primarily responsible for the occurrence of several viral related malignancies in the immunosuppressed transplant population [20]. Penile cancer is the most notable virally-mediated genitourinary cancer and is associated with Human Papilloma Virus (HPV) infection and has a high incidence both in-situ as well as invasive penile cancer [28]. While Human herpes virus-8 (HHV-8), Epstein-Barr virus (EBV) and other viruses are associated with post-transplant immunosuppression, they are not known to be associated with any genitourinary cancers.

Cytotoxicity Associated with Immunosuppression

There has been a high incidence of several cancers associated with the use of T cell depleting agents such as thymoglobulin and anti T cell antibody (OKT3) in induction therapy or during the treatment of acute rejection [29]. Using the Australian and New Zealand Transplant Registry, Lim et al. [30] found that, kidney transplant recipients experiencing acute rejection requiring T-cell depleting antibody, had an increased risk for overall cancer and genitourinary cancer of 1.4 and 2 fold respectively compared to those without rejection. Similarly, Cyclosporine A (CsA) and Tacrolimus , both CNIs, have been noted to have higher cancer incidence compared to mTOR inhibitors [31] through multiple mechanisms affecting tumor genesis mediated via transforming growth factor (TGF)-1β [32], vascular endothelial growth factor (VEGF) [33], and interleukin (IL)-6 pathways [34]. Further, CsA also increases cancer incidence by decreasing DNA repair mechanisms [35].

Azathioprine is a classified carcinogen which is known to cause direct mutagenesis of the DNA mismatch repair mechanism (MMR) inducing microsatellite instability (MSI) [36,37]. Though the precise mechanisms involved in genitourinary cancers is unknown, this effect along with immunosuppressant nephrotoxicity could explain the increased incidence of some of the late onset cancers in transplanted kidneys or in the native kidneys of recipients of other organ transplants [6,38].

Role of end stage organ failure and other factors

While the ill effects of immunosuppression play a role in the development of many cancers in transplant recipients, the role of pre-transplant end stage renal failure cannot be entirely overlooked in renal transplant recipients. The association of renal cancer with acquired renal cystic disease (ACKD) following prolonged dialysis is well known [18] and so is the high incidence of urothelial malignancies in patients with analgesic nephropathy (aristolochic acid) induced renal failure [39,40]. The association of uremia and dialysis with impaired immune function, chronic infection and inflammation, and the retention of carcinogenic compounds results in a milieu favoring carcinogenesis [41]. End stage renal disease associated cancers like renal and urothelial cancers can manifest as recurrent cancers in the renal transplant population [18]. Several other factors also need to be considered including the increasing age of the transplant population and the existence of cancer risk factors like smoking prior to transplant which by themselves have a significant impact [20,29]. Though donor transmitted malignancies are exceedingly rare (0.01%-0.05%) [42-44], renal cancers (19%) are the single most common malignancy in this peculiar group [44].

Racial differences have also been noted in the incidence of genitourinary cancers in the US population [19]. Longer wait times for transplant for black renal transplant recipients [45] may result in an increased risk of acquired polycystic kidney disease (ACKD) [19], which is a known factor for kidney cancer following transplantation [46]. This coupled with the increased association of obesity and hypertension among black patients of renal cell cancer [47] may also be important [19]. Rigorous prostate cancer screening among black renal transplant recipients, in view of an increased risk, could also have resulted in higher incidence [19].

Presentation, Pathology and Management

Rates of genitourinary malignancies are increased in most solid organ transplant recipients. Data regarding the risk of developing a genitourinary malignancy are most robust in the renal transplant population, though much of the data was reported numerous years ago and may reflect older immunosuppression regimens

Kidney Cancer

Kidney cancer has the highest risk amongst the genitourinary malignancies in all solid organ transplants [6,11]. These tumors are often incidentally detected with rigorous ultrasound based screening in renal transplant recipients [48] in view of the high association of these tumors to ACKD. Though more frequently multifocal (40%) and bilateral (20%) than in the non-transplant population, they tend to be less aggressive pathologically as papillary renal cell carcinomas are more common following renal transplant [48]. The WHO has recognized and separately classified this entity occurring in end stage renal disease to highlight the heterogeneity of this group [49]. Breda et al. [50], reported that these tumors are of lower grade and lower stage and thus exhibit favorable clinical features and outcomes as compared to RCCs in the general population. Similarly, cancer in the allograft has also been found to be more commonly papillary RCC in multicenter studies [51] but the pathology of kidney cancer following other solid organ transplants is not well described.

The treatment of cancers in the native kidneys after renal transplant involves radical nephrectomy, with some even considering bilateral native nephrectomies due to the high incidence of bilateral tumors in this cohort [48]. Treatment of the grafted kidneys tends to focus on nephron sparing principles with the use of partial nephrectomy [48] or minimally invasive percutaneous ablative techniques like radiofrequency ablation [51]. For kidney cancers following solid organ transplant, in the absence of

extensive literature, standard management principles as in the general population should be followed. Metastatic renal cancers are difficult to treat but there have been several therapeutic approaches including manipulation of immunosuppressive therapy after maximum possible surgery, conventional interferon/interleukin therapy, Tyrosine kinase inhibitors (TKIs) or mTOR inhibitors [48,52]. The prognosis is often dismal but in the absence of standard recommendations, mTOR inhibitors like temsirolimus and everolimus appear most promising in view of their mechanism of action [48].

Urothelial Cancer

Macroscopic hematuria is still the commonest presentation for patients with urothelial carcinoma following transplantation [53,54], however, in renal transplant patients due to the high incidence of post-transplant urinary tract infections (UTI), diagnosis can be delayed [54]. Both non-invasive and invasive urothelial malignancies are observed and are reported to be aggressive in the bladder as well as in the upper tract compared to that in the general population [54,55]. Conventional surgical options as well as intravesical therapeutic options can be followed depending upon the disease stage [54-56]. The use of BCG has been relatively controversial in view of the concerns for a limited immune response in an environment of generalized immunosuppression and the need for concomitant prophylactic antitubercular therapy [57]. However, several small series have demonstrated its safe use in carefully selected high risk patients with close surveillance for possible sepsis and the use of prophylactic antibiotics [57]. Radical cystectomy has been found to be feasible in renal as well as liver transplant patients in published series. Particularly in renal transplant patients, the choice for urinary diversion needs special consideration and orthoptic substitution can be considered with creatinine clearance $\geq$ 40ml/min [57].

In patients with upper tract urothelial cancer (UTUC) following a renal transplant, bilateral nephroureterectomy is a viable option. Adjustments in the immunosuppressive management is often needed15 and chemotherapy in the adjuvant setting has been reported without resultant renal compromise [54]. The allograft kidney is rarely the source of urothelial malignancy [56].

Prostate Cancer

Konety et al. [58] described the first significant clinical series of prostate cancer in the transplant population where the diagnosis followed either an abnormal rectal examination (DRE) or an elevated Prostate Specific Antigen (PSA) and the majority of patients had localized as well as well/moderately differentiated pathology. Radical Retropubic Prostatectomy without lymphadenectomy at the side of allograft as well as Radiotherapy with shielding of allograft were feasible alternatives for localized disease in renal transplant patients [58]. In a contemporary series of renal transplant recipients, Pettenati et al. [59], found that most prostate cancers (88%) were localized and did not differ significantly from the standard population in terms of prostate cancer characteristics at diagnosis and rates of biochemical recurrence (BCR). An earlier series, however, had found that prostate cancer in the renal transplant population was more prone to locally advanced disease and early disease recurrence especially with the use of CNI and Azathioprine immunosuppression [60].

Several treatment options remain viable for patients with prostate cancer and renal transplants. Robot-assisted Radical Prostatectomy in localized disease can be performed with certain port placement and other procedural modifications employing trans-peritoneal or extraperitoneal approaches with safe clinical and oncological outcomes [61-64]. Similarly brachytherapy and external beam radiation have been found to have equivalent outcomes in a recent series [65] though there is always a concern for increased incidence of radiation related allograft complications [61]. With the increased detection of low risk

cancers the role of active surveillance and focal therapy are also being explored [65,66] and need further evidence to support their routine usage, though in carefully selected men, may be safe. Hormonal treatment has been employed in conjunction with radiation therapy, however, literature on the management of BCR and metastatic disease in this population is lacking especially with the metamorphosis of current therapeutics and the possible role of immunotherapy.

Testicular Cancer

The presentation and the management of testicular cancer in the transplant population follows management in the standard population [56]. Testicular cancer represents a unique sub-population among transplant recipients, where the use of cytotoxic chemotherapy forms the cornerstone of treatment and therefore provides us with the best data for chemotherapy use in the transplant population. The primary concern is for infective complications in view of added myelosuppression in the existing milieu of immunosuppression and therefore mandates adjustments in the immunosuppressant dosage [56]. Cisplatin, typically nephrotoxic, raises questions in renal transplant recipients but in fact may be preferable to carboplatin due to less myelosuppression [67]. Therefore, given concerns about the toxicity of chemotherapeutic agents, observation in eligible patients may be reasonable. Nevertheless, chemotherapy is well tolerated and comparable to the general population [68] with some reports of the expected deterioration in renal function at variable intervals following treatment [67].

Penile Cancer

Penile cancer in transplant recipients appears to be rare with few reports in the literature, and therefore no special recommendations can be made [56]. Conventional methods can be extended to treat penile cancers in the transplant population.

Outcomes and Prognosis

The data on outcomes of the various management strategies and prognosis in this special group of patients with genitourinary cancers is limited (Table 2). The majority of data are derived from smaller series mostly in renal transplant patients. Tsaur et al. [69], in their 30 year renal transplantation experience, found that genitourinary tumors were second only to skin cancers in incidence and accounted for the most number of deaths (44%). Surgery and other chemotherapeutic measures did not significantly affect the graft function and the 5-years cancer specific survival for prostate, renal, urothelial and germ cell tumors were 85.7%, 83.5%, 67.2% and 50% respectively [69]. In another paper focusing on renal tumors, the same group found that progression free survival at 5-years was 76.8% whereas tumor specific and overall survival at 5 and 10 years were 83.5% and 75.1% respectively [52]. In the UK population, Farrugia reported that cancer after renal transplantation accounted for 18% of all deaths and kidney cancer was the third most common cause of cancer related death (9%) [70]. They identified that increased age, pretransplant history of malignancy and deceased-donor renal transplant as independent predictors of death from cancer.

Authors	Transplant Organ	Outcome Reported	Genitourinary Malignancy		
			Renal	Prostate	Bladder/Urothelial
Tsaur et al. [69]	Renal	CSS (%)	83.5	85.7	67.2
Miao et al. [71]	All SOTs	↓ DSS	Stage IV	Stage II, III, IV	Stage III
D'Arcy et al. [71]	All SOTs	CSM	54.3	14.4	158.6
		HR	0.66	0.71	1.86
		aHR	1.23	1.07	1.85

Table 2: Outcomes of genitourinary malignancies in the transplanted patient.

Note: CSS: 5 year cancer specific survival, SOT: solid organ transplant, ↓DSS: Worse stage stratified disease specific survival compared to SEER database population, CSM: cancer specific mortality rate per 1000 patient years, HR: hazard ratio, aHR: HR calculated after adjusting Cox regression models for sex, age, race, stage and year of diagnosis.

Early series looking at outcomes of patients with prostate cancer have noted a cancer specific mortality of 11% in patients treated with radical prostatectomy [58]. Following treatment with low dose brachytherapy or EBRT in a population comprising of 68% (19/28) patients with intermediate or high-risk prostate cancer, Oh et al. [65] found a 3-years biochemical disease-free survival of 95.8%, 3-years distant metastasis free survival of 93.1% and overall survival of 93.8%. In the series from Kleinclauss et.al [60], 48/62 (80%) patients were alive at a mean follow-up 24.7 ± 24 months out of which 35(72.9%) were disease free and 13(27.1%) had disease recurrence and 7/12 deaths were due to prostate cancer. Interestingly, 5(8.1%) allografts were lost during prostate cancer treatment.

There have been two major population-based studies that have looked at cancer outcomes in the US. The first looked at the Israel Penn International Transplant Tumor Registry (IPTTR) and compared it with the Surveillance, Epidemiology and End Results database (SEER) and found that lower stage renal tumors and higher stage bladder cancers were common in the transplant population and stage III bladder cancer, stage II-IV prostate cancer and stage IV kidney cancer had worse disease specific survivals compared to the general population [71]. Recently, D'Arcy et al. [72] used data from the National Cancer Institute's Transplant Cancer Match study database to describe cancer specific mortality following transplantation. They found that while bladder cancer specific mortality was higher in transplant patients, after adjustments were made for the stage of disease, cancer specific mortality was also increased for prostate cancer patients undergoing treatment with curative intent.

As noted above, reported cases of, penile and testicular cancer are small. As such, there is limited data available on survival statistics for these cancers following transplant.

Genitourinary Cancer Screening following Solid Organ Transplant

Given concerns of reported increased risk of genitourinary cancers following solid organ transplantation, it raises the question of the utility of screening for these cancers in this population. However, the lack of high-quality data has led to a lack of consensus regarding this. Compounding this issue are the multiple recommendations of various societies and clinical practice groups (CPG) with most commenting on the renal transplant population. A systematic review by Acuna et al. [73] found that several screening recommendations existed and these varied by the organ transplanted. While there is a general consensus that screening for skin cancer should be performed in solid organ transplant patients, strong recommendations regarding the utility of screening for other cancers was difficult to make given the limited high quality evidence available and the lack of inclusion of relevant stakeholders in the formulation of the recommendations. Out of the 7 CPG guidelines commenting on prostate cancer, 4 recommended no additional screening whereas 3 recommended yearly PSA and digital rectal examination in recipient's ≥50-years and a 10 year life expectancy [73]. This may also vary with the ongoing changes in practice patterns [74] following the US Preventive Services Taskforce (USPSTF) recommendations in 2012, though it should be noted that the USPSTF recommendations were only for men of average risk. Ultrasound guided based kidney cancer screening in native kidneys following renal transplant is recommended by only one guideline and no recommendations existed for urothelial cancer screening [73]. Some commentators also recommend that the screening guidelines should also incorporate lifestyle

modifications along with screening recommendations as a part of comprehensive preventive care in transplant patients [75]. We believe that a high vigilance is necessary for selected patients at particularly high risk of malignancy following organ transplantation. However, in the absence of high level evidence, the establishment of routine screening programs are not currently recommended.

Future Directions

The significance of genitourinary malignancies in the transplant population will continue to rise primarily for 2 reasons. First, increased graft survival and the increasing average age at transplantation will result in transplant recipients that are older and therefore intrinsically more likely to present with genitourinary malignancies. We therefore anticipate the number of transplant recipients who develop genitourinary malignancies to increase, a population that was relatively small in the past. Second, the continued progress in the field of immuno-oncology and immune therapies will likely increase in the use of these approaches in patients with genitourinary malignancies in the future, testing the balance between efficacy and preserving graft function.

Future work should focus on studies generating evidence-based recommendations for the key issues for patients with malignancy following transplant including the appropriateness for screening, the best treatment algorithms, and ultimately how the risk of malignancy in potential transplant patients affects eligibility for this life saving procedure. Further, incorporating relevant stakeholders in policy making and involving effective lifestyle and other recommendations in the prevention of malignancy in this population will be important moving forward.

References

1. Penn I, Starzl TE (1972) Malignant tumors arising de novo in immunosuppressed organ transplant recipients. Transplantation 14(4): 407-417.
2. Webster AC, Craig JC, Simpson JM, et al. (2007) Identifying high risk groups and quantifying absolute risk of cancer after kidney transplantation: A cohort study of 15 183 recipients. American Journal of Transplantation 7(9): 2140-2151.
3. Hoshida Y, Tsukuma H, Yasunaga Y, et al. (1997) Cancer risk after renal transplantation in Japan. International Journal of Cancer 71(4): 517-520.
4. Kinlen LJ, Sheil AG, Peto J, et al. (1979) Collaborative United Kingdom-Australasian study of cancer in patients treated with immunosuppressive drugs. The British Medical Journal 2(6203): 1461-1466.
5. Shin M, Moon HH, Kim JM, et al. (2013) Comparison of the incidence of de novo malignancy in liver or kidney transplant recipients: Analysis of 2673 consecutive cases in a single center. In Transplantation Proceedings 45(8): 3019-3023.
6. Engels EA, Pfeiffer RM, Fraumeni JF, et al. (2011) Spectrum of cancer risk among US solid organ transplant recipients. JAMA: The Journal of the American Medical Association 306(17): 1891-1901.
7. Hall EC, Pfeiffer RM, Segev DL, et al. (2013) Cumulative incidence of cancer after solid organ transplantation. Cancer 119(12): 2300-2308.
8. Dy GW, Gore JL, Forouzanfar MH, et al. (2017) Global burden of urologic cancers, 1990-2013. European Urology 71(3): 437-446.
9. Butt SUR, Chow B, Shah S, et al. (2019) Renal cell carcinoma in kidney transplant recipients at Guy's and King's college hospital (UK) between 1987-2018. Journal of Clinical Oncology 37(15 Suppl.): e16066-e16066.
10. Sampaio MS, Cho YW, Qazi Y, et al. (2012) Posttransplant malignancies in solid organ adult recipients: An analysis of the

US National transplant database. Transplantation 94(10): 990-998.

11. Collett D, Mumford L, Banner NR, et al. (2010) Comparison of the incidence of malignancy in recipients of different types of organ: A UK registry audit. American Journal of Transplantation 10(8): 1889-1896.
12. Jiang S, Jackson S, Calvert C, et al. (2019) Risk of genitourinary malignancy in the renal transplant patient. World Journal of Urology 37(Suppl. 1): 40.
13. Maggi U, Consonni D, Manini MA, et al. (2013) Early and late de novo tumors after liver transplantation in adults: The late onset of bladder tumors in men. PloS one 8(6): e65238.
14. Kaneko J, Sugawara Y, Tamura S, et al. (2013) De novo malignancies after adult-to-adult living-donor liver transplantation with a malignancy surveillance program: Comparison with a Japanese population-based study. Transplantation 95(9): 1142-1147.
15. Ochoa-López JM, Gabilondo-Pliego B, Collura-Merlier S, et al. (2018) Incidence and treatment of malignant tumors of the genitourinary tract in renal transplant recipients. International Brazilian Journal of Urology 44(5): 874-881.
16. Antunes H, Tavares-da-Silva E, Oliveira R, et al. (2018) De novo urologic malignancies in renal transplant recipients. In Transplantation Proceedings 50(5): 1348-1354.
17. Elkentaoui H, Robert G, Pasticier G, et al. (2010) Therapeutic management of de novo urological malignancy in renal transplant recipients: The experience of the French department of urology and kidney transplantation from Bordeaux. Urology 75(1): 126-132.
18. Vajdic CM, McDonald SP, McCredie MR, et al. (2006) Cancer incidence before and after kidney transplantation. JAMA 296(23): 2823-2831.
19. Hall EC, Segev DL, Engels EA (2013) Racial/ethnic differences in cancer risk after kidney transplantation. American Journal of Transplantation 13(3): 714-720.
20. Acuna SA (2018) Etiology of increased cancer incidence after solid organ transplantation. Transplantation Reviews 32(4): 218-224.
21. Burnet M (1957) Cancer-A biological approach I. The processes of control. II. The significance of somatic mutation. British Medical Journal 1(5022): 779-786.
22. Dunn GP, Bruce AT, Ikeda H, et al. (2002) Cancer immunoediting: From immunosurveillance to tumor escape. Nature Immunology 3(11): 991-998.
23. Schreiber RD, Old LJ, Smyth MJ (2011) Cancer immunoediting: Integrating immunity's roles in cancer suppression and promotion. Science 331(6024): 1565-1570.
24. Rovira J, Renner P, Sabet-Baktach M, et al. (2016) Cyclosporine A inhibits the T-bet–dependent antitumor response of CD8+ T cells. American Journal of Transplantation 16(4): 1139-1147.
25. Araki K, Turner AP, Shaffer VO, et al. (2009) mTOR regulates memory CD8+ T-cell differentiation. Nature 460(7251): 108-112.
26. He X, Smeets RL, Koenen HJ, et al. (2011) Mycophenolic acid-mediated suppression of human CD4+ T cells: More than mere guanine nucleotide deprivation. American Journal of Transplantation 11(3): 439-449.
27. Ben-Horin S, Goldstein I, Fudim E, et al. (2009) Early preservation of effector functions followed by eventual T-cell memory depletion: A model for the delayed onset of the effect of thiopurines. Gut 58(3): 396-403.
28. Madeleine MM, Finch JL, Lynch CF, et al. (2013) HPV-related cancers after solid organ transplantation in the United

States. American Journal of Transplantation 13(12): 3202-3209.

29. Au E, Wong G, Chapman JR (2018) Cancer in kidney transplant recipients. Nature Reviews Nephrology 14(8): 508-520.
30. Lim WH, Turner RM, Chapman JR, et al. (2014) Acute rejection, T-cell-depleting antibodies, and cancer after transplantation. Transplantation 97(8): 817-825.
31. Lim WH, Eris J, Kanellis J, et al. (2014) A systematic review of conversion from calcineurin inhibitor to mammalian target of rapamycin inhibitors for maintenance immunosuppression in kidney transplant recipients. American Journal of Transplantation 14(9): 2106-2119.
32. Hojo M, Morimoto T, Maluccio M, et al. (1999) Cyclosporine induces cancer progression by a cell-autonomous mechanism. Nature 397(6719): 530-534.
33. Guba M, von Breitenbuch P, Steinbauer M, et al. (2002) Rapamycin inhibits primary and metastatic tumor growth by antiangiogenesis: Involvement of vascular endothelial growth factor. Nature Medicine 8(2): 128-135.
34. Tanner JE, Menezes J (1994) Interleukin-6 and Epstein-Barr virus induction by cyclosporine A: Potential role in lymphoproliferative disease. Blood 84(11): 3956-3964.
35. Herman M, Weinstein T, Korzets A, et al. (2001) Effect of cyclosporin A on DNA repair and cancer incidence in kidney transplant recipients. Journal of Laboratory and Clinical Medicine 137(1): 14-20.
36. Karran P, Attard N (2008) Thiopurines in current medical practice: Molecular mechanisms and contributions to therapy-related cancer. Nature Reviews Cancer 8(1): 24-36.
37. Swann PF, Waters TR, Moulton DC, et al. (1996) Role of postreplicative DNA mismatch repair in the cytotoxic action of thioguanine. Science 273(5278): 1109-1111.
38. de Mattos AM, Olyaei AJ, Bennett WM (2000) Nephrotoxicity of immunosuppressive drugs: Long-term consequences and challenges for the future. American Journal of Kidney Diseases 35(2): 333-346.
39. Kliem V, Thon W, Krautzig S, et al. (1996) High mortality from urothelial carcinoma despite regular tumor screening in patients with analgesic nephropathy after renal transplantation. Transplant international 9(3): 231-235.
40. El Kaddouri H, Doerfer A, Broeders N, et al. (2019) Bladder cancer in kidney transplant recipients: A retrospective study. World Journal of Urology 37(Suppl. 1): 140-141.
41. Vamvakas S, Bahner U, Heidland A (1998) Cancer in end-stage renal disease: Potential factors involved. American Journal of Nephrology 18(2): 89-95.
42. Kauffman HM, McBride MA, Cherikh WS, et al. (2002) Transplant tumor registry: Donor related malignancies. Transplantation 74(3): 358-362.
43. Desai R, Collett D, Watson CJ, et al. (2012) Cancer transmission from organ donors-unavoidable but low risk. Transplantation 94(12): 1200-1207.
44. Xiao D, Craig JC, Chapman JR, et al. (2013) Donor cancer transmission in kidney transplantation: A systematic review. American Journal of Transplantation 13(10): 2645-2652.
45. Fan PY, Ashby VB, Fuller DS, et al. (2010) Access and outcomes among minority transplant patients, 1999-2008, with a focus on determinants of kidney graft survival. American Journal of Transplantation 10(4p2): 1090-1107.
46. Marple JT, MacDougall M, Chonko AM (1994) Renal cancer complicating acquired cystic kidney disease. Journal of the American Society of Nephrology 4(12): 1951-1956.
47. Colt JS, Schwartz K, Graubard BI, et al. (2011) Hypertension and risk of renal cell carcinoma among white and black

Americans. Epidemiology 22(6): 797-804.

48. Klatte T, Marberger M (2011) Renal cell carcinoma of native kidneys in renal transplant patients. Current Opinion in Urology 21(5).
49. Moch H, Cubilla AL, Humphrey PA, et al. (2016) The 2016 WHO classification of tumors of the urinary system and male genital organs - Part A: Renal, penile, and testicular tumours. European Urology 70(1): 93-105.
50. Breda A, Luccarelli G, Rodriguez-Faba O, et al. (2015) Clinical and pathological outcomes of renal cell carcinoma (RCC) in native kidneys of patients with end-stage renal disease: A long-term comparative retrospective study with RCC diagnosed in the general population. World Journal of Urology 33(1): 1-7.
51. Cornelis F, Buy X, André M, et al. (2011) De novo renal tumors arising in kidney transplants: Midterm outcome after percutaneous thermal ablation. Radiology 260(3): 900-907.
52. Tsaur I, Obermüller N, Jonas D, et al. (2011) De novo renal cell carcinoma of native and graft kidneys in renal transplant recipients. BJU International 108(2): 229-234.
53. Buzzeo BD, Heisey DM, Messing EM (1997) Bladder cancer in renal transplant recipients. Urology 50(4): 525-528.
54. Kao YL, Ou YC, Yang CR, et al. (2003) Transitional cell carcinoma in renal transplant recipients. World Journal of Surgery 27(8): 912-916.
55. Prabharasuth D, Moses KA, Bernstein M, et al. (2013) Management of bladder cancer after renal transplantation. Urology 81(4): 813-819.
56. Besarani D, Cranston D (2007) Urological malignancy after renal transplantation. BJU International 100(3): 502-505.
57. Tomaszewski JJ, Larson JA, Smaldone MC, et al. (2011) Management of bladder cancer following solid organ transplantation. Advances in Urology 256985: 7.
58. Konety BR, Tiwari A, Howard RJ, et al. (1998) Prostate Cancer in the post-transplant population. Urologic Society for Transplantation and Vascular Surgery. Urology 52: 428-432.
59. Pettenati C, Jannot A-S, Hurel S, et al. (2016) Prostate cancer characteristics and outcome in renal transplant recipients: results from a contemporary single center study. Clinical Transplantation 30(8): 964-971.
60. Kleinclauss F, Gigante M, Neuzillet Y, et al. (2008) Prostate cancer in renal transplant recipients. Nephrology Dialysis Transplantation 23: 2374-2380.
61. Sherer BA, Warrior K, Godlewski K, et al. (2017) Prostate cancer in renal transplant recipients. International Brazilian Journal of Urology 43(6): 1021-1032.
62. Ghazi A, Erturk E, Joseph JV (2016) Modifications to facilitate extraperitoneal robot-assisted radical prostatectomy post kidney transplant. Journal of the Society of Laparoendoscopic Surgeons 16(2): 314-319.
63. Moreno Sierra J, Ciappara Paniagua M, Galante Romo MI, et al. (2016) Robot assisted radical prostatectomy in kidney transplant recipients. Our clinical experience and a systematic review. Urologia Internationalis 97(4): 440-444.
64. Lim K, Autorino R, Veccia A, et al. (2019) Robot assisted laparoscopic prostatectomy in liver transplant recipient. Minerva Urologica e Nefrologica 71: 85-88.
65. Oh SC, Tariq MB, Reddy CA, et al. (2019) Outcomes in organ transplant recipients with prostate cancer treated with radiotherapy. Clinical Genitourinary Cancer 17(1): e162-e166.
66. Aminsharifi A, Simon R, Polascik TJ, et al. (2019) Evaluation and active treatment versus active surveillance of localized prostate cancer in renal transplant patients in the era of low and very low risk prostate cancer. The Journal of Urology

202(3): 469-474.

67. Thankamma AV, Parkinson CA, Butler A, et al. (2007) Management of solid tumors in organ-transplant recipients. The Lancet Oncology 8(10): 921-932.
68. Leibovitch I, Baniel J, Rowland RG, et al. (1996) Malignant testicular neoplasms in immunosuppressed patients. The Journal of Urology 155(6): 1938-1942.
69. Tsaur I, Karalis A, Probst M, et al. (2010) Development of urological cancers in renal transplant recipients: 30-year experience at the Frankfurt Transplant Center. Cancer Science 101(11): 2430-2435.
70. Farrugia D, Mahboob S, Cheshire J, et al. (2014) Malignancy-related mortality following kidney transplantation is common. Kidney International 85(6): 1395-1403.
71. Miao Y, Everly JJ, Gross TG, et al. (2009) De Novo cancers arising in organ transplant recipients are associated with adverse outcomes compared with the general population. Transplantation 87(9): 1347-1359.
72. D'Arcy ME, Coghill AE, Lynch CF, et al. (2019) Survival after a cancer diagnosis among solid organ transplant recipients in the United States. Cancer 125(6): 933-942.
73. Acuna SA, Huang JW, Scott AL, et al. (2017) Cancer screening recommendations for solid organ transplant recipients: A systematic review of clinical practice guidelines. American Journal of Transplantation 17(1): 103-114.
74. Sammon JD, Abdollah F, Choueiri TK, et al. (2015) Prostate-specific antigen screening after 2012 US Preventive Services Task Force Recommendations. JAMA 314(19): 2077-2079.
75. Schmid M, Chun FKH, Trinh QD (2016) Targeted cancer screening after solid-organ transplantation. JAMA Oncology 2(4): 470.