

Bladder Cancer in Renal Allograft Recipients: Risk Factors and Outcomes

S. Medani^{a,*}, P. O'Kelly^a, K.M. O'Brien^b, P. Mohan^a, C. Magee^a, and P. Conlon^a

^aDepartment of Nephrology, Urology & Transplantation, Beaumont Hospital, Dublin, and ^bNational Cancer Registry, Cork, Ireland

ABSTRACT

Background. Solid organ transplant recipients have an increased cancer risk owing to immunosuppression and oncogenic viral infections. We report on the incidence and types of bladder cancer in kidney transplant recipients in Ireland, describing possible additional risk factors and outcomes in these patients.

Methods. We identified kidney transplant recipients diagnosed with de novo bladder cancer between January 1, 1994, and July 31, 2012, by integrating data from the Irish National Cancer Registry and National Renal Transplant Registry. We calculated the standardized incidence ratio (SIR) and examined patient and tumor characteristics and 1-year survival rate.

Results. Fifteen patients were diagnosed with de novo bladder cancer during the study period, representing 0.48% of kidney transplant recipients. The SIR was 2.5 (95% CI, 1.4–4.2; $P < .001$). The mean interval between transplantation and diagnosis of bladder tumor was 8.6 years and mean age at time of diagnosis was 55.7 years. Sixty percent of patients were male. The tumor types were transitional cell carcinoma (9 patients), squamous cell carcinoma (3 patients), adenocarcinoma (1 patient), carcinoma in situ (1 patient), and diffuse large B-cell lymphoma (1 patient). Beside immunosuppression, risk factors associated with bladder cancer were urogenital disease (6 patients), cyclophosphamide exposure (2 patients), BK nephropathy (1 patient), analgesic nephropathy (1 patient), and extensive smoking (1 patient). Eight patients underwent radical cystectomy for invasive tumors, with resection of other pelvic organs in 7 patients. Mortality rate within the first year was 40%.

Conclusion. Bladder cancer occurred more commonly in kidney transplant recipients with a predominance of aggressive tumors and a high mortality. In patients with preexisting risk factors such as urologic abnormalities and cyclophosphamide exposure careful assessment before transplantation and vigilant monitoring posttransplantation with a low threshold for cystoscopy may improve outcomes.

MALIGNANCY IS CURRENTLY a leading cause of death with a functioning graft in solid organ transplant recipients [1,2]. Although it is recognized that immunosuppressive therapy and oncogenic viral infections may confer an increased cancer risk in these patients, little is known about the effects of interaction between these factors and other inherent or environmentally acquired risk determinants of cancer development. Optimal screening strategies for cancer in the setting of solid organ transplantation based on these baseline risks are continuously evolving.

There is limited literature relating to pretransplant and posttransplant screening for bladder cancer in solid organ transplant candidates or recipients who have preexisting identifiable risk factors, such as exposure to cyclophosphamide, and the data to substantiate recommendations for such

*Address correspondence to Samar Medani, Department of Nephrology, Beaumont Hospital, Beaumont Road, Dublin 9, Republic of Ireland. E-mail: smedani@doctors.org.uk

screening are scarce. The Canadian Society of Transplantation consensus guidelines published in 2005 and a draft guideline published in 2011 on the Caring for Australians with Renal Impairment (CARI) website recommend that pretransplant cystoscopic surveillance be considered for those with analgesic nephropathy and those who have received cyclophosphamide therapy [3,4]. These recommendations are based on the clinical practice guidelines for the evaluation of renal transplantation candidates published in the *American Journal of Transplantation* in 2001 [5]. However, the 2009 Kidney Disease: Improving Global Outcomes guideline for the care of kidney transplant recipients did not replicate this recommendation. There is even less guidance on the posttransplantation screening of patients with additional risk factors for bladder malignancy with no prospective data supporting the cost effectiveness of any screening strategies. Experts in the field have again recommended urologic examination in patients who develop de novo microhematuria and have a history of analgesic nephropathy or those who received cyclophosphamide especially if the cumulative dose is >20 g [6]. To date, there are few reports on posttransplantation bladder cancer in the setting of prior cyclophosphamide therapy [7–9] or analgesic nephropathy [10]. Other factors that can potentiate the risk have been less well-defined.

We sought to examine the incidence and risk associations of bladder cancer occurring after renal transplantation in the Irish population, and to raise suggestions for enhanced patient screening in the pretransplantation and posttransplantation course to avoid delays in diagnosis and optimize survival potential.

METHODS

This retrospective, registry-based study looked at bladder cancer incidence among renal transplant recipients (RTRs) in comparison with the entire Irish population. Patients were identified by computerized matching of the Irish National Cancer Registry (NCRI) and the National Renal Transplant registry (NRTR) databases. The medical records and histological reports of patients were accessed for clinical data. The NCRI is a nationwide register of cancers since January 1994. The NRTR includes renal transplants carried out in Ireland since 1964. The study population comprised all patients who underwent kidney transplantation in Ireland from 1964 through July 31, 2012, and who had not died before January 1, 1994. The time at risk was therefore defined as the time from the first transplant or January 1, 1994, if the first transplant occurred before this date, until death of the patient or July 31, 2012, regardless of transplantation outcomes. Only records of first primary bladder cancers that were diagnosed after renal transplantation were included. Patients who were transplanted abroad or subsequently followed up abroad (lost to follow-up) were excluded. We compared the incidence with respect to the general population by calculating the age and gender adjusted standardized incidence ratio (SIR). The SIR was calculated by dividing the actual bladder cancer incidence by the expected cancer rate in the transplant population. Multiplying the person years at risk for kidney transplant patients by the average of gender-specific and age-group-specific yearly cancer incidence rates in the entire population

gives the expected cancer rate in the transplant population. The risk of bladder cancer with time after renal transplantation and survival after diagnosis of bladder cancer were evaluated by Kaplan–Meier survival analyses. Statistical analyses were performed with the SPSS software package (SPSS Inc., Chicago, IL).

RESULTS

Between 1964 and July 31, 2012, 3141 patients underwent 3688 renal transplantations in Ireland, excluding 377 patients who died before 1994, 29 patients who were transplanted abroad and 24 patients who were lost to follow-up. Mean age at the time of first kidney transplant was 41.9 ± 16.3 years; 63% of recipients were male. There were 15 renal allograft recipients with a de novo malignant bladder tumor diagnosed during the study period, 60% of whom were male. Mean age at time of diagnosis of bladder tumor was 55.7 years and mean interval between transplantation and diagnosis of bladder tumor was 8.6 years. The SIR for malignant bladder tumors in kidney transplant recipients was 2.5 (95% CI, 1.4–4.2; $P < .001$).

Table 1 illustrates the patient and tumor characteristics of the identified cases. The time interval between transplantation and diagnosis, treatment received, and survival after diagnosis for each patient are also shown. Transitional cell carcinoma (papillary or invasive urothelial carcinoma) was the commonest tumor type. One third of patients had nonurothelial tumors, including squamous cell carcinoma, adenocarcinoma, and diffuse large B-cell lymphoma. In 11 of the 15 patients (73.3%), an additional risk factor associated with bladder malignancy besides immunosuppression was identified. In 6 patients (40%), the additional risk was attributed to a genitourinary condition or a congenital anomaly associated with increased bladder cancer risk. Prior cyclophosphamide therapy, BK nephropathy, analgesic nephropathy, and extensive smoking were other risk associations seen in this cohort. There were 2 patients who received cyclophosphamide 1 year before transplantation. These additional risk factors are demonstrated in Table 2. Eight patients were treated with radical cystectomy for invasive tumors; 7 of these had aggressive disease necessitating resection of other pelvic organs. Five out of 6 female patients had aggressive tumors and required invasive surgery. Five out of the 9 male patients also had aggressive tumors with a high mortality (80% at 1 year). Overall mortality rate within the first year was 40%. In 5 of the 6 patients who died within the first year of bladder cancer diagnosis, death was owing to tumor-related complications, including neutropenic sepsis, pulmonary embolism, and progression of metastatic disease.

Figure 1 shows the cumulative risk of bladder cancer in RTRs. At 15 years posttransplantation, an estimated 0.9% of our renal transplant population will develop bladder cancer with an incidence rate of 5.6 events per 10,000 patient-years. Estimated survival after diagnosis of bladder cancer is shown in Fig 2, predicting 1- and 5-year survivals of 60% and 36%, respectively.

Table 1. Patient and Tumor Characteristics, Treatment, and Outcomes of Bladder Cancer in Renal Transplant Recipients

| Patient | Patient Characteristics | | | Tumor Characteristics | | | Interval From Transplant to Diagnosis (y) | Treatment | Cancer-related Death/Survival After Diagnosis |
|---------|-------------------------|--------|--|-----------------------|-------|-------|---|---|---|
| | Age at Diagnosis (y) | Gender | Etiology of ESKD | Type | Grade | Stage | | | |
| 1 | 70 | M | Crescentic glomerulonephritis | DLBCL | High | IV | 6 | Chemotherapy | Yes/2 wk |
| 2 | 79 | M | Hypertensive nephrosclerosis | TCC | Low | 0 | 4 | TURBT | No/5 y |
| 3 | 71 | M | Unknown | TCC | Low | 0 | 6 | TURBT | Alive/2 y |
| 4 | 34 | M | Reflux/obstructive uropathy (congenital) | CIS | High | 0 | 13 | TURBT | Alive/6 y |
| 5 | 60 | M | PCKD | TCC | High | 0 | 8 | TURBT | Alive/2.5 y |
| 6 | 24 | M | Reflux/obstructive uropathy (congenital anomaly) | SCC | High | IV | 20 | Cystectomy + bowel resection | Yes/3 mo |
| 7 | 39 | F | Reflux nephropathy | TCC | High | III | 15 | Cysectomy + bilateral native nephrectomy + hysterectomy | Yes/9 mo |
| 8 | 49 | F | Reflux/obstructive uropathy (congenital anomaly) | Urachal Adenoca | High | III | 15 | Pelvic exenteration + Radiotherapy | Alive/8 y 10 mo |
| 9 | 76 | M | Renovascular disease | TCC | High | IV | 6 | TURBT, unfit for further therapy | Yes/3 wk |
| 10 | 28 | F | Reflux/obstructive uropathy (congenital anomaly) | SCC | High | II | 12 | Cystectomy + chemotherapy, nonoperative palliation for recurrence | Yes/2 y |
| 11 | 80 | F | Analgesic Nephropathy | TCC | High | I | 4 | TURBT | No/11 mo |
| 12 | 40 | F | PCKD | TCC | High | IV | 8 | TAH/BSO + cystectomy + transplant nephrectomy | Alive/5 y |
| 13 | 57 | M | IgA nephropathy | TCC | High | IV | 7 | Cystoprostatectomy + transplant nephrectomy | Alive/3 y |
| 14 | 59 | M | Ischemic nephropathy | SCC | High | III | 1.6 | Cystoprostatectomy + chemotherapy | Yes/11 mo |
| 15 | 70 | F | ANCA vasculitis | TCC | High | III | 7 | Anterior pelvic exenteration | Alive/1 y 5 mo |

Abbreviations: Adenoca, adenocarcinoma; CIS, carcinoma in situ; DLBCL, diffuse large B-cell lymphoma; ESKD, end-stage kidney disease; PCKD, polycystic kidney disease; SCC, squamous cell carcinoma; TAH/BSO, total abdominal hysterectomy/Bilateral salpingo-oophorectomy; TCC, transitional cell carcinoma; TURBT, transurethral resection of bladder tumor.

DISCUSSION

Bladder cancer is the fourth most common incident cancer among males in the United States, the United Kingdom, and the Republic of Ireland. It is also the 9th most common

Table 2. Patients With Identifiable Risk Associations for Bladder Cancer in Addition to Immunosuppression

| Patient | Risk Factor |
|---------|---|
| 1 | Cyclophosphamide |
| 2 | Obstructive uropathy (TURP-treated BPH) |
| 4 | Reflux/obstructive uropathy (congenital neurogenic bladder) |
| 6 | Reflux/obstructive uropathy, reconstructive urinary tract surgery (prune belly syndrome) |
| 7 | Vesicoureteric reflux |
| 8 | Reflux/obstructive uropathy, reconstructive urinary tract surgery (ectopia vesicae) |
| 10 | Reflux/obstructive uropathy, reconstructive urinary tract surgery, self-intermittent catheterization (spina bifida) |
| 11 | Analgesic Nephropathy |
| 13 | BK virus nephropathy |
| 14 | Extensive smoking |
| 15 | Cyclophosphamide |

Patient numbers correspond with those in Table 1. Abbreviations: BPH, benign prostatic hyperplasia; TURP, transurethral resection of the prostate.

cancer among females in the United States and the 12th most common for women in Ireland. Observational data have shown not only worldwide increased bladder cancer incidence in RTRs (11–32; [Supplementary Appendix](#)), but also more aggressive disease with poorer outcomes when compared with the general population [21,33]. The incidence of bladder cancer in RTRs varies depending on the population studied from 0.08% to 2.8%, which is 2–3 times greater than in the general population. These findings are consistent with our present case series. Excluding Chinese populations, a male predominance is seen across all other population groups; females tend to present with higher stage tumors. With the exception of the study by Kamal et al [17] illustrating a high prevalence of schistosomiasis related squamous cell bladder cancer in the Egyptian population, posttransplant bladder cancer cases reported in the literature are mostly transitional cell carcinoma (TCC) and the vast majority of studies report exclusively TCC cases. Our case series includes a patient with adenocarcinoma and another with lymphoma of the bladder as well as 3 cases with squamous cell carcinoma, which were reported in a recent paper by Davis et al [34] on squamous cell bladder cancer after diseased donor renal transplantation. Apart from the increased incidence, we observed important differences in the statistics of bladder cancer in RTRs

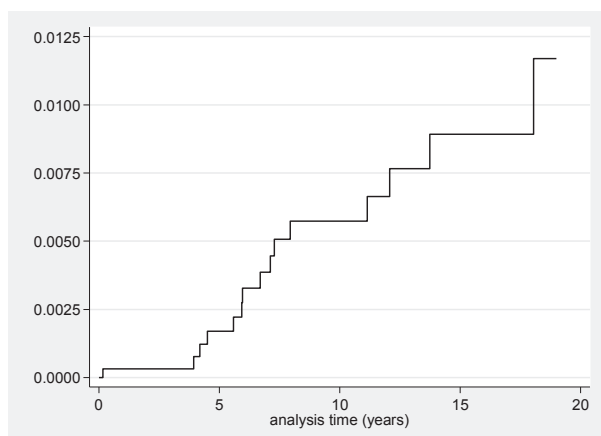


Fig 1. Cumulative incidence of bladder cancer in renal transplant recipients.

compared with the general Irish population. Bladder cancer in RTRs occurred at an earlier age; mean age was 56 compared with a mean age of 70 at the time of diagnosis in the general population. The younger mean age of the transplant population mitigates the significance of this large age discrepancy. However, more disconcertingly, we found that two thirds of those RTRs diagnosed with bladder cancer had muscle invasive disease at diagnosis with a 1-year overall survival of 60%. In the general Irish population, 25% of bladder cancer cases were classified as muscle invasive (stages 2–4) throughout the study period; 35% were superficial tumors and carcinoma in situ, and the remaining 40% were unstaged or classified as neoplasms of uncertain behavior. The 1-year survival after diagnosis of bladder cancer in the general population was 72%, notwithstanding that these were older patients and bladder cancer was reported to be the cause of death in approximately one half of these patients only. Approximately 70% of those diagnosed with bladder cancer in the Irish general population are male, and in 70%, the tumor is a TCC.

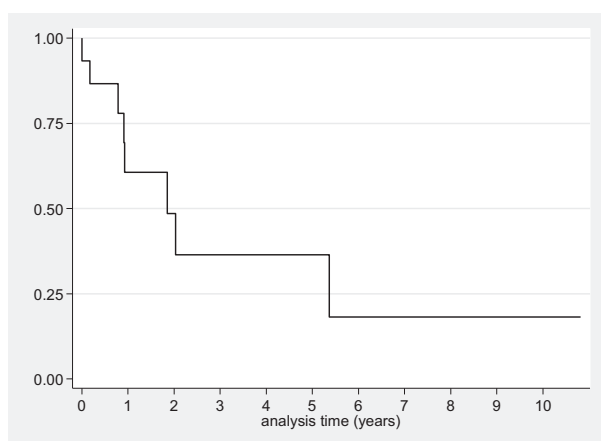


Fig 2. Patient survival after bladder cancer diagnosis in kidney transplant recipients.

Traditional environmental risk factors associated with bladder malignancy include smoking, radiation, occupational exposures, and, in the case of squamous cell carcinoma, urinary schistosomiasis [35,36]. The post-transplantation immunosuppression status of transplant recipients is thought to result in impaired DNA repair mechanisms and impaired protection against oncogenic viruses, further increasing the risk for a variety of neoplastic conditions, including bladder cancer. Although a causal relationship has not been unequivocally proven, human papillomavirus virus and the BK polyoma virus have both been implicated in the pathogenesis of bladder cancer [37–41]. High level expression of BK polyoma virus large T antigen in tumor tissue, but not in the non-neoplastic urothelium, suggest that BK polyoma virus may play a role in the oncogenic pathway in the post-transplantation setting. In this study, 2 of our patients had biopsy proven condylomata acuminata, 1 before and 1 after diagnosis of bladder cancer; hence, a possible association of human papilloma virus infection, a less recognized risk factor, with the development of their bladder tumors. Both patients however had vesicoureteric reflux and their bladder tumors were not analyzed for human papillomavirus virus infection using polymerase chain reaction. One of these patients had a neurogenic bladder, a longstanding urethral stricture, and urethral warts before diagnosis of a carcinoma in situ of bladder; and had biopsy confirmed condyloma acuminatum from a urethral lesion on follow-up 3 years later. The second patient had spina bifida with an ileal conduit and-biopsy proven condyloma acuminata from cervical and vulval lesions 2 and 5 years, respectively, before the diagnosis of invasive squamous cell bladder cancer.

The increased incidence of cancer of the urinary tract and overall cancer risk in dialysis patients has been demonstrated in previous observational studies [42–47]. Both dialysis-dependent patients and RTRs had a higher proportion of muscle invasive bladder cancer and non-urothelial bladder tumors than the general population in a large, retrospective, US database analysis [21]. This implies that factors related to the underlying renal pathology, such as analgesic abuse, cyclophosphamide exposure, or urogenital disease, as well as the immune dysfunction and nutritional deficiencies associated with uremia and dialysis dependence, may contribute to the higher risk and poorer outcomes in transplant recipients [41,46,48]. The risk of bladder cancer has also been shown to be elevated in men with a history of benign prostatic hyperplasia treated with transurethral resection of prostate [49,50]. Therefore, the status of reaching end-stage kidney disease, underlying genetic, congenital, developmental, and environmental factors, including those related to the primary renal disease, may all interact with superimposed immunologic manipulation in a transplant recipient, amounting to a higher cancer risk profile.

Much of the literature on posttransplantation bladder malignancy originates from China, where a high incidence

of de novo TCC posttransplantation has been consistently reported. Kidney and bladder cancers were found to be the most common posttransplant malignancies in Chinese kidney transplant recipients in Taiwan [29], and bladder cancer had the highest SIR among solid organ malignancies in the Hong Kong renal registry [31]. Exposure to Chinese herbs and arsenic in underground water sources are among the additional endemic risk factors that are implicated in the higher prevalence of urothelial cancer seen in these populations [51,52]. A pattern of female predominance and a higher incidence of synchronous and isolated upper tract involvement were seen in the Chinese population [15,30,31]. A protocol of screening for urothelial cancer including bladder tumors in these higher risk populations was presented in the Congress of the Asian Society of Transplantation in 2005. The accelerated rate of diagnosis of these cancers in the transplant population of this region in the last few years may be partially attributed to detection of early lesions owing to enhanced and intensive screening of asymptomatic patients [53].

In general, the treatment of bladder malignancy in transplant recipients is broadly similar to that instituted in nontransplant patients, with preservation of the renal allograft reported in most case series. Pertinent management issues that arise in and are unique to solid organ transplant recipients include concomitant management of immunosuppression and the consequences and additional morbidity burden of loss of graft function. The use of adjuvant intravesical bacillus Calmette-Guérin for non-muscle-invasive bladder cancer is controversial in transplanted patients but has been reported to be successful with and without prophylactic anti mycobacterial cover [54,55]. Fatal disseminated mycobacterial infection has been reported after intravesical bacillus Calmette-Guérin in immunosuppressed patients [56,57]. Prolonged patient and allograft survivals have been demonstrated after radical surgery for bladder cancer in transplant recipients in our series and other reports. Clearly, however, the aim should be earlier diagnosis of superficial tumors. The discordance between the intensity of medical follow-up that these patients are committed to and the late detection of bladder malignancy calls for concern and urges improvements in clinical practice for earlier identification and treatment of these patients. The finding of residual microscopic hematuria owing to intrinsic or structural renal disease in native kidneys can be a source of confusion and delayed diagnosis. On the other hand, anuric patients on dialysis may present at a later stage owing to absence of frank hematuria, the commonest presenting symptom of bladder malignancy, and for the same reason may potentially be transplanted during an early stage of an undiagnosed bladder tumor.

Enhanced urologic screening has been advocated by various authors for early detection of urothelial malignancy in transplant recipients [15,16,18,20,21,29,31,58]. However, owing to lack of adequate evidence and cost-effectiveness studies as well as interpopulation differences in risk factors, tumor characteristics, incidence, and outcomes, there

is no consensus of a universally accepted, risk-adapted surveillance protocol, and specific screening strategies for selected patient groups have seldom been proposed. In addition to these recommendations for considering pretransplant cystoscopy in patients with a history of analgesic nephropathy or cyclophosphamide exposure [3–6], similar screening of heavy smokers, those with end-stage kidney disease owing to toxic, infectious, or obstructive uropathies, and those with a history of exposure to industrial carcinogens or schistosomiasis has been recommended as part of the pretransplantation urologic evaluation [58]. Surveillance posttransplantation raises more controversy with regard to the optimal screening strategy and perceived potential benefit versus long-term cost considerations. Although some authors suggested screening within the first 4–5 years after transplantation [21,59], the risk period may be extended to considerably longer durations. Bladder cancer occurred at a significantly later stage posttransplantation in our study population, 8 years on average as opposed to 5–6 years in other studies [13,21,31]. Moreover, we have diagnosed bladder cancer at ≤ 20 years posttransplantation, arguing for the need for ongoing monitoring and surveillance. In the Asian populations, a high incidence of synchronous upper tract urothelial carcinomas, an association with use of Chinese herbs and a much higher overall incidence compared with Western countries, mandates unique and more vigorous screening programs aiming at early detection of urothelial cancer in transplant recipients [15,20,30,60].

The development of an effective and cost-efficient, risk-tailored screening strategy for pretransplant and posttransplant bladder cancer is a challenging prospect, but of significant importance given that early stage disease is usually curable. A pragmatic approach is required in the absence of definitive evidence to guide recommendations for surveillance. In a relatively low-risk Western population, current evidence does not justify routine screening of transplant candidates and recipients for urologic cancer; however, increased vigilance must be exercised, particularly in high-risk patients, so that appropriate investigation of microscopic hematuria is instigated without delay. In addition to the standard indications for cystoscopic examination, such as unexplained hematuria, recurrent urinary tract infections, obstructive urinary symptoms, and surveillance for recurrent urothelial cancer, it seems reasonable to adopt a policy of high index of clinical suspicion and low threshold for cystoscopy in patients with any of the risk factors identified in this study. The anticipated improvements in prognosis for patients diagnosed with posttransplantation bladder cancer over time may be informative with regard to the cost considerations and modifications needed for future screening strategies.

To our knowledge, this is the first study to highlight the likely augmented risk of bladder cancer in kidney transplant recipients with underlying genitourinary abnormalities compared with the general renal transplant population. Our institution benefits from being the national renal transplant center where all kidney transplants in Ireland are performed,

which facilitates consistency and enhanced accuracy of clinical data. We also cross-linked our data with the national cancer registry database to calculate the SIR. The limitations of this study include those relating to the retrospective nature of registry data analysis where some relevant information, such as background environmental risk associations, may be missing and cancer incidence may be underreported. Because the inclusion periods of the 2 registries are discordant, the NRTR predating the NCRI by 30 years, the 0.48% incidence of bladder cancer found in RTRs is likely to represent an underestimate of the true incidence as any transplant recipients diagnosed with bladder cancer between 1964 and 1994 were missed. That being said, the incidence of bladder cancer in RTRs was found to be higher in comparison with the Irish general population with a SIR of 2.5; the true incidence and corresponding SIR could be higher. The relatively low incidence of bladder cancer contributes to a reduction in the statistical power of the study. The presence of a preexisting tumor could not be excluded in 1 patient who was diagnosed only 2 months after transplantation during routine cystoscopic removal of a ureteric stent.

In conclusion, RTRs have a 2.5-fold increased risk of bladder malignancy compared with the general population in Ireland, with a high rate of aggressive tumors and cancer-related mortality. As renal allografts in the era of current immunosuppression survive longer, posttransplantation incidence of bladder cancer may rise. Preexisting genitourinary abnormalities, toxic nephropathies, and cyclophosphamide exposure seem to confer additional risk. The issue of screening posttransplantation is difficult to resolve given the low incidence of bladder cancer and further research is needed before routine risk adapted cystoscopic surveillance can be recommended. Vigilance in detecting and evaluating new, unexplained, microscopic and macroscopic hematuria, particularly in high-risk patients, is imperative to facilitate earlier diagnosis.

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Appendix. Recent Studies Including Reports of Primary Bladder Cancer After Renal Transplantation*

| Study, Year Published, Country | Transplant Population [†] | | Interval to Diagnosis (y) | Bladder Cancer | | Incidence of Tumor [‡] /(SIR) | Interval-Specific Survival of Patients |
|---|------------------------------------|---------|---------------------------|-----------------|-----------|--|---|
| | Renal Grafts | RTRs | | Patients | % TCC/CIS | | |
| Wang H-B et al 2002, Taiwan [11] | | 320 | 2.1 | 8 [§] | 100 | 2.5% | 100% at 1 y |
| Kao Y-L et al 2003 Taiwan [12] | | 670 | NR | 15 [§] | 100 | 2.24% | 73% at 1 y |
| Master VA et al, 2004 [13] | | 6288 | 8.9 | 5 | 100 | 0.08% | 60% at 1 y |
| Master VA et al 2004, USA (UNOS) [13] | | 129,238 | 5.2 | 31 | NR | 0.024% | NR |
| Master VA et al, 2004, CTTR [13] | | NR | 6.4 | 135 | NR | NR | NR |
| Liao C-H et al, 2004, Taiwan [14] | | 663 | NR | 6 [§] | 100 | 0.9% | NR |
| Wu M J et al, 2004 Taiwan [15] | | 730 | NR | 20 [§] | 100 | 2.74% | NR |
| Diller R et al, 2005 Germany [16] | 2068 | 1804 | 7.3 | 6 [§] | 100 | 0.33% | 80% at 1 y 40% at 5 y |
| Kamal M et al, 2007, Egypt [17] | 1865 | 1865 | 9.4 | 7 | 57 | 0.37% | NR |
| Besarani et al, 2007 UK (UKTR) [18] | | 10,847 | NR | 48 | NR | 0.44% | NR |
| Villeneuve et al, 2007, Canada (CORR, CCR) [19] | | 11,155 | NR | 24 | NR | 0.22% (2.0) | NR |
| Li X-B et al, 2008 China [20] | 1735 | 1669 | 3.6 | 18 [§] | 100 | 1.08% | 100% at 1 y |
| Ehdaie et al, 2009, USA (SEER-Med) [21] | | 97,942 | 5.2 | 58 | 83 | 0.06% | NR |
| Einollahi et al, 2009, Iran [22] | | 5532 | NR | 7 | 100 | 0.13% | NR |
| Elkentaoui et al, 2010, France [23] | | 1350 | 7.3 | 5 | 100 | 0.37% | 60% at 5 y |
| Tsaur et al, 2010 Germany [24] | | 1990 | 6.9 | 18 | 100 | 0.90% | 85% at 1 y [¶] 67% at 5 y [¶] |
| Melchior et al, 2011, Germany [25] | | 802 | 2.3 | 6 | 100 | 0.75% | NR |
| Hwang et al, 2011, Korea [26] | | 1695 | 6.6 | 8 | NR | 0.47% | NR |
| Cox J et al, 2011 USA [27] | | 5920 | 5.4 | 8 | 100 | 0.13% | NR |
| Tomaszewski et al 2011, USA [28] | | 2925 | NR [#] | 8 | 100 | 0.27% | NR |
| Li W-H et al, 2012 Taiwan (NHIRD) [29] | | 4716 | NR | 72 | NR | 1.53% (42.9) | NR |
| Chiang et al, 2012, Taiwan [30] | 770 | | NR | 22 [§] | 100 | NR ^{**} | NR |
| Cheung et al, 2012, Hong Kong [31] | 4895 | 4674 | 4.8 | 12 [§] | NR | 0.26% (8.2) | NR |
| Rogers et al, 2012, UK [32] | | 1647 | 5.9 | 8 | 100 | 0.48% | 83% at 5 y 72% at 10 y |

Abbreviations: CCR, Canadian Cancer Registry; CORR, Canadian Organ Replacement Registry; CTTR, Cincinnati Transplant Tumor Registry; NHIRD, National Health Insurance Research Database in Taiwan; NR, not reported (intervals to diagnosis and death in series that include patients with upper urinary tract TCC only are not included unless they have reported those intervals for the subset of patients with bladder cancer); RTRs, renal transplant recipients; SEER-Med, Surveillance, Epidemiology and End Results- Medicare database; SIR, standardized incidence ratio; ratio of the observed-to-expected number of incident cancers; TCC/CIS, transitional cell carcinoma/carcinoma in situ; UKTR, United Kingdom Transplant Registry; UNOS, United Network for Organ Sharing.

*Studies since 2000 including >3 renal transplant recipients diagnosed with bladder cancer included.

[†]Most papers reported the number of renal transplant recipients (RTRs), although some papers reported the number of renal transplants with or without the number of RTRs.

[‡]Incidence per patients.

[§]Series include patients with synchronous upper tract tumors.

^{||}After excluding 1 patient in whom TCC developed 33 years after transplantation, mean time to diagnosis was 2.8 years.

[¶]Tumor-specific survival reported for 20 patients in total including those with upper tract transitional cell carcinoma.

[#]Mean interval of 39 months between transplantation and bladder cancer diagnosis was recorded for a series including 3 additional patients who received liver transplants in this paper.

^{**}The reported incidence of all urothelial cancers including those in the kidney and/or ureter only was 4.55% of renal transplantations. Only 7 patients (20%) had bladder cancer alone. All cancers were transitional cell carcinomas with a sarcomatoid variant in 1 case.