



Published in final edited form as:

Am J Transplant. 2018 January ; 18(1): 245–252. doi:10.1111/ajt.14530.

Treatment for Presumed BK Polyomavirus Nephropathy and Risk of Urinary Tract Cancers among Kidney Transplant Recipients in the United States

Gaurav Gupta, MD¹, Sarat Kuppachi, MD², Roberto S. Kalil, MD², Christopher B. Buck, PhD³, Charles F. Lynch, MD PhD², and Eric A. Engels, MD MPH³

¹Virginia Commonwealth University, Richmond, United States

²University of Iowa, Iowa City, United States

³National Cancer Institute, Bethesda, United States

Abstract

Recent case series describe detection of BK polyomavirus (BKV) in urinary tract cancers in kidney transplant recipients, suggesting that BKV could contribute to the development of these cancers. We assessed risk for urinary tract cancers in kidney recipients with or without treatment for presumed BKV nephropathy (tBKVN) using data from the United States Transplant Cancer Match Study (2003–2013). Among 55,697 included recipients, 2015 (3.6%) were reported with tBKVN. Relative to the general population, incidence was similarly elevated (approximately 4.5-fold) for kidney cancer in recipients with or without tBKVN, and incidence was not increased in either group for prostate cancer. In contrast, for invasive bladder cancer, incidence was more strongly elevated in recipients with versus without tBKVN (standardized incidence ratios 4.5 vs. 1.7; N=48 cases), corresponding to an incidence rate ratio (IRR) of 2.9 (95%CI 1.0–8.2), adjusted for sex, age, transplant year, and use of polyclonal antibody induction. As a result, recipients with tBKVN had borderline increased incidence for all urothelial cancers combined (renal pelvis, ureter, and bladder cancers: adjusted IRR 2.2, 95%CI 0.9–5.4; N=89 cases). Together with reports describing BKV detection in tumor tissues, these results support an association between BKV and urothelial carcinogenesis among kidney transplant recipients.

Introduction

Kidney transplant recipients have an elevated risk for cancer compared with the general population (1). Defective immune surveillance related to immunosuppressive medication use has been linked with an increased risk of virus-related malignancies, e.g., Epstein-Barr virus-related lymphomas, human papillomavirus-associated anogenital cancers, and human herpesvirus 8-associated Kaposi's sarcoma (2). Kidney transplant recipients also have an

Corresponding Author: Eric A. Engels, MD MPH, Infections and Immunoepidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 9609 Medical Center Drive, Room 6E226, Bethesda, MD 20892, engelse@exchange.nih.gov. Telephone: 240-276-7186.

Disclosure

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

increased risk of developing some urinary tract cancers, including renal cell carcinoma, bladder cancer, and ureteric cancer (2–4). For unclear reasons, risk of prostate cancer is reduced among transplant recipients (1, 5).

BK polyomavirus (BKV, also known as human polyomavirus 1) can cause BKV nephropathy (BKVN) among kidney transplant recipients (6). Approximately 70–90% of healthy people are infected with BKV (6). BKV acquisition generally occurs in childhood, and the virus is thought to establish a lifelong chronic infection in the epithelium of the urinary tract. Intermittent asymptomatic low-level BK viremia in the range of 10–15% has been reported in immunocompetent individuals, but prospective screening studies suggest that 30–50% of kidney recipients develop BK viremia after transplantation, with a peak incidence in the first 2–12 months (6–8). Viremia sometimes progresses to viremia (usually after a gap of a few weeks), with a reported incidence of 5–15%. Although the progress to viremia closely mirrors the onset of BKVN, the incidence of biopsy-proven BKVN is reported to be only 1–5%, likely due to the focal nature of BKV disease (9–11). BKVN often leads to renal allograft loss, and a substantial body of literature exists about this association and its management (8, 12). Typical treatment regimens for BKVN involve reducing the level of immunosuppressive therapy. Rarely, BKV has also been associated with hemorrhagic cystitis or ureteral stenosis in kidney recipients (12).

BKV belongs to the polyomavirus family, other members of which have well-known oncogenic effects in rodents (7, 13). Some members of *Polyomaviridae* are associated with cancer in host animals ranging from mice to raccoons (14). BKV likewise causes various types of cancer, including nephroblastoma, in experimentally challenged rodents (13). Over the last few years, Merkel cell polyomavirus has been demonstrated to be the causative agent for the majority of Merkel cell carcinomas in humans (15). Notably, BKV has been linked to aggressive urinary tract cancers in kidney transplant recipients in a large number of recent case reports (16–34), as summarized by Papadimitriou et al. (35). These reports provide evidence of BKV in the tumors as demonstrated by immunohistochemical staining for BKV proteins, polymerase chain reaction (PCR) testing for BKV DNA, or detection of chromosomally integrated BKV through whole genome shotgun sequencing of the tumor.

Importantly, no population-wide studies have investigated the association of BKVN with the risk of developing urinary tract cancers. In this study, we used linked registry data from the United States to perform a detailed comparison of risk for post-transplant urinary tract cancers among kidney recipients with or without treatment for presumed BKVN.

Methods

The study cohort consisted of kidney transplant recipients (including recipients of other organs simultaneous with a kidney) in the Transplant Cancer Match (TCM) Study, a linkage of the US transplant registry (Scientific Registry of Transplant Recipients, SRTR) with 17 state and regional cancer registries (see Table 1 note). The main exclusion criterion was missing information on the treatment for presumed BKVN (which we abbreviate “tBKVN”), as reported by transplant centers between 6 months and 2 years after transplant. Specifically, our analyses used the SRTR variable TFL_BK_THERAPY, which captures whether a

recipient was treated for BKVN (based on definitive or presumptive clinical information). Since data on tBKVN were first collected for transplants beginning in 2003, we excluded earlier transplants. Kidney recipients infected with human immunodeficiency virus were also excluded. Based upon these criteria, out of a total of 289,495 kidney transplants in the TCM Study, 55,697 were included in the analysis.

Urinary tract cancers (cancers of the kidney, renal pelvis, ureter, urinary bladder, prostate) were identified through linkage with the cancer registries. All invasive cancers at these sites (not merely first occurrences) were assessed. For bladder cancer only, we also assessed *in situ* cancers, because these are commonly diagnosed and ascertained by cancer registries.

Transplant recipients were classified according to the presence of tBKVN using the first reported value for TFL_BK_THERAPY in the interval of 6 months to 2 years post-transplant. Follow-up for cancer started on the date of this report or start of cancer registry coverage, whichever occurred last. Because follow-up did not start until the reported value of TFL_BK_THERAPY, all cancer diagnoses occurred after ascertainment of tBKVN status. Patients were censored at death, failure of the transplanted kidney, subsequent transplant, loss of follow-up, or last date of cancer registry coverage (whichever occurred first).

We calculated the incidence of each urothelial cancer (defined as the number of outcomes per 1000 person-years of follow-up) in kidney recipients with and without tBKVN. We compared cancer incidence in kidney recipients to the incidence expected based on general population rates using standardized incidence ratios (SIRs). SIRs utilized general population rates stratified by sex, age, race/ethnicity, calendar year, and cancer registry. General population rates were obtained from data provided by participating cancer registries, except for Hispanics (which were not uniformly captured). For Hispanics, we obtained general population rates from Surveillance, Epidemiology, and End Results (SEER) cancer registries (<https://seer.cancer.gov/>). However, because SEER does not distinguish between *in situ* and invasive bladder cancer cases, SIR estimates excluded Hispanics when *in situ* and invasive bladder cancer were evaluated separately.

We also used Poisson regression to compare the incidence of graft failure due to BKVN or cancer among kidney transplant recipients according to tBKVN status as defined above. For cancer, we present unadjusted incidence rate ratios (IRRs) and results adjusted for potential confounders including sex, age, calendar year of transplant, and baseline induction immunosuppressive regimen. Because Poisson regression models did not require expected counts, we were able to include all transplants in the analyses of *in situ* and invasive bladder cancer.

We also conducted a sensitivity analysis that considered tBKVN to be present if there was ever a SRTR report of tBKVN, regardless of when it occurred after transplant or in relation to cancer diagnosis. This approach increased the sensitivity of ascertainment of tBKVN and the number of cancer cases considered to have tBKVN. However, it does not account for duration of time spent following tBKVN, and some tBKVN reports could have occurred after cancer diagnosis.

We also describe selected cancer cases in recipients with tBKVN. For bladder cancer cases, we report the tumor histology, grade, and stage at diagnosis. For kidney cancers, we describe whether cases arose in the native vs. donor kidneys based on a review of case documentation by cancer registry staff.

Results

Among 55,697 kidney recipients included in this study, 2015 (3.6%) had an indication of tBKVN in the period 6 months to 2 years post-transplant (Table 1). Although differences were not large, compared with recipients without tBKVN, recipients with tBKVN were more likely to be male (69.7% vs. 60.1%), elderly (age >65 years; 16.0% vs. 12.8%), and of non-Hispanic black race/ethnicity (26.1% vs. 22.5%). A large majority of patients received only a kidney (92.8% in both groups). Diabetes was more common as an indication for transplant among recipients without tBKVN (9.2% vs. 4.4%). Recipients with tBKVN were transplanted in more recent years than recipients without tBKVN (2010–2013: 23.7% vs. 11.4%). As a result, recipients with tBKVN had shorter follow-up (mean 2.10 vs. 3.10 years).

As also shown in Table 1, recipients with tBKVN were more likely to have received polyclonal antibody induction (51.8% vs. 41.3%). They were also slightly more likely to have received baseline maintenance immunosuppression with tacrolimus and/or mycophenolate (94.3% vs. 88.7%) and corticosteroids (72.7% vs. 69.7%). Mammalian target of rapamycin (mTOR) inhibitor use was more common in recipients who did not develop tBKVN (7.7% vs 2.3%). During follow-up, 173 (16.6%) recipients with tBKVN and 327 (1.5%) recipients without tBKVN were reported to develop graft failure due to BKVN (unadjusted IRR 19.3, 95% CI 16.1–23.2).

A total of 584 incident cases of urinary tract cancers (including *in situ* bladder cancer) were identified in the study cohort (Table 2). When compared to the general population, incidence for kidney cancer was similarly elevated (~4.5-fold) in recipients with or without tBKVN, and incidence was not increased in either group for prostate cancer. Renal pelvis and ureteral cancers were rare (N=7 and N=2 total cases, respectively).

In contrast, for bladder cancer, including both invasive and *in situ* cases (N=80), incidence appeared more strongly elevated in recipients with tBKVN than in those without tBKVN (SIRs 2.1 vs. 1.4, Table 2). The SIR for invasive bladder cancer, in particular, appeared much higher in the recipients with tBKVN than in those without tBKVN (4.5 vs. 1.7). There were no cases of *in situ* bladder cancer in the recipients with tBKVN. In Poisson regression models in which all invasive bladder cancer cases were included, recipients with tBKVN had a higher incidence of invasive bladder cancer than those without tBKVN (adjusted IRR, 2.9, 95% CI 1.0–8.2) (Table 3). As a result, there was also a borderline increase in incidence for all urothelial cancers as a group (renal pelvis, ureter, and all bladder cancers: adjusted IRR 2.2, 95% CI 0.9–5.4).

The four invasive bladder cancers in recipients with tBKVN were all transitional cell carcinomas. One case described as having undifferentiated grade had spread regionally

beyond the bladder at the time of diagnosis. The other cases were diagnosed at localized stage and were described as being well differentiated, poorly differentiated, or of unknown differentiation, respectively. These four cancers were diagnosed at a median of 3.4 years (range 1.1–4.2 years) after tBKVN and 4.4 years post-transplant (range 1.8–5.1 years). The seven kidney cancers in recipients with tBKVN were described as renal cell carcinomas (N=3) or adenocarcinomas (N=4). Data on four of these cases were available with regards to the involved kidney. Two cases were bilateral, involving both native kidneys, and two were unilateral involving one native kidney.

Of the 327 recipients without tBKVN (based upon their first report during the 6-month to 2-year window post-transplant) who were later reported to have graft loss due to BKVN, 157 (48%) had at least one SRTR report during follow-up indicating positive tBKVN after the baseline assessment. In a sensitivity analysis that considered all follow-up reports of tBKVN regardless of timing, 9 recipients with tBKVN developed invasive bladder cancer, compared with 71 recipients without tBKVN (0.3% vs. 0.1%; $p=0.05$ by the Fisher exact test). No other cancer was associated with tBKVN in the sensitivity analysis (data not shown).

Discussion

BKVN is an important cause of long-term kidney allograft loss (6, 8, 12). Notably, BKV has also been linked to aggressive urinary tract cancers in kidney transplant recipients in case reports (35, 36). In our study, we aimed to provide results from a rigorous population-based study to examine the association of tBKVN in kidney recipients with subsequent risk of urinary tract cancers. We report that patients with tBKVN had an almost three-fold increased incidence for bladder cancers when compared with patients without tBKVN (adjusted IRR 2.9, Table 3).

The association with bladder cancer in our study is consistent with previous case reports describing detection of BKV in 12 bladder cancer tumors from kidney transplant recipients (16, 18, 23–29, 31). Likewise, a recent single center study found a 12-fold elevated risk of bladder cancer in kidney transplant recipients with evidence of BKV-associated decoy cells in urine, BK viremia, or biopsy-proven BKVN (36). Of the 11 bladder cancers in the recipients with BKVN, four showed immunohistochemical evidence for the presence of the virus within tumor cells. Similar to these prior reports, the four bladder cancers seen in our tBKVN group were all invasive transitional cell carcinomas. In contrast to the somewhat frequent detection of BKV in bladder cancers from transplant recipients, BKV is present only rarely in bladder cancers that arise in the general population (34, 37). Among other urothelial cancers in transplant recipients, five additional cases of BKV detection have been described, including four of the allograft renal pelvis and, one involving the transplant ureter (17, 19–21, 30). Cancers of the renal pelvis and ureter were too rare to analyze separately in our study, but there was no indication of an association with tBKVN.

The incidence of kidney and prostate cancers was similar in our study between recipients with or without tBKVN. Although our results do not suggest the involvement of BKV in these cancers, other studies have reported the detection of BKV in cases of renal cell carcinoma (RCC) among transplant recipients. Two cases were poorly differentiated RCCs

and two were collecting duct carcinomas, one each of a native kidney and a transplanted kidney; additional details on the clinical and pathologic features of these cases are provided in the published reports (38–41). In our study, the four kidney cancers in recipients with tBKVN for which we had data were all diagnosed in the native kidney.

Case reports have used a range of methods to detect BKV in urinary tract cancers. Studies that used only PCR may have detected BKV only in adjacent or infiltrating normal cells, whereas use of immunohistochemistry can demonstrate that the virus is present in tumor cells. Using high-throughput sequencing of tumor DNA obtained from a urothelial carcinoma arising in a renal allograft, Kenan et al. demonstrated that BKV, similar to Merkel cell polyomavirus, can integrate into the human chromosome, which may lead to mutations within the viral non-coding control region that are important for oncogenesis (29, 30). In addition, the viral early genes (in particular, the large tumor antigen [LTA_g]) can transform host cells in culture, primarily through inactivation of cellular tumor suppressor genes (7, 13, 35). Of interest, Das and colleagues demonstrated LTA_g expression in precancerous prostatic lesions (42). On the other hand, in a study examining the association of BKV with prostate cancer, although several cases were positive for BKV by PCR, none showed expression of the LTA_g (43). These observations leave open the formal possibility that BKV LTA_g expression might be transiently involved in early stages of the development of prostate cancer.

A strength of our study is that its population-based design captures data from a large fraction of kidney transplants performed in the US during 2003–2013. In addition, the linkage with cancer registries provided reliable data on incident cancers (44). We used the variable TFL_BK_THERAPY in the SRTR database to identify recipients with tBKVN. We assessed this at only one early point in time (6 months to 2 years post-transplant) to maximize subsequent follow-up, and because BKVN is usually an early diagnosis post-transplant (12). We also sought to optimize the reliability of the reporting, as later transplant center reports may less consistently capture clinical details.

Several factors support the validity of our assessment of BKVN status using tBKVN reported by the SRTR. First, the cumulative incidence of tBKVN in our study (3.6%) is consistent with results for BKVN reported in prior studies (1–5%) (8, 12). Secondly, recipients with tBKVN were more likely to have received T-cell depletion induction (51.8% vs. 41.3%) and less likely to have received mTOR inhibitors (2.3% vs. 7.7%) when compared with those without tBKVN. These observations are consistent with previous reports on this topic suggesting that T-cell depletion induction is strongly correlated with increased incidence of BKVN, and that mTOR inhibitor use might be protective (45). Thirdly, recipients with tBKVN were much more likely to progress to graft failure attributed to BKVN (unadjusted IRR 19.3, 95% CI 16.1–23.2). Our results also showed a similar association between tBKVN and bladder cancer in a sensitivity analysis in which we included all diagnoses of tBKVN regardless of when they were reported. We also observed an inverse association between diabetes mellitus and tBKVN, although published findings on the relationship between diabetes and BKVN have been variable (46, 47).

There are also limitations to our study. Because of the relative rarity of tBKVN, the number of cancer cases expected in this group was small, which limited our ability to assess associations with less common cancers. In addition, recipients with tBKVN had relatively short follow-up (mean 2.1 person-years). The four bladder cancers observed in recipients with tBKVN occurred at a median of 4.9 years post-transplant, and many of the urothelial cancers observed in association with BKV in the literature have occurred later, e.g., at a median 5.9 years post-transplant (range 2–11 years) as summarized by Papadimitriou et al. (35). Thus, it is possible that we missed associations of tBKVN with urinary tract malignancies that will become apparent after longer follow-up. Finally, we were unable to capture asymptomatic BK viremia or viremia, so it is possible that we did not capture the full impact of BKV infection relevant for cancer.

To conclude, our results, when taken in conjunction with reports describing BKV detection in tumor tissue, support an etiologic role for BKV in urothelial carcinogenesis, especially with respect to bladder cancer. Our results confirm the rarity of urinary tract cancers even in patients with tBKVN but still underscore the need for clinicians to be aware of this association and focus on minimizing development of BKVN with careful prospective monitoring of BKV viremia and appropriate adjustment of immunosuppressive regimens. Finally, our results highlight the importance of ongoing research to understand mechanisms by which BKV could cause cancer and identify risk factors among patients with BKV infection for urinary tract cancers.

Acknowledgments

This research was supported in part by the Intramural Research Program of the National Cancer Institute. The authors gratefully acknowledge the support and assistance provided by individuals at the Health Resources and Services Administration (Monica Lin), the SRTR (Ajay Israni, Bertram Kasiske, Paul Newkirk, Jon Snyder), and the following cancer registries: the states of California (Tina Clarke), Colorado (Jack Finch), Connecticut (Lou Gonsalves), Florida (Brad Wohler), Georgia (Rana Bayakly), Hawaii (Brenda Hernandez), Iowa, Illinois (Lori Koch), Kentucky (Jaclyn Nee), Michigan (Glenn Copeland), New Jersey (Xiaoling Niu), New York (Amy Kahn), North Carolina (Chandrika Rao), Texas (Leticia Noguera), and Utah (Janna Harrell), and the Seattle-Puget Sound area of Washington (Margaret Madeleine). We also thank analysts at Information Management Services for programming support (David Castenson, Matthew Chaloux, Michael Curry, Ruth Parsons).

The views expressed in this paper are those of the authors and should not be interpreted to reflect the views or policies of the National Cancer Institute, Health Resources and Services Administration, SRTR, cancer registries, or their contractors.

The SRTR is currently operated under contract number HHS250201500009C (Health Resources and Services Administration) by the Minneapolis Medical Research Foundation, Minneapolis, MN. Previously the SRTR was managed under contracts HHS250201000018C and HHS234200537009C. The following cancer registries were supported by the SEER Program of the National Cancer Institute: California (contracts HHSN261201000036C, HHSN261201000035C, and HHSN261201000034C), Connecticut (HHSN261201300019I), Hawaii (HHSN261201000037C, N01-PC-35137, and N01-PC-35139), Iowa (HSN261201000032C and N01-PC-35143), New Jersey (HHSN261201300021I, N01-PC-2013-00021), Seattle-Puget Sound (N01-PC-35142), and Utah (HHSN261201300017I). The following cancer registries were supported by the National Program of Cancer Registries of the Centers for Disease Control and Prevention: California (agreement 1U58 DP000807-01), Colorado (U58 DP000848-04), Georgia (U58DP003875-01), Illinois (U58DP003883-03), Maryland (U58DP12-1205 3919-03), Michigan (U58DP003921-03), New Jersey (U58/DP003931-05-00), New York (U58DP003879), North Carolina (U58DP000832) and Texas (U58DP000824-04). Additional support was provided by the states of California, Colorado, Connecticut, Illinois, Iowa, Massachusetts (Massachusetts Cancer Prevention and Control Cooperative Agreement 5458DP003920), New Jersey, New York (including the Cancer Surveillance Improvement Initiative), Texas, Utah, and Washington, as well as the University of Utah and Fred Hutchinson Cancer Research Center in Seattle, WA.

Abbreviations

BKV	BK polyomavirus
IRR	incidence rate ratio
LTA_g	large tumor antigen
mTOR	mammalian target of rapamycin
PCR	polymerase chain reaction
RCC	renal cell carcinoma
SEER	Surveillance, Epidemiology, and End Results
SIR	standardized incidence ratio
SRTR	Scientific Registry of Transplant Recipients
tBKVN	BKV nephropathy
TCM	Transplant Cancer Match

References

1. Vajdic CM, McDonald SP, McCredie MR, van Leeuwen MT, Stewart JH, Law M, et al. Cancer incidence before and after kidney transplantation. *Jama*. 2006; 296(23):2823–2831. [PubMed: 17179459]
2. Wimmer CD, Rentsch M, Crispin A, Illner WD, Arbogast H, Graeb C, et al. The janus face of immunosuppression - de novo malignancy after renal transplantation: the experience of the Transplantation Center Munich. *Kidney Int*. 2007; 71(12):1271–1278. [PubMed: 17332737]
3. Kamal MM, Soliman SM, Shokeir AA, Abol-Enein H, Ghoneim MA. Bladder carcinoma among live-donor renal transplant recipients: a single-centre experience and a review of the literature. *BJU international*. 2008; 101(1):30–35. [PubMed: 17850360]
4. Zhou M, Zhu Y, Wang L, Wang Y, Fu S, Min Z. Urological malignancy as a complication of renal transplantation: a report of twelve clinical cases. *Clin Transpl*. 2006:395–398. [PubMed: 18365395]
5. Engels EA, Pfeiffer RM, Fraumeni JF Jr, Kasiske BL, Israni AK, Snyder JJ, et al. Spectrum of cancer risk among US solid organ transplant recipients. *Jama*. 2011; 306(17):1891–1901. [PubMed: 22045767]
6. Hirsch HH, Steiger J. Polyomavirus BK. *Lancet Infect Dis*. 2003; 3(10):611–623. [PubMed: 14522260]
7. Dalianis T, Hirsch HH. Human polyomaviruses in disease and cancer. *Virology*. 2013; 437(2):63–72. [PubMed: 23357733]
8. Hirsch HH, Randhawa P. Practice ASTIDCo. BK virus in solid organ transplant recipients. *Am J Transplant*. 2009; 9(Suppl 4):S136–146. [PubMed: 20070673]
9. Nankivell BJ, Renthawa J, Sharma RN, Kable K, O'Connell PJ, Chapman JR. BK Virus Nephropathy: Histological Evolution by Sequential Pathology. *Am J Transplant*. 2017; 17(8):2065–2077. [PubMed: 28371308]
10. Leboeuf C, Wilk S, Achermann R, Binet I, Golshayan D, Hadaya K, et al. BK Polyomavirus-Specific 9mer CD8 T Cell Responses Correlate With Clearance of BK Viremia in Kidney Transplant Recipients: First Report From the Swiss Transplant Cohort Study. *Am J Transplant*. 2017

11. Drachenberg CB, Papadimitriou JC, Chaudhry MR, Ugarte R, Mavanur M, Thomas B, et al. Histological Evolution of BK Virus-Associated Nephropathy: Importance of Integrating Clinical and Pathological Findings. *Am J Transplant*. 2017; 17(8):2078–2091. [PubMed: 28422412]
12. Hariharan S. BK virus nephritis after renal transplantation. *Kidney Int*. 2006; 69(4):655–662. [PubMed: 16395271]
13. Abend JR, Jiang M, Imperiale MJ. BK virus and human cancer: innocent until proven guilty. *Seminars in cancer biology*. 2009; 19(4):252–260. [PubMed: 19505653]
14. Dela Cruz FN Jr, Giannitti F, Li L, Woods LW, Del Valle L, Delwart E, et al. Novel polyomavirus associated with brain tumors in free-ranging raccoons, western United States. *Emerging infectious diseases*. 2013; 19(1):77–84. [PubMed: 23260029]
15. Chang Y, Moore PS. Merkel cell carcinoma: a virus-induced human cancer. *Annual review of pathology*. 2012; 7:123–144.
16. van Aalderen MC, Yapici U, van der Pol JA, de Reijke TM, van Donselaar-van der Pant KA, Florquin S, et al. Polyomavirus BK in the pathogenesis of bladder cancer. *The Netherlands journal of medicine*. 2013; 71(1):26–28. [PubMed: 23412820]
17. Saleeb R, Faragalla H, Yousef GM, Stewart R, Streutker CJ. Malignancies arising in allograft kidneys, with a first reported translocation RCC post-transplantation: A case series. *Pathology, research and practice*. 2015; 211(8):584–587.
18. Pino L, Rijo E, Nohales G, Frances A, Ubre A, Arango O. Bladder transitional cell carcinoma and BK virus in a young kidney transplant recipient. *Transpl Infect Dis*. 2013; 15(1):E25–27. [PubMed: 23231013]
19. Oikawa M, Hatakeyama S, Fujita T, Murakami R, Hagiwara K, Narita T, et al. BK virus-associated urothelial carcinoma of a ureter graft in a renal transplant recipient: a case report. *Transplant Proc*. 2014; 46(2):616–619. [PubMed: 24656027]
20. McDaid J, Farkash EA, Steele DJ, Martins PN, Kotton CN, Elias N, et al. Transitional cell carcinoma arising within a pediatric donor renal transplant in association with BK nephropathy. *Transplantation*. 2013; 95(5):e28–30. [PubMed: 23503509]
21. Li JY, Fang D, Yong TY, Klebe S, Juneja R, Gleadle JM. Transitional cell carcinoma in a renal allograft with BK nephropathy. *Transpl Infect Dis*. 2013; 15(6):E270–272. [PubMed: 24103071]
22. Lavien G, Alger J, Preece J, Alexiev BA, Alexander RB. BK Virus-Associated Invasive Urothelial Carcinoma With Prominent Micropapillary Carcinoma Component in a Cardiac Transplant Patient: Case Report and Review of Literature. *Clinical genitourinary cancer*. 2015; 13(6):e397–399. [PubMed: 25998557]
23. Hill P, Slavina J, Goodman D. High-grade urothelial carcinoma in a kidney transplant recipient with BK virus infection. *NDT plus*. 2009; 2(3):246–249. [PubMed: 25984002]
24. Geetha D, Tong BC, Racusen L, Markowitz JS, Westra WH. Bladder carcinoma in a transplant recipient: evidence to implicate the BK human polyomavirus as a causal transforming agent. *Transplantation*. 2002; 73(12):1933–1936. [PubMed: 12131691]
25. Bialasiewicz S, Cho Y, Rockett R, Preston J, Wood S, Fleming S, et al. Association of micropapillary urothelial carcinoma of the bladder and BK viruria in kidney transplant recipients. *Transpl Infect Dis*. 2013; 15(3):283–289. [PubMed: 23551580]
26. Alexiev BA, Papadimitriou JC, Chai TC, Ramos E, Staats PN, Drachenberg CB. Polyomavirus (BK)-associated pleomorphic giant cell carcinoma of the urinary bladder: a case report. *Pathology, research and practice*. 2013; 209(4):255–259.
27. Alexiev BA, Drachenberg CB, Papadimitriou JC. Polyomavirus-cystitis associated with in situ and invasive urothelial carcinoma in a heart transplant recipient: evidence suggesting sequential progression/evolution from infection to carcinoma. *Transplantation*. 2015; 99(1):e3–4. [PubMed: 25525923]
28. Roberts IS, Besarani D, Mason P, Turner G, Friend PJ, Newton R. Polyoma virus infection and urothelial carcinoma of the bladder following renal transplantation. *British journal of cancer*. 2008; 99(9):1383–1386. [PubMed: 18971934]
29. Alexiev BA, Randhawa P, Vazquez Martul E, Zeng G, Luo C, Ramos E, et al. BK virus-associated urinary bladder carcinoma in transplant recipients: report of 2 cases, review of the literature, and proposed pathogenetic model. *Hum Pathol*. 2013; 44(5):908–917. [PubMed: 23317548]

30. Saquib R, Barri YM, Saad R, Savino DA, Rice KM, Hays SR, et al. Transitional cell carcinoma of renal allograft associated with BK virus infection. *Dialysis & Transplantation*. 2009; 38(12):518–519.
31. Kuppachi S, Holanda D, Eberlein M, Alexiev B, Tyler AJ, Wissel MC, et al. An Unexpected Surge in Plasma BKPyV Viral Load Heralds the Development of BKPyV-Associated Metastatic Bladder Cancer in a Lung Transplant Recipient With BKPyV Nephropathy. *Am J Transplant*. 2017; 17(3): 813–818. [PubMed: 27647675]
32. Kenan DJ, Mieczkowski PA, Burger-Calderon R, Singh HK, Nickeleit V. The oncogenic potential of BK-polyomavirus is linked to viral integration into the human genome. *J Pathol*. 2015; 237(3): 379–389. [PubMed: 26172456]
33. Kenan DJ, Mieczkowski PA, Latulippe E, Cote I, Singh HK, Nickeleit V. BK Polyomavirus Genomic Integration and Large T Antigen Expression: Evolving Paradigms in Human Oncogenesis. *Am J Transplant*. 2016
34. Comprehensive molecular characterization of urothelial bladder carcinoma. *Nature*. 2014; 507(7492):315–322. [PubMed: 24476821]
35. Papadimitriou JC, Randhawa P, Rinaldo CH, Drachenberg CB, Alexiev B, Hirsch HH. BK Polyomavirus Infection and Renourinary Tumorigenesis. *Am J Transplant*. 2016; 16(2):398–406. [PubMed: 26731714]
36. Liu S, Chaudhry MR, Berrebi AA, Papadimitriou JC, Drachenberg CB, Haririan A, et al. Polyomavirus Replication and Smoking Are Independent Risk Factors for Bladder Cancer After Renal Transplantation. *Transplantation*. 2016
37. Rollison DE, Sexton WJ, Rodriguez AR, Kang LC, Daniel R, Shah KV. Lack of BK virus DNA sequences in most transitional-cell carcinomas of the bladder. *International journal of cancer*. 2007; 120(6):1248–1251. [PubMed: 17192899]
38. Narayanan M, Szymanski J, Slavcheva E, Rao A, Kelly A, Jones K, et al. BK virus associated renal cell carcinoma: case presentation with optimized PCR and other diagnostic tests. *Am J Transplant*. 2007; 7(6):1666–1671. [PubMed: 17511691]
39. Neirynek V, Claes K, Naesens M, De Wever L, Pirenne J, Kuypers D, et al. Renal cell carcinoma in the allograft: what is the role of polyomavirus? *Case reports in nephrology and urology*. 2012; 2(2):125–134. [PubMed: 23197968]
40. Dufek S, Haitel A, Muller-Sacherer T, Aufricht C. Duct Bellini carcinoma in association with BK virus nephropathy after lung transplantation. *J Heart Lung Transplant*. 2013; 32(3):378–379. [PubMed: 23321158]
41. Emerson LL, Carney HM, Layfield LJ, Sherbotie JR. Collecting duct carcinoma arising in association with BK nephropathy post-transplantation in a pediatric patient. A case report with immunohistochemical and in situ hybridization study. *Pediatr Transplant*. 2008; 12(5):600–605. [PubMed: 18652620]
42. Das D, Wojno K, Imperiale MJ. BK virus as a cofactor in the etiology of prostate cancer in its early stages. *J Virol*. 2008; 82(6):2705–2714. [PubMed: 18160432]
43. Lau SK, Lacey SF, Chen YY, Chen WG, Weiss LM. Low frequency of BK virus in prostatic adenocarcinomas. *APMIS : acta pathologica, microbiologica, et immunologica Scandinavica*. 2007; 115(6):743–749.
44. Yanik EL, Nogueira LM, Koch L, Copeland G, Lynch CF, Pawlish KS, et al. Comparison of cancer diagnoses between the US solid organ transplant registry and linked central cancer registries. *Am J Transplant*. 2016
45. Hirsch HH, Yakhontova K, Lu M, Manzetti J. BK Polyomavirus Replication in Renal Tubular Epithelial Cells Is Inhibited by Sirolimus, but Activated by Tacrolimus Through a Pathway Involving FKBP-12. *Am J Transplant*. 2016; 16(3):821–832. [PubMed: 26639422]
46. Trofe-Clark J, Sawinski D. BK and Other Polyomaviruses in Kidney Transplantation. *Seminars in nephrology*. 2016; 36(5):372–385. [PubMed: 27772622]
47. Thangaraju S, Gill J, Wright A, Dong J, Rose C, Gill J. Risk Factors for BK Polyoma Virus Treatment and Association of Treatment With Kidney Transplant Failure: Insights From a Paired Kidney Analysis. *Transplantation*. 2016; 100(4):854–861. [PubMed: 27003098]

Table 1

Characteristics of Kidney Transplant Recipients with or without Treatment for Presumed BK Polyomavirus Nephropathy in the US Transplant Cancer Match Study

Characteristic		Recipients with tBKVN (% of total)	Recipients without tBKVN (% of total)	P-value
Total		2,015 (100.0)	53,682 (100.0)	
Gender	Male	1,405 (69.7)	32,242 (60.1)	<0.0001
	Female	610 (30.3)	21,440 (39.9)	
Age at Transplant, years	0–34	402 (20.0)	11,238 (20.9)	<0.0001
	35–49	544 (27.0)	16,092 (30.0)	
	50–64	746 (37.0)	19,505 (36.3)	
	65+	323 (16.0)	6,847 (12.8)	
Race/Ethnicity	White, Non-Hispanic	1,027 (51.0)	27,592 (51.4)	<0.0001
	Black, Non-Hispanic	526 (26.1)	12,086 (22.5)	
	Hispanic	321 (15.9)	10,308 (19.2)	
	Asian/Pacific Islander	141 (7.0)	3,696 (6.9)	
Transplanted Organ	Kidney	1,870 (92.8)	49,820 (92.8)	0.9975
	Kidney and other	145 (7.2)	3,862 (7.2)	
Reason For Transplant	Glomerular diseases	556 (27.6)	14,259 (26.6)	0.3038
	Hypertension	445 (22.1)	11,433 (21.3)	0.3973
	Polycystic kidneys	174 (8.6)	4,815 (9.0)	0.6060
	Diabetes	89 (4.4)	4,951 (9.2)	<0.0001
	Other	782 (38.8)	19,384 (36.1)	0.0133
Kidney Re-Transplant	Retransplant	230 (11.4)	5,409 (10.1)	0.0505
Calendar Year of Transplant	2003–2006	638 (31.7)	30,032 (55.9)	<0.0001
	2007–2009	900 (44.7)	17,528 (32.7)	
	2010–2013	477 (23.7)	6,122 (11.4)	
Induction Therapy	Polyclonal	1,043 (51.8)	22,197 (41.3)	<0.0001
	Alemtuzumab	207 (10.3)	6,550 (12.2)	0.0092
	Anti-IL2R	496 (24.6)	14,532 (27.1)	0.0148
	Any induction	1,816 (90.1)	46,250 (86.2)	<0.0001
Maintenance Regimen	Tacrolimus and/or MMF	1,980 (98.3)	51,270 (95.5)	<0.0001
	Cyclosporine and/or azathioprine	91 (4.5)	4,656 (8.7)	<0.0001
	Maintenance mTOR inhibitor	47 (2.3)	4,137 (7.7)	<0.0001
	Maintenance corticosteroids	1,464 (72.7)	37,416 (69.7)	0.0046

Abbreviations: tBKVN: treatment for presumed BK polyomavirus nephropathy; IL2R: interleukin 2 Receptor; MMF: mycophenolate mofetil; mTOR: mammalian target of rapamycin.

The Transplant Cancer Match Study links data between the Scientific Registry of Transplant Recipients and 17 cancer registries (California, Colorado, Connecticut, Florida, Georgia, Hawaii, Iowa, Illinois, Kentucky, Maryland, Michigan, New Jersey, New York, North Carolina, Texas, Utah, and the Seattle-Puget Sound area of Washington).

* Because the transplant was the unit of analysis, people with more than one transplant are included multiple times in the table. The median age at transplant for recipients with tBKVN was 51 years. For recipients without tBKVN, the median age at transplant was 49 years. All categories are mutually exclusive and exhaustive, so that sums are all equal to total number of transplants, except for reason for transplant. Because recipients

could have more than one reason for transplant indicated, p-values compare the recipients with and without tBKVN separately with respect to each reason.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 2

Standardized Incidence Ratios for Urinary Tract Cancers among Kidney Transplant Recipients with or without Treatment for Presumed BK Polyomavirus Nephropathy

Cancer	Recipients with tBKVN		Recipients without tBKVN	
	N	SIR (95%CI)	N	SIR (95%CI)
Kidney	7	4.5 (1.8–9.2)	228	4.6 (4.0–5.2)
Renal pelvis	1	13 (0.3–74)	6	2.5 (0.9–5.5)
Ureter	0	0 (0–86)	2	1.4 (0.2–5.2)
Bladder*	4	2.1 (0.6–5.4)	76	1.4 (1.1–1.7)
Invasive	4	4.5 (1.2–12)	44	1.7 (1.2–2.3)
<i>In situ</i>	0	0 (0–4.2)	24	0.9 (0.6–1.4)
All urothelial sites (renal pelvis, ureter, bladder)	5	2.5 (0.8–5.8)	84	1.4 (1.1–1.7)
Prostate [†]	6	0.6 (0.2–1.3)	254	0.9 (0.8–1.0)
Total	18	1.3 (0.8–2.1)	566	1.4 (1.3–1.6)

Abbreviations: tBKVN, treatment for presumed BK polyomavirus nephropathy; CI, confidence interval; SIR, standardized incidence ratio.

* Bladder cancer cases include both invasive and *in situ* cancers, unless otherwise specified. SIR analyses for *in situ* and invasive bladder cancer separately exclude Hispanic recipients, because expected counts for these recipients could not be calculated. As a result, six cases of invasive bladder cancer and two cases of *in situ* bladder cancer in recipients without tBKVN could not be included in the SIR calculations for those outcomes.

[†] Analysis is restricted to males.

Table 3

Incidence Rate Ratios Comparing Incidence of Urinary Tract Cancers among Kidney Transplant Recipients with or without Treatment for Presumed BK Polyomavirus Nephropathy

Cancer	Incidence per 1000 person-years, recipients with tBKVN	Incidence per 1000 person-years, recipients without tBKVN	Unadjusted analysis		Adjusted analysis*	
			IRR (95%CI)	p-value	IRR (95%CI)	p-value
Kidney	1.4	1.3	1.1 (0.5–2.4)	0.77	1.0 (0.5–2.2)	0.91
Renal pelvis	0.2	0.0	--	--	--	--
Ureter	0.0	0.0	0	--	--	--
Bladder total	0.8	0.4	1.9 (0.7–5.3)	0.20	1.9 (0.7–5.2)	0.22
Invasive	0.8	0.3	2.9 (1.1–8.1)	0.04	2.9 (1.0–8.2)	0.04
<i>In situ</i>	0.0	0.1	0	--	--	--
All urothelial sites	1.0	0.5	2.2 (0.9–5.4)	0.09	2.2 (0.9–5.4)	0.09
Prostate [†]	1.7	2.3	0.7 (0.3–1.7)	0.46	0.7 (0.3–1.7)	0.47
Total	3.6	3.1	1.2 (0.7–1.9)	0.53	1.1 (0.7–1.7)	0.82

Abbreviations: tBKVN, BK polyomavirus nephropathy; CI, confidence interval; IRR, incidence rate ratio. Confidence intervals and p-values are based on the Wald statistic.

* Models are adjusted for sex, age, calendar year of transplant, and use of polyclonal antibody induction.

[†] Analysis is restricted to males. Analyses were based on 4982 person-years in kidney recipients with tBKVN (3473 person-years among males) and 182,092 person-years in kidney recipients without tBKVN (108,242 person-years among males).