Renal cancer in recipients of kidney transplant

Prajwal Dhakal, Smith Giri, Krishmata Siwakoti, Supratik Rayamajhi, Vijaya Raj Bhatt
1Michigan State University, East Lansing, MI; 2The Yale New Haven Hospital, New Haven, CT; 3University of Tennessee, Memphis, TN; 4University of Nebraska Medical Center, Omaha, NE, USA

Abstract

The aim of our study is to determine characteristics and outcomes of kidney cancer in renal transplant recipients. MEDLINE database was searched in June 2015 to identify cases of kidney cancer in renal transplant recipients. We include also a new case. Descriptive statistics were used for analysis. Forty-eight (48) recipients reported in 25 papers met the eligibility criteria. The median age was 47 years (range 9-66); 27% were females. Chronic glomerulonephritis, cystic kidney disease and hypertension were common indications for renal transplant. Among donors 24% were females and the median age was 52.5 years (17-73); 62% of kidney cancers were donor-derived. The median interval between transplant and cancer diagnosis was shorter for cancer of recipient versus donor origin (150 vs. 210 days). Clear cell carcinoma was diagnosed in 17%; 25% had metastasis at diagnosis. Kidney explantation or excision was done in 90% and 84% of cases with and without metastasis respectively. The median survival was 72 months. Actuarial 1-year and 5-year survival rates were 73.4% and 55.1% respectively. Among the recipients from 7 donors who subsequently developed malignancy, 57% were dead within a year. Kidney transplant recipients have a small risk of kidney cancer, which affects younger patients and occurs within a year of transplant, likely due to immunosuppression. Whether the use of older donors may increase the likelihood needs further investigation. The presence of metastasis, explantation or excision of affected kidney and development of cancer in donors predict outcomes. The results may guide patient education and informed decision-making.

Materials and Methods

A systematic search of MEDLINE database (via PubMed) was conducted in July 2015 to identify articles describing a new diagnosis of kidney cancer following kidney transplant. The following terms were utilized for selecting the articles: (Kidney Transplantation OR Renal Transplantation OR Organ Transplantation) AND (malignant OR cancer OR tumor) AND (transplantation). The bibliography of each article was hand-searched for additional reports. Only reports published in English language were included. A total of 420 searches, 24 articles met the eligibility criteria (Figure 1). Additionally, we also describe an original case report.

During analysis, details of the patient, transplant history, diagnosis of kidney cancer, therapy, complications and outcomes were obtained until the last follow-up of the patient.

Results

A 55-year-old male presented to emergency department complaining of abdominal pain, distention, as well as nausea and vomiting of 2 days’ duration. He had a bilateral kidney transplant one year ago for end stage renal disease secondary to chronic hypertension. His post-transplant course was complicated by ureteral strictures, enterocutaneous fistula and recurrent small bowel obstructions. The patient was on mycophenolate mofetil, prednisone and tacrolimus to avoid graft rejection. He had a history of heavy smoking, alcohol consumption and cocaine use, but had quit one year ago. Physical examination revealed heart rate of 109 beats/min, blood pressure of 134/96 mm Hg, respiratory rate of 20/min and temperature of 36.6°C. On abdominal examination, there was diffuse tenderness and high-pitched bowel sounds. Rest of the examination was normal.

Laboratory studies included white blood cell count of 10,200/μL with 78% granulocytes, hemoglobin of 16.6 g/dL and platelet count of 155,000/μL. He had a creatinine of 1.04 mg/dL, blood urea nitrogen of 13 mg/dL, sodium of 138 mmol/L, potassium of 3.3 mmol/L, and chloride of 100 mmol/L. Ultrasonography (USG) of right kidney demonstrated a transplanted kidney with a heterogeneous hyperechoic mass measuring 5.5×4.9×5.6 cm. Computed tomography (CT) scan of abdomen revealed right lower quadrant transplanted kidney with a new complex enhancing mass.
Review of reported cases

A total of 48 patients reported in 25 articles (along with our case report) met the eligibility criteria (Table 1). The median age of recipients was 47 years (range 9-66), and 27% were females. The cause for renal transplant were: chronic glomerulonephritis (22%, n=6),

Poly cystic kidney disease (11%, n=3),

Hypertension (11%, n=3),

IgA nephropathy (8%, n=2),

Renal pelvis carcinoma with left nephrectomy (4%, n=1),

Nephronophthisis (4%, n=1),

Congenital nephrotic syndrome (4%, n=1),

Amyloid disease (4%, n=1),

Intestinal disease (4%, n=1),

Neurogenic bladder (4%, n=1),

Obstructive uropathy (4%, n=1) and ESRD of unknown origin (8%, n=2).

The median age of donors was 52.5 years (range 17-73) with 24% of them being females. Where data was available, 60% (n=22) of the donors were cadaver.

Seven donors were subsequently found to have malignancy including clear cell carcinoma, hypernephroma, anaplastic tumor on nephrostomy scar, metastatic adenocarcinoma with unknown primary, primary hepatocellular carcinoma, metastatic giant and spindle cell carcinoma of thyroid, and a lung tumor. Out of seven, 2 donors were diagnosed with malignancy after 8 months and 10 months of transplantation. One donor had a renal cancer after 8 months and 10 months of transplantation.28,29

Table 1. Kidney cancer in recipients of kidney transplant.

| Variables                                      | Non-metastatic kidney cancer | Metastatic kidney cancer |
|------------------------------------------------|------------------------------|--------------------------|
| Age in years, median (range)                   | 47 (12-64)                   | 48 (27-66)               |
| Female                                         | 40%                          | 29%                      |
| Donor type                                     | Living 55%; Cadaver 45%      | Living 0%; Cadaver 100%  |
| Donor age in years                             | 54 (22-73)                   | 52 (17-68)               |
| Concomitant cancer in the donor                | 13%                          | 20%                      |
| Latency period since kidney transplant (days)  | Median 120 (0-6780)          | Median- 210 (90-2190)    |
| Histology (%RCC)                               | 66                           | 80                       |
| Explantation or excision                       | 90%                          | 84%                      |

Records excluded:
1. Review articles (45)
2. Non cancer related studies (189)
3. Non human studies (40)
4. Non transplant related malignancies (46)

Figure 1. Flow diagram for selection of the articles.

Searches identified through MEDLINE (n=420)

Full-text articles evaluated for eligibility (n=100)

Additional records identified through hand searching (n=12)

Articles included in analysis (n=24)

Records excluded:
1. Non kidney transplants (26)
2. Non renal cancers (48)
3. Articles with no patient level information available (14)
cyst which was excised during the transplant, and subsequently found to be a renal cell carcinoma. Three donors had history of malignancy in other organs with no identified metastasis to kidney at the time of donation. Tunner et al. described a case in which a kidney with resected renal cell carcinoma was transplanted to a man in desperate need of functioning kidney.

The median time interval from transplantation to presentation or diagnosis of the malignancy in recipients was 210 days. The latency period between transplant and cancer diagnosis was 272 days in cancer of recipient origin in comparison to 210 days in those with cancer of donor origin.

Biopsy was done for the diagnosis of cancer in 100% (n=48) of recipients, and 69% (n=33) of the cancers had RCC. The most common type of RCC was clear cell carcinoma (27%, n=9), sarcomatoid (15%, n=5), angiosarcoma (6%, n=2), renal papillary tumor (6%, n=2), anaplastic (6%, n=2), chromophobe (3%, n=1), cystic adenocarcinoma (3%, n=1), anaplastic adenocarcinoma (3%, n=1), giant and spindle cell carcinoma (3%, n=1), and undifferentiated (6%, n=2). The type of renal cell carcinoma was not mentioned in the rest (22%, n=7).

Other tumors (31%, n=15) comprised 31% of the cases which included: undifferentiated cancer (20%, n=3), invasive urothelial carcinoma (7%, n=1), papillary transitional cell carcinoma of bladder (7%, n=1). Thirty-three percent of the tumors were subsequently found to be benign and the type of cancer was not mentioned in the rest (33%, n=5).

Fifty-five percent (n=31) of the tumors were donor in origin, while 39% (n=22) originated from the recipient. The rest (6%, n=3) were determined to be derived from both donor and recipient. For example, one of the tumors in Pedotti et al. had 60% recipient and 40% donor DNA material indicative origin from both donor and recipient cell.

Explantation of the graft or excision of the tumor or a part of the graft, and discontinuation of immunosuppressants along with supportive treatment were used for management in most cases. Explantation or excision was done in 90% of the non-metastatic malignancies, while 84% of metastatic malignancies underwent explanation or excision. Chemotherapy, radiotherapy, or both were also used in 9 cases. While 64% (n=7) of the 9 cases had metastasis, 18% (n=2) had no metastasis, and the status of metastasis was not mentioned in the rest, (18%, n=2). In one case treated with local irradiation, distant metastasis was diagnosed at autopsy. Local irradiation was administered to treat recurrent local malignancy in our case after initial explanation.

The median survival was estimated to be approximately 72 months. Actuarial 1-year and 5-year survival rates were 73.4% and 55.1% respectively. Out of eleven recipients, who died after transplant, 9 were due to malignancy-related causes, while 2 were due to other causes. The recipient in Llamas et al. died 9 months post-transplant due to peritonitis secondary to sarcomatoid neoplasm of renal graft. Metastasis of the cancer was the cause of death in four recipients, while two recipients died due to intracerebral hemorrhage. Death due to invasion of renal cell carcinoma (RCC) aggressively into adjacent tissue accounted for the death in the patient reported by Tunner et al. Among the recipients from 7 donors who subsequently developed malignancy, 57% (n=4), 9,11,15,19 were dead within a year. The cause of death in all these recipients was malignancy-related.

Discussion

Our review revealed post renal transplant malignancy in a total of 48 recipients. RCC, the most common type of kidney cancer in adults, was diagnosed in the majority of our cases. Twenty-seven percent of the renal cell carcinoma were clear cell carcinoma which is the most common RCC type. RCC is also known to be the most frequently reported non-central nervous system (CNS) tumor transmitted by transplantation, followed by melanoma and choriocarcinoma. Twelve percent of the cases in our review, including our case, had a sarcomatoid differentiation. The incidence of tumors with sarcomatoid differentiation in general population is estimated as 1-8%, although as high as 32% has been reported.

In our review, the median age of recipients at diagnosis was 49 years while the median age of donors was 52.5 years. The median age at diagnosis for RCC is 64 in normal population, and is unusual in patients under 40 years of age and rare in children. Immunosuppression in recipients may be one of the factors behind the development of malignancy at an early age. In addition, RCC may also occur in children receiving renal allografts from adults. Chronic glomerulonephritis, hypertension and cystic diseases of kidney were the common factors leading to end stage renal disease in our review. Our case also had a history of chronic hypertension and heavy smoking. In fact, hypertension, smoking, obesity and polycystic kidney disease have been well-recognized risk factors for the development of RCC in normal adults.

The malignancy in post-transplant cases might be due to de novo occurrence, recurrence of malignancy or donor-related malignancy. Compared to 3% in general population, RCC occurs de novo in 4.6% of cancers in organ allograft recipients. Transmission of malignancy in an immunosuppressed recipient usually occurs when the tumor is undetected before the organ donation or it may be misdiagnosed as a benign condition such as cyst. This incidence of tumor transmission may also have risen in recent years with the increased donor age. In our review, more than half of the tumors were donor in origin including both donor-derived and donor-transmitted malignancies. Thirty-nine percent of the tumors in our review were recipient in origin. Nineteen out of the twenty cases were recipient in origin in Pedotti et al., thus, suggesting that donor transmission of solid cancer was an unlikely event in their study. Microchimerism, a phenomenon of harboring small numbers of cells that originated in a genetically different individual, has been described in previous post-transplant cases. Three cases in our review demonstrated microchimerism. In a case review by Mengel et al., two metanephric adenomas demonstrated microchimerism comprising both donor-and recipient-derived tumor cells, however, four other tumors were all of donor origin without chimerism. Thus, they concluded that tumors arising in renal transplants originate completely from graft cells except for metanephric adenomas. One of the cases in Pedotti et al. was also analyzed to be 60% recipient and 40% donor in origin. However, the cancer was considered to be a recipient origin because of greater percentage of recipient DNA.

Different factors such as type, level and extent of immunosuppression, the use of drugs such as cyclosporine and azathioprine, carcinogenic factors such as sun exposure, genetic predisposition to cancer, pretransplantation dialysis, and the presence of particular viral infections are associated with development of de novo neoplasia in transplant recipients. The overall level and extent of immunosuppression, as illustrated by more malignancies after cardiac transplant in comparison to renal transplant, appears to be the principal factor that increases the risk of post-transplant malignancy. This is probably related to decreased immunosurveillance of neoplastic cells and depressed antiviral immune activity. A total of 7 donors in our review
had a history of or were diagnosed after transplant with malignancy. Previous studies have shown that about 45% of recipients of kidney transplant from donors with known or incidentally discovered malignancy develop the malignancy.24 The risk of cancer transmission from donor to recipient is largely similar for all solid organ recipients.50 The median time interval from transplantation to presentation or diagnosis of the malignancy in recipients was 270 days in our review. In a study published by Buell et al., the mean time was approximately 2 months.50 The short latency period may indicate a possibility of undetected cancer at the time of transplantation or rapidity of tumorigenesis in immunosuppressant transplant recipients. Almost two-thirds of the cases underwent explantation of the graft. Eleven percent underwent excision of the tumor of a part of the graft. In our case, explantation was done initially and then local irradiation was performed later to treat local recurrent malignancy. The patient refused chemotherapy but was doing well till last follow-up at 18 months. In one case treated with local irradiation, distant metastasis was diagnosed at autopsy.29 Radiation therapy was used after explantation in 2 prior cases out of which one died,18 while the other remained in good clinical condition waiting for another kidney.13 Although guidelines are lacking, most cases with transplant related renal malignancy are treated primarily with explantation of the graft with chemotherapy and radiation therapy as adjunct in selected cases. Ribal et al.36 have reported successful conservative surgery of renal tumors (nephron sparing) with preservation of graft function, but this is only recommended for single carcinoma less than 4 cm in size. This is the outcome for transplant recipients with neoplastic complications is unclear. We calculated the median survival to be 72 months. Actuarial 1-year and 5-year survival rates were 73.4% and 55.1% respectively. In our review, 25% of deaths were related to malignancy. In a review of data from different sources by Briggs et al.,31 malignancy was thought to account for 9-16% of all deaths in renal transplant recipients. Various factors affect the prognosis of RCC in general. The survival difference is largely due to differences in stage in particular and grade, although cytogenetics also play a role.52-56 Cytogenetic abnormalities such as del(8p)/-8, +12, and +20, p53, and gain of 8q31 have prognostic implications.52,55,56 The prognostic value of cytogenetic changes in RCC in transplant recipients has not been studied. The patient reported here had complex cytogenetic changes and was alive at 18-month follow-up.

Conclusions

Kidney transplant recipients have a small but definite risk of kidney cancer. It affects younger patients and usually occurs within a year of transplant, likely due to immunosuppression. Whether the use of older donors may increase the likelihood needs further investigation. Explantation or excision of the graft is the most important treatment for localized disease, while radiotherapy and chemotherapy may be used as adjunct in select cases. The presence of metastasis, explanation or excision of affected kidney and development of cancer in donors may predict outcomes. The results may guide patient education and informed decision-making.

References

1. Murray J, Gleason R, Bartholomay A. Fourth report of the human kidney transplant registry: 16 September 1964 to 15 March 19651. Transplantation 1965;3:684.
2. Desai R, Collett D, Watson CJ, et al. Cancer transmission from organ donors-unavoidable but low risk. Transplantation 2012;94:1200-7.
3. Xu J, Murphy SL, Kochanek KD, Arias E. Mortality in the United States, 2015. NCHS data brief 2016:1-8.
4. Penn I. Primary kidney tumors before and after renal transplantation. Transplantation 1995;59:480-5.
5. Penn I. Occurrence of cancers in immunosuppressed organ transplant recipients. Clin Transpl 1998:147-58.
6. Bentdal OH, Brekke IB, Lien B, et al. Rapid development of cancer in both kidney grafts after transplantation from a donor with undiagnosed malignant disease. Transplantation Proc 1994;26:1763.
7. Kunisch-Hoppe M, Hoppe M, Bohle RM, et al. Metastatic RCC arising in a transplant kidney. Eur Radiol 1998;8: 1441-3.
8. Llamas F, Gallego E, Salinas A, et al. Sarcomatoid renal cell carcinoma in a renal transplant recipient. Transplant Proc 2009;41:4422-4.
9. Zukoski CF, Killen DA, Ginn E, et al. Transplanted carcinoma in an immunosuppressed patient. Transplantation 1970;9:71-4.
10. Mengel M, Jonigk D, Wilkens L, et al. Chimerism of metanephric adenoma but not of carcinoma in kidney transplants. Am J Pathol 2004;165:2079-85.
11. Tunner WS, Goldsmith EI, Whitsell JC, et al. Urothelial carcinoma transmission via kidney transplantation. Nephrol...
36. Cheville JC, Lohse CM, Zincke H, et al.

35. Shuch B, Said J, La Rochelle JC, et al.

34. de Peralta-Venturina M, Moch H, Amin

33. Penn I. Transmission of cancer from

32. Myron Kauffman H, McBride MA,

31. Pedotti P, Poli F, Longhi E, et al.

29. Mocelin AJ. Letter: inadvertent

28. Myron Kauffman H, McBride MA,

27. Detroz B, Detry O, D’Silva M, et al.

25. Lotan D, Laufer J. Metastatic renal
carcinoma in a pediatric recipient of an
adult cadaveric donor kidney. Am J
Kidney Dis 1995;26:960-2.

26. Matter B, Zukoski CF, Killen DA, Ginn
E. Transplanted carcinoma in an
immunosuppressed patient. Transplantation
1970;9:71-4.

27. Detroz B, Detry O, D’Silva M, et al.
Organ transplantation with undetected
donor neoplasm. Transplant Proc
1991;23:2657.

28. Myron Kauffman H, McBride MA,
Cherikh WS, et al. Transplant tumor
registry: donor related malignancies.
Transplantation 2002;74:358-62.

29. Mocelin AJ. Letter: inadvertent
transplant of a malignancy. Transplantation
1975;19:430.

30. Kauffman HM. Malignancies in organ
transplant recipients. J Surg Oncol
2006;94:431-3.

31. Pedotti P, Poli F, Longhi E, et al.
Epidemiologic study on the origin of
cancer after kidney transplantation.
Transplantation 2004;77:426-8.

32. Myron Kauffman H, McBride MA,
Cherikh WS, et al. Transplant tumor
registry: donor related malignancies.
Transplantation 2002;74:358-62.

33. Penn I. Transmission of cancer from
organ donors. Ann Transplant 1997;2:7-
12.

34. de Peralta-Venturina M, Moch H, Amin
M, et al. Sarcomatoid differentiation in
renal cell carcinoma: a study of 101
cases. Am J Surg Pathol 2001;25:275-
84.

35. Shuch B, Said J, La Rochelle JC, et al.
Cytoreductive nephrectomy for kidney
cancer with sarcomatoid histology: is
up-front resection indicated and, if not,
is it avoidable? J Urol 2009;182:2164-
71.

36. Cheville JC, Lohse CM, Zincke H, et al.
Sarcomatoid renal cell carcinoma: an
examination of underlying histologic
subtype and an analysis of associations
with patient outcome. Am J Surg Pathol
2004;28:435-41.

37. Tomera KM, Farrow GM, Lieber MM.
Sarcomatoid renal carcinoma. J Urol
1983;130:657-9.

38. Siemer S, Hack M, Lehmann J, et al.
Outcome of renal tumors in young adults.
J Urol 2006;175:1240-4.

39. Thompson RH, Ordonez MA, Iasonos
A, et al. Renal cell carcinoma in young
and old patients: is there a difference? J
Urol 2008;180:1262-6.

40. Cook A, Lorenzo AJ, Salle JL, et al.
Pediatric renal cell carcinoma: single
institution 25-year case series and initial
experience with partial nephrectomy. J
Urol 2006;175:1456-60.

41. Cumberbatch MG, Rota M, Catto JW,
La Vecchia C. The role of tobacco
smoke in bladder and kidney carcinogenesis: a comparison of
exposures and meta-analysis of incidence and mortality risks. Eur Urol
2016;70:458-66.

42. Adams KF, Leitzmann MF, Albones D,
et al. Body size and renal cell cancer
incidence in a large US cohort study. Am J Epidemiol
2008;168:268-77.

43. Ljungberg B, Campbell SC, Choi HY, et al. The epidemiology of renal cell
carcinoma. Eur Urol 2011;60:615-21.

44. Brenneman JF, Stilmant MM, Babayan
RK, Siroky MB. Acquired renal cystic
disease: implications for the urologist.
Br J Urol 1991;67:342-8.

45. Wetmore JB, Calvet JP, Yu ASL, et al.
Polycystic kidney disease and cancer after renal transplantation. J Am Soc
Nephrol 2014;25:2335-41.

46. Ribal MJ, Rodriguez F, Musquera M, et al. Neophron-sparing surgery for renal
tumor: a choice of treatment in an
allograft kidney. Transplant Proc
2006;38:1359-62.

47. Miao Y, Everly JJ, Gross TG, et al. De
novo cancers arising in organ transplant
recipients are associated with adverse
outcomes compared with the general
population. Transplantation
2009;87:1347-59.

48. Morath C, Mueller M, Goldschmidt H,
et al. Malignancy in renal transplantation. J Am Soc Nephrol
2004;15:1582-8.

49. Buell JF, Gross TG, Woodle ES. Malignancy after transplantation.
Transplantation 2005;80:S254-64.

50. Buell JF, Beebe TM, Trofe J, et al. Donor transmitted malignancies. Ann
Transplant 2004;9:53-6.

51. Briggs JD. Causes of death after renal transplantation. Nephrol Dialysis
Transplant 2001;16:1545-9.

52. Gudbjartsson T, Hardarson S,
Petursdottir V, et al. Histological
subtyping and nuclear grading of renal
cell carcinoma and their implications
for survival: a retrospective nation-wide
study of 629 patients. Eur Urol
2005;48:593-600.

53. Tsui KH, Shvarts O, Smith RB, et al.
Prognostic indicators for renal cell
carcinoma: a multivariate analysis of
643 patients using the revised 1997
tNM staging criteria. J Urol 2000;163:
1090-5.

54. Elfving P, Mandal N, Lundgren R, et al. Prognostic implications of
cytogenetic findings in kidney cancer.
Br J Urol 1997;80:698-706.

55. Gunawan B, Huber W, Holtrup M, et al. Prognostic impacts of cytogenetic
findings in clear cell renal cell
carcinoma: gain of 5q31-qter predicts a
distinct clinical phenotype with
favorable prognosis. Cancer Res 2001;
61:7731-8.

56. Ljungberg B, Bozoky B, Kovaes G, et al. p53 expression in correlation to
patient outcome. Am J Surg Pathol
2001;25:15-20.