Transplant International

Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

Malignancies after kidney transplantation: a 40-year single-center experience in Korea

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Keywords
cancer, kidney transplantation, risk factors.

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Conflicts of Interest
The authors have no conflicts of interest to declare.

Received: 14 January 2011
Revision requested: 7 February 2011
Accepted: 16 April 2011
Published online: 16 May 2011

doi:10.1111/j.1432-2277.2011.01270.x

Summary

Cancer is a well-recognized complication of kidney transplantation (KT), but nearly almost all data have come from Western countries. The aim of this study was to determine the incidence, type, and risk factors of malignancy after KT in Korea. The 1695 patients who underwent KT between 1969 and 2009 were studied retrospectively. Results were compared with a cohort of patients without cancer from the same center. During the follow-up period, 136 of 1695 patients developed 141 post-transplant malignancies (PTM). The cumulative incidence of cancer at 1, 5, 10, 20, and 30 years was 0.64%, 2.42%, 7.89%, 21.49%, and 66.35% respectively. Stomach cancer was the most common PTM. Risk of Kaposi sarcoma, malignant lymphoma, skin cancer, cervical cancer, and renal cell carcinoma was more than 10-times higher in KT recipients. Multivariate logistic regression analysis showed that cancers were clearly associated with recipients' age, recipients' gender, duration of graft function and follow-up period. Our data suggest that most malignancies develop more frequently after KT, but the incidence of individual cancer is different from Western countries. A more vigorous cancer surveillance program should be adapted to risk associated with transplant recipients, especially older, female or long-term follow-up recipients or those with functioning grafts.

Introduction

With the improved long-term outcome of renal allograft recipients, post-transplant malignancy (PTM) has become a leading cause of late death. Compared with an age- and gender-matched population, organ transplant recipients have an increased incidence of malignancies [1–4]. However, the incidence and type of PTM vary among different countries and most data come from Western countries. The aim of this study was to investigate the incidence, type, and risk factors of malignancies after kidney transplantation (KT) in Korea.

Patients and methods

We performed a retrospective cohort study by reviewing the medical records and electronic transplant registry of 1695 KT recipients who underwent follow-up at Seoul St. Mary's Hospital, Catholic University of Korea from March 1969 to February 2009. Our KT program has existed since 1969. A prospective database for these patients has evolved significantly since that time. In its current computerized form, the database contains pre- and post-transplant information for KT recipients, as well as a diagnosis code for all types of secondary diagnoses and related follow-up. All data were registered by a member of the transplantation center. This study was approved by the Institutional Review Board of Seoul St. Mary's Hospital. We investigated the incidence, type and risk factors of malignancy. The patients were divided into two groups on the basis of development of cancer. These two groups were compared with recipients' gender and age at transplantation, donors' gender and age at transplantation, acute rejection episodes, numbers of human leukocyte antigen (HLA) mismatches, type of maintenance immunosuppressive drug, duration of follow-up

period, duration of graft function, and subsequent renal transplantation. The number of person-years at risk of cancer was calculated to compare the cancer risk between KT recipients and the general Korean population. Data for the general population were obtained from *The Annual Report on Cancer Registry of Korea 2007*, supplied by the Ministry of Health & Welfare, Republic of Korea [5]. The expected number of cancers was calculated by multiplying the person-years at risk obtained from the Korean cancer registry annual report. The rate of increase was calculated by the ratio of the observed to expected number of cancer cases. Student's *t*-test for continuous variables and the chi-square test for categorical variables were used to compare data between the two groups, with or without cancer. All data were expressed as mean values ± standard deviation (SD). Kaplan–Meier method and log-rank test were used to compare patients and graft survival rates between the two groups. Data were censored at the time of death or at the last available follow-up. Factors associated with occurrence of malignancy were assessed by univariate and multivariate analyses according to a Cox proportional hazard model. Statistical significance was defined as $P < 0.05$. All statistical analyses were carried out with the SAS software version 9.1 (SAS Institute, Cary, NC, USA).

Results

Patients' characteristics are shown in Table 1. There were 1111 (65.5%) male recipients with a mean follow-up duration of 9.1 ± 6.9 years representing more than 15 400 person-years of follow-up. During the observation period, 141 (8.31%) cases of PTM occurred in 136 KT recipients. The mean age of donors and recipients at the time of transplantation was 38.4 ± 12.6 and 39.9 ± 10.6 years, respectively. A total 1486 (87.6%) cases involved a living donor. Acute rejection developed in 588 (34.7%) recipients. A total of 1604 patients received one graft, 85 received a second graft, and six received a third graft. The maintenance immunosuppressive regimen consisted of (i) azathioprine + prednisolone ($n = 152$), (ii) cyclosporine + azathioprine + prednisolone ($n = 991$), (iii) cyclosporine + mycophenolate mofetil + prednisolone ($n = 340$), and (iv) tacrolimus + mycophenolate mofetil + prednisolone ($n = 212$).

There was no significant difference in donors' age and gender, donor source, number of kidney transplant, number of acute rejection episodes, and number of HLA mismatches. Patients with cancer had a longer follow-up time compared with the non-cancer group (14 ± 6.7 vs. 8.7 ± 6.8 years respectively, $P < 0.001$). The mean duration of graft function in the cancer group also was longer than that in the non-cancer group (11.3 ± 6.2 vs. 5.5 ± 5.3 years respectively, $P < 0.001$). Patients with cancer were older at KT compared with the non-cancer group (39.9 ± 10.6 vs. 36.7 ± 11.8 years respectively, $P = 0.001$). Female recipients had more cancer compared with male recipients. The difference in the male-to-female ratio was statistically significant between the cancer group and non-cancer group (1.3:1 vs. 1.9:1 respectively, $P = 0.014$). There was no significant difference between cyclosporine and tacrolimus in cancer development. However, an azathioprine-based regimen showed a higher incidence of cancer development compared with mycophenolate mofetil ($P = 0.005$). We did not use anti-lymphocyte globulin, anti-thymocyte globulin, and muromonab-CD3 as induction therapy. Instead, we have routinely used interleukin-2 receptor blocker as induction

Table 1. Demographic and clinical characteristics of kidney transplant recipients.

Characteristics	Total patients ($n = 1695$)	Without cancer ($n = 1559$)	With cancer ($n = 136$)	*P*-value
Donor age (years)	38.4 ± 12.6	38.4 ± 12.6	38.3 ± 13.0	0.950
Recipient age (years)	37.7 ± 10.8	36.7 ± 11.8	39.9 ± 10.6	0.001
Gender of recipient % (male/female)	65/35	66/34	56/44	0.014
Gender of donor % (male/female)	58/42	58/42	60/40	0.537
Duration of graft function (years)	8.0 ± 6.5	5.5 ± 5.3	11.3 ± 6.2	<0.001
Duration of follow-up (years)	9.1 ± 6.9	8.7 ± 6.8	14 ± 6.7	<0.001
No. of HLA mismatch	2.93 ± 1.41	2.93 ± 1.41	2.89 ± 1.36	0.747
No. of AR episode % (≥1)	34.7 (588)	34.1 (531)	41.9 (57)	0.744
No. of KT % (>1)	5.4 (91)	5.4 (84)	5.1 (7)	0.678
Donor type % (living/deceased)	87/13	87/13	89/11	0.505
Aza versus MMF (%)	67.5 vs. 32.6	66.5 vs. 33.6	78.7 vs. 21.3	0.005
CsA versus FK506 (%)	78.5 vs. 12.6	78.3 vs. 13.0	80.9 vs. 7.4	0.238

HLA, human leukocyte antigen; AR, acute rejection; KT, kidney transplantation; Aza, azathioprine; MMF, mycophenolate mofetil; CsA, cyclosporine; FK506, tacrolimus.

therapy since 2006 so that follow up period was too short to compare the relation between the presence of induction therapy and incidence of PTM.

A total of 141 cancers were observed in 136 of 1695 (8.3%) KT recipients. Characteristics of the cancer group are shown in Table 2. Stomach cancer ($n = 24$, 17.0%) was the most common PTM, followed by malignant lymphoma ($n = 21$, 14.9%), colorectal cancer ($n = 15$, 10.6%), cervical cancer ($n = 13$, 9.2%), thyroid cancer ($n = 12$, 8.5%), hepatocellular carcinoma ($n = 11$, 7.8%), breast cancer ($n = 8$, 5.7%), bladder cancer ($n = 8$, 5.7%), and renal cell carcinoma ($n = 7$, 5.0%). The cumulative incidence of cancer after KT was 0.64% at 1 year, 2.42% at 5 years, 7.89% at 10 years, 21.49% at 20 years, and 66.35% at 30 years. The cumulative incidences of malignancy increased markedly after the second post-transplantation decade.

The mean age of patients at diagnosis of their cancer was 50.2 ± 11.1 years. Cervical cancer developed at a younger age (40.5 ± 9.2 years), whereas lung cancer occurred at an older age (63.0 ± 9.6 years). The average interval between transplant and diagnosis of cancer was 9.8 ± 6.2 years, with 6.4% ($n = 9$) detected within 1 year, 16.3% ($n = 23$) between 1 and 5 years, 32.6% ($n = 46$) between 6 and 10 years, 39.0% ($n = 55$) between 11 and 20 years, 5.0% ($n = 7$) between 21 and 30 years, and 0.7% ($n = 1$) between 31 and 40 years. The mean time from transplantation to the diagnosis of cancer varied according to the type of malignancy. Cervical cancer, lung cancer, and malignant lymphoma occurred earlier with a mean time of 6.4 ± 4.7, 7.3 ± 4.5, and 8.6 ± 7.0 years, respectively, in contrast to colorectal cancer (14.5 ± 8.5 years) and renal cell carcinoma (11.8 ± 6.0 years). Seven (30%) patients with stomach cancer and three (20%) with colorectal cancer were diagnosed before age 50, and two (25%) patients with breast cancer and four (30%) with cervical cancer were detected before age 40.

Compared with the general Korean population, transplant patients had a 3.3 times higher risk of developing any kind of malignancy. However, the risk of Kaposi sarcoma, malignant lymphoma, skin cancer, cervical cancer, and renal cell carcinoma was more than 10 times higher, whereas several tumors such as colorectal, breast, and liver showed only a slightly increased risk in renal transplant recipients.

Mortality was the outcome in 37.5% ($n = 51$) of the patients with cancer, and it was directly related to cancer in 86.3% ($n = 44$) of them. The overall cumulative patient and graft survival rates in the cancer group and non-cancer group are shown as Kaplan–Meier curves in

Table 2. Type of malignancies.

Type of Ca	No. of Ca	Gender of recipient (male versus female)	Age at Tx (years)	Age at Dx (years)	Time between Tx and Dx (years)	Observed rates of cancer	Expected rates of cancer	Rate of increase
Stomach Ca	24	20 vs. 4	44.3 ± 10.1	55.3 ± 10.4	10.7 ± 5.3	155.0	48.5	3.2
Malignant lymphoma	21	16 vs. 5	40.6 ± 8.6	48.5 ± 9.5	8.6 ± 7.0	135.7	6.8	19.9
Colorectal Ca	15	10 vs. 5	43.0 ± 8.1	57.6 ± 10.5	14.5 ± 8.5	96.9	33.2	2.9
Cervical Ca	13	0 vs. 13	31.6 ± 8.6	40.5 ± 9.2	6.4 ± 4.7	84.0	8.2	10.2
Thyroid Ca	12	5 vs. 7	34.6 ± 9.7	45.7 ± 8.2	10.6 ± 4.6	77.5	21.7	3.6
Hepatocellular Ca	11	8 vs. 3	34.1 ± 9.2	45.5 ± 7.3	11.1 ± 6.6	71.1	29.8	2.4
Breast Ca	8	0 vs. 8	35.3 ± 8.7	45.6 ± 7.7	10.0 ± 5.8	51.7	18.8	2.7
Bladder Ca	8	5 vs. 3	45.3 ± 11.6	52.1 ± 10.4	6.6 ± 3.8	51.7	6.0	8.6
Renal cell Ca	7	4 vs. 3	45.0 ± 12.9	57.0 ± 15.1	11.8 ± 6.0	45.2	4.3	10.5
Skin Ca	6	4 vs. 2	41 ± 13.4	49.8 ± 13.3	8.7 ± 2.5	38.8	3.1	12.5
Kaposi sarcoma	6	2 vs. 4	34.2 ± 9.8	43.7 ± 10.2	9.1 ± 6.2	38.8	0.1	387.6
Lung Ca	4	4 vs. 0	55.3 ± 7.0	63.0 ± 9.6	7.3 ± 4.5	25.8	33.7	0.8
Ureter Ca	1	0 vs. 1	42	56	12.8	6.5	0.5	12.9
Ovarian Ca	1	0 vs. 1	30	34	3.6	6.5	3.2	2.0
Common bile duct Ca	1	1 vs. 0	45	59	14	6.5	8.1	0.8
Gingival Ca	1	0 vs. 1	43	51	8.7	6.5	0.1	64.6
Thymoma	1	0 vs. 1	50	56	5.3	6.5	0.1	64.6
Metastatic tumor of unknown origin	1	1 vs. 0	28	50	20.8	6.5	–	–
Total	141	77 vs. 59	39.9 ± 10.6	50.2 ± 11.1	9.8 ± 6.2	910.9	275.4	3.3

Ca, cancer; Tx, treatment; Dx, diagnosis; Observed rates of cancer, number of cancers per 100 000 patient-years among renal transplant recipients; Estimated rates of cancer, number of cancers per 100 000 patient-years among general population; Rates of increase, observed rates/estimated rates.

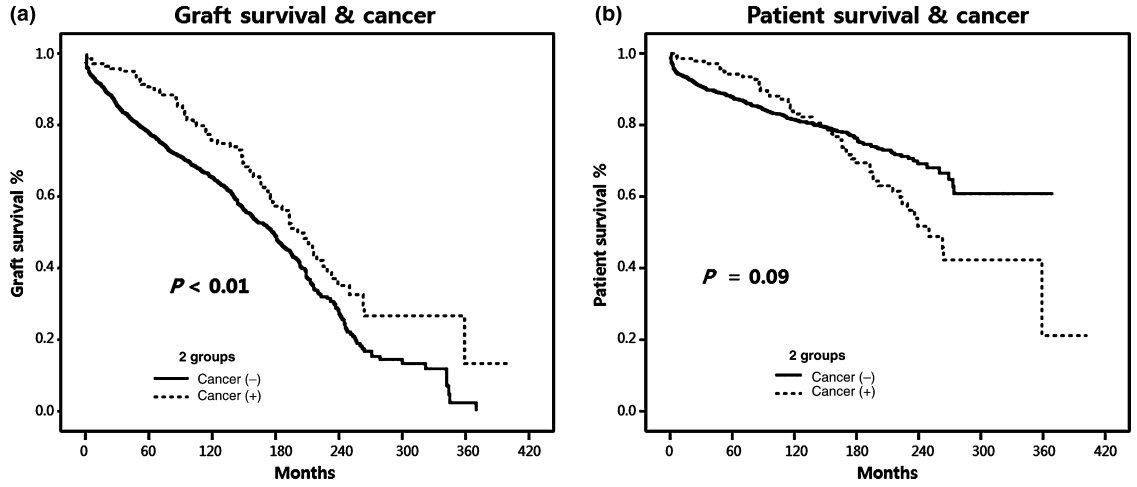

Figure 1 Cumulative graft survival (a) and patient survival rates (b) analyzed by log-rank test.

Fig. 1. The cumulative graft survival rate of KT recipients with cancer was significantly lower than those without cancer ($P < 0.05$). The cumulative patient survival rates with versus without cancer were 97.9% vs. 93.7% at 1 year, 94.2% vs. 87.8% at 5 years, 83.1% vs. 81.5% at 10 years, 51.7% vs. 69.2% at 20 years, and 21.2% vs. 60.8% at 30 years, respectively. The post-transplant cancer group showed a statistically nonsignificant decline ($P = 0.09$) of patient survival rates in the long-term period (>20 years after transplantation).

The cumulative patient survival after diagnosis of cancer was 75.9% at 1 year, 62.4% at 5 years, and 56.8% at 10 years. The 5-year survival rate of all cancer patients was 64.2%. The 5-year survival rate after diagnosis of malignancy were 100% for thyroid, breast, and cervical cancer, 80% for Kaposi sarcoma, 78.8% for cancer of genitourinary tract, 66.7% for malignant lymphoma, and 30.9% for gastrointestinal cancer.

Table 3. Multivariate analysis of risk factors for post-transplant malignancies.

Characteristics	*P*-value	Hazard ratio	95% confidence interval
Recipient age (years)	0.000	1.041	1.022–1.060
Gender of recipient (female)	0.029	1.552	1.046–2.304
Gender of donor (female)	0.914	1.022	0.684–1.528
Duration of graft function (years)	0.000	1.007	1.004–1.009
Duration of follow-up (years)	0.000	1.011	1.008–1.014
Mean number of AR episode	0.958	1.008	0.755–1.344
Donor type (living/deceased)	0.580	1.194	0.636–2.242
Number of KT (>1)	0.932	1.038	0.444–2.426
CsA versus FK506	0.693	0.855	0.392–1.865
Aza versus MMF	0.131	1.582	0.972–2.869

AR, acute rejection; KT, kidney transplantation; CsA, cyclosporine; FK506, tacrolimus; Aza, azathioprine; MMF, mycophenolate mofetil.

According to multivariate logistic regression analysis, cancers were clearly associated with recipient age at transplantation, duration of graft function, follow-up period and female gender (Table 3). However, we were unable to demonstrate any difference among various immunosuppressive agents.

Discussion

Organ transplantation can increase the incidence of cancer through multiple mechanisms and organ transplant recipients have a three- to five-fold excess risk of cancer relative to an age- and gender-matched population, ranging from 4 to 18% (mean, 6%) [1–4,6].

The overall incidence of PTM in our population was 8.3% and transplant recipient had a 3.3-fold higher risk of cancer compared with the general Korean population. Table 3 shows order of incidence of the PTM in our series. The overall cancer incidence in our patients was similar to that of patients in other countries, but the types of malignancy were very different from those in European, Austrian, and North American patients. The most common malignancies in our series were gastrointestinal cancer and cervical cancer; however, in contrast to other studies, we experienced a small number of skin cancers (4.3%). The most common PTM was stomach cancer and the incidence was unusually high in our study (17.0% of PTMs) compared with reports from other countries (0–13% of PTMs) [4,6–10]. An increased incidence of stomach cancer in this study may have resulted from the high prevalence of *Helicobacter pylori* infection in the general Korean population (44.6–66.9%). It is well-known that

most infection-related cancers occur at increased rates in renal transplant recipients and that stomach cancer is associated with *H. pylori* infection [11]. Grulich *et al.* [12] reported that *H. pylori* is estimated to cause more than 60% of all stomach cancer and the rate is roughly double in renal transplant recipients. The incidence of cervical cancer in our study ($n = 13$, 9.2%) was significantly higher than that of Western countries (0.7–5.9%) [2,4,13,14]. The reason for this finding is that the incidence of human papilloma virus (HPV) infection in a general healthy population is higher in Korea than other countries. In Korea, the reported incidence is 43.7–44.8%. The reported regional HPV prevalence is 22.1% in Africa, 20.4% in Central/South America, 11.3% in North America, 8.1% in Europe, and 8.0% in Asia [15]. Skin cancer is the most common malignancy after KT in Western countries [16,17]. In our series, however, skin cancers ranked the 10th among PTMs, with a prevalence of only 4.3% of total PTMs. The reason for the low prevalence rate is that the incidence of skin cancer varies with the amount of sun exposure [18] and our region has limited sun exposure. The average sunshine duration in 2009 was only 2096 h/year [19]. Interestingly, we observed a more than 10-fold increased risk for some specific cancers after KT, such as Kaposi sarcoma, malignant lymphoma, skin cancer, cervical cancer, and renal cell carcinoma. All of these cancers except renal cell carcinoma are associated with infection by oncogenic viruses.

Multivariate analysis showed that the recipient's age at transplantation, duration of graft function, follow-up period, and female gender were significant risk factors for development of PTM in our KT recipients. The duration of graft function was closely related to the duration of immunosuppression and a longer follow-up could potentially allow for the development and detection of a greater number of cancers. The close relationship between the development of malignant disease and long-term immunosuppression has been confirmed in other reports [20,21]. Consistent with our results, recipient's age at transplantation has been extensively reported to be a risk factor for PTM. In contrast to other studies [22,23], we demonstrated that female gender alone is a risk factor for development of PTMs. When we compared age at the last follow-up, there was no difference between male and female patients (43.9 ± 15.2 and 45.0 ± 45.1, respectively). One possible explanation for this finding is that the incidence of cervical cancer was (and is) high in Korea.

Post-transplant malignancy is an important cause of mortality and morbidity after KT. Thus, screening and surveillance for cancer would appear to be appropriate. The overall incidence and risk factors of PTM in our patients was similar to that of patients in other countries. However, the types of malignancy were very different from patients in Europe, Austria, and North America. Although PTM screening recommendations should be tailored in each country according to known factors associated with increased risk for cancer, we propose the following recommendations for PTM screening to Korean, based on our findings. Initial cancer screening including gastroscopy, colonoscopy, abdominal sonography, mammography and Papanicolaou smear should be performed on all recipients before operation to detect pre-existing malignancies and precancerous lesions. After transplantation, we recommend biennial gastroscopy for gastric cancer, annual fecal occult blood test and 5-yearly flexible sigmoidscopy for colon cancer, annual Papanicolaou test for cervical cancer, annual physical examination for skin cancer by dermatologist and biennial mammography and physical examination by a physician for breast cancer in Korea. We do not recommend routine screening for thyroid, renal, hepatic, and skin cancer to recipients who do not have any risk factors. Clearly, prospective, randomized, nation-wide data are needed to further clarify the ideal regimen and better define the time interval after initial screening. However, it seems a relatively short interval between screenings may be necessary.

In conclusion, the incidence of malignancy in the present series is similar to that described elsewhere, but the type of malignancy is significantly different. Stomach cancer is the most common PTM among KT recipients in Korea. Better tailored screening programs for PTM should be offered to all transplant recipients, regarding KT with special focus on older, female, and long-term immunosuppressed renal transplant recipients.

Authorship

J-IK: designed the study, collected and analyzed data, wrote the article. J-KH: collected and analyzed data, analyzed results, wrote the article. I-SM: designed the study, collecting data, edited the article.

Funding

Authors did not receive financial support for this article.

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