Transplant International

Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

Chronologically different incidences of post-transplant malignancies in renal transplant recipients: single center experience

Man Ki Ju,[1,2] Dong Jin Joo,[1,2] Soo Jin Kim,[1,2] Kyu Ha Huh,[1,2] Myoung Soo Kim,[1,2] Kyung Ock Jeon,[2] Hyun Jung Kim,[2] Soon Il Kim[1,2] and Yu Seun Kim[1,2]

1 Department of Surgery, Yonsei University College of Medicine, Seoul, Korea
2 The Research Institute for Transplantation, Yonsei University College of Medicine, Seoul, Korea

Keywords
immunosuppression, kidney transplantation, malignancy.

Correspondence
Myoung Soo Kim MD, Department of Surgery, Yonsei University College of Medicine, 134 Shinchon-Dong, Seodaemun-Ku, Seoul 120-752, Korea.
Tel.: +82 2 2228 2123; fax: +82 2 313 8289;
e-mail: ysms91@yuhs.ac

Received: 9 November 2008
Revision requested: 9 December 2008
Accepted: 14 January 2009

doi:10.1111/j.1432-2277.2009.00846.x

Summary

The incidence of malignancy in transplant recipients is known to be higher than the same in the general population. However, the types of malignancies vary geographically, and the relative risks (RR) for malignancy in transplant recipients, compared with that of the general population, also differ country-by-country. In this study, we investigated the incidence and characteristics of malignancies after renal transplantation in a single center. A total of 2630 renal recipients who underwent surgery between April 1979 and June 2007 were enrolled in this study. The cumulative and interval incidences of malignancies were calculated for every 3 years post-transplantation. One-hundred ninety cases of postrenal transplant malignancies among 177 recipients (6.73%) were reported until 2007. The post-transplant malignancies were detected from 6 to 290 months after transplantation, with a mean duration of 112.6 ± 66.0 months. Skin cancer [35 (18.4%)] was the most common post-transplant malignancy, followed by thyroid [25 (13.2%)], stomach [22 (11.6%)], colorectal [22 (11.6%)], and urologic cancers [19 (10.0%)]. As the post-transplant period increased, the interval incidence of malignancy correspondingly increased. Virus-related malignancies, such as Kaposi's sarcoma and cervical cancer, developed earlier within the post-transplant period, while urologic cancer, colorectal cancer developed late in the post-transplant period. The recipient's age at the time of transplantation was the sole independent risk factor for post-transplant malignancy based on the multivariate analysis (RR = 2.723, $P < 0.0001$ in the >50-year-old age group). We should establish strategies for post-transplant malignancy-screening based on the recipient's age at the time of transplantation, the post-transplant interval, and the national trend of post-transplant malignancy.

Introduction

Immunosuppressive therapy has short- and long-term side-effects, such as infections, cardiovascular accidents, and malignancies [1]. Of these, life-threatening infections have declined attributable to more meticulous immunosuppressive therapy and improved anti-infective therapies. The risk of cardiovascular disease among transplant recipients has been reduced through the aggressive treatment of hypertension and hyperlipidemia and the use of steroid-free immunosuppressive protocols [2]. Indeed, post-transplant malignancies have become an important cause of mortality and are expected to become the leading cause of death within the next 20 years [2]. The incidence of

malignancy in renal transplantation recipients ranges from 2.3% to 31% [2–6]. The incidence of malignancy in transplant recipients is known to be higher than that in the general population, with three to five times the relative risk (RR) [2,6]. In immunosuppressed patients, virus-related malignancies, such as lymphoma, Kaposi's sarcoma, and cervical cancer, are more common than that in the general population [7–9]. However, the types of malignancies vary geographically and the relative risk compared with the general population also varies by country. There have been many reports from Western countries on post-transplant malignancies, but there have only been a few reports that have focused on the Asian population [10–12]. This study was designed to investigate the incidence, characteristics, and risk factors for malignancy in Korean renal transplant recipients, who have different characteristics from Western renal transplant recipients. Data was collected over a 28-year time-period from a single Korean medical center.

Patients and methods

A total of 2650 renal recipients who underwent transplantation between April 1979 and June 2007 at the Yonsei University Health System (YUHS) were enrolled in this study. However, 20 recipients with previous malignancy history were excluded from study population. So, 2630 renal transplant recipients without a pretransplant history of malignancy were enrolled in the study. After transplantation, all recipients have followed up to YUHS out-patient clinic at least once a month. In every visit to our out-patient clinic, they were checked up in respect of their transplant kidney and health status by physical exam and laboratory test. In addition, they were checked up with 24-h urine analysis, bone densitometry, tumor marker yearly and imaging study, such as ultrasonography or computed tomography if needed. If there were abnormal or suspicious findings, we did more specific examination and consult with the concerned department of our hospital. All examined data and medical problems were entered in the hospital medical record and our transplant database. To identify recipients with post-transplant malignancies, we retrospectively reviewed the medical records of the 2630 recipients in the transplant database. All malignancies were confirmed by pathologic study, except for hepatocellular carcinoma, which was diagnosed by radiologic imaging. Synchronous and metachronous malignancies in other system were counted as different events. The interval and cumulative incidences of the malignancies were calculated as the number of post-transplant malignancies per 100 000 recipients for every 3-year period post-transplant, and compared with the age-standardized incidence (ASR) of malignancy in the Korean general population by gender, which was adopted from the Cancer Incidence in Korea 1999–2001, supplied by the Ministry of Health and Welfare, Republic of Korea [13]. The ASR of malignancy in the Korean general population was based on data from national survey for 3 years, so we set the duration of interval period in this study for 3 years.

We did not use induction immunosuppression therapy, such as anti-thymocyte globulin (ATG), anti-lymphocyte globulin (ALG), and muromonab-CD3 (OKT-3), but we began induction therapy with interleukin-2 receptor antibody (basiliximab) for high-risk recipients only in 1999. We also used maintenance immunosuppression therapy with an azathioprine-based regimen during 1979–1984, and have used cyclosporine since 1984 and tacrolimus since 1998 as the main immunosuppressive agents. Trough levels were maintained between 10 to 12 ng/ml for tacrolimus and 120 to 150 ng/ml for cyclosporine for the first 3 months; thereafter they were gradually reduced to 5–8 and 80–100 ng/ml respectively. Acute rejection was treated with steroid pulse therapy, and treated with ATG/ALG or OKT-3 in steroid-resistant acute rejection.

An analysis of variance (ANOVA) was used to analyze the characteristics of each malignancy. To determine the risk factors for a malignancy, a uni-variate analysis of all the demographic characteristics of the patients was performed. After examining the relationships of individual demographic factors to malignancy, a Cox proportional-hazards model, taking into account the interactions between the demographic factors, was again used to identify the risk factors for a malignancy. The results of the Cox regression test were presented as relative risks, the 95% confidence interval, and *P*-values. In risk factor analysis, we calculate two groups separately by recipient's gender and then calculate all study population for excluding bias of gender-dependent malignancy risk. The incidence and survival rate were calculated by the life-table method and compared with a Wilcoxon test. All statistical analyses were performed using SPSS® 14.0 for Windows (SPSS, Inc., Chicago, IL, USA).

Results

Clinical manifestations

For the time-period considered, 2630 renal transplant recipients without a pretransplant history of malignancy were enrolled in the study. There were 1772 male (67.4%) and 858 female (32.6%) recipients with a mean follow-up duration of 195.3 ± 11.5 months (range, 0–338 months). The mean age of recipients at the time of transplantation was 37.3 ± 11.5 years (2–70). There were 1396 (53.1%) cases involving a living-related donor, 1123 (42.7%) cases involving a living-unrelated donor, and 111 (4.2%) cases

involving a deceased donor kidney transplant. We used dual immunosuppressive regimen in 1391 recipients and triple regimen in 1239 recipients by combination of azathioprine, steroid, calcineurin inhibitor (cyclosporine or tacrolimus), and anti-metabolite (mycophenolate mofetil or mycophenolate sodium). Acute rejection was developed in 799 (30.4%) recipients within 1 year after transplantation. Other clinical manifestations have been shown in Table 1. The overall graft survival rates were 85.1%, 70.9%, and 52.3% for 5, 10, and 20 years after transplantation respectively. The overall patient survival rates were 93.3%, 87.8%, and 78.8% for 5, 10, and 20 years after transplantation, respectively. The post-transplant malignancy did not affect to graft survival rate ($P = 0.2457$) (Fig. 1a). The post-transplant malignancy group showed decline of patient survival rate in long-term period (>10 years after transplantation). But, it was not statistically significant ($P = 0.4619$) (Fig. 1b). The most common cause of graft loss was chronic rejection [319 (40.4%)], followed by patient death [294 (37.3%)]. Infectious disease [126 (41.3%)] was the most common cause of death, and cerebrovascular disease, cardiovascular disease, and malignancy were other major causes of death.

Table 1. Clinical manifestation of study population.

	No. (%)/mean ± SD (range)
Recipient gender, male:female	1772:858 (67.4:32.6)
Recipient age at transplant	37.3 ± 11.5 (2–70)
Donor gender, male:female	1577:1053 (60.0:40.0)
Donor age at transplant	36.3 ± 11.4 (5–69)
Donor type, LRD:LURD:deceased	1396:1123:111 (53.1:42.7:4.2)
Retransplantation, primary:retransplant	2464:166 (93.7:6.3)
Original kidney disease	
Glomerulonepritis	312 (11.9)
Diabetic nephropathy	139 (5.3)
Hereditary nephropathy	29 (1.1)
Reflux nephropathy	57 (2.1)
Vascular disease	9 (0.3)
Systemic disease	33 (1.4)
Others	41 (1.5)
Unkown (no pretransplant biopsy)	2010 (76.4)
Pretransplant treatment	
No dialysis	400 (15.0)
Hemodialysis	1499 (56.6)
Peritoneal dialysis	428 (16.1)
Unknown	330 (12.3)
Induction IS with IL2-R blocker, none:yes	2373:257 (90.2:9.8)
Maintain immunosuppressive agent	
Azathioprine + steroid	127 (4.9)
CNI + steroid	1264 (48.1)
CNI + steroid + anti-metabolite	1239 (47.0)
Acute rejection episodes within 1 year after transplantation	
Before 1995 ($n = 1260$)	419 (33.3)
After 1995 ($n = 1390$)	380 (27.3)
Graft status, survival:fail	1841:789 (70.0:30.0)
Patient status, survival:death	2325:305 (88.4:11.6)

LRD, living-related donor; LURD, living unrelated donor; IL2-R, interleukin-2 receptor; CNI, calcineurin inhibitor.

Diagnosis and classification of post-transplant malignancy

One hundred ninety cases of post-transplant malignancies among 177 recipients were reported until 2007. Synchronous [2 (1.1%)] and metachronous [23 (12.1%)] malignancies in other system were counted as different events. Post-transplant malignancies were detected from 6–290 months after transplantation, with a mean duration of 112.6 ± 66.0 months. The mean age at diagnosis was 49.0 ± 11.6 years (range, 15–72 years). Skin cancer [35 (18.4%)] was the most common post-transplant malignancy, followed by thyroid cancer [25 (13.2%)], stomach cancer [22 (11.6%)], colorectal cancer [22 (11.6%)], urologic cancer [19 (10.0%)], post-transplant lymphoproliferative disorders [PTLD; 12 (6.3%)], and Kaposi's sarcoma [12 (6.3%); Table 2].

Interval and cumulative incidences of post-transplant malignancies

The overall incidence of post-transplant malignancies during the study period was 7.2% (190/2630). As the post-transplant period increased, the interval incidence of malignancies correspondingly increased every 3 years after transplantation. During the first 3 years after transplantation, post-transplant malignancies occurred in only 0.97% of the recipients. During the next 3 years, the interval incidence increased 1.92%, and reached 7.56% 18–21 years after transplantation. By increasing the interval incidence, the cumulative incidence of post-transplant malignancies was exponentially increased. Therefore, the cumulative incidence was 32.83% 21 years after transplantation (Fig. 2). In comparison with the incidence of malignancies (malignancy cases/100 000/3 years) in the general Korean population grouped by gender [14], the first 3-year-interval incidence of malignancies in the male group was 2.7 times higher than those of general population (281.2 cases/100 000/3 years), and this incidence gap between the malignancies in male transplant recipients and male subjects who had not undergone any transplantation in the general population increased to 30.3 times higher, 18 years after transplantation. In the female transplant group, the interval incidence of malignancies was 8.9 times higher in the first 3 years after transplantation and 50.9 times higher 21 years after transplantation (versus those of female subjects in the general

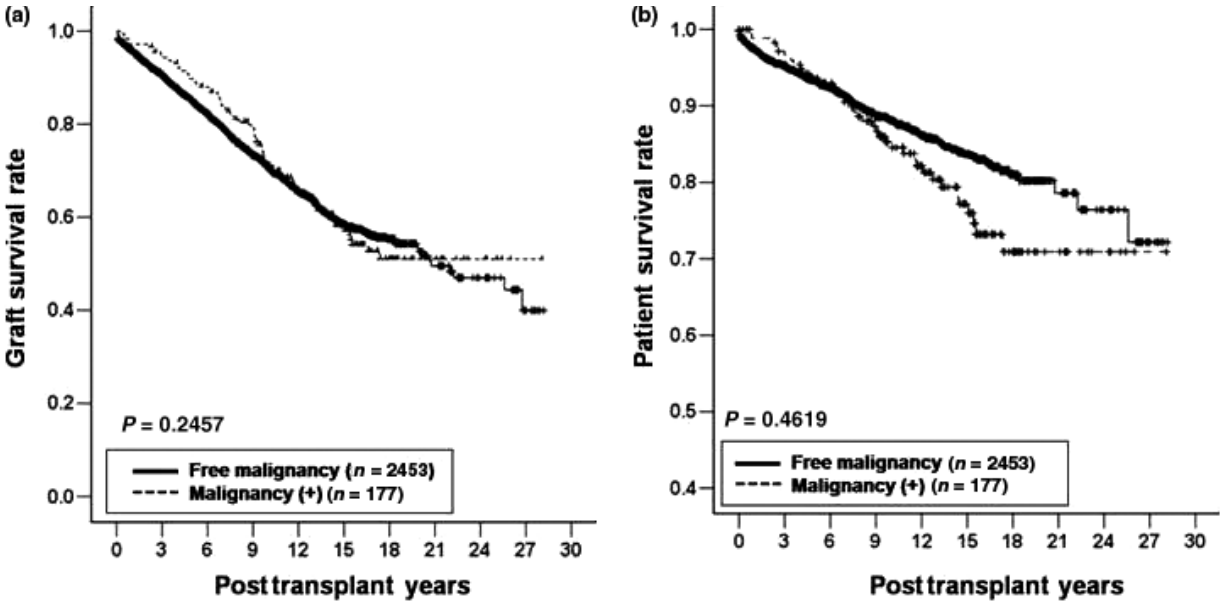


Figure 1 Overall graft survival (a) and patient survival rate (b) was not significantly different between malignancy-free and post-transplant malignancy group (P = 0.2457 and 0.4619, respectively).

population, 160.3 cases/100 000/3 years). There were no reports about age-standardized incidence of Kaposi's sarcoma, PTLD, and skin cancer in the Korean general population. Comparisons of other site-specific malignancy incidences between transplant recipients and Korean general population by post-transplant period have been shown at Table 3.

Risk factors affecting post-transplant malignancies

Univariate analysis showed that gender (female) and age at the time of transplantation (group of individuals aged over 50 years) were significant risk factors (P = 0.002 and 0.0008 respectively) for post-transplant malignancies when considering all study population together. There were no significant differences in connection with donor type, human leukocyte antigen (HLA) matching, ABO blood matching, immunosuppressive agents, episodes of acute rejection, and re-transplantation (P = 0.053, 0.1246, 0.8073, 0.4738, 0.2069, and 0.1877 respectively). Based on the multivariate risk analysis, the recipient's age at the time of transplantation was the sole independent risk factor for post-transplant malignancy (RR = 2.723, $P < 0.0001$ in the >50 years old age-group) especially in male, however no significance in female group. Other multivariate analysis results which were calculated for the two groups separately by recipient's gender and then calculated for all the study population as a whole have been shown in Table 4.

Interval incidence characteristics of site-specific malignancies

We analyzed the characteristics of site-specific malignancies that occurred in more than 10 cases. Cervical cancer and Kaposi's sarcoma occurred in the early post-transplant period (within 6 years after transplantation); thereafter, the occurrence of these malignancies was minimal (Table 3). The mean onset interval from transplantation to cervical carcinoma and Kaposi's sarcoma was 74.4 ± 45.68 and 59.8 ± 58.54 months respectively, which was significantly shorter than the mean onset interval from transplantation to colorectal and urologic cancers (Table 5). Another remarkable demographic characteristic of these malignancies was that the recipients with these malignancies were transplanted in the mid 30s, which was a relatively younger age than for other malignancies, but without statistical significance. A relatively young age at the time of transplantation and a short interval to occurrence of the tumor contributed to the significantly young age at the time of diagnosis of these malignancies ($P < 0.001$; Table 5).

Colorectal and urologic cancers developed late after transplantation in elderly recipients. Early occurrence (within 6 years after transplantation) of these malignancies was rare, but the interval incidence in the late post-transplant period was exponentially increased with the advancing post-transplant period (P = 0.001; Table 5). The mean onset interval from transplantation was

Table 2. Classification of post-transplant malignancies by recipient's gender.

	Male	Female	Total
Classification	No. (%)	No. (%)	No. (%)
Skin			
Squamous cell carcinoma	24 (20.5)	7 (9.6)	31 (16.3)
Basal carcinoma	3 (2.6)	1 (1.4)	4 (2.1)
Endocrine			
Breast	–	10 (13.7)	10 (5.3)
Thyroid	13 (11.1)	12 (16.4)	25 (13.2)
Adrenal/other endocrine	1 (0.9)	–	1 (0.5)
Respiratory			
Lung	5 (4.3)	1 (1.4)	6 (3.2)
Pleura/other respiratory	1 (0.9)	–	1 (0.5)
Gastrointestinal			
Stomach	16 (13.7)	6 (8.2)	22 (11.6)
Small intestine	1 (0.9)	–	1 (0.5)
Colorectal	14 (12.0)	8 (11.0)	22 (11.6)
Liver	2 (1.7)	3 (4.1)	5 (2.6)
Biliary	1 (0.9)	1 (1.4)	2 (1.1)
Urologic			
Kidney	9 (7.7)	1 (1.4)	10 (5.3)
Bladder	2 (1.7)	4 (5.5)	6 (3.2)
Other urologic	3 (2.6)	–	3 (1.6)
Genital			
Ovary/testicle	–	1 (1.4)	1 (0.5)
Cervix	–	12 (16.4)	12 (6.3)
PTLD			
Large B-cell lymphoma	6 (5.1)	1 (1.4)	7 (3.6)
Lymphoid hyperplasia	1 (0.9)	1 (1.4)	2 (1.1)
Burkitt's lymphoma	2 (1.7)	–	2 (1.1)
Anaplastic plasmacytoma	1 (0.9)	–	1 (0.5)
Others			
Kaposi's sarcoma	8 (6.8)	4 (5.5)	12 (6.3)
CNS/PNS	2 (1.7)	–	2 (1.1)
Soft tissue tumor	1 (0.9)	–	1 (0.5)
Metastatic cancer	1 (0.9)	–	1 (0.5)
Total	117 (100.0)	73 (100.0)	190 (100.0)

152.2 ± 65.37 months in colorectal cancer and 139.9 ± 65.06 months in urologic cancer. Additionally, the mean age at transplantation of colorectal and urologic cancers was in the mid-40s ($P < 0.0001$). Therefore, the mean age at diagnosis of colorectal and urologic cancers was 55.0 ± 9.27 and 55.5 ± 9.30 years, respectively, which was significantly older than the other malignancies ($P < 0.0001$). Not only an older age at transplantation, but also the long onset-interval from transplantation contributed to the onset of colorectal and urologic cancers in elderly transplant recipients.

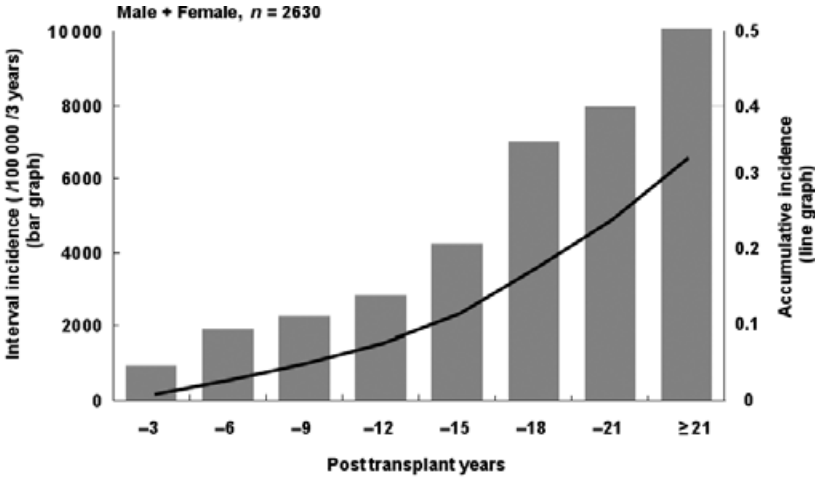
Skin cancer and PTLD had an average interval incidence in the early post-transplant period. But, the interval incidence was increased by the advancing post-transplant period. While significant old age at the time of diagnosis of skin cancer was because of the significant old age at transplantation (44.5 ± 9.29 years old), the significant old age at the time of diagnosis of PTLD was because of the relative late onset (mean onset interval from transplantation was 128.6 ± 71.51 months; Table 5).

Stomach, breast, and thyroid cancers did not exhibit the chronologic difference in the interval incidence in the post-transplant period. Therefore, the mean age at transplantation of these malignancies was directly correlated with the mean age at diagnosis. There was no difference in the incidence of malignancies by gender, with the exception of gender-dependent breast and cervical cancer (Table 5).

Discussion

There have only been a few registries or multi-center studies that have compared the incidence of post-transplant malignancies in renal transplant recipients with the general population. This single-center study had a relatively large study population and a long follow-up duration. The overall post-transplant malignancy incidence of 7.2% in this study is similar to that reported in previous registries or multi-center studies [5,14,15].

Skin cancer is an uncommon malignancy in the general Korean population, accounting for <2% (including melanoma) of the total number of malignancies in both the male and female segments of the general Korean population [13]. But the most common malignancy after kidney transplantation in this study was skin cancer. Thus, the relative incidence of skin cancer in post-transplant recipients is remarkably high compared with the general population. However, this comparison of skin cancer incidence between transplant recipients and Korean general population is subject to certain limitations. The report on cancer registry of Korea [13] does not deal exhaustively with all malignancies in the general Korean population. The program covered only 134 medical centers, about 10% of all the Korean medical institutions, which participated in the national cancer registry program and the program mainly focused on the most widely prevalent malignancies (lung, stomach, colon, liver, and cervix-related malignancies) in Korea. Moreover, this program was not mandatory but only voluntary registry program. Therefore, there was paucity of information about rare malignancies in the general Korean population like skin cancer [13,16]. Many immunosuppressants, especially azathioprine, can increase the risk of skin cancer (particularly squamous cell carcinoma) compared with cyclosporine [17]. Of note, in this study, the proportion of the study population which used azathioprine as the main immunosuppressant was merely 4.9% (127/2630); most of the study population [83.6% (2199/2630)] used cyclosporine as the main immunosuppressant. Therefore, the increased incidence of skin cancer



No. entered	2630	2103	1618	1166	766	435	142	51
No. censored	504	449	420	372	305	272	83	48
No. at risk	2378.0	1878.5	1408.0	980.0	613.5	299.0	100.5	27.0
No. event	23	36	32	28	26	21	8	3

Figure 2 Incidence of post-transplant malignancies: As the post-transplant duration was prolonged, the interval (Bar graph) and cumulative (Line graph) incidence of malignancies was correspondingly increased per 3-year interval. No. event indicates case number of post-transplant malignancy. No. censored indicates case number of follow-up termination without post-transplant malignancy or graft loss without post-transplant malignancy.

was not only with respect to the sub-segment of the study population that was on azathioprine as immunosuppressant but also covered most other recipients who were on cyclosporine.

The incidence of gastrointestinal (GI) tract malignancies, such as stomach-, colon-, and rectal cancer, may be less influenced by the immunosuppressants because the relationship of GI malignancy to viral infection has not been clearly demonstrated [18,19], and GI tract malignancies are less common malignancies in both transplant recipients and the general population in Western countries [5,20,21]. As per an Asian report, GI malignancies are common malignancies in both the general population and post-transplant recipients [9,22]. Moreover, from a systemic point of view, GI tract malignancy was the most common malignancy in this study, just as in the general Korean population [13]. Chen *et al.* [23] reported that renal transplant recipients are at increased risk of gastric adenocarcinoma, which is the most common malignancy in Korea.

As previous studies have reported, lymphomas and Kaposi's sarcomas develop early after transplantation, and GI malignancies develop relatively later [2]. Our results showed similar results. Kaposi's sarcoma and cervical cancer developed in the early post-transplant period, but urologic cancer and colorectal cancer developed in the late post-transplant period. Both Kaposi's sarcoma and cervical cancer are well known virus-related malignancies, so we think that the increased viral replication induced by early potent immunosuppression is the main cause of an early peak in both malignancies. Compared with other studies, PTLD, although not statistically significant, showed a different development pattern by time after transplantation. Many studies have reported that PTLD developed early after transplantation, like Kaposi's sarcoma or other virus-related malignancies [2,24,25]. Indeed, PTLD is closely related to Epstein–Barr virus (EBV) in transplant recipients, with 98% of the cases associated with latent EBV infection [24,25]. In a previous study of PTLD involving 667 renal transplant recipients, there were no significant differences in the incidence of PTLD when comparing patients before and after the introduction of a calcineurin inhibitor, and ALGs had no effect on PTLD risk. However, the occurrence time was shorter in patients treated with a calcineurin inhibitor and ALGs [26]. Our study population had a relatively low immunologic risk, because they were composed of a high proportion of living donors (95.8%) and primary transplantations (93.7%). Therefore, we did not routinely use ALGs as an induction immunosuppressive agent and used a low-dose cyclosporine or tacrolimus protocol. Moreover, the proportion of Kaposi's sarcomas and PTLD in post-transplant malignancies was 6.3% and 4.2%, respectively, in our study, which is far lower than that of other reports [22,27]. However, there is a report about late PTLD development after solid organ transplantation. Cockfield [28] attributed late PTLD to advanced recipient age and a long duration of immunosuppression. Further, the pattern of development of PTLD has a bimodal peak of development. The early peak is because of viral infection related to potent immunosuppression and the late peak is associated with older age and the duration of immunosuppression. Therefore, we suggest that our unexpected result was because of the use of a relatively weak

Table 3. The interval incidence of site-specific malignancy of transplant recipients by post-transplant period; comparison with Korean general population.

Type (*n*)	ASR	Post-transplant years	0–<3	3–<6	6–<9	9–<12	12–<15	15–<18	18–<21	≥21
Breast (10)	21.7	No. at risk	769.0	607.0	460.5	315.0	199.0	95.5	26.0	6.0
		No. event	4	2	1	0	2	1	0	0
		Interval incidence	520	330	220	0	1001	1050	0	0
		Relative risk	23.9	15.2	10.1	0	46.1	48.4	0	0
Cervix (12)	15.5	No. at risk*	768.0	607.0	455.5	311.0	194.0	92.0	25.0	6.0
		No. event	2	6	1	2	1	0	0	0
		Interval incidence†	260	990	220	640	520	0	0	0
		Relative risk‡	16.8	63.9	14.2	41.3	33.5	0	0	0
Thyroid (25)	17.7	No. at risk	2373.0	1882.0	1426.0	1003.5	633.0	314.0	110.0	30.0
		No. event	3	6	3	4	2	5	2	0
		Interval incidence	130	320	210	400	320	1590	1820	0
		Relative risk	7.3	18.1	11.8	22.6	18.8	89.8	102.8	0
Stomach (22)	164.8	No. at risk	2373.0	1885.0	1430.0	1002.0	631.5	310.5	107.5	29.0
		No. event	2	5	7	3	2	2	1	0
		Interval incidence	80	270	490	300	320	640	930	0
		Relative risk	0.5	1.6	2.9	1.8	1.9	3.9	5.6	0
Large intestine (22)	188.3	No. at risk	2373.0	1883.5	1434.0	1010.0	637.5	312.5	107.5	30.5
		No. event	2	0	2	4	6	5	1	1
		Interval incidence	80	0	140	400	940	1600	930	3280
		Relative risk	0.4	0	0.7	2.1	4.9	8.5	4.9	17.4
Urologic (19)	78.1	No. at risk	2373.0	1884.5	1429.0	1006.0	635.5	315.0	112.0	31.5
		No. event	0	4	2	4	3	3	2	1
		Interval incidence	0	210	140	400	470	950	1790	3170
		Relative risk								
Kaposi's sarcoma (12)§	–	No. at risk	2374.5	1883.0	1429.0	1004.0	633.0	313.0	110.0	30.5
		No. event	5	3	2	1	0	1	0	0
		Interval incidence	210	160	140	100	0	320	0	0
PTLD (12)§	–	No. at risk	2373.5	1883.5	1432.0	1006.5	634.5	311.5	109.0	29.0
		No. event	2	0	2	1	4	2	1	0
		Interval incidence	80	0	140	100	630	640	920	0
Skin (35)§	–	No. at risk	2372.5	1881.5	1421.0	995.0	624.0	307.0	109.0	29.5
		No. event	2	9	7	8	4	1	3	1
		Interval incidence	80	480	490	800	640	330	2750	3390

*No. at risk = (no. at start of period + no. at end of period)/2; no. at end of period = (no. at start of period) – (no. event) – (no. censored).
†Interval incidence: post-transplant malignancy cases/100 000/3 years in this study.
‡Relative risk = interval incidence in this study/ASR.
§We could not calculate the rate ratio of Kaposi's sarcoma, PTLD, and skin cancer because there were no reports about their age-standardized incidence of malignancy in the Korean general population.
ASR: age-standardized incidence of malignancy in the Korean general population (malignancy cases/100 000/3 years).

induction immunosuppressive agent, older age at long-term follow-up and, the long-term effect of immunosuppression.

The difference of 'age at diagnosis' among each malignancy group is because of the natural characteristics of each malignancy. For the young age group (15–34 years old), thyroid (22.5%) and breast cancers (17.6%) were the leading and second-most common malignancies among females, according to a Korean report [13], while bladder and colorectal cancers were more common in the old-age group.

Our study provides specific information about the long-term risk of developing a malignancy after kidney transplantation. A few studies have reported the risk of malignancy by the time interval after transplantation [3,15,29]. However, detailed information on interval trends and the cumulative incidence of malignancy have not been clearly reported. Our study showed that as the post-transplant duration increased, the interval incidence of malignancy correspondingly increased, and the cumulative incidence showed exponential increments related to the prolongation of the time interval after transplantation. In our study, in the first 3 years after transplantation, the interval and cumulative incidences of malignancies were 0.97%. However, the interval and cumulative incidences of malignancies increased to 11.11% and 32.8%,

Table 4. Risk factors affecting post-transplant malignancies by recipient gender; multivariate analysis.

	Male (n = 1772)				Female (n = 858)				Total (n = 2630)			
			95% CI of RR				95% CI of RR				95% CI of RR	
Variables	*P*-value	RR	Low	Upper	*P*-value	RR	Low	Upper	*P*-value	RR	Low	Upper
Female gender									0.068	1.328	0.980	1.802
Recipient age												
<30 years old	<0.0001				0.569				0.001			
30–39 years old	0.019	1.992	1.120	3.543	0.305	1.418	0.728	2.761	0.013	1.730	1.121	2.671
40–49 years old	0.006	2.381	1.290	4.394	0.161	1.640	0.821	3.274	0.002	2.039	1.290	3.222
≥50 years old	<0.0001	4.150	2.186	7.878	0.527	1.312	0.565	3.047	<0.0001	2.723	1.663	4.457
Donor type												
Living related	0.168				0.931				0.222			
Living unrelated	0.810	1.053	0.693	1.601	0.708	0.908	0.547	1.507	0.910	1.019	0.740	1.402
Deceased	0.061	2.762	0.953	8.011	0.992	1.010	0.134	7.641	0.086	2.254	0.892	5.696
ABO blood type matching, compatible	0.266	1.288	0.825	2.011	0.786	0.914	0.476	1.753	0.411	1.165	0.809	1.677
Re-transplantation	0.072	0.163	0.022	1.178	0.709	1.312	0.315	5.464	0.119	0.399	0.126	1.268
Main IS agent												
Azathioprine	0.596				0.521				0.298			
Cyclosporine-A	0.547	1.260	0.594	2.670	0.453	1.766	0.400	7.793	0.310	1.413	0.725	2.757
Tacrolimus	0.571	0.542	0.066	4.490	0.942	0.927	0.120	7.174	0.592	0.695	0.184	2.627
Acute rejection within 1 year	0.736	1.079	0.694	1.675	0.323	1.292	0.777	2.146	0.371	1.163	0.835	1.619

IS, immunosuppression; RR, relative risk; CI, confidence interval.

Table 5. Characteristics of site-specific post-transplant malignancies incidence.

Malignancy type	Difference in incidence by gender	Age at transplant (years old)	Onset interval (post-transplant months)	Age at diagnosis (years old)
Breast	Female restrictive	29.6 ± 12.12	78.8 ± 71.92	36.1 ± 11.74
Cervix	Female restrictive	34.2 ± 7.97	74.4 ± 45.68	40.4 ± 5.07
Thyroid	Equal P = 0.1035*	34.7 ± 10.0	115.8 ± 67.84	44.4 ± 8.99
Stomach	Equal P = 0.9890	38.2 ± 9.23	101.9 ± 61.23	46.6 ± 8.54
Large intestine	Equal P = 0.6478	42.3 ± 9.65	152.2 ± 65.37	55.0 ± 9.27
Urologic	Equal P = 0.6989	43.9 ± 10.01	139.9 ± 65.06	55.5 ± 9.30
Kaposi's sarcoma	Equal P = 0.9427	38.7 ± 12.54	59.8 ± 58.54	43.7 ± 13.65
PTLD	Equal P = 0.7352	40.7 ± 13.36	128.6 ± 71.51	51.4 ± 14.13
Skin	Equal P = 0.4453	44.5 ± 9.29	115.9 ± 64.48	54.1 ± 8.04
Mean comparison analysis of age and onset interval	*P*-value by ANOVA Significant difference by multiple comparison	P < 0.0001 Breast, thyroid versus large intestine, urologic, skin	P = 0.001 Cervix, KS versus large intestine, urologic	P < 0.0001 Breast, cervix, thyroid, KS versus large intestine, urologic, skin, PTLD

KS, Kaposi sarcoma; PTLD, post-transplant lymphoproliferative disease.
**P*-value of 'Difference of incidence by gender' was calculated by comparison of life-table survival analysis (Wilcoxon method).

respectively, 21 years (seventh 3-year interval period) after transplantation. The serial increase in the interval incidence was because of 'advancing age' and the 'long-term use of immunosuppressants.' Many studies have focused on the 'age at the time of transplantation,' and our study also showed that the 'age at the time of transplantation'

(especially an age >50 years) was a potent independent risk factor for developing a malignancy by both univariate and multivariate analyses. Consistent with our results, the 'age at the time of transplantation' has been extensively reported to be a risk factor for post-transplant malignancy in other studies [15,29]. However, the native effect of 'advancing age' itself has been neglected. Advancing age is a high-risk factor for malignancy, with persons >65 years of age accounting for 60% of the newly diagnosed malignancies and 70% of all malignancy-related deaths [30]. As graft and patient survival rates increase, the recipients advance in age. As recipients grow older, the risk of post-transplant malignancies simultaneously increases. Agraharkar *et al.* [29] reported that a post-transplant period of >10 years was a risk factor for the development of a malignancy. We should be concerned with the risk of post-transplant malignancies in the long-term follow-up of renal transplant recipients.

Many prior studies have focused on the relationship between post-transplant malignancy and the immunosuppressive therapy used as a factor that may contribute to the risk of post-transplant malignancy [31–33]. But, we could not find any relationship between the type of immunosuppressive agent or induction therapy and the development of a post-transplant malignancy in this study. However, our study did show an increase in the cumulative incidence of post-transplant malignancy as time passed after transplantation, which could be explained by the overall or cumulative effect of using immunosuppressive agents [34,35]. It has recently been suggested that newer agents, such as mycophenolate mofetil and sirolimus, are not linked with post-transplant malignancies and might have anti-tumor properties [36,37], but the long-term results are still not clear.

In close agreement with other registries or multi-center studies, we found that the 'age at the time of transplantation' has a significant relationship with an increase in the risk of post-transplant malignancy. However, our study also showed a few novel and different results from these previous studies. First, we could not find any relationship between the type of immunosuppressive agent or induction therapy and the development of a post-transplant malignancy. We also found that not only the cumulative incidence, but also the interval incidence of post-transplant malignancy, was correspondingly increased as the time interval after transplantation increased. Finally, we suggest that as most malignancies develop more frequently after renal transplantation than in the general population, we should make efforts toward the prevention and early detection of post-transplant malignancies in renal transplant recipients. Our results regarding the common types, development timing, and incidence by time interval after transplantation can help these efforts to detect and prevent post-transplant malignancies.

Authorship

MSK: designed this study. MKJ and MSK: performed this study. SJK, DJJ, KHH, KOJ, and HJK: collected the data. SIK and YSK: contributed important advice to this study. MKJ: wrote the article.

References

1. Stratta P, Morellini V, Musetti C, *et al.* Malignancy after kidney transplantation: results of 400 patients from a single center. *Clin Transplant* 2008; **22**: 424.
2. Buell JF, Gross TG, Woodle ES. Malignancy after transplantation. *Transplantation* 2005; **15**: S254.
3. Andrés A. Cancer incidence after immunosuppressive treatment following kidney transplantation. *Crit Rev Oncol Hematol* 2005; **56**: 71.
4. Kauffman HM, Cherikh WS, McBride MA, Cheng Y, Hanto DW. Post-transplant de novo malignancies in renal transplant recipients: the past and present. *Transpl Int* 2006; **19**: 607.
5. Kasiske BL, Snyder JJ, Gilbertson DT, Wang C. Cancer after kidney transplantation in the United States. *Am J Transplant* 2004; **4**: 905.
6. Available at: http://www.ctstransplant.org/ (last accessed on July 2008).
7. de Jong-Tieben LM, Berkhout RJ, ter Schegget J, *et al.* The prevalence of human papillomavirus DNA in benign keratotic skin lesions of renal transplant recipients with and without a history of skin cancer is equally high: a clinical study to assess risk factors for keratotic skin lesions and skin cancer. *Transplantation* 2000; **69**: 44.
8. Nobbenhuis MA, Walboomers JM, Helmerhorst TJ, *et al.* Relation of human papillomavirus status to cervical lesions and consequences for cervical-cancer screening: a prospective study. *Lancet* 1999; **354**: 20.
9. Vajdic CM, McDonald SP, McCredie MR, *et al.* Cancer incidence before and after kidney transplantation. *JAMA* 2006; **296**: 2823.
10. Imao T, Ichimaru N, Takahara S, *et al.* Risk factors for malignancy in Japanese renal transplant recipients. *Cancer* 2007; **109**: 2109.
11. Hoshida Y, Aozasa K. Malignancies in organ transplant recipients. *Pathol Int* 2004; **54**: 649.
12. Samhan M, Al-Mousawi M, Donia F, Fathi T, Nasim J, Nampoory MR. Malignancy in renal recipients. *Transplant Proc* 2005; **37**: 3068.
13. Ministry of Health & Welfare, Republic of Korea. *Cancer Incidence in Korea 1999–2001*. Korea: Ministry of Health & Welfare, 2005: 38–49 pp.

14. London NJ, Farmery SM, Will EJ, Davison AM, Lodge JP. Risk of neoplasia in renal transplant patients. *Lancet* 1995; **346**: 403.
15. Birkeland SA, Løkkegaard H, Storm HH. Cancer risk in patients on dialysis and after renal transplantation. *Lancet* 2000; **355**: 1886.
16. TY Lee, HK Cho, KH Kim. A study of the completeness of Korean Cancer Registry. *J Korean Soc Health Stat* 2003; **28**: 67.
17. Gutierrez-Dalmau A, Campistol JM. Immunosuppressive therapy and malignancy in organ transplant recipients: a systematic review. *Drugs* 2007; **67**: 1167.
18. Selgrad M, Malfertheiner P, Fini L, Goel A, Boland CR, Ricciardiello L. The role of viral and bacterial pathogens in gastrointestinal cancer. *J Cell Physiol* 2008; **216**: 378.
19. Persing DH, Prendergast FG. Infection, immunity, and cancer. *Arch Pathol Lab Med* 1999; **123**: 1015.
20. Chapman J, Webster AC. *Cancer Report: ANZDATA Registry 2004 Report*: 99 pp. Available at: http://www.anzdata.org.au/ (last accessed on July 2008).
21. Port F. Standardized incidence ratio: the rate of de novo malignancies by site and transplanted organ compared to population-based controls. Paper presented at: *Third Annual ASTS/Winter Symposium*, Miami, FL, 2003.
22. Hoshida Y, Tsukuma H, Yasunaga Y, *et al.* Cancer risk after renal transplantation in Japan. *Int J Cancer* 1997; **71**: 517.
23. Chen J, Cheong JH, Hyung WJ, *et al.* Gastric adenocarcinoma after renal transplantation. *Hepatogastroenterology* 2004; **51**: 895.
24. Shroff R, Rees L. The post-transplant lymphoproliferative disorder – a literature review. *Pediatr Nephrol* 2004; **19**: 369.
25. Cao S, Cox K, Esquivel CO, *et al.* Posttransplant lymphoproliferative disorders and gastrointestinal manifestations of Epstein-Barr virus infection in children following liver transplantation. *Transplantation* 1998; **66**: 851.
26. Birkeland SA, Hamilton-Dutoit S. Is posttransplant lymphoproliferative disorder (PTLD) caused by any specific immunosuppressive drug or by the transplantation per se? *Transplantation* 2003; **76**: 984.
27. Dantal J, Pohanka E. Malignancies in renal transplantation: an unmet medical need. *Nephrol Dial Transplant* 2007; **22**(Suppl. 1): i4.
28. Cockfield SM. Identifying the patient at risk for post-transplant lymphoproliferative disorder. *Transpl Infect Dis* 2001; **3**: 70.
29. Agraharkar ML, Cinclair RD, Kuo YF, Daller JA, Shahinian VB. Risk of malignancy with long-term immunosuppression in renal transplant recipients. *Kidney Int* 2004; **66**: 383.
30. Berger NA, Savvides P, Koroukian SM, *et al.* Cancer in the elderly. *Trans Am Clin Climatol Assoc* 2006; **117**: 147.
31. Mihalov ML, Gattuso P, Abraham K, Holmes EW, Reddy V. Incidence of post-transplant malignancy among 674 solid-organ-transplant recipients at a single center. *Clin Transplant* 1996; **10**: 248.
32. Barrett WL, First MR, Aron BS, Penn I. Clinical course of malignancies in renal transplant recipients. *Cancer* 1993; **72**: 2186.
33. Dharnidharka VR, Sullivan EK, Stablein DM, Tejani AH, Harmon WE, North American Pediatric Renal Transplant Cooperative Study (NAPRTCS). Risk factors for posttransplant lymphoproliferative disorder (PTLD) in pediatric kidney transplantation: a report of the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS). *Transplantation* 2001; **71**: 1065.
34. Diehl V, Hauch P, Harris N. Hodgkin's disease. In: DeVita VT, Hellman S, Rosenberg SA, eds. *Cancer: Principles and Practice of Oncology*. Philadelphia, PA: Lippincott Williams & Wilkins, 2001: 2339 pp.
35. Yarchoan R, Little RF. Immunosuppression-related malignancies. In: DeVita VT, Hellman S, Rosenberg SA, eds. *Cancer: Principles and Practice of Oncology*. Philadelphia, PA: Lippincott Williams & Wilkins, 2001: 2575 pp.
36. Kauffman HM, Cherikh WS, Cheng Y, Hanto DW, Kahan BD. Maintenance immunosuppression with target-of-rapamycin inhibitors is associated with a reduced incidence of de novo malignancies. *Transplantation* 2005; **80**: 883.
37. Campistol JM, Eris J, Oberbauer R, *et al.* Sirolimus therapy after early cyclosporine withdrawal reduces the risk for cancer in adult renal transplantation. *J Am Soc Nephrol* 2006; **17**: 581.

