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# Incidence, Site and Risk Factor of Post-Transplant Malignancies – Analysis of 771 Renal Transplant Recipients for 40 Years in Japanese Single Center

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## Abstract

**Backgrounds:** A number of studies have observed increased cancer incidence rates among renal transplant recipients. However, the interval from transplant and the site of malignancies quite vary by era and region.

**Methods:** We retrospectively reviewed the records of 771 renal transplant recipients in Kyoto Prefectural University of Medicine between 1970 and 2010. 172 were done in conventional era (1970.4-1982.3), and 599 were done in calcineurin inhibiter (CNI) era (1982.4-). Overall incidence, site and risk factor of malignancies were analyzed.

**Results:** A total of 63 (8.2%) kidney recipients developed 66 malignancies. Graft-loss censored cumulative incidence in CNI era at 5, 10 and 20 years were 3.6%, 6.8% and 13.9%, while those in conventional era were 1.8%, 4.9% and 19.5%. Sites of malignancies occurring within three years following transplantation were breast, stomach, uterus, liver, leukemia, adult T cell lymphoma (ATL), Kaposi Sarcoma and post transplant lymphoproliferative disorder (PTLD). Univariate analysis showed age at the time of transplantation (≧50 y.o., OR=7.011, p<0.01), diabetic nephropathy (OR=6.657, p<0.01), ABO-incompatible transplant (OR=5.785, p<0.01) and use of mycophenolate mofetil (OR=4.510, p<0.01) were significant risk factors to develop malignancies within 5 years. Among them, age at the time of transplantation (OR=4.645, p<0.05) and diabetic nephropathy (OR=4.311, p=<0.05) were independent risk factors by multivariate analysis.

**Conclusions:** Thus, recent potent immunosuppressive regimen shortened the interval between malignancy and transplantation, increasing viral-related malignancies. In the long-term follow-up, it is crucial to pay special attention to those who have risk factors to develop them.

**Keywords:** Complication; Immunosuppression; Kidney transplantation; Malignancy

## Introduction

Because newly developed immunosuppressive strategies have steadily reduced the frequency of acute rejection, kidney transplant recipients tends to survive longer than ever with continuous immunosuppression. Therefore, post-transplant malignancy has become an important issue which causes considerable morbidity and mortality [1,2]. The etiology of post-transplant malignancy is believed to be multifactorial and might involve impaired immunosurveillance and depressed antiviral immune activity of kidney recipients. Although conventional immunosuppressive drug have been linked with posttransplant malignancy, newer agents have not and indeed may have antitumor properties [3-6].

Although a number of studies have demonstrated increased cancer incidence rates, the interval from transplant and the site of malignancies were quite different by the era and the region [7-10]. Then, these studies have been limited by relatively small sample sizes, short follow-up intervals or focused on fewer cancer sites. As we have conducted kidney transplantation since 1970, retrospective study of these recipients has been performed to elucidate the incidence, site and risk factor of malignancies after renal transplantation in Japanese population, in which clinical characteristics are different from western countries.

## Materials and Methods

We retrospectively reviewed the records of 771 renal transplant recipients who received the first renal allograft (excluding re-transplant) at Kyoto Prefectural University of Medicine between 1970 and 2010 and recorded the incidence and types of *de novo* malignancies that developed in these patients. The mean age at transplant of all recipients was 35 ± 13 (4-70) years old. 536 (69.5%) were male and 235 (30.5%) were female. 695 (90.1%) were living donor transplant and 76 (9.9%) were deceased donor transplant. They were divided into two groups according to the immunosuppressive era; conventional era (1970.4-1982.3: n=172), when CNI had not been introduced yet, and CNI era (1982.4-: n=599), when CsA or Tac were used in combination with or without antimetabolite and antibody induction.

Cumulative incidence studies were performed with the Kaplan-Meier method. Graft-loss censored cumulative incidence was defined as the incidence among graft survivors under continuing immunosuppression. Therefore, when graft-loss censored cumulative incidence was calculated, the date of graft loss without malignancies was identified as the endpoint of malignancy-free survival and malignancies after induction of dialysis was not counted.

To determine risk factors for malignancy, univariate analysis

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of demographic characteristics, including gender, age at the time of transplantation, pre-transplant chronic renal failure duration, original disease, donor source, blood-type incompatibility, experience of acute rejection and type of immunosuppression used, was first performed with a Cox proportional-hazards model. After examining the relations of individual demographic factors, a Cox proportional-hazards model taking into account interactions among demographic factors was again used to identify risk factors for malignancy using SPSS software. The statistical significance of the difference in non-parametric data was analyzed using Student's *t* test. Statistical significance was set at $P < 0.05$.

## Results

### Site, interval, therapy and prognosis of malignancies

A total of 63 (8.2%) kidney recipients out of 771 developed 66 malignancies. Twenty-seven were included in conventional era and 36 were in calcineurin inhibiter (CNI) era. The mean age at diagnosis of malignancy was 47 ± 11 (12-66) years old. Forty-two (66.7%) were male and 21 (33.3%) were female. Fifty-five (83.3%) were living-donor transplant and eight (16.7%) were deceased-donor transplant. The average interval between transplantation and development of malignancy was 133 ± 89 (7-340) months. The tumors included 13 skin cancers, 12 gastro-intestinal tract cancers, 9 liver cancers, 6 breast cancers, 6 renal cell carcinomas, 5 leukemia, 5 lymphoma and 10 others (Figure 1). Nineteen cases died of cancer, and 5 died of other disease. Nine were living after re-induction into dialysis, and 30 were living with functioning graft. Mortality was high in liver cancer (89%) and leukemia (100%). Of 61 solid tumors, 45 (74%) were treated with surgical resection with or without radiation and/or chemotherapy, while remaining 16 (26%) tumors were not resected because other therapy was suitable or lesion was too advanced to be resected.

### Cumulative incidence of malignancies by era

Cumulative incidence of malignancies of all 771 kidney recipients at 5, 10, 20, 30 years were 2.2%, 4.5%, 10.5% and 13.8%, respectively. Graft-loss censored cumulative incidence, which was calculated to see the incidence of malignancies among graft survivors under continuing immunosuppression, of all recipients in 5, 10, 20, 30 years were 2.8%, 6.3%, 16.3% and 26.2%, respectively (Figure 2a). Graft-loss censored cumulative incidence in CNI era at 5, 10 and 20 years were 3.6%, 6.8% and 13.9%, while those in conventional era were 1.8%, 4.9% and 19.5%, showing early higher incidence in CNI era outstripped by conventional era by 12 years (Figure 2b). Site of malignancies in CNI era occurring within 3 years following transplantation, which was never observed in conventional era, were breast, stomach, uterus, liver, leukemia, adult T cell lymphoma (ATL), Kaposi Sarcoma and post transplant lymphoproliferative disorder (PTLD) (Table 1).

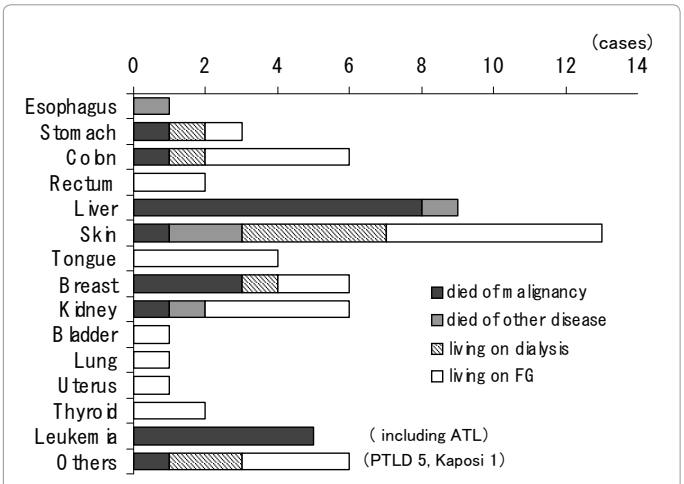


**Figure 1:** Site and prognosis of post-transplant malignancy FG: functioning graft, ATL: adult T-cell leukemia, PTLD: post-transplant lymphoproliferative disorder.

### Risk factor of post-transplant malignancies

Univariate analysis showed conventional immunosuppression (OR=2.912, p<0.01) was significant risk factors to develop malignancies during total period after transplant, while use of CsA (OR=0.494, p<0.01) and basiliximab (OR=0.092, p<0.01) were significant negative risk factors. However, as this analysis included bias influenced by observation period, we next looked at the risk factor to develop malignancies within 5 years after transplant. Univariate analysis showed age at the time of transplantation (≧50 years old, OR=7.011, p<0.01), diabetic nephropathy as an original disease (OR=6.657, p<0.01), ABO-incompatible transplant (OR=5.785, p<0.01) and use of mycophenolate mofetil (MMF) (OR=4.510, p<0.01) were shown to be significant risk factors to develop malignancies within 5 years (Table 2). Among them, age at the time of transplantation (OR=4.645, p<0.05) and diabetic nephropathy (OR=4.311, p<0.05) were found to be independent risk factors by multivariate analysis (Table 3).

## Discussion

Recent progress in immunosuppressive strategy have decreased the rate of acute rejection and substantially improved graft survival in renal transplantation. In spite of these encouraging trends, long-term

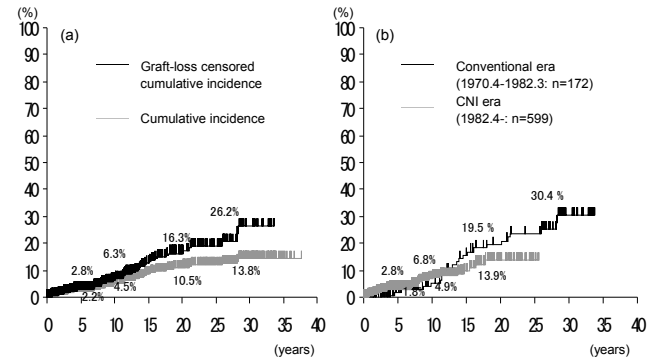


**Figure 2:** (a) Cumulative and Graft-loss censored cumulative incidence of post-transplant malignancy (b) Graft-loss censored cumulative incidence of post-transplant malignancy in conventional and CNI era.

| |
|---|
| Conventional era (1970.4-1982.3) : 0/27 |
| CNI era (1982.4-2007.10) :11/36 |
| Breast (1) |
| Stomach (1) |
| Uterus (1) ---Human Papilloma virus |
| Liver (2) ---Hepatitis C virus |
| Leukemia (1) |
| ATL (1) ---HTLV |
| Kaposi Sarcoma (1) --- HHV-8 |
| PTLD (3) ---EB virus |

CNI: Calcineurin Inhibitor, ATL: Adult T-Cell Leukemia, HTLV: Human T-Cell Leukemia Virus, HHV-8: Human Herpes Virus-8, PTLD: Post-Transplant Lymphoproliferative Disorder, EB: Epstein-Barr

**Table 1:** Malignancy occurring within 3 years following renal transplantation.

| | Total period | | Within 5 years | |
|---|---|---|---|---|
| | OR (95%CI) | P | OR (95%CI) | p |
| Male | 0.866 (0.501-1.498) | 0.607 | 1.322 (0.422-4.144) | 0.630 |
| Age (≧50y.o.) | 1.226 (0.634-2.372) | 0.544 | 7.011 (2.560-19.196) | <0.001 |
| Age (≦20y.o.) | 0.484 (0.172-1.365) | 0.161 | 0.492 (0.064-3.774) | 0.486 |
| HD (≧10years ) | 1.275 (0.526-3.091) | 0.590 | 1.716 (0.380-7.737) | 0.476 |
| Preemptive | 0.751 (0.315-1.795) | 0.518 | 2.494 (0.787-7.901) | 0.108 |
| Deceased donor | 0.599 (0.211-1.697) | 0.329 | 1.276 (0.284-5.722) | 0.740 |
| Diabetic Nephropathy | 1.266 (0.436-3.678) | 0.664 | 6.657 (2.045-21.667) | <0.001 |
| AR(+) | 0.813 (0.451-1.466) | 0.490 | 0.554 (0.156-1.963) | 0.353 |
| ABO-i | 1.024 (0.394-2.657) | 0.961 | 5.785 (1.940-17.244) | <0.001 |
| Immunosuppression | | | | |
| Tac | 0.701 (0.338-1.455) | 0.337 | 2.659 (0.950-7.438) | 0.053 |
| CsA | 0.494 (0.293-0.831) | 0.007 | 0.692 (0.257-1.865) | 0.465 |
| MMF | 0.606 (0.282 -1.302) | 0.195 | 4.510 (1.663-12.225) | 0.001 |
| Bas | 0.092 (0.022-0.380) | <0.001 | 0.437 (0.098-1.940) | 0.263 |
| Rit | 0.365 (0.049-2.719) | 0.304 | 1.611 (0.206-12.602) | 0.646 |
| Conventional | 2.912 (1.712-4.954) | <0.001 | 0.491 (0.110-2.184) | 0.340 |

OR: Odds Ratio, CI: Confidence Interval, HD: Hemodialysis, AR: Acute Rejection, ABO-i: ABO-incompatible, Tac: Tacrolimus, CsA: Cyclosporine, MMF: Mycophenolate Mofetil, Bas: Basiliximab, Rit: Rituximab. *Conventional: CNI was not applied, but only antimetabolite and steroid was used

**Table 2:** Risk factor for post-transplant malignancy assessed by univariate analysis.

| | OR (95%CI) | p |
|---|---|---|
| Age (≧ 50y.o.) | 4.645 (1.120-10.853) | 0.031 |
| Diabetic Nephropathy | 4.311 (1.078-13.583) | 0.038 |
| ABO-i | 1.313 (0.589-7.527) | 0.252 |
| MMF | 2.112 (0.740 -7.575) | 0.146 |

**Table 3:** Risk factor for post-transplant malignancy within 5 years assessed by multivariate analysis.

survival following transplantation has remained largely unchanged with considerable number of death with functioning graft. High mortality among renal-transplant recipient is attributed mainly to increased risks of cardiovascular disease and malignancy while infectious disease becomes less lethal. In North America [11,12], Europe [13] and Australia/New Zealand [14], the incidence of malignancy among renal transplant recipients ranges from 7% to 14.9%.

In our present follow-up study, the incidence of malignancy was 8.2% in renal transplant recipients. This incidence is slightly higher than the incidence of 6.8% reported in 1998 by Kishikawa et al. [15] and 6% in 2007 by Imao et al. [16] from other Japanese institutes, conceivably reflecting the longer follow-up period as long as up to 40 years in the present study. Thus, a post-transplant period was reported to be a risk factor for the development of malignancy [17]. Therefore, care must be taken to the risk of malignancy in long-term survivors after renal transplantation.

The site of malignancy occurring in our series was quite similar with those reported from other Japanese institutes where gastrointestinal and renal cancers were frequent. The difference was that our most common site was skin while fewer patients had skin cancer in other Japanese institutes. They suggested that the low incidence of skin cancer is a characteristic of Asian patients [16], referring to the Chinese results reported by Tang et al. [18]. The reason why skin cancer was most common in our series as seen in western countries was not obvious, but possible reason was that our previous patients frequently came from south part of Japan where there were much sun exposures.

On the other hand, malignancy occurring in the early period after transplantation had special characteristics. As shown in Table 2, 8 out of 11 malignancies were known to be associated with oncogeneic virus such as human papilloma virus, hepatitis C virus, human T-cell leukemia virus, human herpes virus-8 and Epstein-Barr virus. These results suggested that depressed antiviral immune activity caused by recent immunosuppressive regimen facilitated the occurrence of viral-related malignancy in relatively early period following transplantation in our population.

Multivariate analysis in the present study showed that age at the time of transplantation was independent risk factors to develop malignancies within 5 years. Consistent with our results, 'age at the time of transplantation' has been reported to be a risk factor for malignancy in western countries [11,18-20] and in other Japanese institutes [15,16]. We also found that diabetic nephropathy as the cause of end stage renal disease is clearly a risk factor for malignancy. Although Webster et al. [14] reported otherwise, the risk of malignancies in general population is reported to be increased from earlier stages of glucose metabolism abnormalities, with a linear relationship between cancer risk and plasma insulin levels [21,22], indicating justification of our results.

A correlation between the use of immunosuppressant and the development of malignancy has been reported by many authors. In our results, use of tacrolimus (Tac) was a relatively high risk factor of malignancy in 5 years (OR=2.659, p=0.053), while use of cyclosporine (CsA) was relatively low risk factor (OR=0.692, p=0.465). In experimental model, CsA [23,24] and Tac [25,26] exerted both progressive and suppressive effect for tumor growth. As for clinical data, according to a US multicenter study of renal transplantation [27], the incidence of malignancy was not significantly different in CsA and Tac group. A meta-analysis of 30 recent studies also showed no significant difference between two groups [28]. However, one study showed that the incidence of lymphoma 2 years after transplantation was about double in the Tac group than in the CsA group [29]. It is also reported that the use of Tac is associated with a high risk of PTLD [30]. In contrast, Kauffman et al. [31] found no difference in the incidence of PTLD between CsA and Tac regimen and even found significantly less incidence in the rates of any cancer, nonskin, nonlymphoid solid cancer, and nonmelanoma skin cancer in Tac regimen. Thus, which CNI become more oncogeneic after transplantation is still controversial.

Although conventional immunosuppressive drug have been linked with posttransplant malignancies, newer agents such as MMF [3,4] and sirolimus [5,6] have not and indeed may have antitumor properties. Actually, Leckel et al. [4] showed that MMF prevented receptor-dependent tumor dissemination in vitro. However, in our patients, use of MMF was significant risk factors to develop malignancies within 5 years by univariate analysis, although multivariate analysis did not find it as an independent risk factor. It is possible that depressed antiviral immune activity by MMF might facilitate the occurrence of viral-related malignancy which was seen relatively early period following transplantation. However, another interpretation of these results was that the cumulative dose of immunosuppression was a risk for malignancies, therefore ABO-incompatibility and MMF itself might not be the point, but the higher dose of cumulative immunosuppression used in these patients.

The limitation of present study is that the number of the population is quite small, so the conclusions about risk factors to develop malignancies should be evaluated cautiously. However, this study is relevant because most of these kinds of studies are from western countries.

In conclusion, our results demonstrated that recent potent immunosuppressive regimen shortened the interval between

transplantation and increased viral-related malignancies. In the long-term follow-up, it is crucial to pay special attention to the groups that have risk factors to develop malignancies. More importantly screening for malignancy should be performed periodically after renal transplantation to detect malignancy at an early stage [32-35].

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