Outcomes of Kidney Transplantation Performed by Urologists in Collaboration with Nephrologists: a Small Single Center Experience

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Abstract

To evaluate the outcomes of kidney transplantations performed by general urologists in collaboration with nephrologists by analyzing the clinical results. We retrospectively reviewed the medical records of 164 kidney transplantations performed at our center from July 1998 to December 2015. We obtained demographic data, anthropometric information, laboratory findings, and patient/graft survival data. The recipients included 99 (66.1%) men with a median ± standard deviation (SD) age of 41 ± 14.5 years, whereas the donors included 65 (40.1%) men with a median ± SD age of 59 ± 10.8 years. Among the recipients, chronic glomerulonephritis (non-biopsied glomerular injury, n = 42) was the most common primary disease that progressed to end-stage kidney disease, followed by IgA nephropathy (n = 33), and diabetic nephropathy (n = 20). Kaplan-Meier graft survival rate was 83.7% at 10 years after transplantation, which is comparable to the nationwide rate of 84.9% at 10 years after living-donor kidney transplantation. Graft survival rate in the ABO blood type incompatible subgroup was 90.5% at 10 years after transplantation, which was not significantly different from 82.2% rate in the ABO blood type compatible subgroup. Donors aged ≥60 years were defined as old-age donors. This old-age donor subgroup showed a significantly lower graft survival rate of 70.5% at 10 years after transplantation compared with 93.1% in donors aged less than 60 years (p = 0.02). Although the number of kidney transplantations at our center was small, outcomes comparable to nationwide outcomes could be achieved through the collaboration of urologists with nephrologists.

Key words
kidney transplantation, urologist, nephrologist

Introduction

In Japan, kidney transplantation has traditionally been performed by surgeons or urologists; however, nephrologists have actively begun to cooperate in kidney transplantations as a part of the medical team, contributing to improvement in the quality of kidney transplantation and reducing the burden of surgeons and urologists in performing the procedure. At our center, kidney transplantations are performed by urologists in collaboration with nephrologists. Nephrologists manage the chronic kidney disease patients from diagnosis to end-stage kidney disease on hemodialysis or peritoneal dialysis. Preoperatively, kidney donor and recipient candidates are evaluated by nephrologists, whereas urologists play a key role in donor and recipient surgery and perioperative management including control of immunosuppression. Postoperatively, donors and recipients were followed up through collaboration between the urologists and nephrologists. We retrospectively reviewed the outcomes of kidney transplantation at our center by analyzing the clinical results in both donors and recipients.
Patients and Methods

From July 1998 to November 2015, 162 consecutive kidney transplantations (154 living and 8 cadaveric donors) were performed at our center. Immunosuppression was induced using treatment with the following drugs: calcineurin inhibitors (tacrolimus or ciclosporin), mycophenolate mofetil, basiliximab, steroids for ABO blood type-compatible recipients, and those drugs plus rituximab with double filtration plasmapheresis and/or plasma exchange sessions for ABO blood type incompatible recipients. Information on demographics, anthropometric information, laboratory findings, and patient/graft survival data was retrospectively investigated for all 164 donors and recipients, and data related to graft function were investigated for the 147 recipients with a functioning graft.

Statistical analyses

We used the Cox proportional hazards model to estimate the risk of graft loss. Survival curves were generated by the Kaplan-Meier method, with results considered significant at the 5% level (p < 0.05). All statistical calculations were analyzed using JMP version 9 for Windows software. This study was performed with the approval of the local institutional ethical committee (approval number 3227).

Results

Donor and recipient age, original disease of end-stage kidney disease, duration of dialysis, and donor source

The recipients included 99 (66.1%) men with a median ± standard deviation (SD) age of 41 ± 14.5 years, and the donors included 65 (40.1%) men with a median ± SD age of 59 ± 10.8 years. Fig. 1a shows the original diseases of the recipients. Chronic glomerulonephritis (non-biopsied glomerular injury, n = 42) was the most common primary disease that progressed to end-stage kidney disease, followed by IgA nephropathy (n = 33), diabetic nephropathy (n = 20), and nephrosclerosis (n = 12). Fig. 1b indicates the duration of dialysis. The median ± SD duration of dialysis was 19.7 ± 59.6 months, including 22 pre-emptive kidney transplantations. An analysis of the relationship of the donors with the recipients is shown in Fig. 1c. Of the 164 donors, mothers (n = 52) were the most common donors, spouses (n = 49) were the second common and cadaveric donor accounted for only 5% of the donors owing to the extreme shortage of cadaveric donors in Japan.

Patient and graft survival rates

Kaplan-Meier survival rates of the recipients were 98.2%, 96.3%, and 95.0% at 1, 5, and 10 years after transplantation, respectively. Overall graft survival rates in the recipients were 96.3%, 92.2%, and 84.6% at 1, 5, and 10 years after transplantation, respectively, which are comparable to the respective nationwide rates of 97.2%, 92.3%, and 84.9% at 1, 5, and 10 years after living-donor kidney transplantation. The respective graft survival rates at 1, 5 and 10 years at transplantation in the ABO blood type compatible subgroup were 96.8%, 90.9%, and 82.2% and were not different from those in the ABO blood type incompatible subgroup at 94.3%, 90.5%, and 90.5%. Donors aged 60 years or older were defined as old-age donors, and this old-age donor subgroup showed significantly lower graft survival rates of 93.3%, 87.9%, and 70.5% at 1, 5, and 10 years after transplantation, respectively, than those of donors aged less than 60 years with respective survival rates of 98.8%, 95.6%, and 93.1% after 1, 5, and 10 years of transplantation (log-rank, p = -0.02).

Other investigated factors did not affect the graft survival rate (Table 1).

Pre- and post-transplant body weight of the recipients

Bodyweight of the recipients significantly increased from a preoperative weight of 59.1 ± 13.6 (37.3–111.0) kg to 61.9 ± 15.6 (33.5–111.0) kg post-operatively (p = 0.0031).

Post-transplant serum creatinine level and estimated glomerular filtration rate (eGFR)

Post-transplant levels of serum creatinine and the eGFR are shown in Fig. 3. Male recipients tended to have a higher serum creatinine level than female recipients although the eGFR values were similar.

Blood pressure of the recipients in the outpatient clinic

In the outpatient follow-up clinic, 80% of the recipients needed antihypertensive drugs. Mean blood pressure of the male recipients was controlled to 125 (±10.8)/79.3 (±8.2) mmHg, whereas that of the female recipients was controlled to 117 (±12.3)/74.3 (±9.8) mmHg. Calcium channel blockers were the most commonly administered antihypertensives, comprising of 42% of the total antihypertensives administered. Angiotensin receptor blockers were also commonly used, accounting for 41% of all antihyper-
Fig. 1a  Original disease of the recipients in ESKD

Fig. 1b  Duration of dialyses

Fig. 1c  Donor source
Fig. 2  Overall patient and graft survival rate (n = 164)

Table 1. Subgroup Analysis of Graft Survival Rate

| Factor                      | Yes | No | Kaplan-Meier analysis | Cox proportional hazard analysis |
|-----------------------------|-----|----|-----------------------|----------------------------------|
|                             |     |    | 10-year survival      | Log rank | HR | p   | 95%CI |
| Diabetic                    |     |    |                       |          |    |     |      |
| Yes                         | 86.1|    | 0.4690                | Diabetic | 0.94| 20.52|
| No                          | 84.9|    | 0.8363                | Unrelated donor | 0.84| 3.27 |
| Relationship                |     |    |                       |          |    |     |      |
| Yes                         | 84.9|    | 0.8363                | Unrelated donor | 0.84| 3.27 |
| No                          | 83.9|    |                       |          |    |     |      |
| Donor age                   |     |    |                       |          |    |     |      |
| >=60                        | 72.4|    | 0.0267*               | >=60     | 0.027*| 10.440|
| <60                         | 93.4|    | 3.20                  |          |    |     |      |
| Blood type                  |     |    |                       |          |    |     |      |
| Compatible                  | 83.6|    | 0.5755                | Incompatible | 0.588 | 3.98 |
| Incompatible                | 90.8|    | 0.724                 |          |    |     |      |
| Acute rejection             |     |    |                       |          |    |     |      |
| Yes                         | 89.4|    | 0.832                 | AR+      | 0.830 | 2.732 |
| No                          | 83.1|    | 0.872                 |          |    |     |      |
| Cytomegalovirus infection   |     |    |                       |          |    |     |      |
| Yes                         | 86.1|    | 0.991                 | CMV+     | 0.992 | 3.353 |
| No                          | 86.1|    | 1.007                 |          |    |     |      |
| Body mass index             |     |    |                       |          |    |     |      |
| >=25                        | 82.1|    | 0.798                 | >=25     | 0.801 | 3.413 |
| <25                         | 86.4|    | 1.161                 |          |    |     |      |
| Donor nephrectomy           |     |    |                       |          |    |     |      |
| Laparo                      |     |    |                       | Laparo   | 0.203 | 1.460 |
| Open                        |     |    |                       |          |    |     |      |

Abbreviations; HR, hazard ratio; CI, confidence interval

**Factors related to metabolic syndrome**

Table 2 lists the factors related to metabolic syndrome in the recipients. Ischemic heart disease, that required intervention with coronary artery catheterization was encountered in 7.8% of the male recipients and 1.8% of the female recipients. All recipients who required coronary intervention are alive with a functioning kidney graft and no recurrence of ischemic heart disease.

**Serum uric acid level**

Serum uric acid level in the male recipients was controlled to 6.4 ± 1.3 mg/dL, whereas that in the female recipients was controlled to 5.8 ± 1.1 mg/dL. Febuxostat was administered to 78.9% of the recipients with hyperuricemia, and 21.9% were administered allopurinol to control serum uric acid levels. No recipient experienced uric acid urinary tract stone disease or attacks of gout.
Serum Cr level (mg/dl)

Fig. 3 Post-transplant serum creatinine level and eGFR

Table 2. Metabolic Syndrome-related Factors

| Factor                              | Male (n = 90) | Female (n = 57) | Total (n = 147) |
|-------------------------------------|---------------|----------------|-----------------|
| Obese                               | 33 (36.7%)    | 15 (26.3%)     | 48 (32.6%)      |
| BMI > 25                             |               |                |                 |
| Post-transplant diabetes mellitus   | 21 (23.3%)    | 6 (10.5%)      | 32 (21.8%)      |
| New-onset diabetes after transplantation | 3 (3.3%)     | 3 (5.3%)       | 6 (4.1%)        |
| Hypertension (use of anti-hypertensives) | 76 (84.4%)   | 41 (71.9%)    | 117 (79.6%)     |
| Dyslipidemia (use of statins)       | 40 (44.4%)    | 25 (43.9%)     | 65 (44.2%)      |
| Ischemic heart disease              | 7 (7.8%)      | 1 (1.8%)       | 8 (5.4%)        |

Post-transplant viral infections in the recipients

Table 3 summarizes information regarding the post-transplant viral infections in the recipients. Cytomegalovirus infection was the most common infection, accounting for 76% of all infections.

Post-transplant malignancies in the recipients

Table 4 summarizes post-transplant malignancies that developed in 12 recipients. One recipient with colon cancer, a 63-year-old man, died of the disease after surgery and chemotherapy. Another recipient with thyroid cancer, a 52-year-old woman, died from sepsis on dialysis without evidence of cancer. The other recipients have functioning grafts and are alive with no evidence of recurrence or metastases of their cancers.

Recipient deaths

Seven (4.3%) of the 164 recipients died after transplantation. Cause and time of death post-transplant are summarized in Table 5. We could not find any tendency related to the causes of deaths of the re-
Table 3. Post-transplant Viral Infections in the Recipients

| Virus | n | Treatment | Outcome               |
|-------|---|-----------|-----------------------|
| CMV   | 45| Reduction of immunosuppression + anti-CMV | Cured in all cases |
| BK    | 4 | Reduction of immunosuppression | Alive with functioning graft in all cases |
| JC    | 1 | None | Stable graft function |
| VZV   | 3 | Reduction of immunosuppression + aciclovir | Cured in all cases |
| EBV   | 1 | Reduction of immunosuppression | Alive with functioning graft |
| HBV   | 0 | Two recipients received prophylactic entecavir | Alive with normal liver and graft function |
| HCV   | 0 | Two recipients received prophylactic entecavir | Alive with normal liver and graft function |

Table 4. Post-transplant Malignancies in the Recipients (1)

| Age | Sex | Organ                        | Years post-transplant | Treatment | Outcome               |
|-----|-----|-------------------------------|-----------------------|-----------|-----------------------|
| 34  | M   | Bilateral upper UT and urinary bladder | 9                     | Surgery Chemotherapy | Alive without cancer |
| 65  | M   | Native kidney cancer          | 16                    | Surgery   | Alive without cancer |
| 52  | F   | Thyroid                       | 6                     | Surgery   | Died without cancer  |
| 49  | F   | Breast (bilateral)            | 9                     | Surgery Radiation | Alive without cancer |
| 34  | F   | Ovary                         | 4                     | Surgery Chemotherapy | Alive without cancer |
| 41  | F   | Colon                         | 6                     | Surgery   | Alive without cancer |
| 64  | M   | Thyroid                       | 9                     | Surgery   | Alive without cancer |
| 49  | F   | Cervix                        | 2                     | Surgery   | Alive without cancer |
| 43  | M   | Skin Dermatofibrosarcoma protuberans | 6                  | Surgery   | Alive without cancer |
| 63  | M   | Colon                         | 6                     | Surgery Chemotherapy | Died of cancer |
| 46  | M   | Brain (gliosarcoma)           | 1                     | Surgery Chemotherapy | Alive without cancer |
| 51  | F   | Stomach                       | 5                     | Surgery   | Alive without cancer |

Discussion

This paper reports the overall results of kidney transplantation at our center, which is performed in collaboration with urologists and nephrologists. Because kidney transplantation is already an established
cipients.

**Newly developed disease in the donors**

Table 6 lists newly developed disease in the donors. No donation-related disease was observed.
Table 5. Recipient Deaths

| Age/Sex | Cause of death                                      | Time post-transplant |
|---------|----------------------------------------------------|----------------------|
| 40/male | Cardiopulmonary arrest (unknown cause)              | 26 days              |
| 20/male | Traffic accident                                    | 4 years              |
| 68/male | Infectious endocarditis                             | 62 days              |
| 68/female | Thrombotic microangiopathy                       | 10 days              |
| 63/male | Colon cancer                                       | 6 years              |
| 67/female | Interstitial lung disease                        | 3 years              |
| 52/female | Sepsis due to blood access catheter (on hemodialysis) | 13 years            |

Table 6. Newly Developed Disease in Donors

| Disease               | N | Treatment          | Outcome                        |
|-----------------------|---|--------------------|--------------------------------|
| Cerebral infarction   | 1 | Medical            | Cured                          |
| Prostate cancer       | 2 | Radiation (1) Anti-androgen (1) | Relapse: 0                     |
| Colon cancer          | 1 | Chemotherapy       | Died 2 years after donation    |
| B cell lymphoma       | 1 | Chemotherapy       | Cured                          |
| Pyogenic osteomyelitis| 1 | Antibiotics        | Died 9 years after donation    |
| Colon cancer          | 1 | Endoscopic submucosal dissection | Completely resected          |

Although various factors can affect the long-term outcomes of kidney transplantation such as the presence of acute rejection\(^1\), HLA mismatches\(^2\), and graft size mismatches\(^3\), we found only donor age to be a predictive factor for graft survival in our data. This may be due to the small sample size of our series, the shorter duration of follow-up, and the non-detection of subclinical chronic antibody-mediated rejection. We understand that early detection of antibody production in recipients and pathological confirmation of antibody-mediated rejection followed by adequate anti-rejection therapy should be immediately introduced in our transplantation program.

Kidney grafts from old age donors have lower survival rates because older donors have naturally impaired kidney function\(^4\). Our data showed the
same tendency in the recipients, thus, supporting the findings of previous reports. We are preparing a pathological study of zero and one hour graft biopsies to analyze the reasons for impaired graft function and the lower survival rate in recipients receiving a kidney from old-age donors.

Although the number of recipients was small, we found that graft survival in the ABO blood type-incompatible kidney transplant recipients was the same or better than that in the ABO blood type-compatible recipients. Use of low dose of rituximab (100 mg/kg body weight x 2 preoperatively) and the reduction of antibodies with double filtration plasmapheresis or plasma exchange, which we previously reported appears to be a safe and effective method to establish a standard regimen for an ABO blood type-incompatible kidney transplantation.

To improve the long-term results of kidney transplantation, medical control of factors related to metabolic syndrome including blood pressure, body weight, blood glucose level, serum lipid level, and serum uric acid level, are thought to be essential for preventing graft dysfunction and loss due to non-immunological reasons. Because physicians are specialized in these areas, it is reasonable that kidney transplant recipients should be followed up in cooperation with nephrologists. We previously reported that the blood pressure of transplant recipients was better controlled when we worked in cooperation with nephrologists during follow-up. Although the values of these above-mentioned parameters in our recipients were almost all acceptable, whether the long-term graft survival rate can be improved based on this level of control of factors related to metabolic syndrome is not known. Longer follow-up is needed.

Of our 164 kidney transplant recipients, 12 (7.3%) were diagnosed as having malignancy. As the follow-up period increases, malignancies are more likely to occur in kidney transplant patients, so we have to carefully monitor for malignancies, especially in recipients with follow-up periods of 10 years or longer. Early detection and early treatment are mandatory for recipient malignancies.

We reported outcomes of kidney transplantation at our center that were generally comparable to the nationwide results. Nevertheless, efforts are still required to improve the outcomes of kidney transplantations in the future, especially by focusing on chronic antibody-mediated rejection, factors related to metabolic syndrome, and de novo malignancies after transplantation.

References

1) Lentine KL, Gheorghian A, Axelrod D, Kalsekar A, L’italien G, Schnitzler MA. The Implications of Acute Rejection for Allograft Survival in Contemporary U.S. Kidney Transplantation. Transplantation 2012; 94: 369–376.
2) Süsal C, Opelz, G. Current role of human leukocyte antigen matching in kidney transplantation. Current Opinion in Organ Transplantation 2013; 18: 438–444.
3) Dick AS, Mercer LD, Smith JM, McDonald RA, Young B, Healey PJ. Donor and recipient size mismatch in adolescents undergoing living donor renal transplantation affect long-term graft survival. Transplantation 2013; 96: 555–559.
4) Lim WH, Clayton P, Wong G, Campbell SB, Cohney S, Russ GR, Chadban SJ, McDonald SP. Outcomes of Kidney Transplantation From Older Living Donors. Transplantation 2013; 95: 106–113.
5) Chikaraishi T, Sasaki H, Tsutsumi H, Miyano S, Nakazawa R, Nakano T, Kitajima K, Kudo H, Takahashi T, Sato Y, Kimura K. ABO Blood Type Incompatible Kidney Transplantation Without Splenectomy Prepared With Plasma Exchange and Rituximab. Transplant Proc 2008; 40: 3445–3447.
6) Matsui K, Sasaki H, Chikaraishi T, Shibagaki Y, Hanada K, Yasuda T, Kimura K. Impact of internist’s participation in the management of kidney transplant recipients. Ishoku 2011; 46: 335–342.