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KIDNEY RESEARCH AND CLINICAL PRACTICE

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Changing pattern and safety of pretransplant malignancy in kidney transplant recipients

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Introduction

- Since the first kidney transplantation (KT) was successfully performed between identical twins in a Western country in 1954, advances in immunosuppressive (IS) agents have improved short-term outcomes of allografts, reducing acute rejection.
- Unfortunately, IS agents also cause many unwanted complications, including:
  - increased tumors
  - new-onset diabetes after transplantation
  - opportunistic infections
  - hair loss
  - neuropathy
  - paradoxically, nephrotoxicity

Introduction

- Malignancy in kidney transplant recipients (KTRs) is an important issue:

  The third most common cause of death

  Related to graft and patient survival during the late period after KT

- Previous reports have revealed a higher incidence of cancer in KTRs than in the general population worldwide.
- Therefore, present guidelines recommend regular surveillance to screen for cancer in KTRs.

Introduction

- Due to advances in medical therapy, an extension of life span has been achieved in populations worldwide, including patients with end-stage renal disease (ESRD).
- In addition to an increasingly aging population, advances in medical equipment and an accumulation of experience have led to an increase in the number of patients with cancer diagnosis and treatment, in parallel with the increase in tumor incidence associated with aging.
- The incidence of cancer has also increased over time in Korea.
- **As a result, the number of KT candidates receiving cancer treatment before transplantation is increasing.**

Introduction

- Guidelines for KT candidates emphasize more frequent cancer screening among older patients.
- **Patients with pretransplant malignancies were not considered KT candidates in the past.**
- An increase in cancer-free survival has increased the demand for transplant among ESRD patients with a previous malignancy to achieve freedom from lifelong dialysis.
- Therefore, the consensus KT guidelines were changed to permit transplantation on a **case-by-case** basis.

Methods

- Retrospective, observational study
- The Catholic University of Korea, Seoul St. Mary's Hospital, Keimyung University Kidney Institute.
- In each center, both pre- and posttransplant data of KT included donor and recipient information registered in a computerized system.
- KTRs with **pretransplant** malignancies were **divided into three eras** based on the progression of the nationwide regular surveillance system in Korea, the first era as before and including 1998, the second era as between 1999 and 2006, and the third era as 2007 and beyond

Methods

We investigated the proportion of KTRs with:

- Pretransplant malignancies
- Cancer type of pretransplant malignancies
- Cancer-free intervals until KT in KTRs with pre- transplant malignancies
- posttransplant outcomes
- Eight KTRs among these patients experienced allograft failure.
- All tumors were confirmed by histopathological and radiological findings.
- Patients were diagnosed with only one cancer type.

Immunosuppression Therapy

- Maintenance IS agents in the two centers consisted of azathioprine and corticosteroids until 1984.
- After that time, IS agents consisted of cyclosporine, as a calcineurin inhibitor, combined with corticosteroids, with or without azathioprine.
- Tacrolimus was introduced in 1998.
- Mycophenolate mofetil was introduced in 1999 for treatment of patients.
- However, since 2001, mycophenolate mofetil has been administered as an initial maintenance strategy.

Immunosuppression Therapy

- **The target trough levels during the first 3 months:**

a. tacrolimus: 8 to 12 ng/mL

b. Cyclosporine: 150 to 300 ng/mL

- **The target trough level after the 3rd month:**

a. Tacrolimus 3 to 8 ng/mL

b. Cyclosporine 50 to 100 ng/mL

Induction therapy and desensitization strategy

- In May 2002, **basiliximab →** was introduced for most patients.
- **Anti-thymocyte globulin →** in highly immunized patients.
- At both centers, in 2009, a tailored desensitization strategy was initiated with **combination** therapy consisting of **rituximab, plasmapheresis**, and **intravenous immunoglobulin** for **ABO-incompatible** KT and for transplantation in **highly sensitized** patients.

Results

Table 1. Clinical characteristics of total patients before KT

Characteristic	Total (1969–2016, n = 3,748)	First era (1969–1998, n = 1,591)	Second era (1999–2006, n = 638)	Third era (2007–2016, n = 1,519)	*P* value
Male	2,267 (60.5)	1,042 (65.5)	366 (57.4)	859 (56.6)	< 0.001
Age at KT (yr)	40.6 ± 12.3	36.1 ± 11.7	39.4 ± 11.1	45.9 ± 11.5	< 0.001
Dialysis modality (HD/PD/pre-emptive)	2,685/617/443 (71.6/16.5/11.8)	1,227/205/156 (77.1/12.9/9.8)	464/132/42 (72.7/20.7/6.6)	994/280/245 (65.4/18.4/16.1)	< 0.001
Dialysis vintage (months)	30.4 ± 42.9	15.1 ± 18.8	28.0 ± 38.1	48.8 ± 55.5	< 0.001
Primary renal disease					
Chronic GN	2,373 (63.3)	1,293 (81.3)	411 (64.4)	669 (44.0)	< 0.001
DM	408 (10.9)	60 (3.8)	54 (8.5)	294 (19.4)	
HTN	328 (8.8)	101 (6.3)	42 (6.6)	185 (12.2)	
ADPKD	97 (2.6)	12 (0.8)	15 (2.4)	70 (4.6)	
SLE	52 (1.4)	7 (0.4)	13 (2.0)	32 (2.1)	
Other	85 (2.3)	26 (1.6)	26 (4.1)	33 (2.2)	
Unknown	404 (10.8)	91 (5.7)	77 (12.1)	236 (15.5)	

Data are presented as number (%), mean ± standard deviation, or number only.

ADPKD, autosomal dominant polycystic kidney disease; DM, diabetes mellitus; GN, glomerulonephritis; HD, hemodialysis; HTN, hypertension; KT, kidney transplantation; PD, peritoneal dialysis; SLE, systemic lupus erythematosus.

Results

(*Proportion of kidney transplant recipients with pretransplant malignancies)*

- The mean age of the total patients was 40.6 years
- The proportion of males was approximately 60%
- A total of 1.9% (72 patients) of KTRs among the total patients were cured of pretransplant malignancies.
- No patients with cancer underwent transplantation prior to 1998.

Results

A total of 1.1% (7 patients) of KT patients with pretransplant malignancies underwent transplantation between 1999 and 2006.
The percentage of those patients increased to 4.3% (65 patients) during the third era. **The proportion of KTRs with pretransplant malignancies significantly increased over time (P < 0.001).**

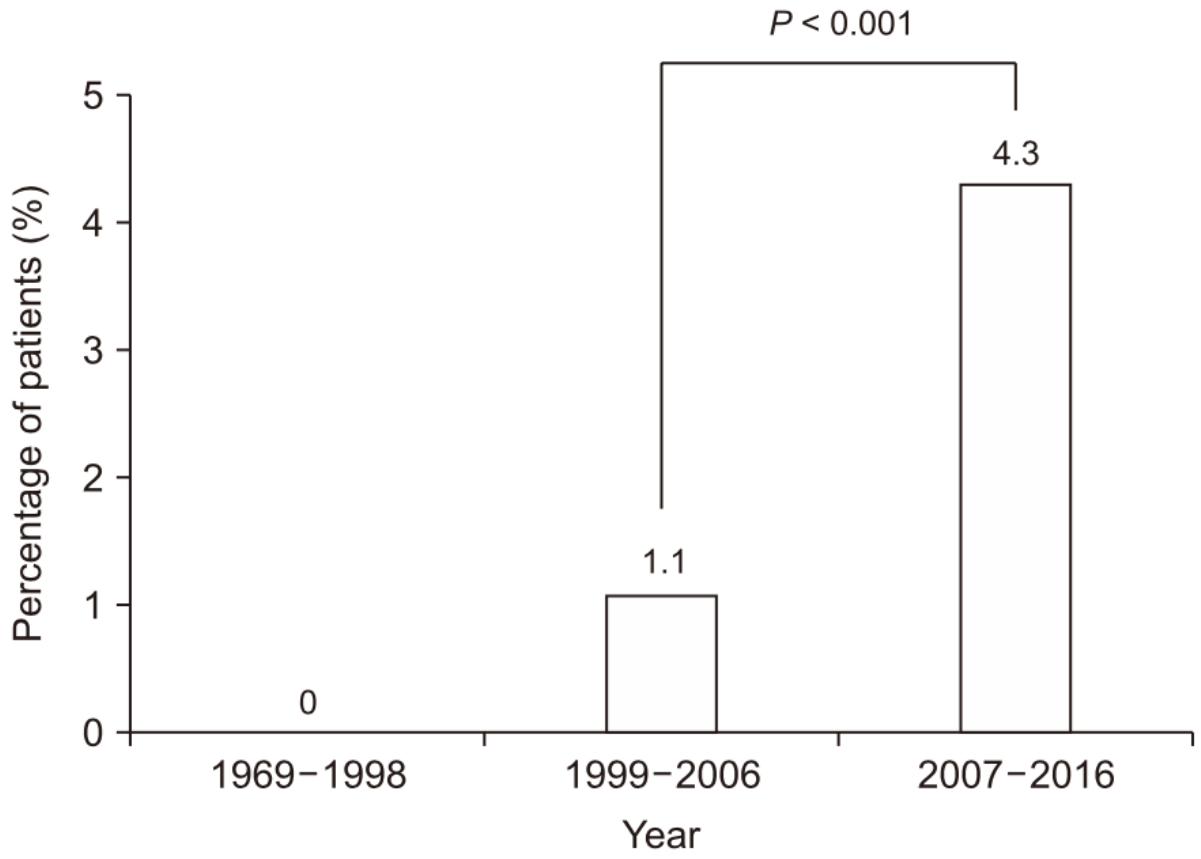


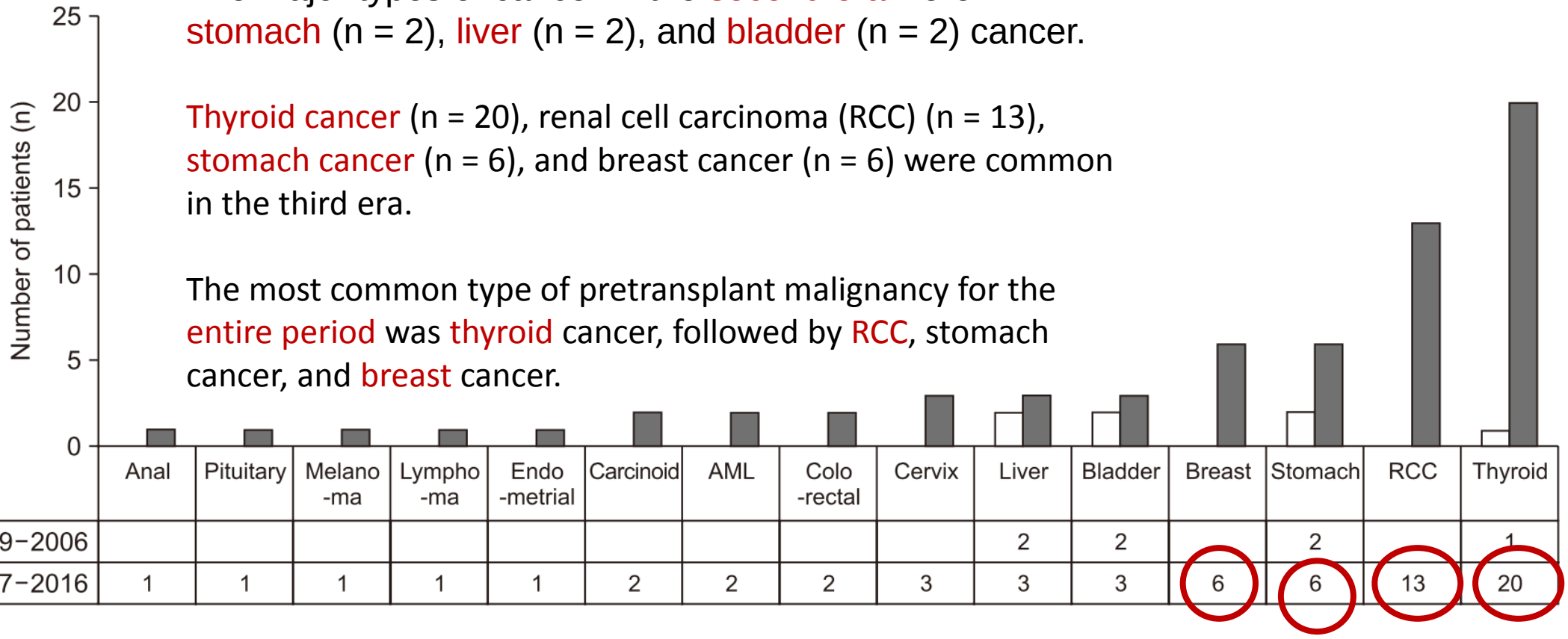
Figure 1. The incidence of pretransplant malignancies in kidney transplant recipients over time.

Results *(changing in cancer type)*

The major types of cancer in the second era were stomach (n = 2), liver (n = 2), and bladder (n = 2) cancer.

Thyroid cancer (n = 20), renal cell carcinoma (RCC) (n = 13), stomach cancer (n = 6), and breast cancer (n = 6) were common in the third era.

The most common type of pretransplant malignancy for the entire period was thyroid cancer, followed by RCC, stomach cancer, and breast cancer.



	Anal	Pituitary	Melano -ma	Lympho -ma	Endo -metrial	Carcinoid	AML	Colo -rectal	Cervix	Liver	Bladder	Breast	Stomach	RCC	Thyroid
1999–2006										2	2		2		1
2007–2016	1	1	1	1	1	2	2	2	3	3	3	6	6	13	20

Figure 2. Changes in pretransplant cancer types in kidney transplant recipients over time.
AML, acute myeloid leukemia; RCC, renal cell carcinoma.

Table 2. Cancer-free interval until KT based on cancer type

Cancer type	Pretransplant case (n)	Mean cancer-free interval until KT (mo)
Pituitary gland	1	112.5
Thyroid	21	47.6
Breast cancer	6	113.0
GI tract		
Stomach	8	71.2
Colorectal	2	96.6
Liver	5	51.5
Urological		
RCC	13	65.0
Bladder	5	30.1
Gynecological		
Cervical	3	163.0
Endometrial	1	135.4
Anal	1	89.0
Hematological		
AML	2	72.5
Lymphoma	1	294.6
Melanoma	1	30.0
Carcinoid tumor	2	25.1

AML, acute myeloid leukemia; GI, gastrointestinal; KT, kidney transplantation; RCC, renal cell carcinoma.

Table 3. Type and incidence of *de novo* and recurrent cancers

	De novo cancer	Recurrent cancer
Stomach	44	
Lymphoma	34	
Thyroid	23	
Colorectal	22	
Liver	18	
Breast	16	1
Cervix	15	
Head and neck	15	
Lung	11	
Bladder	10	2
RCC	10	
Urothelial	8	
Biliary and pancreas	7	
Kaposi sarcoma	7	
Other hematologic malignancy	7	
Skin	3	
Prostate	3	
Ovary	2	
Adrenal	1	
Anus	1	
Thymic carcinoma	1	
MUO	1	
Total	259	3

MUO, metastasis of unknown origin; RCC, renal cell carcinoma.

Discussion

- The results of this study demonstrated that the number of KTRs treated for pretransplant malignancy has increased over time, and **the common cancer types before KT have changed.**
- **The most common cancer types in KTRs with pretransplant malignancies were thyroid cancer and RCC**.
- ***However, the recurrence rate of cancer was not increased in KTRs with pretransplant malignancies.***

The most important finding of this study

- The proportion of KTRs with pretransplant malignancies **increased** over time.
- No cancer patients were reported for approximately 30 years prior to 1998.
- However, the proportion of cancer patients was 1.1% during the next 10 years and markedly increased to 4.3% during the final 10 years.
- **The reason for this trend may be inferred from previous reports based on the regional population.** The **National Cancer Screening Program (NCSP)** was initiated in 1999; Thereafter, the cancer types monitored by the NCSP gradually expanded, and the number of beneficiaries also increased over time.
- The number of participants who were also potential beneficiaries continuously increased during this time.

Discussion

- The national surveillance strategy **includes the entire adult population aged 40 to 66 years for cancer screenings according to the policy of "The Life Transition Period Health Examination at the Korea Association of Health Promotion"** instituted in 2007.
- Additionally, life span extension has occurred in all populations, including ESRD patients.
- Both an increment of the aging population and advances in medical techniques have contributed to cancer diagnoses and cures.

Discussion

- The **outcome** of these factors has been an **increase in the detection of cancer in the regional population over time** .
- In particular, early cancer detection has gradually increased, while the mortality from each type of cancer has decreased.
- These findings suggest **that we may encounter an increased number of KTRs with pretransplant malignancies** in the near future.
- Thus, it is important to address the issue of safety associated with posttransplant cancer development in KTRs with pretransplant malignancies.

Pretransplant malignancies were barriers to KT in the past

- An unestablished guideline for KT candidates cured of pretransplant cancer
- Inappropriate living donors
- A limited number of deceased donors
- The introduction of the desensitization protocol.
- Some patients waited a long time for their children to reach adulthood in order to be a donor or to find another suitable deceased donor.
- Recently, other patients have been allowed to undergo KT after desensitization, resulting in the development of an acceptable strategy to treat KTRs with pretransplant malignancy over time.

The cancer types observed have also changed

- In this study, the most common pretransplant malignancy found was **thyroid cancer**, followed by **RCC**.
- These two cancers have recently shown an increasing incidence.
- Indeed, not only was the cancer **incidence** distinct compared to those of other countries, but the **pattern** was different from that in the general population in Korea.
- In domestic studies of CKD patients before dialysis and ESRD patients on dialysis, there were high incidences of colorectal, stomach, kidney, lung, thyroid, breast, prostate, and liver cancers.

The cancer types observed have also changed

- The difference in prevalence of common cancer incidence and pre- transplant malignancy in renal transplant recipients may be related to the **age-related** distribution of carcinoma patients, **the cancer-free interval**, and the **increase in patient condition or mortality between the waiting periods during treatment**.
- The major burden of these cancers affects the NCSP.
- The local population showed the highest incidence of gastric cancer, followed by thyroid, colorec- tal, and lung malignancies over the past 15 years.

The cancer types observed have also changed

- The number of patients with **small thyroid cancers** rapidly increased, and these patients underwent **thyroidectomy** in considerable numbers, according to recent regional data. Therefore, marked increases in thyroid cancer were observed in this study.
- Most subjects in the current study underwent dialysis for **more than 5 years prior to KT**. The presence of ESRD and its duration are independent risk factors for RCC. Therefore, RCC is the second leading cause of pretransplant malignancy in this study.

Interestingly, all thyroid cancer and RCC patients had the same type of cancer, papillary cell type and clear cell type, respectively

The mean cancer-free interval before KT

- **The mean cancer-free interval before KT i**n the total patient group was 70.2 months, which was a substantial cancer-free interval despite the wide range of cancer types.
- Considering previous guidelines, this interval also complied with the criteria.
- Therefore, the favorable results of the current study were possibly due to achieving a cure for each cancer and a sufficient cancer- free interval.

The other interesting finding in the present study was:

- The lack of a significant difference in the cancer incidence of KTRs with pretransplant malignancies compared to that of KTRs without pretransplant malignancies.
- Only 3 patients in this study developed recurrent cancers
- No patient developed de novo cancer.
- The low incidence of posttransplant malignancies among KTRs with pretransplant malignancies was inconsistent with the results found in other studies.
- This discrepancy may be due to the slightly younger mean age of our patients

conclusion

- The number of KTRs with pretransplant malignancies is gradually increasing, and changes in the type of cancer presented have been observed.
- This observational study suggests that KT in patients who have been cured of **pretransplant malignancies** and have achieved a **sufficient cancer-free** interval **may be safe** with **regard to recurrent and de novo cancer during the posttransplant period**.
- Regular surveillance based on the present guide- line is equally helpful for detecting cancer in KTRs with and without pretransplant malignancies.

conclusion

- **The most important finding of this study was that the proportion of KTRs with pretransplant malignancies increased over time.**
- No cancer patients were reported for approximately 30 years prior to 1998.
- However, the proportion of cancer patients was 1.1% during the next 10 years and markedly increased to 4.3% during the final 10 years.

Some Limitations of This Study

- **First**, cancer staging was not performed in this study.
- **Second**, the follow- up duration may not have been sufficient to analyze the incidence of all tumors. However, the mean follow-up time in the pretransplant malignancy group was approximately 5 years.
- Therefore, this duration may provide evidence that contradicts the high incidence of malignancy reported during the early period after KT in previous studies.

Some Limitations of This Study

- **Third**, despite cancer work-up before KT and regular posttransplant cancer screening, the issue of patient adherence may have affected cancer incidence. Although additional investigations of malignancies before transplantation are needed, we aimed to assess whether transplantation is safe after cancer treatment in KTRs with pretransplant malignancies compared to those without pretransplant malignancies. Nevertheless, the results of the current study showed that pretransplant cancer screening requires different strategies based on regional data, which may allow safer transplantation in KT candidates with pretransplant malignancies.