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Solid-type RCC originating from native kidneys in renal transplant recipients should be monitored cautiously

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Summary

Incidental hemodialysis-related renal cell carcinoma (id-RCC) has been reported to have a good prognosis. However, we have observed rapid progression of id-RCC in some renal transplant patients. Operative indications for id-RCC detected via computed tomography (CT) immediately before renal transplantation (RTx) remain unclear. The purpose of this study was to examine the effects of immunosuppression on the progression of solid-type RCC (s-RCC) and cystic-type RCC (c-RCC). We divided 202 patients with id-RCC into four groups as follows: Group 1, s-RCC with RTx (n = 17); Group 2, c-RCC with RTx (n = 27); Group 3, s-RCC without RTx (n = 53); and Group 4, c-RCC without RTx (n = 105). Five-year cancer specific survival (CSS) rates were significantly worse in Group 1 than Group 3 (79.6% and 100%, respectively, P = 0.012), as were non-recurrence rates (NRRs) (59.2 and 100%, respectively, $P < 0.001$). In contrast, 5-year CSS rates were similar in Group 2 and Group 4 (100% and 95.7%, respectively, P = 0.295) as were NRR (100% and 98.7%, respectively, P = 0.230). Solid-type RCC should be removed immediately after RTx, and more carefully monitored for recurrence during follow-up.

Introduction

Patients with end-stage renal disease (ESRD) have a higher incidence of renal cell carcinoma (RCC) than individuals with normal renal function. In Japan, many ESRD patients on long-term dialysis have received renal transplantation (RTx). The mean waiting periods for RTx from a deceased donor is more than 15 years [1]. According to Kasiske *et al.* [2], renal transplant recipients have an approximate 15-fold greater risk of RCC than the general population and a 1.4-fold greater risk than patients on the transplant waiting list. Although patients on long-term dialysis have a high risk of RCC [3], incidental dialysis-related RCC (id-RCC) has a relatively good prognosis and low recurrence rate [4,5]. After removal of tumor, a waiting period of at least 2 years before transplant has been suggested for most types of tumors. For id-RCC, however, there is no recommendation for disease-free intervals before RTx [6] or for post-RTx screening of patients who received radical nephrectomy [7,8]. We performed radical nephrectomy concurrently with or shortly before RTx.

Immunosuppressive therapy can spur rapid progression owing to complex interactions between the effects of depressed immunosurveillance, the actions of pro-oncogenic viruses, and possibly the direct carcinogenic effects of immunosuppressive drugs [9]. We have experienced cases of incidental solid-type RCC (s-RCC) that metastasized shortly after RTx.

In Japan, many incidental RCCs are detected via computed tomography (CT) or ultrasonography in pre-transplant examinations of long-term dialysis patients. We sometimes wonder whether we should first have

nephrectomy and then have enough disease-free intervals before renal transplantation, and how much we should monitor carefully after RTx. To address these issues, we determined the effects of post-RTx immunosuppressive therapy on RCC progression, which seemed to be accelerated in s-RCC.

Materials and methods

We performed a retrospective study to investigate the relationship between immunosuppression after RTx and s-RCC progression. Clinical and laboratory data were obtained from our electronic database and patient medical records. We obtained patients consent and IRB approved (No. 3111).

Patients

From 2000 through 2013, we performed radical nephrectomies on 202 patients with id-RCC. There were no metastases in any areas including the lymph nodes. id-RCC was classified as s-RCC ($n = 70$) or cystic-type RCC (c-RCC) ($n = 132$) according to preoperative CT and macroscopic tumor findings. One reason for this division is that c-RCC such as those associated with acquired cystic disease of the kidney (ACDK) has a good prognosis in renal transplant recipients [10]. Figure 1a shows representative images of s-RCC and c-RCC detected via CT. Figure 1b shows macroscopic images of s-RCC and c-RCC. s-RCC and c-RCC were subdivided as follow: Group 1, s-RCC with RTx ($n = 17$); Group 2, c-RCC with RTx ($n = 27$); Group 3, s-RCC without RTx ($n = 53$); and Group 4, c-RCC without RTx ($n = 105$). Patients in Group 1 and Group 2 ($n = 44$) received renal transplants within two years after or before radical nephrectomy. We compared age, sex, median follow-up period, pathological T (pT) stage, and histological grade and subtype in the four groups. pT stages were similarly combined ('pT1a, b' and 'pT2,3'). Histological grades 1 and 2 were combined and referred to as 'G1, G2'. We also compared overall survival (OS), cancer-specific survival (CSS), and nonrecurrence rate (NRR) between Groups 1 and 3 (to assess s-RCC development in renal transplant recipients versus HD patients) and between Groups 2 and 4 (to assess c-RCC development in renal transplant recipients versus HD patients).

Immunosuppressive regimen

The immunosuppressive regimen used at our institution has been described in detail elsewhere [11,12]. In brief, all 44 recipients received a triple immunosuppressive protocol consisting of tacrolimus (FK), mycophenolate mofetil (MMF), and methylprednisolone (MP). Patients received 0.15 mg/(kg•day) FK for 7 days before RTx; the dose was adjusted to maintain whole-blood trough levels of 8–12 ng/ml for 1–2 months postoperatively and at 7–9 ng/ml thereafter. Patients received 2000 mg/day MMF for 7 days before RTx, and 1000–1500 mg/day 1 month postoperatively depending on white blood cell counts. Patients received 20 mg/day MP for 7 days before RTx and 500 mg/day MP on the day of the operation; the dose was then tapered to 6–8 mg/day within 1–2 months after RTx. If recipients had donor-specific antigen or ABO incompatible state, we performed splenectomies until 2003 and after then administered rituximab during renal transplant surgery for desensitization. We did not administer antithymocyte globulin.

Statistical analysis

All analyses were performed using, JMP PRO software (version 11.2, SAS Institute Inc., Cary, NC, USA). Numerical variables were expressed as mean ± standard deviation and median (range), and categorical variables were expressed as percentages. Differences in continuous and categorical variables were assessed using the Student's *t*-test or the Mann–Whitney *U*-test and chi-squared tests. We evaluated OS, CSS, and NRR during the 5 years after nephrectomy by use of the Kaplan–Meier estimate. Differences between two groups were assessed using the Wilcoxon signed-rank test. We also described details of recurrence patients. P values < 0.05 were considered statistically significant.

Results

Comparative analysis of the survival and recurrence rates in s-RCC (Group 1 versus Group 3)

Table 1a shows the characteristics of Group 1 and Group 3. P values comparing the groups were calculated using the statistical methods noted in the footnotes. Groups 1 and 3 consisted of 76.5% and 71.6% men, respectively ($P = 0.133$). Mean age was 53.1 ± 10.4 in Group 1 and 58.1 ± 11.4 in Group 3 ($P = 0.113$). Mean time between HD and nephrectomy was 173.1 ± 104.3 months in Group 1 and 144.8 ± 98.6 months in Group 3 ($P = 0.315$). Mean follow-up duration was 45.6 ± 43.4 months in Group 1 and 44.7 ± 41.0 months in Group 3 ($P = 0.912$.) As indicated by the P values, none of the above parameters were significantly different between the two groups.

Table 2a shows the post-nephrectomy characteristics of the s-RCC groups. There were no significant difference in pT stage: pT1a, b rates were 76.5% and 86.8%, and pT2,3 rates were 23.5% and 13.2% in Group 1 and 3, respectively ($P = 0.327$). There were also no significant differences in histological grade [76.5% and 90.6% (G1, G2) and 23.5% and 9.4% (G3) in Groups 1 and 3, respectively; $P = 0.153$] or histological subtype [70.6% and 79.3% (clear cell carci-

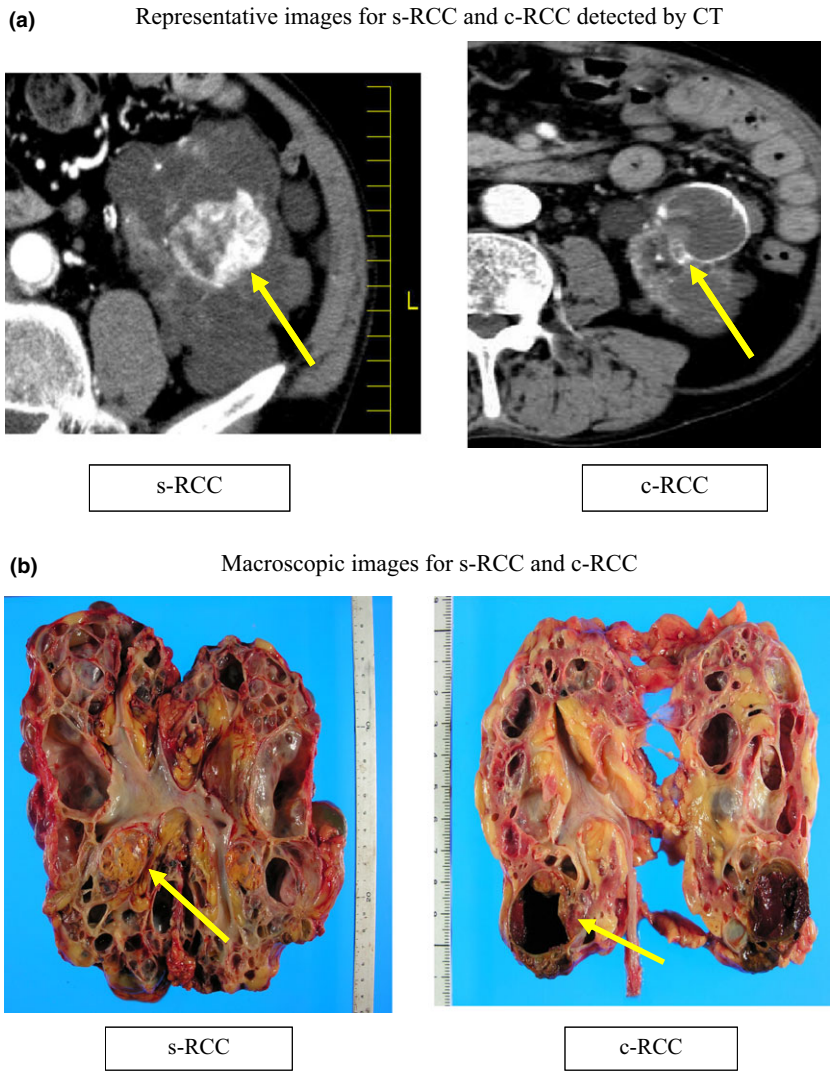

Figure 1 (a) Shows representative images of solid-type RCC (s-RCC) and cystic-type RCC (c-RCC) detected via CT. (b) shows macroscopic images of s-RCC and c-RCC.

noma) and 29.4% and 13.2% (papillary carcinoma) in Groups 1 and 3, respectively; $P = 0.129$]. Death rates were also similar in Groups 1 and 3: 11.8% and 9.4%, respectively ($P = 0.784$). Recurrence rates, however, were notably higher in Group 1 (23.5%) than Group 3 (0%) ($P < 0.001$).

Comparative analysis of the survival and recurrence rates in c-RCC (Group 2 versus Group 4)

Table 1b shows the characteristics of Group 2 and Group 4. Groups 2 and 4 consisted of 88.9% and 83.8% men, respectively ($P = 0.498$). Follow-up duration was 67.9 ± 45.0 months in Group 2 and 57.6 ± 10.9 months in Group 4 ($P = 0.145$). There was a significant difference between Groups 2 and 4 in terms of age (49.3 ± 13.2 years and 57.6 ± 10.9 years, respectively; $P = 0.001$) and time between HD and nephrectomy (128.4 ± 79.4 months and 194.7 ± 99.1 months, respectively; $P = 0.002$).

Table 2b shows the post-nephrectomy characteristics of the c-RCC groups. There was no significant difference in pT stage [88.9% and 94.3% (pT1a, b) and 11.1% and 5.7% (pT2,3) in Groups 2 and 4, respectively; $P = 0.349$] or histological grade [96.3% and 91.4% (G1, G2) in Groups 2 and 4, respectively; $P = 0.358$]. Death rates were also similar in the two groups (7.4% in Group 2 and 15.2% in Group 4, $P = 0.261$), as were recurrence rates (0% in Group 2and 3.8% in Group 4, $P = 0.172$). In contrast, rates of clear cell and papillary RCC were significantly different between Group 2 (88.9% and 11.1%, respectively) and Group 4 (62.9% and 24.8%, respectively) ($P = 0.007$).

Table 1. Characteristics of patients with (a) s-RCC and (b) c-RCC.

	Group 1	Group 3	*P* value
(a)			
N	17	53	
Male (%)	13 (76.5)	38 (71.6)	0.133*
Age	53.1 ± 10.4	58.1 ± 11.4	0.113*
HD, month	173.1 ± 104.3	144.8 ± 98.6	0.315†
Follow-up, months	46.0 ± 43.4	44.7 ± 41.0	0.912†
	Group 2	Group 4	*P* value
(b)			
N	27	105	
Male (%)	24 (88.9)	88 (83.8)	0.498*
Age	49.3 ± 13.2	57.6 ± 10.9	0.001†
HD, months	128.4 ± 79.4	194.7 ± 99.1	0.002†
Follow-up, months	67.9 ± 45.0	49.4 ± 41.4	0.145†

*Chi-squared tests.
†Student's *t*-tests.

s-RCC patients receiving renal transplants have worse CSS rates and NRR than the other groups

OS rates

Five-year OS rates were 79.6% in Group 1 and 83.0% in Group 3 ($P = 0.785$) (Fig. 2a). They were 100% in Group 2 and 83.2% in Group 4 ($P = 0.050$) (Fig. 2b). The differences in OS rates between the paired groups were not significant.

CSS rates

Five-year CSS rates were 79.6% in Group 1 and 100% in Group 3 ($P = 0.012$) (Fig. 3a). They were 100% in Group 2 and 95.7% in Group 4 ($P = 0.295$) (Fig. 3b). The difference between Groups 1 and 3 was significant, whereas the difference between Groups 2 and 4 was not.

Non-recurrence rates

Five-year NRRs were 59.2% in Group 1 and 100% in Group 3 ($P < 0.001$) (Fig. 4a). They were 100% in Group 2 and 98.7% in Group 4 ($P = 0.230$) (Fig. 4b). The difference in NRR between Groups 1 and 3 was highly significant, whereas the difference between Groups 2 and 4 was not significant.

Patients with rapidly progressing recurrent RCC

Table 3 shows the characteristics of patients with rapidly progressing recurrent RCC. There were four such patients in Group 1 and four in Group 4. Three of the four patients in Group 4 had relatively good prognosis. Among all eight patients with recurrence, four had clear cell carcinomas, one had a papillary type 1 tumor, and three had papillary type 2 tumors. The median recurrence-free period was 27 months (range, 17–116 months) in Group 4 but only 8 months (range, 4–30 months) in Group 1. During our observation period, two patients with recurrence in Group 1 (50%) died because of RCC exacerbation within 3 years of nephrectomy; their median survival period was 28.5 months (range, 25–32 months).

Discussion

Immunosuppressive therapy is thought to promote rapid cancer progression and intensive immunosuppression regimens used to prevent and treat allograft rejection may increase malignancy rates [9]. According to previous reports, the risk of RCC was approximately 15–100 times greater in RTx patients than in the general population [2,13]. Other reports, however, suggest that RCC originating in the native kidney of renal transplant recipients have a more favorable outcome than RCC in dialysis patients [14]. Early detection of RCC is important. Previous reports recommend that patients should regularly receive ultrasonography to detect RCC on the native kidney during the first month after RTx and every 5 years thereafter in the absence of cysts (which are the source of RCC), or every 2 years in the presence of cysts [10,15]. Because cysts regress in ACDK patients and kidneys return to baseline atrophic size, renal transplant recipients with RCC may have a better prognosis than ESRD patients without RTx [16]. Thus, it is unclear whether immunosuppressive therapy has an oncogenic effect that causes rapid progression of RCC. Our study showed that s-RCC had lower CSS rates and NRR in patients receiving immunosuppressive therapy (Group 1) than in those undergoing HD (Group 3). However, there was no difference in OS among the four groups. This may reflect the death of most HD patients due to causes other than RCC recurrence and progression (e.g., stroke, cardiovascular disease, and metabolic abnormalities). Our results suggest that s-RCC progressed rapidly under immunosuppressive therapy.

The solid and cystic types of RCC are not well defined or differentiated, and it is possible that s-RCC is a progressed form of c-RCC. To resolve this problem, we compared background of Group 1 and Group 2. We could deny this possibility because pT stage was similar between Group 1 and Group 2 ($P = 0.279$, not reported in tables). Moreover, the favorable CSS rates and NRR of Group 3 indicate that tumor formation *per se* does not affect tumor progression. We therefore suggest that immunosuppressive therapy promotes s-RCC progression in renal transplant recipients. c-RCC, on the other hand, is presumably not affected by immunosuppressive therapy because Group 2 had similar CSS rates and NRR as Group 4.

There are some limitations in our study. First, the patients in Groups 2 and 4 differed significantly in several respects. Patients in Group 2 were younger than those in Group 4, and the duration of HD was longer in Group 4

Table 2. Post-nephrectomy characteristics of the (a) s-RCC groups. (b) c-RCC groups.

			Group 1	Group 3	*P* value
(a)					
N			17	53	
pT stage (%)	T1a, b		13 (76.5)	46 (86.8)	0.327*
	T2–3		4 (23.5)	7 (13.2)	
Histological grade (%)	G1–2		13 (76.5)	48 (90.6)	0.153*
	G3		4 (23.5)	5 (9.4)	
Histology	Clear cell		12 (70.6)	42 (79.3)	0.129*
	Papillary		5 (29.4)	7 (13.2)	
		Type 1	1	0	
		Type 2	4	7	
	Others		0	4 (7.6)	
Death (%)			2 (11.8)	5 (9.4)	0.784*
Recurrence (%)			4 (23.5)	0 (0)	<0.001*
			Group 2	Group 4	*P* value
(b)					
N			27	105	
pT stage (%)	T1a, b		24 (88.9)	99 (94.3)	0.349*
	T2–3		3 (11.1)	6 (5.7)	
Histological grade (%)	G1–2		26 (96.3)	96 (91.4)	0.358*
	G3		1 (3.7)	9 (8.6)	
Histology	Clear cell		24 (88.9)	66 (62.9)	0.007*
	Papillary		3 (11.1)	26 (24.8)	
		Type 1	2	15	
		Type 2	1	11	
	Others		0	13 (12.4)	
Death (%)			2 (7.4)	16 (15.2)	0.261*
Recurrence (%)			0 (0)	4 (3.8)	0.172*

*Chi-squared tests.

than Group 2, which may affect tumor development. However, the CSS rates and NRR in both groups were mostly favorable, suggesting that these differences did not appreciably skew the results.

Second, the number of cases was small, and the follow-up period was relatively short. Determination of whether immunosuppressive therapy causes rapid progression of s-RCC requires additional studies with larger cohorts and longer follow-ups.

Lastly, we did not directly compare Group 1 and Group 2. Such a comparison would clearly tell us whether s-RCC progresses more rapidly than c-RCC under immunosuppressive therapy. We attempted this comparison and found that 5-year CSS rates (79.6% in Group 1 versus 100% in Group 2) and NRR (59.2% in Group 1 versus 100% in Group 2) appeared to be statistically different. However, these groups had some statistical differences relevant to tumor progression, such as nephrectomy time before or after RTx, interval between HD and RTx, and histological grade [9,17]. For these reasons, we did not include data comparing Groups 1 and 2 in our study.

Reducing dose of immunosuppressive agents in renal transplant recipients diagnosed with RCC is a difficult decision. There are no randomized control trials assessing medication reduction or withdrawal in such patients. Reducing immunosuppressant doses can cause acute or chronic rejection and graft failure in some situations and may preclude use of anticancer drug, available to patients with good renal function [8,9]. Recent reports show that mTOR inhibitors have both immunosuppressive and anticancer effects in patients with non-melanoma skin cancer and Kaposi's sarcoma [9,18]. Further examination is needed to assess the

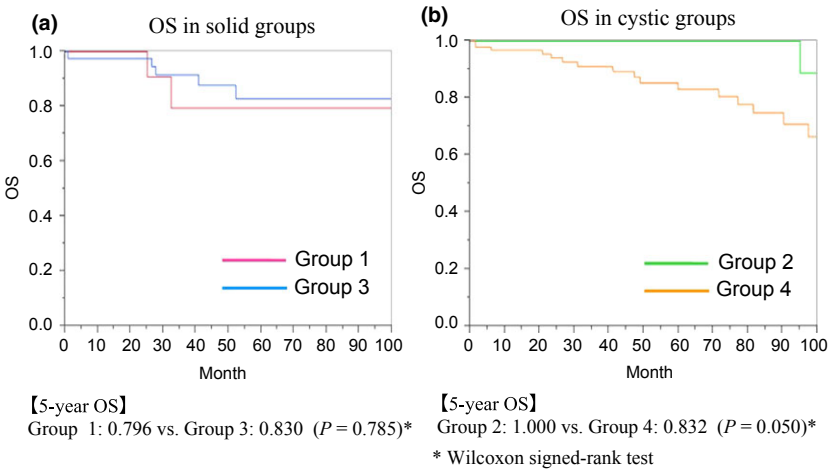

Figure 2 (a, b) Show the OS rates by use of Kaplan–Meier estimate, respectively. (a) Shows that 5-year OS rates were not significantly different between Groups 1 and 3 (79.6% and 83.0%, $P = 0.785$). (b) Shows that 5-year OS rates were marginally significantly different between Groups 2 and 4 (100% and 83.2%, $P = 0.050$).

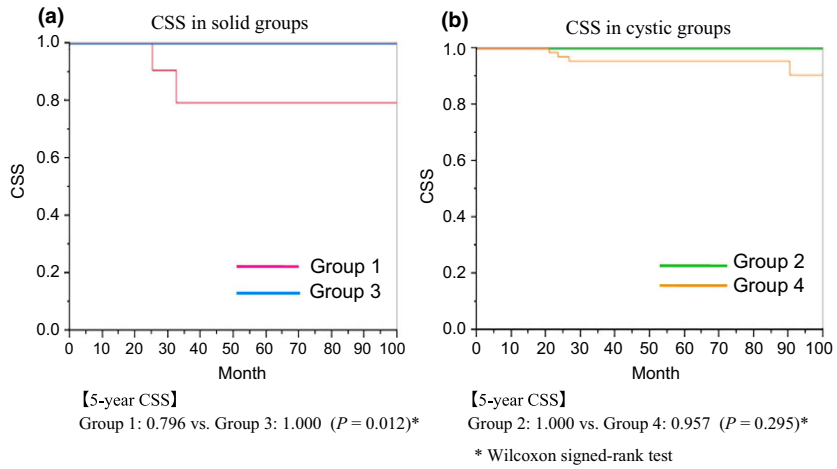

Figure 3 (a, b) Show the CSS rates by use of Kaplan–Meier estimate, respectively. (a) Shows that 5-year CSS rates were significantly different between Groups 1 and 3 (79.6% and 100%, $P = 0.012$). (b) Shows that 5-year CSS rates were not significantly different between Groups 2 and 4 (100% and 95.7%, $P = 0.295$).

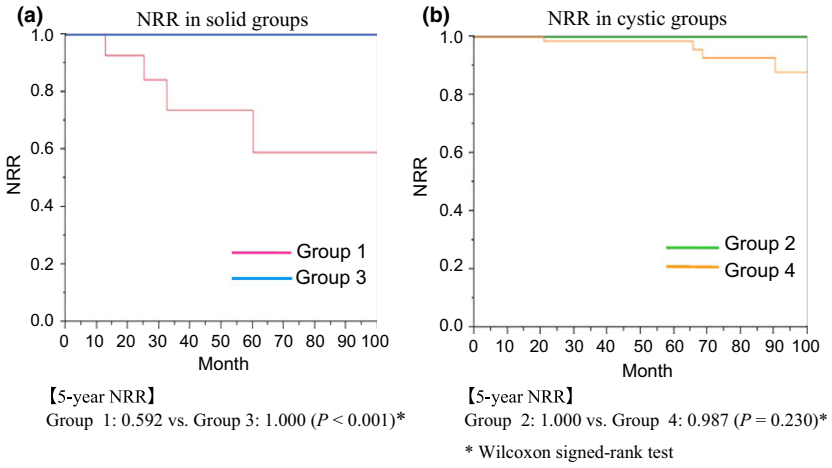

Figure 4 (a, b) Show the NRR by use of Kaplan–Meier estimate, respectively. (a) Shows that 5-year NRRs were significantly different between Group 1 and Group 3 (59.2% and 100%, $P < 0.001$). (b) Shows that 5-year NRRs were not significantly different between Groups 2 and 4 (100% and 98.7%, $P = 0.230$).

Table 3. Characteristics of patients with rapidly progressing recurrent RCC.

No.	Age	Sex	Group	Pre- or Post-Tx or HD	pT stage	Histology	Grade	Recurrence-free period	Recurrence site	Survival period
1	64	M	1	Post	pT3aN0M0	Papillary type 2	G3	10	Lung and bone	25
2	64	M	1	Post	pT2bN0M0	Clear cell	G2	4	Lung	32
3	55	M	1	Post	pT2bN0M0	Clear cell	G3	6	Lung, bone, liver, and skin	12*
4	67	M	1	Pre	pT1aN0M0	Papillary type 2	G2	30	Lung, liver, brain	60*
5	44	M	4	HD	pT1aN0M0	Clear cell	G1	116	Adrenal	151*
6	75	M	4	HD	pT1aN0M0	Clear cell	G3	17	Lung	20
7	55	M	4	HD	pT1aN0M0	Papillary type 1	G1	25	Retroperitoneum	68*
8	59	M	4	HD	pT2aN0M0	Papillary type 2	G2	29	Liver	65*

*Patients are alive.

applicability of mTOR inhibitors for RCC patients after RTx.

It is generally believed that a disease-free period before RTx is not needed when incidental RCC has been found and removed [6]. Institutions all over the world perform renal transplants at the same time as nephrectomy. However, in s-RCC cases, we should be particularly vigilant after RTx because renal transplant patients can rapidly develop s-RCC despite nephrectomy as shown in our study. Some guidelines state that there is no need for active follow-up examinations to detect RCC [7,8]. We suggest performance of follow-up ultrasonography or CT in patients with medical history of s-RCC or a diagnosis of incidental s-RCC after RTx.

In transplant recipients, s-RCC progressed rapidly under immunosuppressive conditions. A waiting period after nephrectomy may be needed before RTx in ESRD patients with s-RCC. Closer monitoring of potential recurrence than previously advised is also warranted for renal transplant recipients with RCC, especially those with a medical history of s-RCC.

Conclusions

The occurrence of s-RCC after RTx reduces CSS rates and NRR. ESRD patients with s-RCC should receive an adequate waiting period before RTx because immunosuppressive therapy tends to exacerbate s-RCC progression. We also believe that renal transplant recipients with s-RCC should be carefully followed up even after nephrectomy.

Authorship

MR: designed retrospective study, collected and analyzed the data, and wrote the manuscript. HI: designed the study, performed research, and collected and analyzed the data. TT and TS: collected the data. KT: designed the study and collected the data. TK: oversaw the study, collected the data, and is the corresponding author.

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