The impact of primary region resection on the therapeutic outcome of combination regimens for metastatic renal cell carcinoma

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Abstract. The present study aimed to clarify the relationship between the therapeutic outcome of combination regimens, including immune checkpoint inhibitors (ICIs) and/or tyrosine kinase inhibitors (TKIs), and cytoreductive nephrectomy (CN) for metastatic renal cell carcinoma (mRCC). The present study retrospectively assessed the association between treatment efficacy and prognosis with or without CN, and the timing of CN in 151 patients treated with combination regimens for mRCC who were categorized as intermediate/poor risk. The first-line regimens included the ICI-ICI and ICI-TKI regimens in 98 and 53 cases, respectively. In patients with recurrence after radical surgery (n=66), the 50% PFS times of the ICI-ICI and the ICI-TKI groups were 33.6 months and not reached (NR) (P=0.4032), respectively, and the 50% OS times were 53.7 months and NR (P=0.6886), respectively. Among the 38 patients with metastasis from the initial diagnosis who underwent upfront CN, the 50% PFS times of the ICI-ICI and the ICI-TKI groups were 10.5 and 8.2 months (P=0.5806), respectively, and the 50% OS times were NR and 15.8 months (P=0.0587), respectively. Among the 51 patients who did not receive upfront CN, the 50% PFS time of the ICI-TKI group was significantly higher than that in the ICI-ICI group (4.1 months and NR, respectively; P=0.0210), and the 50% OS times were 29.8 months and NR (P=0.7343), respectively. In conclusion, according to the analysis of real-world data, good therapeutic efficacy can be achieved with any regimen in patients with recurrence after radical surgery. In addition, improved results could be achieved through treatment with ICI-TKI in patients without upfront CN.

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Introduction

Renal cell carcinoma (RCC) accounts for 3-5% of all cancer cases worldwide, and while improved screening has increased the detection of early stage disease, a total of 20-30% of patients with RCC are diagnosed with metastases at the initial presentation (1). Although in the past, there was no systemic therapy regimen that could be expected to be effective enough for patients with advanced RCC, the advent of molecular-targeted agents, including tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICIs), has changed the treatment of metastatic RCC (mRCC) (2,3). Furthermore, combination regimens of the aforementioned drugs have been introduced over several years, and the prognosis of patients with mRCC has improved (4-8). The combination regimens approved by the health insurance system in Japan can be broadly classified into two types: Regimens combining two ICIs (ipilimumab and nivolumab; ICI-ICI) and regimens combining a TKI with an ICI (ICI-TKI). Four ICI-TKI regimens have been introduced: Avelumab + axitinib, pembrolizumab + axitinib, nivolumab + cabozantinib, and pembrolizumab + lenvatinib. All regimens have been shown to improve treatment efficacy and prognosis through randomized control trials (RCTs) (4-8). While the introduction of multiple effective systemic treatment options has been encouraging, nephrectomy as a treatment approach has been controversial (9-14). A number of retrospective studies have demonstrated the benefit of upfront cytoreductive nephrectomy (CN) in mRCC treated with TKIs (9,10) and ICIs (11,12); however, several RCTs have shown negative data for upfront CN in mRCC treated with TKIs (13,14). It is important to clarify the association between treatment efficacy and surgical therapy to select the optimal systemic treatment regimen. The present study aimed to determine the relationship between the therapeutic outcome of combination regimens, including ICIs and/or TKIs, and CN for mRCC.

Materials and methods

Patients. Inclusion criteria for the present study included: i) Treatment of mRCC between January 2018 and June 2022 at Kobe University Hospital or affiliated institutes: Hyogo Prefectural Amagasaki General Medical Center (Amagasaki, Japan), Hyogo Cancer Center (Akashi, Japan), Japanese Red Cross Society Himeji Hospital (Himeji, Japan), Kobe City Medical Center West Hospital (Kobe, Japan), Hyogo Prefectural Kakogawa Medical Center (Kakogawa, Japan), Kansai Rosai Hospital (Amagasaki, Japan), Kita-harima Medical Center (Himeji, Japan) and Yodogawa Christian Hospital (Osaka, Japan), from January 2018 to June 2022; ii) treatment with a combination regimen including TKI or ICI as first-line therapy; and iii) mRCC classified as intermediate or poor risk by the International mRCC Database Consortium (IMDC) (15). Exclusion criteria included: i) Treatment with a combination regimen as presurgical therapy; and ii) unknown pathology. A total of 8/172 patients with mRCC whose pathological diagnosis was not determined, and a total of 13/172 patients who were categorized as favorable risk, were excluded. As a result, 151 patients were included in the current study, and were retrospectively studied by reviewing the relevant clinicopathological data. Ethics approval was granted by the Ethics Committee of Kobe University (approval no. B230087).

Patients treated with ipilimumab + nivolumab, and those treated with either avelumab + axitinib, pembrolizumab + axitinib, nivolumab + cabozantinib or pembrolizumab + lenvatinib, were divided into the ICI-ICI and ICI-TKI groups, respectively. Clinicopathological data, including age, sex, pathological findings, Karnofsky performance status (KPS) score (16), metastasis status, choice of first-line regimen and IMDC risk, were evaluated for all patients, and the distribution of these parameters in each group was compared. The objective response (OR), OR rate (ORR), and the progression-free survival (PFS) and overall survival (OS) times for each group were determined. These analyses were performed for all patients, and patients were further classified into three patterns: Recurrence after primary tumor resection diagnosed as RCC (pattern A), mRCC at initial diagnosis with upfront CN (pattern B) and mRCC at initial diagnosis without upfront CN (pattern C).

Statistical analysis. The differences in the distribution of categorical variables between the groups were analyzed using a χ^2 test, and when >20% of expected counts were ≤5, they were analyzed using Fisher's exact test. Tumor responses were determined by investigator assessment on the basis of RECIST version 1.1 (17). The PFS and OS times were determined using the Kaplan-Meier method, and the differences between the two groups were analyzed using log-rank test. All statistical analyses were conducted using Statview (version 5.0; Abacus Concepts, Inc.), and $P<0.05$ was considered to indicate a statistically significant difference.

Results

All patients. The median age of the patients was 71 years (range, 30-86 years). The median observation period was 16.6 months (range, 1-93.8 months). The first-line regimens were the ICI-ICI and ICI-TKI regimens in 98 and 53 cases, respectively. The number of patients with lymph node metastasis in the ICI-ICI group was significantly higher than that in the ICI-TKI group (Table IA). There was no statistically significant difference in either PFS or OS between the two regimen groups when all patients were assessed (Fig. 1).

Patients' characteristics in each pattern. Patterns A, B and C consisted of 62, 38 and 51 patients, respectively. The frequency of patients with non-clear histology, low KPS, multiple metastatic organs, bone metastasis, lymph node metastasis and poor IMDC risk was significantly lower in pattern A than in the other two patterns (Table II). The frequency of patients with poor IMDC risk in pattern B was significantly lower than that in pattern C (Table II). There was no significant difference in the background of patients between the ICI-ICI and the ICI-TKI groups in every pattern, except for a higher number of patients with lymph node metastasis in the ICI-ICI group in pattern B and C, and a higher number of patients with liver metastasis in the ICI-TKI group in pattern C (Table IB-D).

Treatment outcomes in each pattern. In the ICI-TKI group of pattern C and in that of all patients, the ORR [the frequency of patients with complete response (CR) or partial response (PR) as the best OR] was significantly higher, while the frequency of patients with CR and that with progressive disease (PD) as the best OR were significantly lower than that in the ICI-ICI group (Table III). In pattern A, the 50% PFS times of the ICI-ICI and the ICI-TKI groups were 33.6 months and not reached (NR) (Fig. 2A), respectively, and the 50% OS times were 53.7 months and NR, respectively (Fig. 2B). In pattern B, the 50% PFS times of the ICI-ICI and ICI-TKI groups were 10.5 and 8.2 months (Fig. 3A), respectively, and the 50% OS times were NR and 15.8 months, respectively (Fig. 3B). In pattern C, the 50% PFS time in the ICI-TKI group was significantly better than that in the ICI-ICI group (4.1 months and NR, respectively; Fig. 4A), and the 50% OS time was 29.8 months and NR, respectively (Fig. 4B).

Discussion

The introduction of molecular-targeted agents and ICIs has changed the therapeutic strategy of systemic therapy for mRCC in recent years. The use of various combination regimens with these agents has notably contributed to improved efficacy of treatment for patients with mRCC (4-8). The increase in therapeutic options has enabled the selection of treatment approaches that are expected to be effective for patients with diverse backgrounds (18,19). While the number of treatment options has increased, selecting the most appropriate therapy can be challenging. A previous study attempted to characterize every regimen by comparing results from multiple RCTs using network meta-analysis (20). To the best of our knowledge, no RCTs that directly compare first-line combination regimen options for mRCC have been performed; therefore, analyses derived from real-world data will be important in making treatment selections.

Table I. Comparison of characteristics of patients between the ICI-ICI (n=98) and ICI-TKI (n=53) groups.

A, All patients (n=151)

Characteristics	ICI-ICI, n (%)	ICI-TKI, n (%)	P-value	Total, n (%)
Age, years				
≥70	54 (55.1)	31 (58.5)	0.6887	85 (56.3)
≤69	44 (44.9)	22 (41.5)		66 (43.7)
Sex				
Male	76 (77.6)	43 (81.1)	0.6073	119 (78.8)
Female	22 (22.4)	10 (18.9)		32 (21.2)
Histological type				
Clear	72 (73.5)	45 (84.9)	0.1083	117 (77.5)
Non-clear	26 (26.5)	8 (15.1)		34 (22.5)
KPS score, %				
≥80	82 (83.7)	37 (69.8)	0.0467	119 (78.8)
<80	16 (16.3)	16 (30.2)		32 (21.2)
No. of metastatic disease sites				
1	35 (35.7)	20 (37.7)	0.8054	55 (36.4)
≥2	63 (64.3)	33 (62.3)		96 (63.6)
Metastatic disease sites				
Lung	58 (59.2)	33 (62.3)	0.712	91 (60.3)
Bone	32 (32.7)	23 (43.4)	0.1904	55 (36.4)
Lymph node	44 (44.9)	11 (20.8)	0.0033	55 (36.4)
Adrenal gland	9 (9.2)	6 (11.3)	0.6752	15 (9.9)
Liver	14 (14.3)	11 (20.8)	0.3074	25 (16.6)
Pancreas	6 (6.1)	4 (7.6)	0.7412	10 (6.6)
Brain	5 (5.1)	6 (11.3)	0.7563	11 (7.3)
IMDC risk				
Intermediate	56 (57.1)	27 (50.9)	0.4649	83 (55.0)
Poor	42 (42.9)	26 (49.1)		68 (45.0)
First-line regimen				
Ipilimumab + nivolumab	98 (100.0)	0 (0.0)		98 (64.9)
Avelumab + axitinib	0 (0.0)	19 (35.8)		19 (12.6)
Pembrolizumab + axitinib	0 (0.0)	11 (20.8)		11 (7.3)
Nivolumab + cabozantinib	0 (0.0)	20 (37.7)		20 (13.2)
Pembrolizumab + lenvatinib	0 (0.0)	3 (5.7)		3 (2.0)

B, Patients with recurrence after radical surgery for renal cell carcinoma (n=62)

Characteristics	ICI-ICI, n (%)	ICI-TKI, n (%)	P-value	Total, n (%)
Age, years				
≥70	20 (50.0)	14 (63.6)	0.3019	34 (54.8)
≤69	20 (50.0)	8 (36.4)		28 (45.2)
Sex				
Male	30 (75.0)	17 (77.3)	0.8415	47 (75.8)
Female	10 (25.0)	5 (22.7)		15 (24.2)
Histological type				
Clear	34 (85.0)	19 (86.4)	>0.9999	53 (85.5)
Non-clear	6 (15.0)	3 (13.6)		9 (14.5)
KPS score, %				
≥80	37 (92.5)	17 (77.3)	0.1190	54 (87.1)
<80	3 (7.5)	5 (22.7)		8 (12.9)

Table I. Continued.

B, Patients with recurrence after radical surgery for renal cell carcinoma (n=62)

Characteristics	ICI-ICI, n (%)	ICI-TKI, n (%)	P-value	Total, n (%)
No. of metastatic disease sites				
1	19 (47.5)	10 (45.5)	0.8773	29 (46.8)
≥2	21 (52.5)	12 (54.5)		33 (53.2)
Metastatic disease sites				
Lung	19 (47.5)	13 (59.1)	0.3822	32 (51.6)
Bone	7 (17.5)	7 (31.8)	0.197	14 (22.6)
Lymph node	11 (27.5)	4 (18.2)	0.5409	15 (24.2)
Adrenal gland	2 (5.0)	2 (9.1)	0.6104	4 (6.5)
Liver	10 (25.0)	3 (13.6)	0.3481	13 (21.0)
Pancreas	3 (7.5)	3 (13.6)	0.6566	6 (9.7)
Brain	1 (2.5)	1 (4.5)	>0.9999	2 (3.2)
IMDC risk				
Intermediate	30 (75.0)	16 (72.7)	0.8449	46 (74.2)
Poor	10 (25.0)	6 (27.3)		16 (25.8)
First-line regimen				
Ipilimumab + nivolumab	40 (100.0)	0 (0.0)		40 (64.5)
Avelumab + axitinib	0 (0.0)	8 (36.4)		8 (12.9)
Pembrolizumab + axitinib	0 (0.0)	5 (22.7)		5 (8.1)
Nivolumab + cabozantinib	0 (0.0)	9 (40.9)		9 (14.5)
Pembrolizumab + lenvatinib	0 (0.0)	0 (0.0)		0 (0.0)

C, Patients with metastatic renal cell carcinoma at initial diagnosis who underwent upfront cytoreductive nephrectomy (n=38)

Characteristics	ICI-ICI, n (%)	ICI-TKI, n (%)	P-value	Total, n (%)
Age, years				
≥70	13 (52.0)	8 (61.5)	0.5748	21 (55.3)
≤69	12 (48.0)	5 (38.5)		17 (44.7)
Sex				
Male	18 (72.0)	10 (76.9)	>0.9999	28 (73.7)
Female	7 (28.0)	3 (23.1)		10 (26.3)
Histological type				
Clear	17 (68.0)	11 (84.6)	0.2698	28 (73.7)
Non-clear	8 (32.0)	2 (15.4)		10 (26.3)
KPS score, %				
≥80	22 (88.0)	9 (69.2)	0.2025	31 (81.6)
<80	3 (12.0)	4 (39.8)		7 (18.4)
No. of metastatic disease sites				
1	7 (28.0)	6 (46.2)	0.2631	13 (34.2)
≥2	18 (72.0)	7 (53.8)		25 (65.8)
Metastatic disease sites				
Lung	19 (76.0)	9 (69.2)	0.7092	28 (73.7)
Bone	6 (24.0)	3 (23.1)	>0.9999	9 (23.7)
Lymph node	14 (56.0)	2 (15.4)	0.0140	16 (42.1)
Adrenal gland	1 (4.0)	2 (15.4)	0.2651	3 (7.9)
Liver	2 (8.0)	2 (15.4)	0.5959	4 (10.5)
Pancreas	1 (4.0)	0 (0.0)	>0.9999	1 (2.6)
Brain	1 (4.0)	2 (15.4)	0.2651	3 (7.9)

Table I. Continued.

C, Patients with metastatic renal cell carcinoma at initial diagnosis who underwent upfront cytoreductive nephrectomy (n=38)

Characteristics	ICI-ICI, n (%)	ICI-TKI, n (%)	P-value	Total, n (%)
IMDC risk				
Intermediate	17 (68.0)	5 (38.5)	0.0802	22 (57.9)
Poor	8 (32.0)	8 (61.5)		16 (42.1)
First-line regimen				
Ipilimumab + nivolumab	25 (100.0)	0 (0.0)		25 (65.8)
Avelumab + axitinib	0 (0.0)	9 (69.2)		9 (23.7)
Pembrolizumab + axitinib	0 (0.0)	4 (30.8)		4 (10.5)

D, Patients with metastatic renal cell carcinoma at initial diagnosis who did not undergo upfront cytoreductive nephrectomy (n=51)

Characteristics	ICI-ICI, n (%)	ICI-TKI, n (%)	P-value	Total, n (%)
Age, years				
≥70	21 (63.6)	9 (50.0)	0.3444	30 (58.8)
≤69	12 (36.4)	9 (50.0)		21 (41.2)
Sex				
Male	28 (84.8)	16 (88.9)	>0.9999	44 (86.3)
Female	5 (15.2)	2 (11.1)		7 (13.7)
Histological type				
Clear	21 (63.6)	15 (83.3)	0.2025	36 (70.6)
Non-clear	12 (36.4)	3 (16.7)		15 (29.4)
KPS score, %				
≥80	23 (69.7)	11 (61.1)	0.5342	34 (66.7)
<80	10 (30.3)	7 (38.9)		17 (33.3)
No. of metastatic disease sites				
1	9 (27.3)	4 (22.2)	0.7502	13 (25.5)
≥2	24 (72.7)	14 (77.8)		38 (74.5)
Metastatic disease sites				
Lung	20 (60.6)	11 (61.1)	0.9718	31 (60.8)
Bone	19 (57.6)	9 (50.0)	0.6033	28 (54.9)
Lymph node	19 (57.6)	5 (27.8)	0.0416	24 (47.1)
Adrenal gland	6 (18.2)	2 (11.1)	0.6959	8 (15.7)
Liver	2 (6.1)	6 (33.3)	0.0171	8 (15.7)
Pancreas	2 (6.1)	1 (5.6)	>0.9999	3 (5.9)
Brain	3 (9.1)	3 (16.7)	0.6524	6 (11.8)
IMDC risk				
Intermediate	9 (27.3)	6 (33.3)	0.6499	15 (29.4)
Poor	24 (72.7)	12 (66.7)		36 (70.6)
First-line regimen				
Ipilimumab + nivolumab	33 (100)	0 (0.0)		33 (64.7)
Avelumab + axitinib	0 (0.0)	2 (11.1)		2 (3.9)
Pembrolizumab + axitinib	0 (0.0)	2 (11.1)		2 (3.9)
Nivolumab + cabozantinib	0 (0.0)	11 (61.1)		11 (21.6)
Pembrolizumab + lenvatinib	0 (0.0)	3 (16.7)		3 (5.9)

KPS, Karnofsky performance status; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; ICI, immune checkpoint inhibitor; TKI, tyrosine kinase inhibitor.

Table II. Characteristics of patients in pattern A (n=62), pattern B (n=38) and pattern C (n=51).

Characteristics	Pattern A, n (%)	Pattern B, n (%)	Pattern C, n (%)	P-value, pattern A vs. patterns B + C	P-value, pattern B vs. pattern C	Total,n (%)
Age, years						
≥70	34 (54.8)	21 (55.3)	30 (58.8)	0.7639	0.7370	85 (56.3)
≤69	28 (45.2)	17 (44.7)	21 (41.2)			66 (43.7)
Sex						
Male	47 (75.8)	28 (73.7)	44 (86.3)	0.4513	0.1350	119 (78.8)
Female	15 (24.2)	10 (26.3)	7 (13.7)			32 (21.2)
Histological type						
Clear	53 (85.5)	28 (73.7)	36 (70.6)	0.0495	0.7479	117 (77.5)
Non-clear	9 (14.5)	10 (26.3)	15 (29.4)			34 (22.5)
KPS						
≥80%	54 (87.1)	31 (81.6)	34 (66.7)	0.0375	0.1169	119 (78.8)
<80%	8 (12.9)	7 (18.4)	17 (33.3)			32 (21.2)
No. of metastatic organs						
1	29 (46.8)	13 (34.2)	13 (25.5)	0.0274	0.3709	55 (36.4)
≥2	33 (53.2)	25 (65.8)	38 (74.5)			96 (63.6)
Metastatic disease sites						
Lung	32 (51.6)	28 (73.7)	31 (60.8)	0.0698	0.2029	91 (60.3)
Bone	14 (22.6)	13 (34.2)	28 (54.9)	0.0032	0.0527	55 (36.4)
Lymph node	15 (24.2)	16 (42.1)	24 (47.1)	0.0091	0.6422	55 (36.4)
Adrenal gland	4 (6.5)	3 (7.9)	8 (15.7)	0.2789	0.3409	15 (9.9)
Liver	13 (21.0)	4 (10.5)	8 (15.7)	0.2235	0.5457	25 (16.6)
Pancreas	6 (9.7)	1 (2.7)	3 (5.9)	0.2077	0.6329	10 (6.6)
Brain	2 (3.2)	3 (7.9)	6 (11.8)	0.2011	0.7272	11 (7.3)
IMDC risk						
Intermediate	46 (74.2)	22 (57.9)	15 (29.4)	<0.0001	0.0070	83 (55.0)
Poor	16 (25.8)	16 (42.1)	36 (70.6)			68 (45.0)
First-line regimen						
Ipilimumab + nivolumab	40 (64.5)	25 (65.8)	33 (64.7)	0.9341	0.9155	98 (64.9)
Avelumab + axitinib	8 (12.9)	9 (23.7)	2 (3.9)	0.9211	0.0077	19 (12.6)
Pembrolizumab + axitinib	5 (8.1)	4 (10.5)	2 (3.9)	0.7583	0.3954	11 (7.3)
Nivolumab + cabozantinib	9 (14.5)	0 (0.0)	11 (21.6)	0.7005	0.0020	20 (13.2)
Pembrolizumab + lenvatinib	0 (0.0)	0 (0.0)	3 (5.9)	0.2691	0.2577	3 (1.9)

Pattern A, patients with recurrence after radical surgery for renal cell carcinoma; pattern B, patients with metastatic renal cell carcinoma at initial diagnosis who underwent upfront cytoreductive nephrectomy; pattern C, patients with metastatic renal cell carcinoma at initial diagnosis who did not undergo upfront cytoreductive nephrectomy. Comparisons among the groups were analyzed using χ^2 test or Fisher's exact test. KPS, Karnofsky performance status; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium.

ORR was significantly higher in the ICI-TKI group than that in the ICI-ICI group, whereas there was no significant difference in either PFS or OS times when comparing all patients. However, the backgrounds of patients who had post-operative recurrence after radical surgery for low-stage RCC, and those who had metastasis from the initial diagnosis as high-stage RCC were considered to be different. In addition, since the physician decides whether to perform upfront CN on the basis of a comprehensive evaluation of the patient's condition, the pathophysiology of mRCC may notably vary between those cases where upfront CN was performed and those where it was not performed. In particular, the IMDC classification has been reported to be useful in the prognostic stratification of patients treated with combined regimens (21). The notable difference in the distribution of IMDC classification among the three patterns suggests that they should be separately examined.

First, in patients with recurrence after radical surgery (pattern A), satisfactory PFS and OS times, and ORR were obtained regardless of the selection of the first-line regimen, and no patient in the ICI-TKI group had PD as the best response. The proportion of patients with parameters that

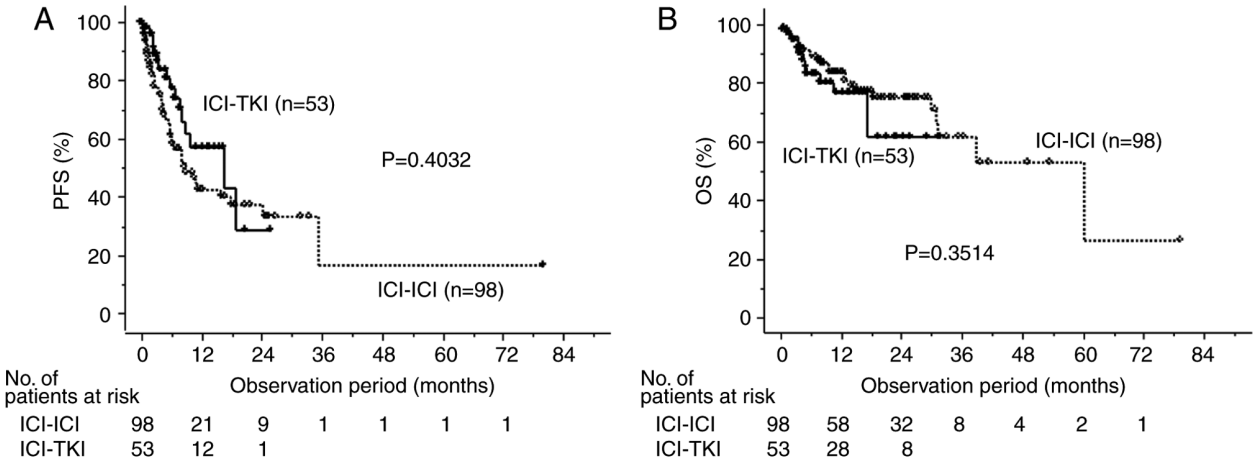

Figure 1. (A) PFS and (B) OS stratified by first-line regimen in all patients with metastatic renal cell carcinoma. PFS, progression-free survival; OS, overall survival; TKI, tyrosine kinase inhibitor; ICI, immune checkpoint inhibitor.

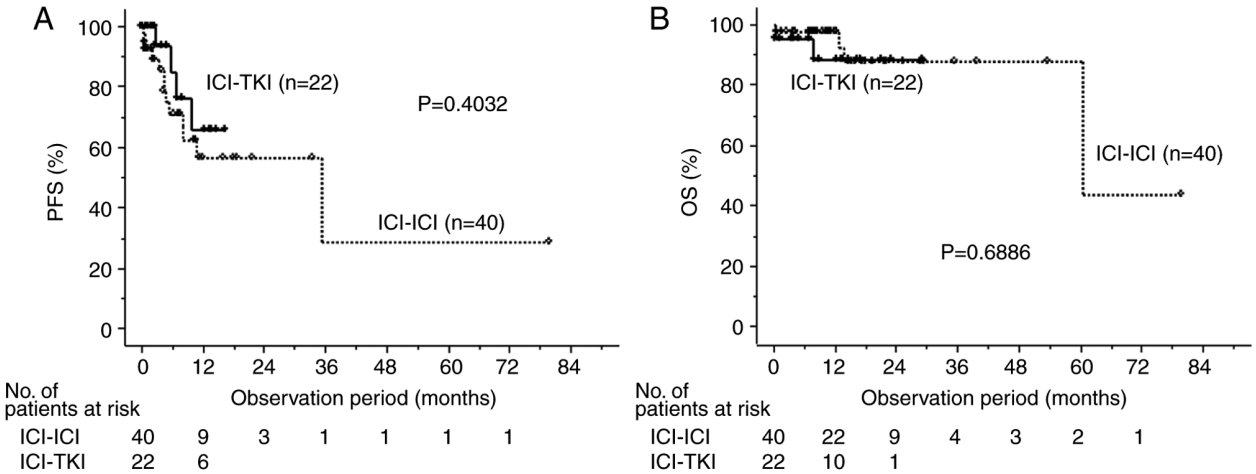

Figure 2. (A) PFS and (B) OS stratified by first-line regimen in those patients with metastatic renal cell carcinoma who showed recurrence after radical surgery. ICI, immune checkpoint inhibitor; TKI, tyrosine kinase inhibitor; PFS, progression-free survival; OS, overall survival.

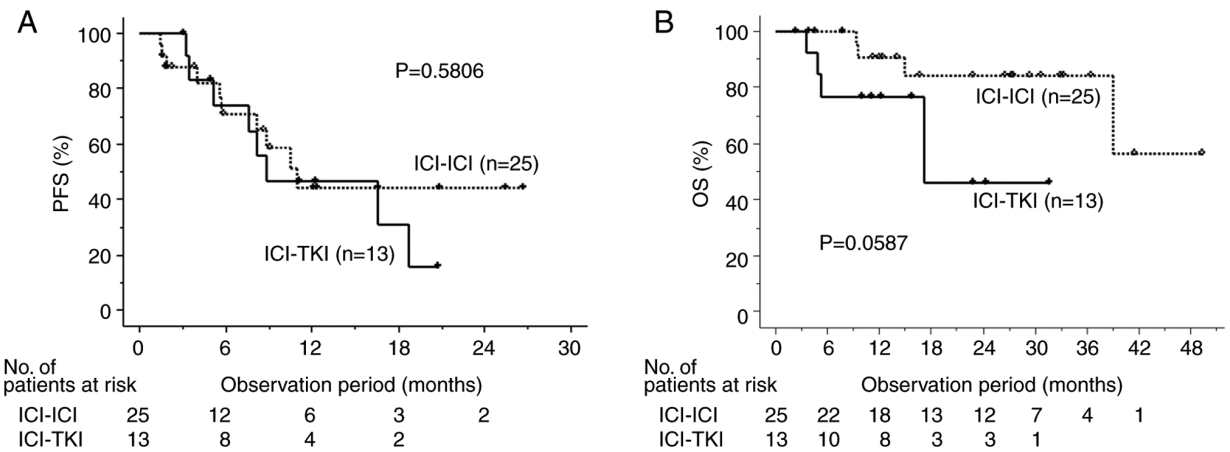

Figure 3. (A) PFS and (B) OS stratified by first-line regimen in those patients with metastatic renal cell carcinoma who underwent upfront cytoreductive nephrectomy. PFS, progression-free survival; OS, overall survival; TKI, tyrosine kinase inhibitor; ICI, immune checkpoint inhibitor.

seemed to represent a poor prognosis, including non-clear histology, poor KPS and poor IMDC risk classification, was significantly lower in pattern A than in other patients with mRCC at initial diagnosis. Additionally, since recurrence was detected during regular follow-up, the frequency of patients with multiple sites of metastatic disease was also

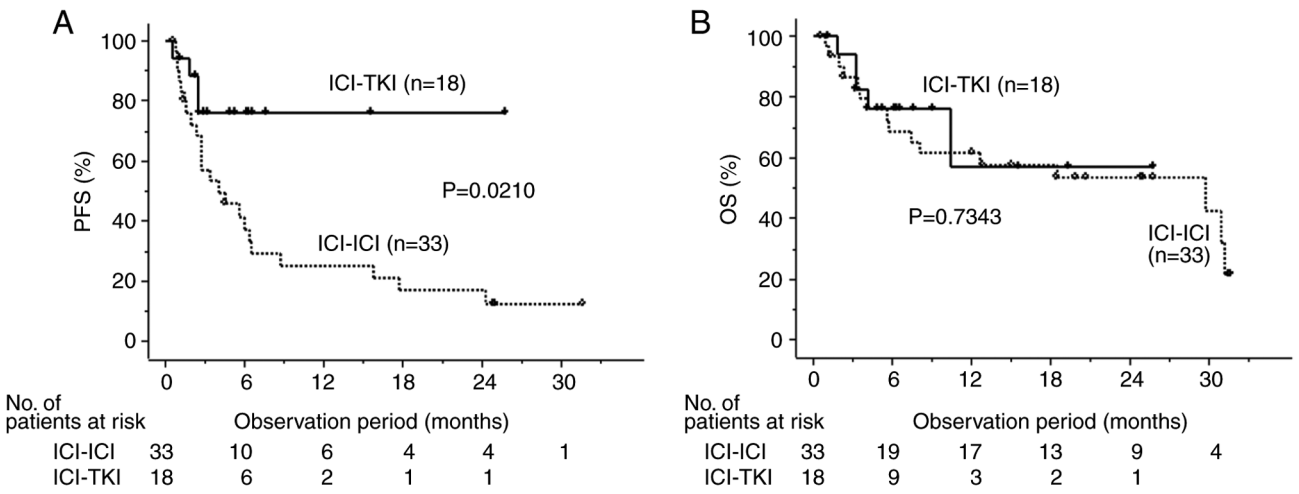

Figure 4. (A) PFS and (B) OS stratified by first-line regimen in those patients with metastatic renal cell carcinoma who did not undergo upfront cytoreductive nephrectomy. PFS, progression-free survival; OS, overall survival; TKI, tyrosine kinase inhibitor; ICI, immune checkpoint inhibitor.

significantly lower. These characteristics of metastatic status were considered to be one of the reasons for the difference of treatment efficacy and prognosis of patients in pattern B compared with those in pattern C. The treatment outcome trends in ORR and PFS differed significantly between patients with and without upfront CN in patients with mRCC. Patients in pattern B, i.e. those with mRCC who underwent upfront CN, showed no difference in ORR, or PFS or OS times between the ICI-ICI and the ICI-TKI groups.

Second, the frequency of poor IMDC risk cases was significantly lower in pattern B compared with that in pattern C, indicating a tendency to choose upfront CN when the overall condition of the patient was good. A total of ~40% of patients in the ICI-ICI group had no recurrence, reflecting a trend towards improved OS in the ICI-ICI group. The results of the current study suggested that treatment with ICI-ICI may be more likely to be effective in such cases with relatively improved conditions (22). These results are consistent with a previously reported sub-analysis of an RCT showing the efficacy of ipilimumab + nivolumab therapy for mRCC by the number of IMDC risk factors (23).

In contrast to pattern B, in patients with mRCC who did not undergo upfront CN (pattern C), PFS times and ORR in the ICI-TKI group were significantly higher than those in the ICI-ICI group. Patients in pattern C had more advanced disease with multiple metastases than those patients in pattern B, and it was hypothesized that for many of these patients in pattern C they would not exhibit a durable response, which is an important feature of the effect of ICI-ICI therapy. Despite significant differences in ORR and PFS times, there was no significant difference in OS times between the two groups. It is biologically reasonable to assume that TKI-naïve patients who receive ICI-ICI as first-line therapy will have an improved response when they receive TKI in the second line or later, and that the ICI-TKI group will have fewer options for substantial therapy. A previous study also reported that even though ORR was higher in the ICI-TKI group, there was no difference in OS times between these regimens because there were fewer post-treatment options, and since the ICI-ICI group did not receive TKIs in first-line therapy, better efficacy of TKIs in subsequent therapy after failure of first-line therapy can be expected (24). However, patients in the ICI-TKI group, which offers good PFS times and ORR even in patients with poor IMDC risk, are more likely to choose surgical and radiotherapeutic options, including deferred CN and metastasectomy, for shrinking primary tumors and metastases, compared with the ICI-ICI group. These options are likely to become further available with increasing proficiency in the use of various systemic combination regimens and collaboration with other departments. In the current study, patients who were administered for the purpose of presurgical therapy were excluded, and deferred CN was performed in only one patient. The OS times may be further improved by multidisciplinary treatment with these aggressive interventions in the future.

The present study has several limitations. It is based on the analysis of real-world data and is a retrospective study with a relatively small sample size. Additionally, different regimens are included within the ICI-TKI group. The choice of regimen and whether to perform upfront CN depend on patient background, as the decision is made by the physician, taking into account the patient's overall medical condition, thus leading to potential selection bias in each regimen. Further analyses with a larger volume and longer follow-up period are warranted to confirm the findings of the present study.

In conclusion, the outcomes following treatment with ICI-ICI and ICI-TKI regimens were detected in patients with mRCC, including in those who exhibited recurrence after radical surgery, and those who did and did not undergo upfront CN before systemic therapy. Therapeutic efficacy could be achieved with any regimen in patients with recurrence after radical surgery, whereas improved results of PFS and ORR were archived with ICI-TKI in patients without upfront CN. The efficacy of systemic treatment is more promising than in the past decade; to further improve the effectiveness of treatment it is necessary to understand the characteristics of each regimen, and work towards multidisciplinary treatment with surgery and radiation therapy.

Table III. OR of first-line therapy in all patients (n=151), and patterns A (n=58), B (n=38) and C (n=42).

A, All patients (n=151)

	First-line combination regimen	
OR	ICI-ICI, n (%) (n=92)	ICI-TKI, n (%) (n=46)
CR	14 (15.2)	1 (2.2)
PR	28 (30.4)	30 (65.2)
SD	28 (30.4)	11 (23.9)
PD	22 (23.9)	4 (8.7)

B, Pattern A, recurrence after radical surgery (n=58)

	First-line combination regimen	
OR	ICI-ICI, n (%) (n=39)	ICI-TKI, n (%) (n=19)
CR	9 (23.1)	1 (5.3)
PR	12 (30.8)	13 (68.4)
SD	12 (30.8)	5 (26.3)
PD	6 (15.4)	0 (0.0)

C, Pattern B, mRCC with upfront CN (n=38)

	First-line combination regimen	
OR	ICI-ICI, n (%) (n=25)	ICI-TKI, n (%) (n=13)
CR	5 (20.0)	0 (0.0)
PR	8 (32.0)	7 (53.8)
SD	8 (32.0)	4 (30.8)
PD	4 (16.0)	2 (15.4)

D, Pattern C, mRCC without upfront CN (n=42)

	First-line combination regimen	
OR	ICI-ICI, n (%) (n=28)	ICI-TKI, n (%) (n=14)
CR	0 (0.0)	0 (0.0)
PR	8 (28.6)	10 (71.4)
SD	8 (28.6)	2 (14.3)
PD	12 (42.9)	2 (14.3)

ICI, immune checkpoint inhibitor; TKI, tyrosine kinase inhibitor; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; OR, overall response; mRCC, metastatic renal cell carcinoma; CN, cytoreductive nephrectomy; Best objective response of ICI-ICI group and that of ICI-TKI one were compared. Table IIIA P-values: CR, 0.0204; CR + PR, 0.0159; PD, 0.0376; Table IIIB P-value: CR, 0.1421; CR + PR, 0.1472; PD: 0.1634; Table IIIC P-value: CR, 0.1440; CR + PR, >0.9999; PD, 0.9616; Table IIID P-value: CR + PR, 0.0188; PD, 0.0886.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

ToT, JH, HU, NW, KH, YN, YO and MF contributed to the conception and design of the study, providing supervision and drafting the manuscript. JF, TaT, YB and TH contributed to the conception and design of the study, acquisition of data and drafting the manuscript. JT and YS contributed to the conception and design of the study, acquisition of data, drafting and critical revision of the manuscript, and clinical analysis. YS and YO confirm the authenticity of the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The protocol of the current study was approved by the Ethics Committee of Kobe University (approval no. B190010 and B230087), and was carried out according to the approved guidelines. No informed consent was obtained due to data anonymization as no identifying information associated with the participants was included.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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