Oncological outcomes classified according to metastatic lesions in the era of molecular targeted drugs for metastatic renal cancer

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Abstract. Since the introduction of molecular targeted agents for the treatment of metastatic renal cell cancer (mRCC), several treatment outcomes, including those from our facilities, have been reported. However, the outcome of these drugs, classified by the metastatic organs, is not well known. The present study reported the treatment results of molecular-targeted agents as classified by the metastatic organ at Osaka City University Graduate School of Medicine. A total of 180 consecutively treated patients who had received molecular targeted agents for metastatic renal cancer for 3 or more months were retrospectively analyzed. The overall survival was calculated and compared according to the Memorial Sloan-Kettering Cancer Center (MSKCC) criteria, the number of metastatic organs, and metastatic lesions. The median overall survival of patients with mRCC treated by molecular targeted agents was 34 months. A significant difference in survival rate between groups was found according to the MSKCC criteria. Patients with single metastatic organ lived significantly longer compared with those with metastases in multiple organs. Patients with pancreatic metastasis had a good response to molecular targeted drugs. Pancreatic metastasis, the number of metastatic organs, and MSKCC criteria were independent risk factors for overall survival. Treatment of mRCC by molecularly targeted agents did not show any difference by metastatic organs except for the pancreas, although its efficacy depends on the number of metastatic organs and the MSKCC classification.

Introduction

In 2017, six molecular targeted agents were approved for the treatment of metastatic renal cell carcinoma (mRCC) in Japan (1). Results of large-scale clinical trials (2-7), as well as from our institution (8), and other investigators in Japan (9-12) have reported real-world clinical data showing an improvement in the survival rate of patients with mRCC. However, it is uncertain for which type of patient will this treatment be effective. Differences in survival rates according to the Memorial Sloan Kettering Cancer Center (MSKCC) criteria (13) and the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) model (14) are being studied. Motzer *et al* reported that Eastern Cooperative Oncology Group performance status, serum hemoglobin level, time from diagnosis to treatment, and corrected calcium, alkaline phosphatase, and lactate dehydrogenase levels were significant independent predictors for survival (15). It was also reported that the prognostic factors used in the MSKCC classification are robust and applicable in the contemporary era of targeted therapy. Although these models correlated well with cancer survival, only a few reports presented the survival rate as classified by metastatic organ. In the cytokine therapy era, there was minimal variation in the metastatic organ among Japanese patients (16,17). Liver, bone, lymph node, and brain metastases were independent risk factors for mRCC due to interferon-α administration. However, the relationship between metastatic organ and mRCC treatment using molecular targeted drugs (10,18,19) are not well studied. Therefore, we aimed to investigate the survival rate classified according to the metastatic lesion in the molecular targeted agents era for mRCC in Japanese patients.

Patients and methods

We retrospectively analyzed 180 consecutively treated patients who had received molecular targeted drugs for mRCC. Regarding administration of first-line drugs, sunitinib 50 mg was administered orally (PO) every day over 2 or 4 weeks, followed by a 1- or 2-week washout period. Dose reductions, if needed, were made in decrements of 12.5 mg. Sorafenib was administered continuously at a full dose of 400 mg PO twice a day, with an allowed dose reduction of 200 mg (2,3). Temsirolimus was administered at a full dose of 25 mg div weekly (7). For second-line drugs, everolimus was administered continuously at a full dose of 10 mg PO per day (4). Axitinib was administered continuously at a full dose of 10 mg PO per day, with allowed dose escalation of up to 20 mg, and dose reduction of up to 2 mg (20). According to the therapeutic

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strategy in our institute, sorafenib is used as the first-line therapy and sunitinib or everolimus as the second-line therapy. From 2010 onward, we usually used sunitinib as the first-line therapy, and from 2012 onward, we usually used axitinib as the second-line therapy.

We calculated the overall survival (OS), OS classified according to the MSKCC criteria (21), the number of metastatic organs, the metastatic lesion, and presence or absence of nephrectomy. OS period commenced from treatment with the initial targeted therapy. OS was estimated using the Kaplan-Meier method, and the differences were determined using the log-rank test. Cox proportional stepwise multivariate analysis was used to evaluate the association between the number of metastatic organ, metastatic site, MSKCC criteria, presence or absence of nephrectomy and OS.

Response assessment was performed by using computed tomography or magnetic resonance imaging scans every 10-12 weeks, and evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1, and the change in the pancreatic tumor size was calculated by the fraction of decrease or increase in the sum of the largest diameter of the target lesions (22). A P-value <0.05 was considered statistically significant. All statistical analyses were performed using Microsoft Excel® (Microsoft, Redmond, Washington, USA). Permission to access the database for review of the medical records of these patients was approved by the Local Research Ethics Committee at Osaka City University (approval number 3441).

Results

The median age of the patients was 67 years (range: 35-84) Other patient characteristics and treatments are shown in Table I. Patients belonging to the intermediate risk class accounted for about 50% of all risk classes. The number of metastatic organs was almost evenly allocated to single or multiple. Lungs were the most common metastatic organ, followed by lymph nodes and bone. The median OS was 34 months (Fig. 1). Fig. 2 shows the OS classified by the MSKCC criteria. Patients in the favorable group had a significantly prolonged survival than those in the other groups; conversely, the patients in the poor group had significantly shorter survival time compared to those in the other groups (favorable: Not reached; intermediate 31.0 months; poor: 11.0 months). In univariate analysis, patients who performed nephrectomy or cytoreductive nephrectomy had a significantly prolonged survival than those who did not performed. Concerning the intermediate risk class (126 patients in total), this was subdivided into Intermediate group 1 (64 patients) and intermediate group 2 (62 patients). The median age of intermediate group 1 was 67 years (range: 40-80); that of intermediate group 2 was 69 years (range: 39-83). The other patient characteristics and treatments are detailed in Table II.

Patients who had a single metastatic organ lived significantly longer than those with multiple metastatic organs (Fig. 3). OS classified according to metastatic lesions was analyzed using univariate logistic regression (Table II). Patients with pancreatic metastasis had a good response to molecular targeted drugs. Other metastatic lesions did not have a significant impact on the patients' survival. In multivariate analysis,

Table I. Patients characteristics and treatments (N=180).

Characteristics	No. of patients	Percentage
Sex		
Male	140	
Female	40	
Age, years (median)	66	range, 35-84
MSKCC		
Favorable	44	24.3%
Intermediate	99	55.2%
Poor	37	20.5%
No. of metastatic organ		
Single	98	54.1%
Multiple	82	45.9%
Sites of metastasis		
Lung	127	46.7%
Lymph node	54	20.0%
Bone	51	18.8%
Pancreas	14	5.1%
Liver	13	4.8%
Brain	13	4.8%
Prior nephrectomy		
Yes	165	91.6%
No	15	8.4%
Molecular targeted agents		
1st		
Sunitinib	108	
Sorafenib	66	
Temsilorimus	6	
2nd		
Everolimus	30	
Axitinib	33	
Sunitinib	20	
Temsilorimus	14	
Sorafenib	2	
3rd		
Everolimus	21	
Sunitinib	7	
Axitinib	7	
Sorafenib	5	
Temsirolimus	5	
Pazopanib	3	
4th		
Everolimus	21	
Sunitinib	7	
Axitinib	7	
Sorafenib	5	
Temsirolimus	5	
Pazopanib	3	
5th		
Axitinib	3	
Sorafenib	2	

MSKCC, Memorial Sloan Kettering Cancer Center.

Table II. Results of the Cox proportional stepwise multivariate analysis for the association between the clinicopathological variables and cause specific survival.

Comparison	Overall survival (months) (median)	Unadjusted		Adjusted	
		HR (95% CI)	P-value	HR (95% CI)	P-value
Lung vs. other organs	31.0 vs. 34.0	1.03 (0.74-1.42)	0.846		
Lung only vs. other organs	36.0 vs. 31.0	0.66 (0.40-1.07)	0.097		
Pancreas vs. other organs	not reached vs. 31.0	0.20 (0.04-0.80)	0.024	0.22 (0.05-0.94)	0.042
Brain vs. other organs	15.0 vs. 34.0	1.66 (0.81-3.38)	0.163		
Lymph node vs. other organs	28.0 vs. 34.0	1.15 (0.76-1.74)	0.496		
Liver vs. other organs	15.0 vs. 34.0	1.88 0.83-4.26)	0.129		
Bone vs. other organs	15.0 vs. 34.0	1.23 (0.80-1.89)	0.334		
Single organ vs. multiple organs	44.4 vs. 32.3	0.53(0.33-0.84)	0.007	0.51 (0.33-0.82)	0.005
MSKCC					
Favorable vs. others	not reached vs. 26.0	0.07(0.02-0.25)	<0.001	0.10 (0.03-0.33)	<0.001
Poor vs. others	12.0 vs. 53.0	4.21(2.52-7.02)	<0.001	2.33 (1.39-3.93)	0.001
Nephrectomy					
Yes vs. no	35 vs. 13	0.46(0.23-0.93)	0.030		

MSKCC, Memorial Sloan Kettering Cancer Center.

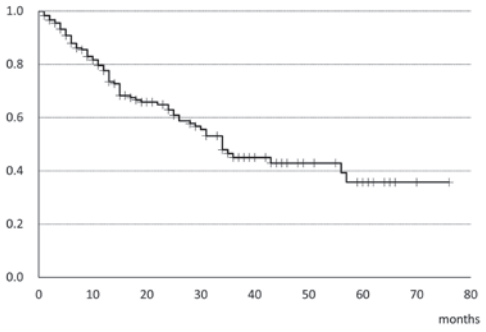

Figure 1. Overall survival of all patients with metastatic renal cell carcinoma after receiving molecular targeted drugs.

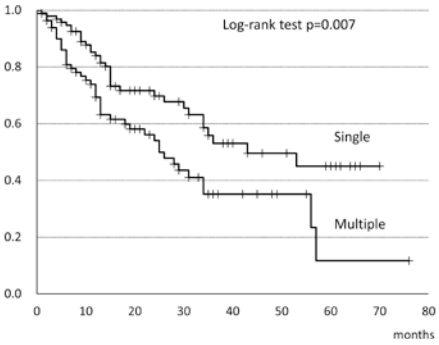

Figure 3. Overall survival according to single or multiple metastatic organs.

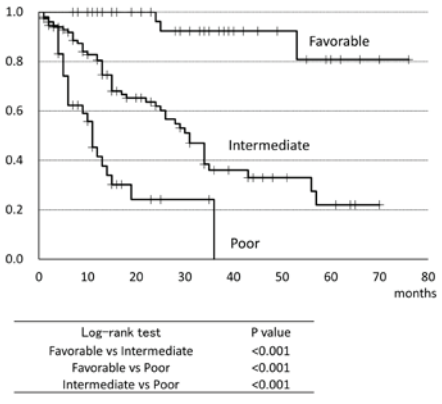

Figure 2. Overall survival according to the Memorial Sloan-Kettering Cancer Center criteria.

Figure 4. Maximal percentage changes in pancreatic tumor size from baseline in the 10 evaluable patients with pancreatic metastasis.

pancreatic metastasis, the number of metastatic organs, and MSKCC criteria were independent risk factors for OS.

Next, we focused on pancreatic metastasis due to RCC. The characteristics of patients with pancreatic metastasis and other metastasis are shown in Table III. Three out of 14 cases

Table III. Characteristics of patients with or without pancreatic metastasis.

	Pancreatic metastasis (N=14)	Other metastasis (N=166)	P-value
Other metastatic organs			
Lung	10	117	
Liver	1	12	
Brain	1	11	
Lymph node	4	50	
Bone	3	48	
Others	6	27	
None	3	-	
Time from diagnosis to metastasis (months)	81 (1.5-182.5)	37.4 (0-232.4)	0.004

had metastases confined only to the pancreas; however, all the 3 cases had multiple pancreatic metastases in pancreatic head and there was no indication for surgical resection. In patients with pancreatic metastasis, the time from diagnosis to metastasis was significantly longer than in cases with other metastasis (unpaired t test, Welch's test). The maximum reduction from the baseline of the pancreatic tumors in the 10 evaluable patients is shown in Fig. 4. Partial remission was achieved in 6 cases.

Discussion

Treatment of mRCC has changed over the last few years, and treatment by molecular targeted drugs has become common (2-4,6,7,20). Although a number of treatment outcomes have been reported in the real-world setting (10,23), there are only few reports on the treatment outcomes classified according to metastatic lesion (19). We retrospectively investigated the treatment outcome by metastatic lesion with molecular targeted drugs, and consequently, identified that pancreatic metastasis had better response compared to metastasis to other organs in the molecular targeted therapy era.

In the cytokine therapy era, there was minimal variation in the metastatic organ in Japanese patients (17). It was reported that lymph node, bone, hepatic, and brain metastasis correlated with progression on univariate analysis, but not on multivariate analysis. Shinohara *et al* (16) reported that liver or bone metastasis were independent risk factors. In the targeted therapy era, McKay *et al* reported that the presence of bone and liver metastasis had a negative impact on survival (19), and another report indicated that lymph node metastases was associated with poor prognosis in mRCC patients treated with targeted therapy (24). In Japanese patients, liver metastasis was an independent factor for OS (10). However, patients with pancreatic metastasis were very few among the population, and the relationship between survival and pancreatic metastasis was not studied in these previous studies. Yuasa *et al* reported that the pancreatic metastasis (N=20) occurs a long time (median 7.8 years) after nephrectomy, and that the OS of these patients is long (median not reached, 10 year survival rate; 80%) (25), although, among 20 patients, only 6 patients were treated by molecular targeted drugs. Only Grassi *et al* (26) and Kalra *et al* (27) reported that pancreatic metastasis is an independent prognostic variable in the targeted therapy era. We also identified that OS of patients with pancreatic metastasis was longer than that of those with metastasis to other organs (not reached vs. 31 months, respectively) in Japanese patients. According to our findings, the reason that pancreatic metastasis might carry good prognosis is that pancreatic metastasis occurred late, showed good response to molecular targeted drugs, and few patients were classified to have poor prognosis according to the MSKCC criteria. In fact, our study showed that time to pancreatic metastasis was longer than that to other metastases (81 vs. 37.4 months, respectively), and 60% of patients with pancreatic metastasis achieved partial response. Moreover, no patients with pancreatic metastasis were classified as poor risk in our study population. As opposed, Chrom *et al* (28) recently reported that the presence of pancreatic metastasis was not an independent prognostic factor.

OS for patients with mRCC treated by molecular targeted drugs was 34 months, this result is comparable to other reports by Japanese investigators (10,12). According to the MSKCC criteria (13), survival rates in each group were clearly stratified. IMDC criteria, which is another risk classification, is now often adapted to mRCC; however, some of our study participants had no available neutrophil/lymphocyte ratio, especially those who were diagnosed before 2010; hence, we did not investigate the IMDC risk. Although MSKCC criteria was established in the cytokine therapy era, our results showed that it can be applied efficiently, even in the era of molecular targeted drugs (21).

Next, we investigated the relationship between the number of metastatic organ and OS. OS for patients who had one metastatic organ was superior to those with multiple organs. Gerlinger *et al* mentioned that intratumor heterogeneity can lead to underestimation of the tumor genomics landscape portrayed from single tumor-biopsy samples, and may present major challenges to personalized-medicine and biomarker development (29). Therefore, it can be said that it is a reasonable result that the prognosis is better if the metastatic lesion is in a single organ. As might be expected, a single metastasis in a single organ must be enucleated because complete resection of RCC metastases may be associated with log-term survival (30,31), and we also performed metastatectomy in such cases. In this study, the patient recruited was inoperable due to the presence of multiple metastases in a single organ.

Despite that the cases who underwent metastasis resection were not included, the prognosis was better in the single organ metastasis group than in the multiple organ group; it is said that early detection and prompt treatment of metastasis are useful.

This study was a retrospective study and thus has certain limitations. Treatment strategy for mRCC patients is changing across time, so there is minimum variation due to the class of molecular targeted drugs. Treatment with immune checkpoint inhibitors has also increased, and future investigation is necessary.

In conclusion, the presence of pancreatic metastasis in patients with mRCC treated with molecular targeted therapy has a positive impact on survival. The site of metastasis may possibly be used for risk-stratification of patients with mRCC.

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Availability of data and materials

The datasets during and/or analysed during the current study available from the corresponding author on reasonable request.

Authors' contributions

YS and ST conceived and designed the study and were major contributors in writing the manuscript. TI, MK, NN, TN and TY designed the study and revised the manuscript. SY analyzed and interpreted the data.

Ethics approval and consent to participate

Permission to access the database for review of the medical records of these patients was approved by the Local Research Ethics Committee at Osaka City University (approval no. 3441).

Consent for publication

Not applicable.

Competing interests

Dr Satoshi Tamada received remuneration for a lecture from Pfizer Japan (Tokyo, Japan), Bayer Japan (Tokyo, Japan) and Novartis Pharma Japan (Tokyo, Japan). The other authors have declared that they have no competing interests.

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