Responses to Targeted Therapy among Organs Affected by Metastasis in Patients with Renal Cell Carcinoma are Organ-Specific

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Purpose: Previous reports showed that targeted therapy efficacy varied due to different metastatic organs in patients with metastatic renal cell carcinoma (mRCC). This study aimed to further evaluate the response and progression-free time (PFT) of individual metastatic organs.

Materials and Methods: Data from mRCC patients, who were treated with sunitinib between January 2008 to December 2018, were retrospectively reviewed. Individual metastatic organs were assessed separately by The Response Evaluation Criteria in Solid Tumors criteria.

Results: We evaluated response heterogeneity and PFT as characteristics of 281 individual organs affected by mRCC in 213 patients. The objective response rates in these organs were 72.7% in pancreas, 63.7% in spleen, 14.3% in adrenal glands, 13.5% in bone and soft tissue, 11.6% in lymph nodes, 11.6% in lungs, and 9.1% in liver. The median PFT was 15.2 months (95% confidence interval [CI] 2.7–27.7 months) for adrenal glands, 13.2 months (95% CI 3.5–22.9 months) for bone and soft tissue, 9.0 months (95% CI 7.6–10.4 months) for lymph nodes, 8.6 months (95% CI 6.3–10.9 months) for lungs, and 5.2 months (95% CI 2.9–7.5 months) for liver. Median PFT was not reached in pancreas and spleen, but was > 22.8 months and > 20.6 months, respectively.

Conclusion: Our results indicated that organs affected by metastasis may have individual responses to sunitinib treatment. The pancreas and spleen may have the best responses, and liver may have the worst response. Further research is needed to verify these findings.

Keywords: metastasis; objective response rate; organ; renal cell carcinoma; targeted therapy

INTRODUCTION

Renal cell carcinoma (RCC) accounts for 3% of malignant tumors in adults; approximately 17% of patients with RCC harbor distant metastases at the time of the initial diagnosis[1-3]. The organs most commonly affected by RCC metastasis are the lungs, lymph nodes, and bones[4]. Targeted therapy is the mainstay in the treatment of patients with metastatic RCC (mRCC), as it results in improvements in quality of life and survival [5,6]. Sunitinib, one of the multitarget receptor-tyrosine-kinase inhibitors (TKIs), has been the gold-standard first-line treatment for mRCC for over 10 years[7,8].

Our clinical practice of sunitinib-based treatment revealed the possibility of organ-specific responses to metastatic lesions. To date, there is no published evidence relating to this potential response heterogeneity in patients with mRCC who receive targeted therapy. Understanding any organ-specific variations in response and prognosis would be important for the personalization of mRCC patient treatments. In this paper, we demonstrated organ-specific differences in objective response rates (ORRs) and progression free time (PFT) that were indicative of response heterogeneity.

PATIENTS AND METHODS

Ethics Statement

This retrospective study focused on the evaluation of the efficacy and clinical outcomes of first-line sunitinib treatment in patients with mRCC, and was reviewed and approved by the Ethics Committee of the Domain-Specific Review Board (ID Num: NCC2016XQ-22).

Study Population

Patients with mRCC who were treated in our institute between January 2008 and December 2018 were retrospectively identified. The medical records of all patients with mRCC who were treated with sunitinib were reviewed. Among them, 213 patients with diagnoses of

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Table 1. Patient characteristics at baseline.

Characteristics	n (%)
Total patients	213
Gender	
Male	139 (65.3)
Female	74 (34.7)
Median age (range), year	55 (17–76)
ECOG	
0	148 (69.5)
1	53 (24.9)
> 1	12 (5.6)
MSKCC	
Good	102 (47.9)
Intermediate	72 (33.8)
Poor	39 (18.3)
Prior surgery	
Yes	165 (77.5)
No	48 (22.5)
Sites of disease (by organs)	
Lung	95 (33.8)
Lymph node	69 (24.6)
Bone and soft tissue	52 (18.5)
Liver	22 (7.8)
Adrenal gland	21 (7.5)
Pancreas	11 (3.9)
Spleen	11 (3.9)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; MSKCC, Memorial Sloan-Kettering Cancer Center

clear-cell RCC (ccRCC) who had detailed imaging data collected every two cycles of sunitinib treatment, and had not received other systemic treatments or metastasectomy, were included in the study. Sunitinib was administered at a dosage of 50 mg once daily, on a 4/2 (on/off) schedule. Dosages were reduced or interrupted only in cases of treatment intolerance, in which case stepwise dose reductions occurred in 12.5 mg increments. All patients had complete imaging data and follow-up information. Characteristics including age, sex, Memorial Sloan Kettering Cancer Center (MSKCC) criteria, and Eastern Cooperative Oncology Group (ECOG) Performance Status[9].

Radiological Assessment

Computed tomography (CT) or magnetic-resonance imaging (MRI) scanning was performed every 4–8 weeks, and the Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 criteria were used for evaluation of the responses of the lesions in every organ affected by metastasis[10]. Patients with measurable disease at baseline were collected. The tumor burden was assessed in centimeters of the tumor diameter by the sum of five measurable diseases for each metastatic organ at baseline according to RECIST 1.1. The best response of each individual organ was determined (complete response [CR] was better than partial response [PR], which was better than stable disease [SD], which was better than progressive disease [PD]), with the proviso that the response had to have been maintained for $\geq$ 28 days.

All CT and MRI data were reviewed by two independent genitourinary radiologists. Organs with metastases at the beginning of sunitinib treatment were evaluated throughout the treatment period, and the efficacy was recorded for each individual organ. Metastatic lesions that appeared during sunitinib treatment were considered to be primary drug-resistant lesions, and were not included in the study. Brain metastasis was not investigated, because in our institution nearly all brain metastases were treated with radiotherapy or surgical resection. Evaluation continued until death, the end of follow-up, or the replacement of sunitinib with a second-line targeted therapy or another systemic therapy.

Statistical Analysis

The chi-square test was used to compare the difference of distribution data between the groups; non-normally distributed continuous data were compared using the Mann-Whitney U test. PFT for each organ, progression-free survival (PFS) and overall survival (OS) from the initiation of sunitinib were analyzed by the Kaplan–

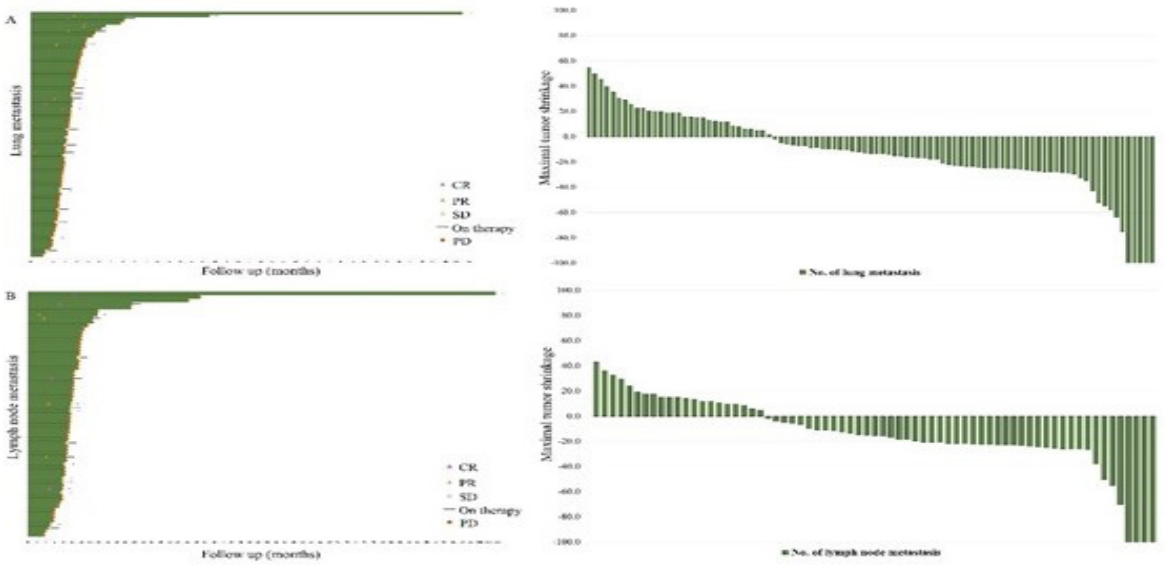

Figure 1. Responses and maximal tumor shrinkage of lung metastasis **(A)** and lymph node metastasis **(B)** assessed by RECIST1.1. The green-shaded area corresponds to follow-up time (months). The positioning of the markers with different colors indicates the point of complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). The arrow (on therapy) indicates continuing treatment with sunitinib.

Table 2. The distribution of MSKCC scores, tumor burden, and dose changes based on different metastatic organs

Metastatic organs n (%)	MSKCC risk classification			Median tumor burden (IQR), cm	Dose reduction or interruption n (%)
	Low	Intermediate	Poor		
Lung	46 (48.4)	31 (32.6)	18 (19.0)	4.3 (2.3–5.6)	48 (50.5)
Lymph node	38 (55.1)	21 (30.4)	10 (14.5)	4.0 (2.4–5.1)	33 (47.8)
Bone and soft tissue	19 (36.5)	15 (28.9)	18 (34.6)	3.8 (2.1–4.8)	20 (38.5)
Liver	6 (27.3)	6 (27.3)	10 (45.4)	4.1 (2.6–5.5)	10 (45.5)
Adrenal gland	7 (33.3)	8 (38.1)	6 (28.6)	3.9 (1.8–4.9)	11 (52.4)
Pancreas	3 (27.3)	5 (45.4)	3 (27.3)	3.8 (1.4–5.0)	4 (36.4)
Spleen	3 (27.3)	3 (27.3)	5 (45.4)	3.6 (1.9–4.5)	3 (27.3)
P value	0.071	0.068	0.714		

Abbreviations: MSKCC, Memorial Sloan-Kettering Cancer Center; IQR, interquartile range.

Meier method and the log-rank test. The deadline for follow-up was October 2019. Statistical analysis was performed using SPSS statistics for Windows, version 23.0 (IBM Corp. Armonk, NY, USA), and differences were considered statistically significant if $P < 0.05$.

RESULTS

Patient characteristics

The patient characteristics are summarized in **Table 1**. A total of 213 metastatic ccRCC patients, with a measurable response to sunitinib, were included in the study. This population consisted of 139 men (65.3%) and 74 women (34.7%), with a median age of 55 years (range 17–76 years). The numbers of patients with ECOG scores of 0, 1, and > 1 were 148 (69.5%), 53 (24.9%), and 12 (5.6%), respectively. Good, intermediate, and poor MSKCC risk levels were assessed in 102 (47.9%), 72 (33.8%), and 39 (18.3%) patients, respectively. In 165 patients (77.5%), nephrectomy was performed prior to sunitinib treatment. We only statistically analyzed target organs that were identified in >10 participants, which meant that 281 individual organs were available for analysis. These organs were lung in 95 patients (33.8%), lymph node in 69 (24.6%), bone and soft tissue in 52 (18.5%), liver in 22 (7.8%), adrenal gland in 21 (7.5%), pancreas in 11 (3.9%), and spleen in 11 (3.9%). There was no difference in MSKCC risk distribution between metastatic organs ($P = 0.071$) (**Table 2**). The median tumor burden for lung, lymph node, bone and soft tissue, liver, adrenal gland, pancreas, and spleen was 4.3 cm (interquartile range [IQR]: 2.3-5.6), 4.0 cm (IQR: 2.4-5.1), 3.8 cm (IQR: 2.1-4.8), 4.1 cm (IQR: 2.6-5.5), 3.9 cm (IQR: 1.8-4.9), 3.8 cm (IQR: 1.4-5.0), and 3.6 cm (IQR:1.9-4.5), respectively. Difference of tumor burden between metastatic organs was not statistically observed ($P = 0.068$) (**Table 2**).

Organ-specific treatment efficacy for metastasis

The treatment responses in each individual organs are shown in Figure 1; the best responses and ORRs for each organ type are summarized in Table 3. For lung metastasis, the median times to CR, PR, and SD were 8.6 months, 7.4 months, and 4.3 months, respectively (**Figure 1A**). For lymph-node metastasis, the median times to CR, PR, and SD were 5.6 months, 3.6 months, and 4.2 months, respectively (**Figure 1B**). For bone and soft-tissue metastasis, the median times to CR, PR, and SD were 7.5 months, 8.6 months, and 4.6 months, respectively (**Figure 2A**). For adrenal metastasis, the median time to CR was 6.4 months, only one patient achieved PR (in 4.3 months), and the median time to SD was 2.6 months (**Figure 2B**). For liver metastasis, the median times to PR and SD were 6.9 months and 2.6 months, respectively (**Figure 3A**). For pancreas metastasis, the median times to CR, PR, and SD were 6.9 months, 6.5 months, and 2.4 months, respectively (**Figure 3B**). For spleen metastasis, the median times to CR, PR, and SD were 10.2 months, 3.0 months, and 2.8 months, respectively (**Figure 3C**).

Clinical Outcomes of Metastases in Different Organs

The final follow-up was in October 2019. The median overall follow-up period was 32.0 months (range, 2.6–125.8 months). Median PFS was 10.7 months (95% confidence interval [CI] 9.9–11.4 months) and median OS was 28.3 months (95% CI 26.5–30.1 months) (Supplementary file). Dose interruption and reduction due to adverse events were required in 30.5% (65/213) and 47.4% (101/213) of patients, respectively. The rate of dose reduction or treatment discontinuation for lung, lymph node, bone and soft tissue, liver, adrenal gland, pancreas, and spleen was 50.5% (48/95), 47.8% (33/69), 38.5% (20/52), 45.5% (10/22), 52.4% (11/21), 36.4% (4/11), and 27.3% (3/11), respectively. Difference of the rates was not significant ($P = 0.714$) (**Table 2**).

Kaplan–Meier analysis revealed that median PFT was 8.6 months (95% CI: 6.3-10.9) for lung metastasis, which was similar to lymph node metastasis with 9.0 months (95% CI: 7.6-10.4) ($P = 0.762$). Median PFT was 13.2 months (95% CI: 3.5-22.9) for bone and soft tissue metastasis, which was slightly shorter than adrenal metastasis with 15.2 months (95% CI: 2.7-27.7) ($P = 0.501$). Median PFT of liver metastasis was 5.2 months (95% CI: 2.9-7.5), which was shorter than other organs ($P < 0.001$). Median PFT was not reached in pancreas and spleen, but was > 22.8 months and > 20.6 months, respectively. An overall comparison of all the PFT curves for each organ is shown in Figure 4.

DISCUSSION

It is clear that different therapeutic effects of targeted therapy in the treatment of patients with mRCC are partly correlated with individual metastatic organs. In this study, we further evaluated the response and PFT of each organ individually. We found that metastasis in different organs resulted in organ-specific PFTs and responses to sunitinib.

Tumor burden has been shown to be a prognostic factor in mRCC[11-13]. In this study, we evaluated the tumor burden separately based on the metastatic organs. The results showed that the median tumor burden between different organs was relatively consistent with 4.3 cm

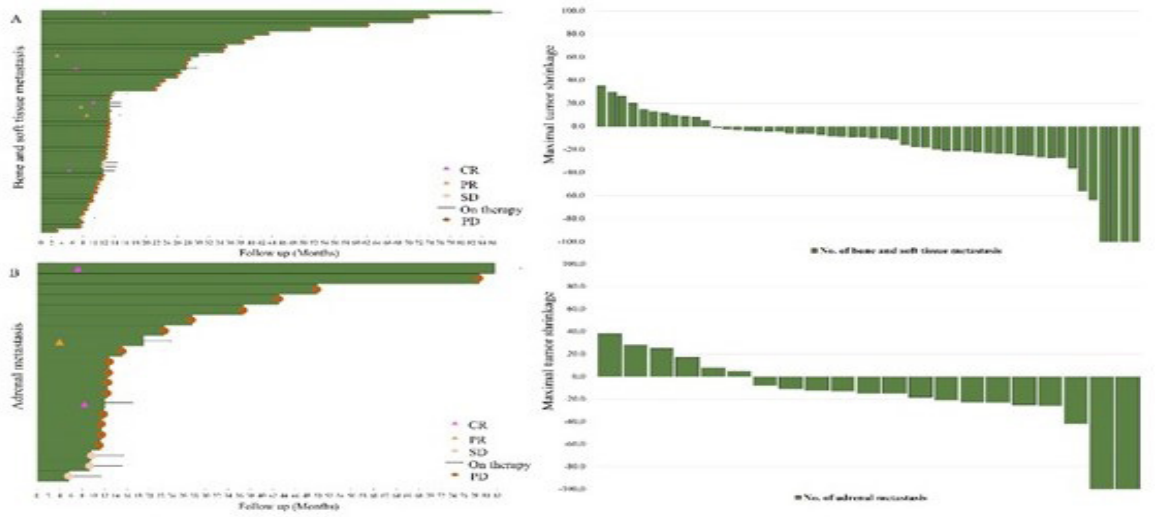

Figure 2. Responses and maximal tumor shrinkage of bone and soft tissue metastasis **(A)** and adrenal metastasis **(B)** assessed by RECIST1.1. CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

in lung, 4.0 cm in lymph node, 3.8 cm in bone and soft tissue, 4.1 cm in liver, 3.9 cm in adrenal gland, 3.8 cm in pancreas, and 3.6 cm in spleen. However, the efficacy of sunitinib varied among organs. Previous results have suggested that the biological behaviors of organs affected by metastasis and the corresponding microenvironments may be related to the efficacy of antiangiogenic therapy[14-16]. In the present study, although all of the metastases originated from ccRCC, the therapeutic responses were organ specific. The ORRs were from 72.7% in the pancreas to 9.1% in the liver. The wide range of ORRs may reflect heterogeneity among the metastatic tumors or the relationship between the growth of metastatic tumors and neovascularization in the various organs. Identification of organ-specific differences in the efficacy of targeted therapies may ena-

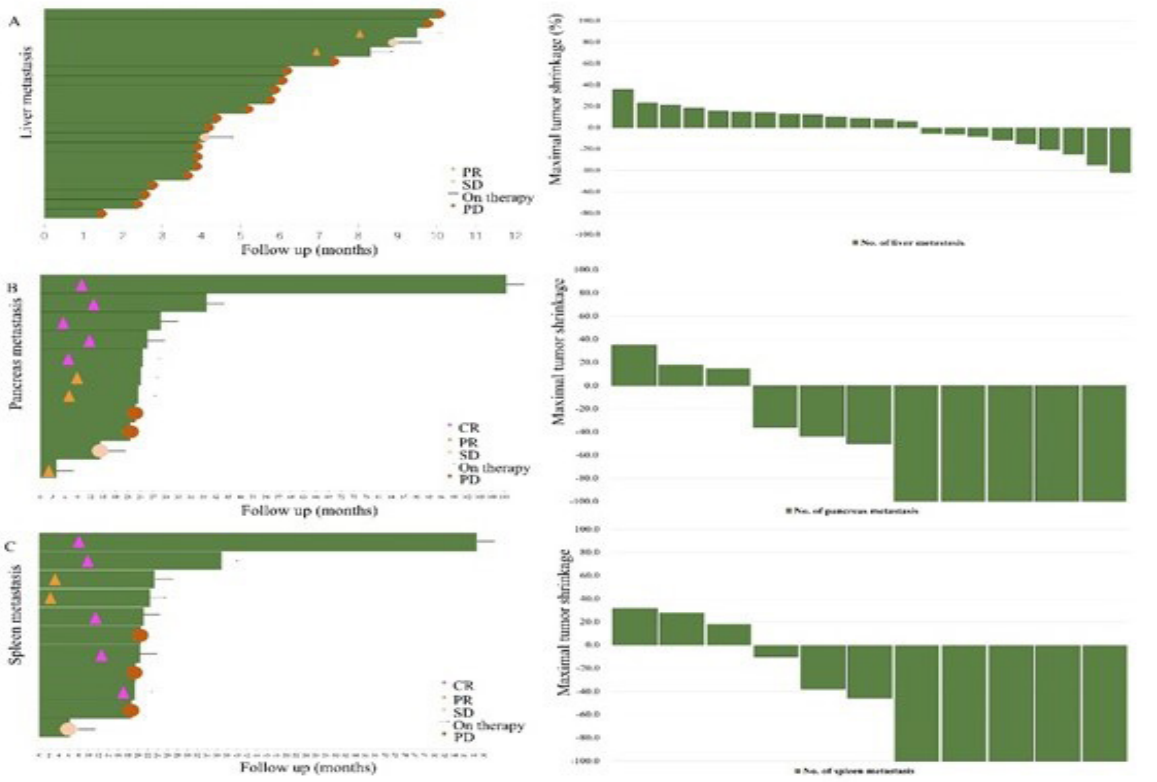

Figure 3. Response and maximal tumor shrinkage of liver metastasis **(A)**, pancreas metastasis **(B)** and spleen metastasis **(C)** assessed by RECIST1.1. CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

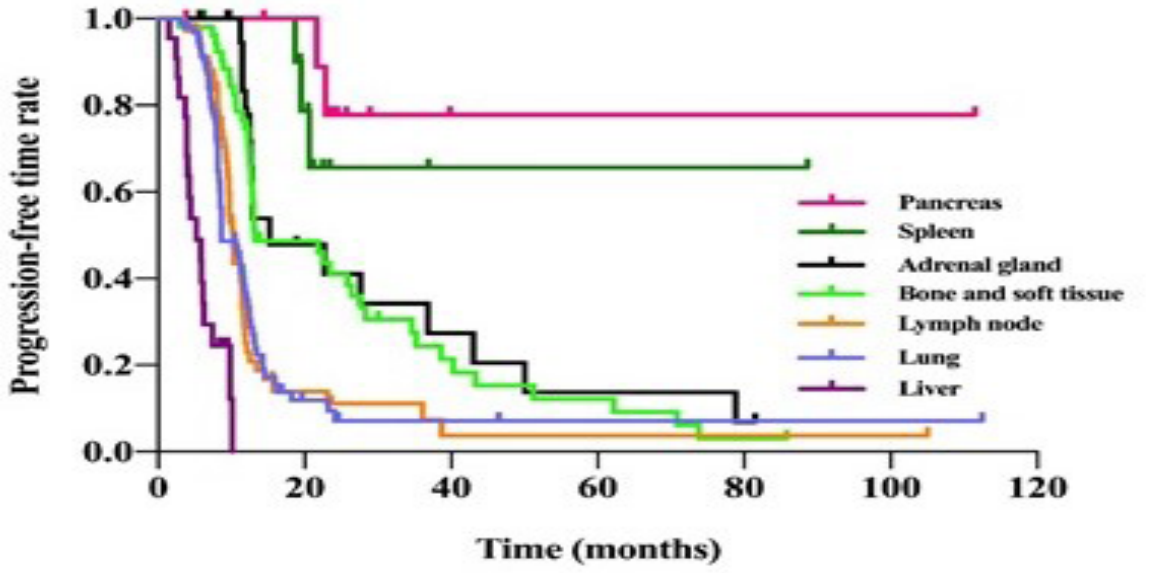

Figure 4. Kaplan–Meier analysis of organ-specific progression free time.

ble a breakthrough in individualized therapy.

The lung is the primary major target organ of metastasis in mRCC, as it is involved in ~45% of cases[4]. In a previous study of patients with mRCC and metastases solely to the lung[17], targeted therapy was found to result in a relatively stable PFS (10.6 months), which is similar to that observed in our study (8.6 months). The lung is an organ with an abundant blood supply, and an anti-angiogenic probably could be more effective. However, we found that lung metastasis had a worse response and shorter PFT than bone and soft tissue, adrenal gland, spleen, or pancreas metastasis. In addition, lymph-node metastasis had a similar PFT to lung metastasis, with a median PFT of 9.0 months. It has previously been suggested that surgical resection is beneficial for isolated lymph-node metastases[18]. In our population, patients with lymph-node metastasis receiving sunitinib mostly had metastases to retroperitoneal lymph nodes that were accompanied by metastases to other organs. For these patients, metastatic lymph node excision may not benefit from surgery. From the above results, we considered that patients with lung and lymph node metastasis treated with sunitinib may have poor prognosis, and be more suitable for immunotherapy or immunotherapy combined with targeted therapy. However, clinical research validation with large cohorts is needed.

Previous studies reported that some selected patients with adrenal-gland metastasis underwent surgery as an alternative treatment option[19,20]. Differently, in our study we found that the organ-specific median PFT for adrenal-gland metastasis was 15.2 months longer than lung, lymph node, and liver metastasis; this suggested that surgical treatment of adrenal-gland metastasis may be not a priority and can be postponed if other metastases are also well controlled. Bone and soft-tissue metastasis had a similar response to adrenal-gland metastasis, with a median PFT of 13.2 months. Bone and soft tissue metastasis has previously been shown to have a negative effect on the outcome in patients with ccRCC who are treated with sunitinib, due to skeletal-related events, including pain, impending fractures, nerve compressions, hypercalcemia, and pathological fractures[21]. Considering the relatively long PFT and stable response associated with bone metastasis in patients with mRCC, we suggest that local therapy may prevent the occurrence of skeletal-related events and may improve the therapeutic effects associated with targeted therapy. In this regard, radiotherapy has been shown to have promising effects on short-term pain control, prevention of fractures, and avoidance of the need for surgery in patients with RCC and multiple bone metastases[22].

In our study population, the ORR and PFT for liver metastasis were only 9.1% and 5.2 months, respectively. The association of poor outcomes with liver metastasis in patients with mRCC who are undergoing targeted therapy is supported by previous findings[23,24]. Therefore, it may be beneficial for patients with liver metastasis to also receive adjuvant treatment, such as surgery, transarterial chemoembolization, or radioablation[25-27]. In addition, immune checkpoint inhibitors may also be applicable.

The pancreas and spleen are infrequently affected by metastasis in mRCC, and published reports relating to these types of metastasis involve cases of isolated and metachronous lesions, for which surgical resections have been recommended[28-32]. However, we found that metastases in the pancreas and spleen had favorable responses to sunitinib, compared with other organs, suggesting that targeted therapy is a suitable treatment for these lesions, and that surgery or other systematic therapies may not be necessary.

A limitation of our study was that it was a retrospective study involving a limited number of cases. A prospective, observational study with a larger population may be needed to confirm (or refute) our findings. In addition, further exploration of the possible mechanisms underlying the organ-specific responses of metastases is needed.

CONCLUSIONS

The present study found organ-specific responses of

metastases to sunitinib treatment. Metastases in the pancreas and spleen may have the best responses, and liver metastasis may have the worst. We suggest that other therapies may be explored for the optimal treatment of liver, lung, and lymph-node metastasis. Further prospective validation is needed to confirm these findings.

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Availability of Data and Materials

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

CONFLICT OF INTEREST

The authors report no conflict of interest.

APPENDIX

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