

Survival Outcomes After Adding Stereotactic Body Radiotherapy to Metastatic Renal Cell Carcinoma Patients Treated With Tyrosine Kinase Inhibitors

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Objective: Long-lasting control is rarely achieved with tyrosine kinase inhibitors (TKI) alone in metastatic renal cell carcinoma (mRCC). Our study aimed to investigate the survival outcomes of adding stereotactic body radiotherapy (SBRT) to TKI in mRCC.

Materials and Methods: From September 2015 to September 2018, 56 patients treated with TKI received SBRT for 103 unresectable lesions. A total of 24 and 32 patients were irradiated before and after TKI failure, respectively. Overall survival (OS) was calculated from metastases. Progression-free survival (PFS) was calculated from SBRT.

Results: Overall, 10, 32, and 12 patients had International Metastatic Renal Cell Carcinoma Database Consortium favorable, intermediate, and poor risk. Median follow-up was 21.7 months (range, 5.1 to 110.6 mo). Median OS was 61.2 months. The median PFS was 11.5 months, while the 2-year LC rate was 94%. Sixteen (34%) lesions achieved complete response (CR) in patients irradiated before TKI failure, whereas only 4 (7%) lesions yielded CR in those irradiated after TKI failure ($P=0.001$). The median PFS in CR group was significantly longer than that of non-CR group (18.9 vs. 7.1 mo; $P=0.003$). The 5-year OS in CR group was 86%, compared with 48% in non-CR group ($P=0.010$). Four (7%) patients experienced Grade 3 toxicity.

Conclusions: Adding SBRT to TKI is safe and seems to improve survival in mRCC. Patients irradiated before TKI failure have higher CR rate, and the favorable local response might turn into survival benefit.

Key Words: metastatic renal cell carcinoma, stereotactic body radiotherapy, tyrosine kinase inhibitor, survival

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Although targeted therapy has substantially improved the prognosis of patients with metastatic renal cell carcinoma (mRCC), survival rates seem to plateau, despite the development of targeted agents. The objective response rate (ORR) after targeted monotherapy ranges from 10% to 30%, with complete and durable responses being rarely observed.^{1–3} The combined use of immunotherapy and targeted therapy has improved survival time and doubled the ORR; however, complete response (CR) remains rare, accounting for about 3% cases.⁴

Definitive local therapy directed against metastatic sites represents an important component of multidisciplinary treatment. Local therapy is not only an indispensable symptom palliation approach, but also an effective way to eradicate metastatic tumor deposits. Complete metastasectomy combined with targeted therapy could prolong overall survival (OS); however, perioperative targeted therapy is associated with an increasing incidence of wound-related complications.⁵ In addition, metastasectomy is only feasible in carefully selected patients, and those with unfavorable tumor size, site, local extent, comorbidity, or functional status lose their potential chance to benefit. By contrast, radiotherapy is a less selective form of local therapy.

Radiotherapy was reserved for symptom relief because of the dogma that renal cell carcinoma is radioresistant. Stereotactic body radiotherapy (SBRT) could overcome radioresistance by intensified dose delivery, emphasizing long-term local control (LC) rather than short-term palliation. Previous studies suggested that SBRT could yield a noninferior LC compared with surgical resection (1-year LC, 80% to 90%), and is preferred when patients present with risk factors.^{6–9} SBRT coupled with targeted therapy might provide additional benefit given their synergetic action. A previous study demonstrated that concurrent targeted therapy and SBRT is safe and offers superior LC compared with SBRT or targeted therapy alone.¹⁰

Previous studies have primarily focused on LC after SBRT; therefore, there is a lack of data regarding the survival benefits and the timing of SBRT when combined with targeted therapy. Therefore, we conducted this study to investigate the survival outcomes and the potential efficacy of the combination strategy.

METHODS AND MATERIALS

Patient Eligibility

The medical records of 350 consecutive patients with mRCC treated with tyrosine kinase inhibitor (TKI) between 2013 and 2018 were reviewed retrospectively. Eligible patients

were adults (≥ 18 y of age) who underwent SBRT for at least 1 unresectable metastatic lesion at the discretion of the genitourinary multidisciplinary team. SBRT was indicated in patients with oligometastases or oligoprogression, or in patients with multiple metastases who required local therapy for symptom relief or tumor burden reduction. Those with spinal instability or rapidly progressive neurological deficit who received SBRT after surgical intervention were also included. Patients were excluded if they were followed up for <2 months, received TKI after SBRT for systemic disease progression or were treated with conventionally fractionated radiotherapy. Finally, 56 patients were included in the analysis.

TKI Administration

All patients were treated systemically with TKI for mRCC. Sunitinib, sorafenib, and axitinib were the most frequently chosen TKI. Sunitinib was administered orally in a 6-week cycle at 50 mg daily for 4 weeks. Sorafenib was given orally at a dose of 400 mg twice daily, and axitinib was given at 5 mg twice daily. The TKI dose was not withheld or reduced during SBRT.

SBRT Procedure

SBRT was indicated for curative intent, major tumor burden, or symptom relief. For patients treated with curative intent, all metastatic sites at the time of SBRT were irradiated. Tumor burden was defined as the sum of the longest unidimensional diameter of target lesions according to Response Evaluation and Criteria in Solid Tumors (RECIST) version 1.1. Major tumor burden was defined as the largest lesion accounting for at least 50% of the tumor burden in each patient. Symptom relief was performed in frail patients with disseminated metastases to relieve pain, spinal cord compression, or bleeding. A total of 103 unresectable lesions were irradiated.

SBRT was performed using Volumetric Intensity Modulated Arc Therapy planning. All patients underwent 3 mm slice thickness contrast-enhanced computed tomography (CT) and/or magnetic resonance imaging simulation scanning with site-specific immobilization. Four-dimensional CT simulation scans were performed in lung metastatic lesions, allowing for visualization of tumor motion. Biologically effective dose (BED) was calculated using linear-quadratic model with $\alpha/\beta = 5$.⁹ The most common fractionation scheme was 35 to 45 Gy delivered in 5 fractions, which was prescribed in 84% patients (Supplementary Table 1, Supplemental Digital Content 1, <http://links.lww.com/AJCO/A296>). Normal tissue dose constraints were in accordance with the United Kingdom consensus since 2018. Before that, BED was calculated for dose constraints. Prescription dose was required to cover $>95\%$ of the target; however, normal tissue protection had priority over target coverage. Cone beam CT was mandatory for daily image-guided radiation therapy during SBRT.

Outcomes and Statistical Analysis

Clinical examination and follow-up scans were recommended every 3 months for the first 2 years; however, early scans might be ordered for patients' complaints. OS was defined as the time from the diagnosis of metastatic disease until last follow-up or death from any cause. Progression-free survival (PFS) was measured from the initiation of SBRT until disease progression or death. LC and distant PFS were defined as freedom from in-field and out-field progression after SBRT, respectively. Irradiated sites were independently assessed for treatment response. Bone metastases were evaluated using The University of Texas MD Anderson Cancer Center (MDA)

criteria,¹¹ and the rest were evaluated using Response Evaluation and Criteria in Solid Tumors version 1.1. Toxicities were graded according to Common Terminology Criteria for Adverse Events rating scale (CTCAE 4.0). Categorical data were compared using a χ^2 test. Survival rates were estimated using the Kaplan-Meier method and compared using the log-rank test. A hazard ratio with a 95% confidence interval for univariate and multivariate analyses was calculated using the Cox proportional hazard model. A P -value <0.05 was considered significant. SPSS version 23 (IBM Corp., Armonk, NY) was used for the statistical analyses.

RESULTS

Patient Characteristics

The clinical features of the patients are summarized in Table 1. Among the 56 patients, 26 (46%) had synchronous metastases. Ten (18%), 32 (57%), and 12 (21%) patients were categorized as International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) favorable, intermediate, and poor risk, respectively at the diagnosis of mRCC. Patients had predominantly clear-cell type disease, with >5 metastatic lesions before SBRT. Bone was the most common metastatic site, followed by the lungs and lymph nodes. Only 4 patients presented with brain metastases.

Treatment Characteristics

The treatment characteristics of the patients were summarized in Table 2. First-line targeted therapy comprised sunitinib, axitinib, or sorafenib in 91% of the patients. Thirty-eight (68%) patients switched to second-line therapy after systemic disease progression. Two patients changed to second-line TKI because of drug intolerance, and 2 patients discontinued systemic treatment because of intolerable toxicity caused by the first-line TKI. All of these patients were treated with first-line sunitinib. Nephrectomy was performed in 84% of

TABLE 1. Patient Characteristics (N = 56)

	Patients, n (%)
Age (y)	
Median (range)	55 (22-86)
Sex	
Male	44 (78.6)
Female	12 (21.4)
Synchronous metastases	26 (46.4)
IMDC score	
Favorable	10 (17.9)
Intermediate	32 (57.1)
Poor	12 (21.4)
Unknown	2 (3.6)
Nonclear cell pathology	22 (39.3)
Sarcomatoid features	10 (17.2)
Metastatic sites before SBRT	
≤ 5 sites	26 (46.4)
> 5 sites	30 (53.6)
Metastatic location before SBRT	
Bone	46 (82.1)
Lung	31 (55.4)
Lymph node	23 (41.4)
Brain	4 (7.1)
ECOG 0-1 before SBRT	27 (48.2)

ECOG indicates Eastern Cooperative Group; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; SBRT, stereotactic body radiotherapy.

TABLE 2. Therapeutic Characteristics (N=56)

	Patients, n (%)
First-line therapy	
Sunitinib	25 (44.6)
Axitinib	13 (23.2)
Sorafenib	13 (23.2)
Others	5 (9.0)
Nephrectomy	47 (83.9)
Metastasectomy	21 (37.5)
SBRT indication	
Curative	18 (32.1)
Major tumor burden	20 (35.7)
Symptom relief	18 (32.1)
Concurrent targeted therapy	
First-line therapy	35 (62.5)
Second-line therapy	21 (37.5)

SBRT indicates stereotactic body radiotherapy.

the patients, and ~38% of the patients underwent incomplete metastasectomy. The sequence of systemic and local therapy for each patient was presented in Figure 1.

The median number of irradiated metastases was 1 (range, 1 to 6), and the median BED was 104 Gy (range, 50 to 165 Gy) (Supplementary Table 1, Supplemental Digital Content 1, <http://links.lww.com/AJCO/A296>). The majority of irradiated lesions were located in bones, accounting for 71% of cases. The median time between the initiation of first-line TKI and SBRT was 5.3 months (range, 0 to 58.9 mo). Twenty-four (43%) patients received SBRT before TKI failure, whereas 32 (57%) patients received SBRT after TKI failure.

Response and Disease Control

CR, partial response, stable disease, and progressive disease were observed in 20 (19%), 67 (65%), 13 (13%), and 3 (3%) lesions after SBRT, leading to an ORR of 84%. In patients irradiated before TKI failure, 16 (34%) lesions achieved CR, whereas only 4 (7%) lesions yielded CR in patients irradiated after TKI failure ($P=0.001$). At last follow-up, 3 lesions (located on the vertebra, pleura, and adrenal gland, respectively) developed progressive disease. The 1-year and 2-year LC rates were 98% and 94%, respectively. The median BED was not different between the CR (104 Gy; range, 50 to 165 Gy) and the non-CR (104 Gy; range, 59 to 134 Gy; $P=0.099$) lesions.

Survival and Prognostic Factors

At a median follow-up of 21.7 months (range, 5.1 to 110.6 mo), 18 patients died. All deaths were tumor-related. The median OS was 61.2 months, with 2-year and 5-year OS rates of 71% and 58%, respectively. The median PFS was 11.5 months, mainly for out-field progression. Thirty-two patients had out-field progression after SBRT, and the median distant PFS was 5.0 months (Fig. 2). The 2-year OS of patients treated for curative intent, major tumor burden, and symptom relief were 93%, 68%, and 58%, respectively ($P=0.032$). Patients who achieved CR at irradiated sites after SBRT had a more favorable prognosis. The median PFS in CR group was significantly longer than that of non-CR group (18.9 vs. 7.1 mo; $P=0.003$). The 5-year OS in CR group was 86%, compared with 48% in non-CR group ($P=0.010$; Fig. 2).

In univariate analysis, IMDC high-risk group, sarcomatoid features, CR after SBRT, ECOG >1 were significant prognostic factors for OS. No difference in OS was found between

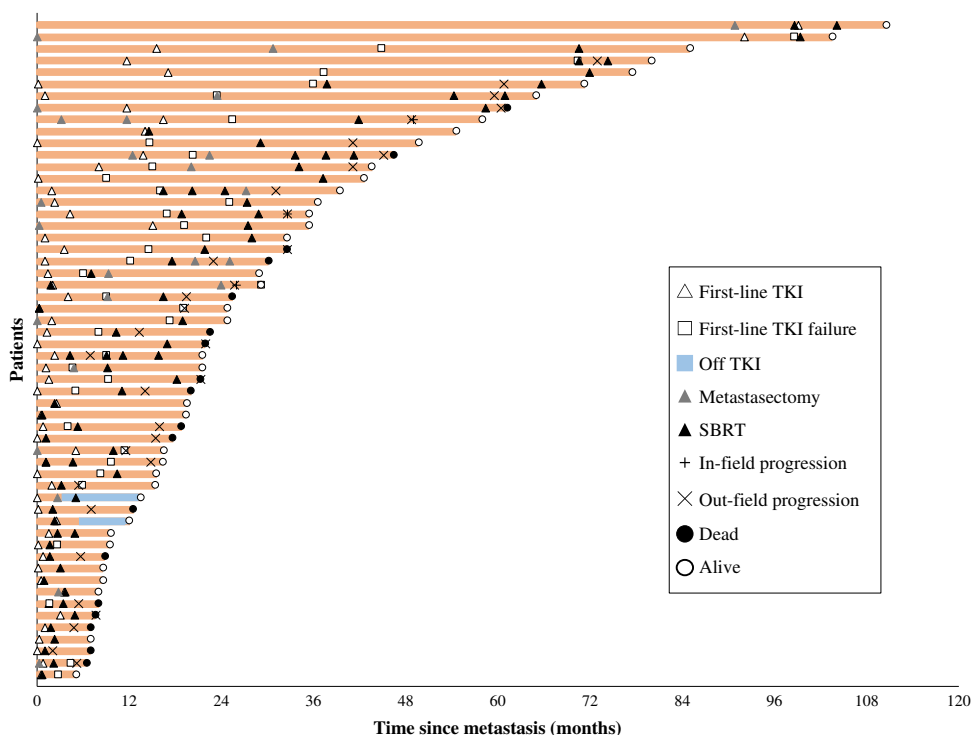


FIGURE 1. Swimmer plot of time since metastases (N = 56). Individual patients are depicted as lines. Two patients who discontinued TKI due to toxicity are demonstrated as blue lines. SBRT indicates stereotactic body radiotherapy; TKI, tyrosine kinase inhibitor.

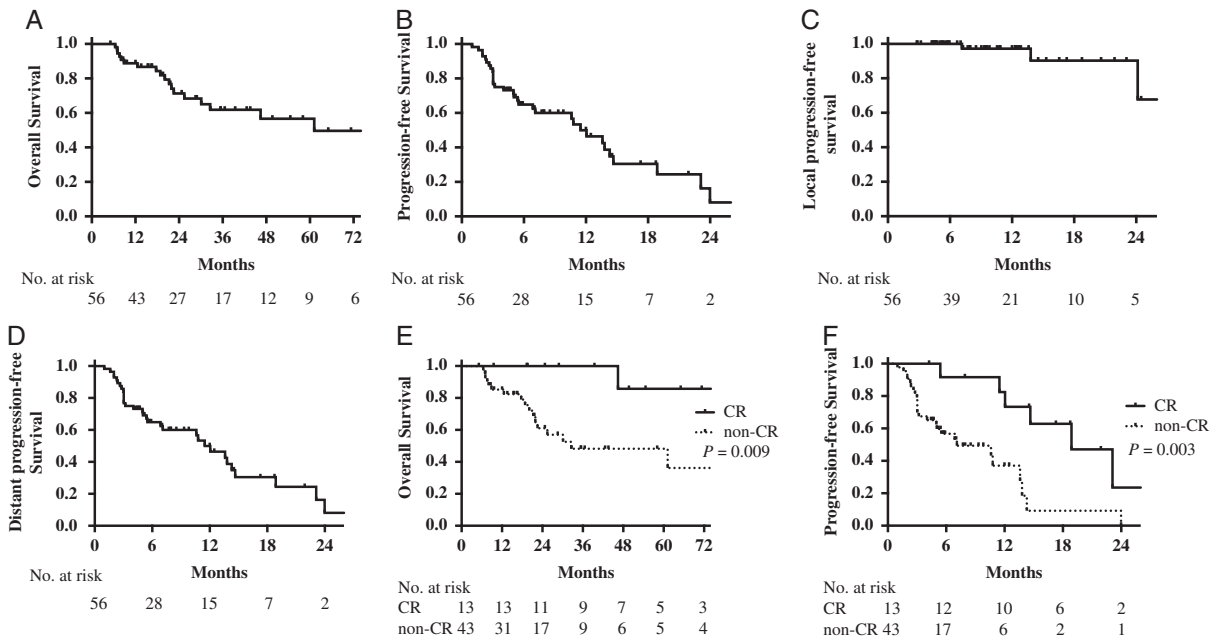


FIGURE 2. Survival outcomes of metastatic renal cell carcinoma patients treated with SBRT combined with TKI (N=56). A, Overall survival. B, Progression-free survival. C, Local progression-free survival. D, Distant progression-free survival of all patients. Overall survival (E) and progression-free survival of patients who achieved local CR and non-CR after SBRT (F). CR indicates complete response; SBRT, stereotactic body radiotherapy; TKI, tyrosine kinase inhibitors.

the concurrent first-line TKI and the concurrent second-line TKI group ($P=0.249$). In multivariate analysis, only CR after SBRT was associated with OS (hazard ratio 0.08; 95% confidence interval, 0.01-0.70; $P=0.023$; Table 3).

Toxicity

Treatment-related toxicities are presented in Table 4. Toxicity occurred in 30 (54%) patients. There were 5 cases of Grade 3 toxicity in 4 patients, and 60% were Grade 3 anemia. One patient with neural invasion before radiotherapy suffered from late radiation-related neuropathy. One patient with pretreatment skin invasion developed skin perforation in addition to Grade 3 anemia, and received skin flap surgery after radiotherapy. One patient with a prior history of multiple pulmonary bullae developed bronchopleural fistula 7 months after radiotherapy. Among the patients

with Grade 3 toxicity, half were treated concurrently with axitinib, and the others received concurrent sunitinib.

DISCUSSION

Local treatment has become increasingly popular to treat patients with oligometastatic mRCC; however, its role in patients with nonoligometastatic disease remains controversial.¹² Our study focused exclusively on the survival benefit of patients treated with combined TKI and SBRT in both the oligometastatic setting and nonoligometastatic setting. SBRT combined with TKI was safe and there was no need to pause the targeted therapy several weeks before SBRT. We also observed superior local treatment response in patients irradiated before TKI failure, and better local treatment response was associated with improved OS. Thus, we suggest the adoption of SBRT early in the course of systemic treatment, preferably before TKI failure.

Acquired resistance will inevitably occur at a median of 6 to 12 months in patients treated with TKI.^{1-3,13,14} Sequential targeted therapy has prolonged the median OS of patients with mRCC to about 30 months; however, cross-resistance after

TABLE 3. Prognostic Factors of Overall Survival

Variables	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	P	HR (95% CI)	P
Sarcomatoid				
Yes vs. no	3.50 (1.30-9.40)	0.013	1.21 (0.33-4.41)	0.768
ECOG PS				
> 1 vs. 0-1	3.37 (1.20-9.51)	0.022	2.90 (0.82-10.3)	0.099
IMDC risk				
High vs. low/favorable	4.74 (1.70-13.2)	0.003	2.65 (0.67-10.5)	0.165
CR after SBRT				
Yes vs. no	0.11 (0.01-0.83)	0.032	0.08 (0.01-0.70)	0.023

CR after SBRT indicates complete response after stereotactic radiotherapy for irradiated sites; ECOG PS, Eastern Cooperative Group performance status; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium.

TABLE 4. Treatment-related Toxicity

	Grade 1	Grade 2	Grade 3
Skin	3	—	1
Alopecia	1	—	—
Skin induration	1	—	—
Gastrointestinal	14	4	—
Neuropathy	2	3	1
Pneumonitis	3	—	—
Neutropenia	11	7	—
Anemia	3	2	3
Thrombocytopenia	3	1	—
Bronchopleural fistula	—	2	—

first-line TKI failure creates a bottleneck to further improve survival outcomes.^{15–17} Thus, systemic therapy alone is insufficient for optimal mRCC management. When assessing the survival outcomes, the median OS of our patients (61.2 mo) was unexpectedly high compared with patients treated with targeted agents alone. Previous studies in patients treated with TKI combined with complete metastasectomy or SBRT demonstrated similar survival benefit (median OS 51 to 66 mo).^{9,18,19} Although the result is only exploratory, we believe that the clear survival improvement was realized by the incorporation of local treatment. Complete metastasectomy, a well-recognized local therapy, could reduce the risk of mortality by 51%, even in the era of targeted therapy.¹⁹ However, up to 25% of patients receiving metastasectomy suffered from major postoperative complications, and perioperative discontinuation of targeted agents would lead to a rapid increase in angiogenesis.^{20,21} SBRT has been shown to be noninferior to metastasectomy, especially in patients with risk factors.⁹ In addition, there was no need to pause TKI during SBRT, ensuring uninterrupted benefit from the combined therapy. Therefore, with improved systemic control and advanced treatment techniques, SBRT might be considered in patients with less favorable risk profiles.

Our study considered sites with major tumor burden as target for SBRT, based on the evidence that tumor burden is a significant prognostic factor.^{22–24} Heterogenous responses of different metastatic sites within individual patients are frequently observed during TKI treatment, among which larger lesions exhibit inferior response rates.²⁵ Furthermore, the development of local resistance is the initial step for systemic progression in most cases, and bulky lesions have a higher proportion of clonal and subclonal alterations that might drive TKI resistance.^{26,27} Theoretically, irradiation to the major tumor burden could reduce the chance of developing resistant clones or subclones and could maintain TKI sensitivity. A previous study suggested that a 1 cm increase in the tumor burden elevates the risk of progression by 4.5% and death by 5%.²³ A greater percentage of tumor burden removal is associated with improved PFS.²⁸ Indeed, our study suggests that those who yielded CR at irradiated sites had more favorable survival outcomes. Thus, cytoreductive radiotherapy for non-oligometastatic patients is promising, and the site and extent of tumor burden removal is worthy of further investigation.

For patients treated with the combined therapy, SBRT delivered before TKI failure resulted in superior PFS, OS, and CR rates. Multivariate analyses revealed that SBRT timing was an independent prognostic factor for survival outcome. Consideration of the use of SBRT early in the course of treatment is encouraged²⁹; however, the use SBRT before TKI requires further discussion. mRCC has a variable spectrum of biological behavior, and patients with certain driver events show rapid systemic progression and extremely short survival.²⁷ On the one hand, TKI could sift out resistant lesions that may benefit from local intervention in patients with multiple metastases. On the other hand, initial TKI could identify patients with rapid progression, who require intensive systemic treatment, rather than local treatment. As observed in the SURTIME and CARMENA trials, cytoreductive nephrectomy (CN) before TKI had a significantly inferior survival outcome compared with sunitinib followed by CN (32.4 vs. 15 mo); however, delaying CN for symptom control could only achieve a median OS of 18.4 months.^{13,30} Thus, TKI followed by SBRT before systemic progression is likely to be the ideal temporal combination.

All of the patients in the present study received concurrent TKI during SBRT, and treatment was well tolerated, despite

common concerns about severe toxicity. Only 5 Grade 3 events were observed, 4 of which were myelosuppression. Previous studies suggested that Grade 3 toxicity after SBRT is 0% to 7% in mRCC, and the few studies focusing on combined modality therapy in mRCC found 0% to 7% Grade 3 toxicities following concurrent treatment.^{6,9,29,31} Meta-analyses showed that the vast majority of evaluated TKI do not alter the adverse effect profile of SBRT when administered concurrently; however, liver SBRT in conjunction with sorafenib should be administered with caution.³²

Our study is limited by its retrospective nature and the relatively small sample size. However, in the absence of prospective randomized trials, our study contributes useful information regarding combined modality therapy for mRCC. In addition, patients with oligometastatic mRCC comprised a relatively small proportion of the series, which might represent a more real-world clinical situation. Thirdly, our patients were treated at a large academic center that has more access to investigational drugs. Thus, results might be difficult to replicate in small centers.

CONCLUSIONS

The present study evaluated survival outcomes and toxicity profiles after combining SBRT with TKI. Our findings suggest that adding SBRT to TKI is safe and seems to improve survival in patients with mRCC. Patients irradiated before TKI failure have higher CR rate, and the favorable local treatment response might turn into survival benefit.

REFERENCES

- Escudier B, Eisen T, Stadler WM, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med*. 2007;356:125–134.
- Hutson TE, Lesovoy V, Al-Shukri S, et al. Axitinib versus sorafenib as first-line therapy in patients with metastatic renal-cell carcinoma: a randomised open-label phase 3 trial. *Lancet Oncol*. 2013;14:1287–1294.
- Motzer RJ, Hutson TE, Cella D, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. *N Engl J Med*. 2013;369:722–731.
- Buchler T, Bortlicek Z, Poprach A, et al. Outcomes for patients with metastatic renal cell carcinoma achieving a complete response on targeted therapy: a registry-based analysis. *Eur Urol*. 2016;70:469–475.
- Chapin BF, Delacroix SE Jr, Culp SH, et al. Safety of presurgical targeted therapy in the setting of metastatic renal cell carcinoma. *Eur Urol*. 2011;60:964–971.
- De Meerleer G, Khoo V, Escudier B, et al. Radiotherapy for renal-cell carcinoma. *Lancet Oncol*. 2014;15:e170–e177.
- Altoos B, Amini A, Yacoub M, et al. Local control rates of metastatic renal cell carcinoma (RCC) to thoracic, abdominal, and soft tissue lesions using stereotactic body radiotherapy (SBRT). *Radiat Oncol*. 2015;10:218.
- Franzese C, Franceschini D, Di Brina L, et al. Role of Stereotactic body radiation therapy for the management of oligometastatic renal cell carcinoma. *J Urol*. 2019;201:70–75.
- Stenman M, Sinclair G, Paavola P, et al. Overall survival after stereotactic radiotherapy or surgical metastasectomy in oligometastatic renal cell carcinoma patients treated at two Swedish centres 2005–2014. *Radiother Oncol*. 2018;127:501–506.
- Kao J, Chen CT, Tong CC, et al. Concurrent sunitinib and stereotactic body radiotherapy for patients with oligometastases: final report of a prospective clinical trial. *Target Oncol*. 2014;9:145–153.
- Costelloe CM, Chuang HH, Madewell JE, et al. Cancer response criteria and bone metastases: RECIST 1.1, MDA and PERCIST. *J Cancer*. 2010;1:80–92.
- Dabestani S, Marconi L, Hofmann F, et al. Local treatments for metastases of renal cell carcinoma: a systematic review. *Lancet Oncol*. 2014;15:e549–e561.

13. Mejean A, Ravaud A, Thezenas S, et al. Sunitinib alone or after nephrectomy in metastatic renal-cell carcinoma. *N Engl J Med*. 2018;379:417–427.
14. Rini BI, Escudier B, Tomczak P, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. *Lancet*. 2011;378:1931–1939.
15. Eichelberg C, Vervenne WL, De Santis M, et al. SWITCH: a randomised, sequential, open-label study to evaluate the efficacy and safety of sorafenib-sunitinib versus sunitinib-sorafenib in the treatment of metastatic renal cell cancer. *Eur Urol*. 2015;68:837–847.
16. Knox JJ, Barrios CH, Kim TM, et al. Final overall survival analysis for the phase II RECORD-3 study of first-line everolimus followed by sunitinib versus first-line sunitinib followed by everolimus in metastatic RCC. *Ann Oncol*. 2017;28:1339–1345.
17. Juengel E, Kim D, Makarevic J, et al. Molecular analysis of sunitinib resistant renal cell carcinoma cells after sequential treatment with RAD001 (everolimus) or sorafenib. *J Cell Mol Med*. 2015;19:430–441.
18. Rausch S, Kruck S, Walter K, et al. Metastasectomy for metastatic renal cell carcinoma in the era of modern systemic treatment: C-reactive protein is an independent predictor of overall survival. *Int J Urol*. 2016;23:916–921.
19. Yu X, Wang B, Li X, et al. The significance of metastasectomy in patients with metastatic renal cell carcinoma in the era of targeted therapy. *Biomed Res Int*. 2015;2015:176373.
20. Griffioen AW, Mans LA, de Graaf AMA, et al. Rapid angiogenesis onset after discontinuation of sunitinib treatment of renal cell carcinoma patients. *Clin Cancer Res*. 2012;18:3961–3971.
21. Meyer CP, Sun M, Karam JA, et al. Complications after metastasectomy for renal cell carcinoma: a population-based assessment. *Eur Urol*. 2017;72:171–174.
22. Basappa NS, Elson P, Golshayan AR, et al. The impact of tumor burden characteristics in patients with metastatic renal cell carcinoma treated with sunitinib. *Cancer*. 2011;117:1183–1189.
23. Iacovelli R, Lanoy E, Albiges L, et al. Tumour burden is an independent prognostic factor in metastatic renal cell carcinoma. *BJU Int*. 2012;110:1747–1753.
24. Stein A, Bellmunt J, Escudier B, et al. Survival prediction in everolimus-treated patients with metastatic renal cell carcinoma incorporating tumor burden response in the RECORD-1 trial. *Eur Urol*. 2013;64:994–1002.
25. Crusz SM, Tang YZ, Sarker SJ, et al. Heterogeneous response and progression patterns reveal phenotypic heterogeneity of tyrosine kinase inhibitor response in metastatic renal cell carcinoma. *BMC Med*. 2016;14:185.
26. Basler SM, Kroeze SG, Guckenberger M. SBRT for oligoprogressive oncogene addicted NSCLC. *Lung Cancer*. 2017;106:50–57.
27. Turajlic S, Xu H, Litchfield K, et al. Tracking cancer evolution reveals constrained routes to metastases: TRACERx Renal. *Cell*. 2018;173:581–594.
28. Barbastefano J, Garcia JA, Elson P, et al. Association of percentage of tumour burden removed with debulking nephrectomy and progression-free survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted therapy. *BJU Int*. 2010;106:1266–1269.
29. Miller JA, Balagamwala EH, Angelov L, et al. Spine stereotactic radiosurgery with concurrent tyrosine kinase inhibitors for metastatic renal cell carcinoma. *J Neurosurg Spine*. 2016;25:766–774.
30. Bex A, Mulders P, Jewett M, et al. Comparison of immediate vs deferred cytoreductive nephrectomy in patients with synchronous metastatic renal cell carcinoma receiving sunitinib: the SURTIME randomized clinical trial. *JAMA Oncol*. 2019;5:164–170.
31. Staehler M, Haseke N, Nuhn P, et al. Simultaneous anti-angiogenic therapy and single-fraction radiosurgery in clinically relevant metastases from renal cell carcinoma. *BJU Int*. 2011;108:673–678.
32. Kroeze SG, Fritz C, Hoyer M, et al. Toxicity of concurrent stereotactic radiotherapy and targeted therapy or immunotherapy: a systematic review. *Cancer Treat Rev*. 2017;53:25–37.