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ORIGINAL ARTICLE

Stereotactic body radiotherapy and tyrosine kinase inhibitors in patients with oligometastatic renal cell carcinoma: a multi-institutional study

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Abstract

Purpose Few studies have determined the viability of stereotactic body radiotherapy (SBRT) and tyrosine kinase inhibitors (TKIs) in the treatment of metastatic renal cell carcinoma (mRCC). We examined the results of RCC patients who had five or fewer lesions and were treated with TKI and SBRT.

Methods The clinical data of 42 patients with 96 metastases treated between 2011 and 2020 were retrospectively evaluated. The prognostic factors predicting overall survival (OS) and progression-free survival (PFS) were assessed in uni- and multivariable analyses.

Results Median follow-up and time between TKI therapy and SBRT were 62.3 and 3.7 months, respectively. The 2-year OS and PFS rates were 58.0% and 51.3%, respectively, and 2-year local control rate was 94.1% per SBRT-treated lesion. In univariable analysis, the time between TKI therapy and SBRT and treatment response were significant prognostic factors for OS and PFS. In multivariable analysis, a time between TKI therapy and SBRT of less than 3 months and complete response were significant predictors of better OS and PFS. Only 12 patients (28.6%) had a systemic treatment change at a median of 18.2 months after SBRT, mostly in patients with a non-complete treatment response after this therapy. Two patients (4.8%) experienced grade III toxicity, and all side effects observed during metastasis-directed therapy subsided over time.

Conclusion We demonstrated that SBRT in combination with TKIs is an effective and safe treatment option for RCC patients with ≤5 metastases. However, distant metastasis was observed in 60% of the patients, indicating that distant disease control still has room for improvement.

Keywords Renal cell carcinoma · Oligometastasis · Tyrosine kinase inhibitor · Stereotactic body radiotherapy · Survival

Introduction

Renal cell carcinoma (RCC) accounts for 3–5% of all adult cancers, with a less than 50% survival rate at 5 years [1]. A third of patients with RCC have metastases at the time of diagnosis, and another third will develop metastases during the course of the disease [2, 3]. Despite the fact that targeted therapy has increased survival and prolonged progression-free survival (PFS) in mRCC patients to 12–15 months, resistance to tyrosine kinase inhibitors (TKIs) is unavoidable, and the depletion of effective systemic agents is only a matter of time [4–6]. As a result, systemic therapy must be combined with other complementary treatment modalities to improve survival, such as metastasis-directed therapy (MDT).

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Previous research has shown that complete metastasectomy improves overall survival (OS) in mRCC patients compared to incomplete or no metastasectomy [7]. However, in the age of targeted therapy, metastasectomy has become less common. On the one hand, the use of perioperative targeted therapy has been associated with an increase in the number of complications that arise during surgical procedures [8]. Furthermore, the interruption of targeted therapy during surgery can cause rapid angiogenesis, which promotes tumor growth [9]. Moreover, metastasectomy is only possible in a subset of patients, and those with an unfavorable tumor size, site, local extent, comorbidity, or functional status are out of luck. Therefore, a more conservative MDT modality is necessary to increase survival without causing an interruption in treatment or complications.

Previously, it was believed that RCC was a radioresistant tumor, and only conventionally fractionated radiotherapy (RT) was used to relieve the symptoms. Stereotactic body radiotherapy (SBRT), which delivers intensified radiation doses in a highly conformal manner in one to five fractions, has the potential to overcome the inherent radioresistance of RCC. Previous studies have suggested that SBRT could result in non-inferior local control (LC) when compared to surgical resection [10–12]. Furthermore, preclinical data have provided a biological basis for mRCC radiosensitivity to SBRT-induced activation of the ceramide pathway and the presence of an immunologically mediated abscopal effect [13, 14].

A previous study demonstrated that the combination of TKIs and SBRT is safe and results in superior LC when compared to SBRT or TKI therapy alone in patients with various types of cancer [15]. Moreover, one prospective trial [16] and a few retrospective studies have determined the viability of SBRT and TKIs in the treatment of mRCC [17–21]. To contribute to this body of knowledge, we present the outcomes of SBRT and TKI use in patients with oligometastatic RCC (five or fewer lesions) and investigate prognostic factors for OS and PFS.

Materials and methods

Patient selection

In this retrospective study, clinical data of 42 biopsy-confirmed RCC patients treated between 2011 and 2020 at two centers were analyzed. An age of 18 years or older, histologic diagnosis of RCC on the primary tumor, an Eastern Cooperative Oncology Group (ECOG) performance score of 0–1, fewer than or equal to five oligometastatic lesions, a controlled primary tumor, an SBRT fraction dose of at least 5 Gy per fraction, and a biologically effective dose (BED) of at least 90 Gy using α/β of 2.63 Gy [22] were the inclusion criteria. Patients were excluded if they had received conventional fractionation, had received immunotherapy or any systemic therapy as a first-line therapy, underwent a complete or incomplete metastasectomy, or had a life expectancy of less than 3 months. SBRT was indicated if the patient had five or fewer oligometastases at the time of diagnosis or oligoprogressive lesions while receiving systemic treatment. All patients gave their written informed consent for treatment. This study was approved by the Baskent University Institutional Review Board (Project no: KA22/313) and supported by the Baskent University Research Fund.

TKI treatment

For mRCC, all patients received systemic TKI therapy. The most commonly used TKI was sunitinib in 23 patients (54.8%) followed by pazopanib in 14 patients (33.3%) and axitinib in 5 (11.9%) patients. Suntinib was given orally in a 6-week cycle at a dose of 50 mg daily for 4 weeks. Pazopanib was given at a single dose of 800 mg/day administered orally, and axitinib at 5 mg twice daily. During SBRT, the TKI dose was not withheld or reduced, except for in cases of serious toxicity caused by the treatment.

Radiotherapy planning and treatment

SBRT was used to treat a total of 96 lesions. We obtained a contrast-enhanced planning computed tomography (CT) with 1.25-mm slice thickness using an Optima 580 computed tomography scanner (GE Healthcare, Waukesha, WI, USA). The patients were placed in supine position with their arms elevated above their heads and immobilized with a BodyFIX® bluebag (Elekta, Stockholm, Sweden). In addition, an abdominal compress was used to minimize target volume motion during treatment for lung and adrenal gland metastasis. For patients with brain metastasis, a thermoplastic mask was used to eliminate movement during treatment.

The SBRT dose regimens were determined based on institutional protocols. The prescribed dosage was determined by the size and location of the lesion. For spinal lesions, 16 or 18 Gy delivered in one fraction was preferred; for non-spinal bone lesions, 20 Gy or 27 Gy delivered in two or three fractions was preferred. Meanwhile, 60 Gy delivered in three or four fractions was prescribed for lung metastasis, 27–30 Gy delivered in three or four fractions was prescribed for adrenal gland metastasis, and 35 Gy delivered in five fractions was prescribed for lymph node metastasis. The prescribed dose for brain metastasis was 18–20 Gy delivered in one fraction, or 24 or 25 Gy in three or five fractions. All treatment plans incorporated previously defined dose constraints for organs at risk [23].

To compensate for setup errors, daily cone-beam CT-guided RT was administered to all patients. Specifically, the patient was positioned using cone-beam CT, and the couch was adjusted online using the Hexapod evo RT System (Elekta AB, Stockholm, Sweden). After automatic matching of the cone-beam CT images to reference CT images, the treating physician repositioned the couch and performed manual refining.

Follow-up

Except for the first visit, which was scheduled 45 days after SBRT for toxicity assessment, patients were followed up every 3 months. At the time of the initial assessment, radiologic responses were collected and classified as complete response (CR), partial response (PR), stable disease (SD), or progression of disease (PD) using the RECIST version 1.1 classification system [24]. Patients who had oligoprogression after MDT in another treated region were considered for additional treatment; another round of SBRT was delivered to patients with progressive lesions who met the dose constraints for critical organs (e.g., the spinal cord, intestines, and kidneys). In patients with advanced disease, a new systemic treatment was started.

The Common Terminology Criteria for Adverse Events, version 4.0, were used to assess acute and late toxicities. Toxicities were reported as the absolute number of patients and their relative rates.

Statistical analysis

SPSS 22.0 (SPSS for Windows, IBM Corp., Armonk, NY, USA) and GraphPad Prism (GraphPad Software, Inc., San Diego, USA) version 9.3.1 were used for statistical analysis. The mean, standard deviation, range, and median were calculated as part of the descriptive analysis. OS was calculated using the time interval between the oligometastasis date and death or last follow-up. The PFS was calculated by taking the time between the last day of MDT to the oligoprogressive lesion and the date of radiological detection of local progression or distant metastasis following SBRT, whichever came first. The OS, PFS, and LC rates were calculated using the Kaplan–Meier method. The log-rank test was used for univariate analysis. Covariates with a p-value less than 0.05 in univariate analysis were included in multivariate analyses using the Cox proportional hazards model. Statistical significance was defined as p-values less than 0.05.

Results

Patient characteristics

Table 1 shows the clinical characteristics of the patients. In total, 42 patients with 96 SBRT-treated lesions were evaluated. The majority of patients (88.1%) were male, had clear cell histology (73.8%), had only one metastasis (52.4%), and had the majority of lesions in their bones (61.8%).

Table 1 Patient and tumor characteristics

Parameter	Patient number	%
Age (years; median, range)	65 (38–81)	
Gender		
Male	37	88.1
Female	5	11.9
Histology		
Clear cell	31	73.8
Non-clear cell	11	26.2
Timing of metastasis		
Synchronous	18	42.9
Metachronous	24	57.1
Number of metastases		
1	22	52.4
2	4	9.5
3	6	14.3
4	2	14.8
5	8	19.0
Site of metastasis		
Bone	26	61.8
Brain	8	19.1
Lung	4	9.5
Adrenal gland	2	4.8
Lymph node	2	4.8
Treatment of primary tumor		
Surgery	21	50.0
Surgery + ChT	20	47.6
Surgery + ChT + RT	1	2.4
Systemic agent (TKI)		
Sunitinib	23	54.8
Pazopanib	14	33.3
Axitinib	5	11.9
Treatment change after MDT		
Yes	12	28.6
No	30	71.4
Treatment response after MDT		
CR	27	64.3
PR	5	11.9
SD	3	7.1
PD	7	16.7

ChT chemotherapy, *RT* radiotherapy, *MDT* metastasis-directed therapy, *TKI* tyrosine kinase inhibitor, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

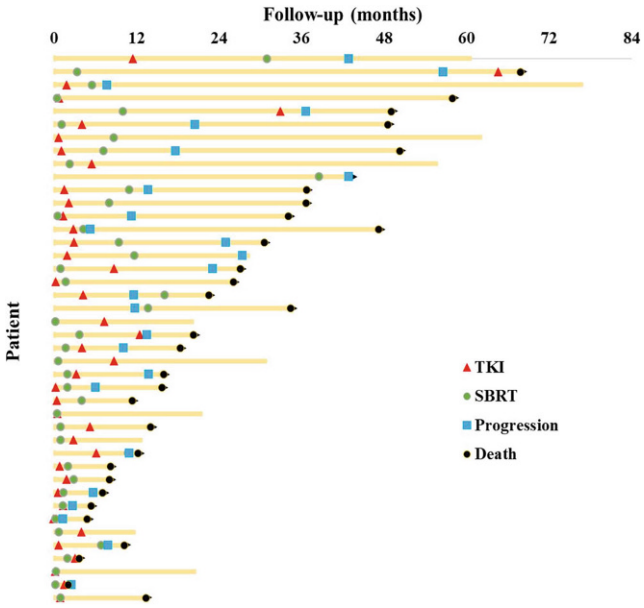

Fig. 1 Swimmer plot diagram demonstrating patient treatment sequence, progression, and death. *TKI* tyrosine kinase inhibitor, *SBRT* stereotactic body radiotherapy

Twenty-four (57.1%) patients had synchronous oligometastasis, while 18 (42.9%) had metachronous oligometastasis. Sunitinib was the most commonly used TKI (23 patients, 54.8%). Fig. 1 depicts the systemic and local therapy sequence for each patient.

The median number of irradiated metastases was 1 (range 1–5) and the median BED was 109.2 Gy (range 90.6–521.5 Gy). The median SBRT fraction and total doses were 8 Gy (range 5–24 Gy) and 24 Gy (range 12–60 Gy), respectively. SBRT was delivered with a median of three (range 1–5) fractions.

Thirty-three patients (78.6%) received SBRT applied to oligometastases followed by TKI therapy, 8 patients (19.0%) received TKI therapy first followed by SBRT applied to metastatic lesions, and 1 patient (2.4%) began TKI therapy together with SBRT. The median time between TKI therapy and SBRT was 3.7 months (range 0–49.6 months).

Treatment outcomes

After a median follow-up of 62.3 months (interquartile range [IQR] 44.3–80.3 months), 11 patients (26.2%) remained alive (7 patients [16.7%] with disease), 29 patients (69.0%) had died of their disease, and 2 patients (5.8%) had died from other causes. The 2-year OS and PFS rates were 58.0% and 51.3%, respectively (Fig. 2). The median OS was 30.5 months (95% CI 15.9–43.1 months) and the median PFS was 25.7 months (95% CI 15.1–34.4 months). At a median follow-up of 17.3 months (95% CI 12.1–36.6 months) after SBRT, 25 patients (59.5%) developed disease progression. Only 2 patients had additional in-field local recurrences in addition to distant metastasis, with all the recurrences being distant metastasis as well. The 2-year LC rate was 94.1% per lesion.

Prognostic factors

The time between TKI therapy and SBRT as well as the treatment response were significant prognostic factors for OS and PFS in univariable analysis (Table 2). Furthermore, clear cell histology was associated with a marginally worse OS compared to non-clear cell histology ($p=0.07$). Patients with a shorter interval between SBRT and TKI therapy (<3 months) had significantly longer median OS (47.2 months vs. 15.7 months; $p=0.01$; Fig. 3a) and PFS (30.5 months vs. 15.1 months; $p=0.04$) than those with a longer interval (≥3 months; Fig. 3c). Median OS in the CR group was 36.6 months, while it was 8 months in the non-CR group ($p=0.02$; Fig. 3b). The median PFS in the CR group was significantly longer than that of the non-CR group (34.4 months vs. 5.0 months; $p=0.001$; Fig. 3d). In multivariable analysis, a time between TKI and SBRT of more than or equal to 3 months as well as non-CR were found to be significant predictors of poorer OS and PFS (Table 2).

After receiving SBRT for oligometastatic lesions, 30 patients (71.4%) remained on the same treatment, while 12 patients (28.6%) had a systemic treatment change at a of

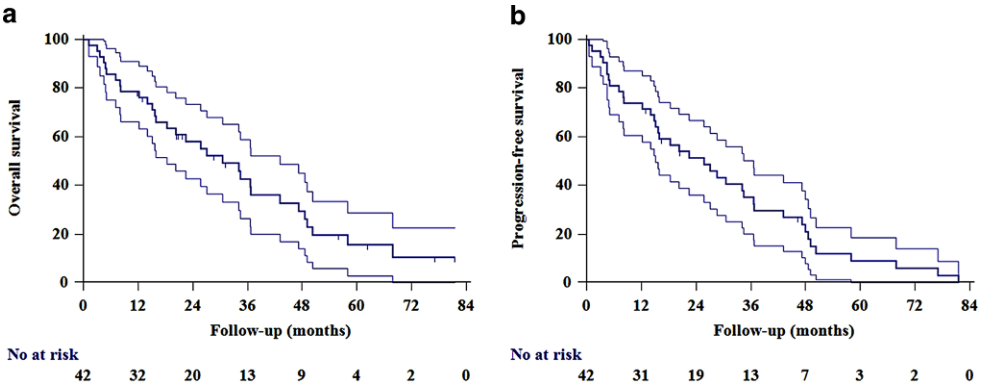

Fig. 2 Kaplan–Meier curves for **a** overall survival and **b** progression-free survival

Table 2 Univariate and multivariate analyses of prognostic factors for overall and progression-free survival

	Overall survival				Progression-free survival			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
Patient characteristics	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Patient age								
≤ 65 years	1	0.36	–	–	1	0.55	–	–
> 65 years	1.40 (0.69–2.85)	–	–	–	1.07 (0.55–2.07)	–	–	–
Gender								
Female	1	0.53	–	–	1	0.88	–	–
Male	1.60 (0.38–6.74)	–	–	–	0.92 (0.32–2.64)	–	–	–
Histology								
Clear cell	1	0.07	–	–	1	0.27	–	–
Non-clear cell	0.38 (0.13–1.08)	–	–	–	0.63 (0.27–1.43)	–	–	–
Site of metastasis								
Bone	1	0.19	–	–	1	0.59	–	–
Non-bone	1.63 (0.79–3.33)	–	–	–	1.21 (0.62–2.36)	–	–	–
Number of metastases								
1	1	0.92	–	–	1	0.49	–	–
> 1	0.96 (0.47–1.96)	–	–	–	1.26 (0.65–2.44)	–	–	–
Timing of metastasis								
Synchronous	1	0.61	–	–	1	0.24	–	–
Metachronous	1.21 (0.59–2.48)	–	–	–	1.49 (0.76–2.91)	–	–	–
RT–TKI time								
< 3 months	1	0.01	1	0.02	1	0.04	1	0.009
≥ 3 months	2.53 (1.23–5.20)	–	2.50 (1.16–5.41)	–	1.98 (1.02–3.83)	–	2.56 (1.26–5.22)	–
Treatment response								
CR	1	0.02	1	0.02	1	0.001	1	< 0.001
Non-CR	2.50 (1.13–5.52)	–	2.79 (1.22–6.40)	–	3.44 (1.69–6.99)	–	4.40 (2.03–9.56)	–
Treatment change								
Yes	1	0.55	–	–	1	0.26	–	–
No	1.26 (0.59–2.69)	–	–	–	1.51 (0.74–3.09)	–	–	–

HR hazard ratio, *RT* radiotherapy, *TKI* tyrosine kinase inhibitor, *CR* complete response

median 18.2 months (range 3.8–35.9 months) after completion of the SBRT: 8 patients switched treatment from a TKI to immunotherapy and 4 patients switched from one TKI to another. Patients with non-CR had higher rates of treatment change compared to those with CR (40.7% vs. 6.7%; $p = 0.03$). However, the time between TKI and SBRT had no effect on treatment modification (33.3% vs. 25.0%; $p = 0.73$).

Toxicity

All patients received their treatment as planned. During SBRT, seven patients (16.8%) experienced grade I toxicities, including four with esophagitis, one with pain, one with diarrhea, and one with dermatitis. Six patients (14.4%) developed grade II toxicity during SBRT. Two of them had esophagitis, while the others had anemia, fatigue, liver toxicity, and dermatitis. Only one patient (2.4%) experienced grade III diarrhea and one (2.4%) had grade III hyperten-

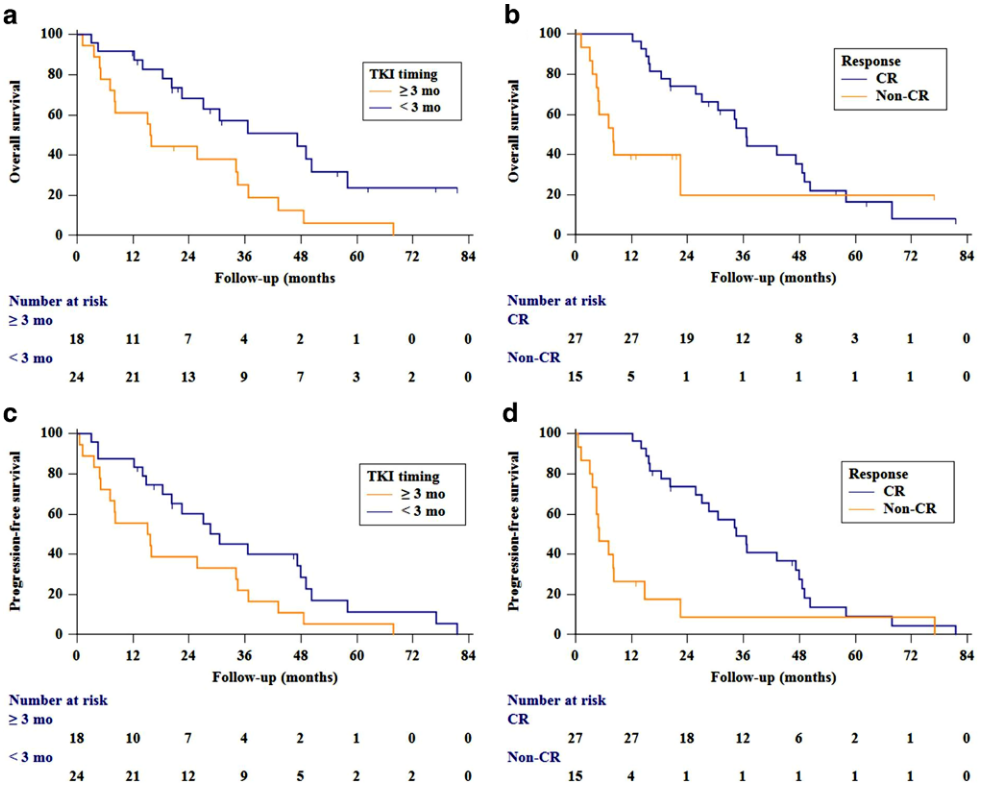

Fig. 3 Overall survival and progression-free survival in patients receiving tyrosine kinase inhibitor (*TKI*) and stereotactic body radiotherapy (SBRT) in ≥3 and <3 months (**a**,**c**), and patients with complete response (*CR*) and non-CR (**b**,**d**)

sion while undergoing SBRT. All of the side effects seen during MDT subsided over time.

Discussion

In this retrospective study, we demonstrated that SBRT applied to oligometastatic sites combined with TKI therapy is an effective and safe treatment option for patients with RCC who have five or fewer metastases. Patients who had CR as well as those who had a shorter time interval between TKI therapy and SBRT had better OS and PFS than their counterparts. SBRT for metastatic lesions results in excellent in-field control rates, but approximately 60% of patients developed disease progression, with all recurrences being distant metastasis. Nearly 30% of patients required a systemic treatment change, with a median time interval before this change of 18.2 months after completion of the MDT, which was more common in patients with non-CR after SBRT. Our findings show that combining SBRT and TKI therapy within a short period of time as well as CR after SBRT improves treatment outcomes.

Even in the era of targeted therapy, complete metastasectomy, a well-known local therapy, could reduce the risk of mortality by approximately 50% [25]. However, up to 25% of patients undergoing metastasectomy experienced significant postoperative complications and stopping targeted agents during surgery would result in a rapid increase in angiogenesis [8, 9]. Stenman et al. [11] demonstrated that SBRT is equivalent to metastasectomy in terms of local disease control and survival, particularly in high-risk mRCC patients. A further advantage of SBRT over metastasectomy is that there is no need to pause TKI administration during SBRT, thus ensuring that the combined therapy provided continuous benefit. According to a meta-analysis of 28 studies conducted by SABR ORCA, SBRT can safely achieve remarkable tumor control in oligometastatic RCC, with an LC rate of approximately 90% and any significant toxicity rate of approximately 1% [26]. Therefore, SBRT may be considered for patients with oligometastasis or oligoprogressive disease due to its potential for improved local control, the advanced treatment technique, and provision of the opportunity to continue systemic treatment.

Previous studies have demonstrated the efficacy of TKIs in conjunction with SBRT in patients with oligometastatic RCC ([16–20]; Table 3). In a phase II prospective multicenter study, Cheung et al. [16] evaluated the use of SBRT in oligoprogressive mRCC patients already receiving TKI therapy and found it to be effective, with a median PFS of 9.3 months and 1-year OS of 92%. Liu et al. [20] compared mRCC patients treated with TKI alone or TKI and SBRT and discovered that the median OS in the TKI and SBRT group was significantly longer than that in the TKI-alone group (63.2 vs. 29.8 months; $p < 0.001$), and only 5 patients

Table 3 Published studies involving patients treated with tyrosine kinase inhibitors (TKIs) and stereotactic body radiotherapy (SBRT) for oligometastatic renal cell carcinoma

Author (year)	*N*	No. of lesions	Site of OM (%)	TKI (%)	Follow-up (months)	OS	PFS	Toxicity (%)
Cheung et al. (2021) [16]	37	57	Lung (37) Bone (26) Lymph node (12) Brain (5) Others (20)	Sunitinib (95) Pazopanib (5)	11.8	1-year: 92%	Median: 9.3 months	No grade ≥ 3 acute or late toxicities
Staehler et al. (2012) [17]	22	33	Bone (45.5) Lymph node (30.3) Local recurrence (12.1) Others (12.1)	Sunitinib (100)	14.3	Median: NR	NA	Gr IV hypertension (4.5)
He et al. (2020) [18]	56	103	Bone (82.1) Lung (55.4) Lymph node (41.4) Brain (7.1)	Sunitinib (44.6) Axitinib (23.2) Sorafenib (23.2) Others (9.0)	21.3	Median: 61.2 months	Median: 11.5 months	Gr III fatigue (5.4), dermatitis (1.8), neuropathy (1.8)
Gebbia et al. (2020) [19]	28	61	Bone (71) Lungs (50) Lymph node (39) Brain (18)	Pazopanib (100)	NA	NA	Median: 14 months	Gr III hypertension (7), diarrhea (4), anemia (4), liver toxicity (7), pneumonitis (4)
Liu et al. (2021) [20]	85	144	Bone (68.1) Lymph node (6.9) Lung (5.6) Brain (2.1) Others (17.3)	NA	25.8	Median: 63.2 months	Median: 9 months	Gr III anemia (7), neutropenia (2), dermatitis (1), hemorrhage (1)
Current study	42	96	Bone (61.8) Brain (19.1) Lung (9.5) Others (9.6)	Sunitinib (54.8) Pazopanib (33.3) Axitinib (11.9)	62.3	Median: 30.5 months	Median: 25.7 months	Gr III diarrhea (2), hypertension (2)

(5.9%) experienced SBRT-related grade III toxicities. He et al. [18] found that in 56 patients treated with TKIs who received SBRT for 103 unresectable lesions, the median OS was 61.2 months, the median PFS was 11.5 months, and the 2-year LC rate was 94%. While these two studies reported very impressive median OS values of approximately 5 years, the median OS in our study was only approximately 30 months, which may be attributable to the longer median follow-up period in our study (62.3 months) compared to the other two studies (21.3 and 25.8 months) [18, 20]. However, our median PFS was higher compared to previous studies, which may be due to the fact that only patients with ≤ 5 metastases were included in the current study, whereas in the study by He et al. [18], 54% of patients had > 5 metastases and only 32% of patients were treated with curative intent, and, in the study by Liu et al. [20], 48% of patients had ≤ 5 metastases.

Although early use of SBRT is encouraged, there is still no agreement regarding when TKI and SBRT should be administered to patients with mRCC. However, in patients with multiple metastases who may benefit from local intervention, TKI may eradicate resistant tumors. Initial TKI, on the other hand, may identify patients with rapid progression who require intensive systemic treatment rather than local treatment. Recently, He et al. [18] found that SBRT given before TKI failure resulted in better PFS, OS, and CR rates than SBRT given after TKI, and, in multivariate analyses, SBRT timing was an independent prognostic factor for survival outcome. In multivariable analysis of the present study, we found that patients receiving TKI therapy and SBRT within 3 months of each other was an independent predictor of improved OS and PFS, supporting the evidence that concurrent use of TKI therapy and SBRT is an effective treatment option for patients with mRCC.

Delaying or changing systemic treatment for mRCC may benefit patients financially as well as in terms of quality of life and the ability to save potentially effective therapies for later stages of the disease; however, it is not without risks. The majority of patients receiving systemic treatment for mRCC have side effects, and immune checkpoint inhibitors in particular have been linked to severe immune-related side effects in up to 40% of patients [27]. The use of MDT may allow for a change in systemic treatment to be postponed [10, 12]. We found that approximately 30% of patients in

our study underwent a systemic therapy change after SBRT applied to a metastatic site—particularly those with CR after MDT—demonstrating the efficacy of local treatment to oligometastatic sites in deferring systemic therapy change.

Previous studies have demonstrated the safety of SBRT in mRCC patients, with rates of grade III toxicity ranging from 0 to 7% [12, 28], while the few studies focusing on combined-modality therapy of TKIs and SBRT in mRCC found 0 to 7% grade III toxicities after concurrent treatment [16, 18, 20]. Furthermore, meta-analyses have revealed that the vast majority of tested TKIs have no effect on the adverse effect profile of SBRT when used concurrently [29]. In line with the literature, we observed grade III toxicity in only 2 patients (4.8%) who received TKI therapy and SBRT sequentially or concurrently.

The limitations of the current study include its small patient population, retrospective design, and some selection biases. Another constraint was a population with varying fractionation schedules and a high degree of diversity. Additionally, there was no control group of TKI-only patients. Nonrandom MDT selection may have been influenced by the clinician's assessment of disease status, the clinician's personal preference for or aversion to specific agents, and/or the patients' anticipated tolerance of treatment side effects. SBRT patients may represent a subset that is healthier and more tolerant of side effects, thereby exaggerating the actual time to progression associated with systemic treatment. Because the vast majority of patients in our study were referred for bone or lung metastases as opposed to intra-abdominal parenchymal metastases or brain metastases, our current findings suggest that application of RT to oligometastatic RCC may be limited. Collectively, these constraints hindered our ability to conduct causal analysis in a clinical setting to guide patient selection, treatment selection, and treatment sequencing. On the other hand, our study had a relatively long follow-up period, only included patients with fewer than or equal to five metastases, and was multicentric.

Conclusion

In this retrospective study, we found that TKI therapy combined with SBRT to oligometastatic sites is an effective and safe treatment option for mRCC patients with five or fewer metastases. The most important finding of this study is that patients with CR to MDT and those receiving TKI and SBRT within less than or equal to 3 months had a better OS and PFS compared to their counterparts. Excellent LC was attained at the oligometastatic site treated with SBRT, but disease progression was seen in the majority of patients 17 months after the end of MDT, with all patients experiencing distant disease progression, and only 2 patients experiencing additional recurrence at the SBRT-treated lesion. This necessitated the use of a successful systemic therapy to improve the treatment outcomes. Prospective studies on SBRT with TKIs for oligometastatic sites are necessary to provide information on how well the disease is controlled and how well patients survive after such a treatment strategy.

Declarations

Conflict of interest C. Onal, E. Oymak, O.C. Guler, B. Tilki, G. Yavas, P. Hurmuz, C. Yavas, and G. Ozyigit declare that they have no competing interests.

Ethical standards All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by the Baskent University Institutional Review Board (project no: KA22/313) and supported by the Baskent University Research Fund.

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