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Objectives

To evaluate the safety and efficacy of stereotactic radiotherapy (SRT) in patients with metastatic renal cell carcinoma (mRCC) concurrently receiving targeted therapy (TT) or immunotherapy.

Patients and Methods

Data on patients with mRCC were extracted from a retrospective international multicentre register study (TOaSTT), investigating SRT concurrent (≤30 days) with TT/immune checkpoint inhibitor (ICI) therapy. Overall survival (OS), progression-free survival (PFS), local metastasis control (LC) and time to systemic therapy switch were analysed using Kaplan–Meier curves and log-rank testing. Clinical and treatment factors influencing survival were analysed using multivariate Cox regression. Acute and late SRT-induced toxicity were defined according to the Common Terminology Criteria for Adverse Events v.4.03.

Results

Fifty-three patients who underwent 128 sessions of SRT were included, of whom 58% presented with oligometastatic disease (OMD). ICIs and TT were received by 32% and 68% of patients, respectively. Twenty patients (37%) paused TT for a median (range) of 14 (2–21) days. ICI therapy was not paused in any patient. A median (range) of 1 (1–5) metastatic tumour was treated per patient, with a median (range) SRT dose of 65 (40–129.4) Gy (biologically effective dose). The OS, LC and PFS rates at 1 year were 71%, 75% and 25%, respectively. The median OS and PFS were not significantly different among patients receiving TT vs those receiving ICIs ($P = 0.329$). New lesions were treated with a repeat radiotherapy course in 46% of patients. After 1 year, 62% of patients remained on the same systemic therapy as at the time of SRT; this was more frequent for ICI therapy compared to TT (83% vs 36%; $P = 0.035$). OMD was an independent prognostic factor for OS ($P = 0.004$, 95% confidence interval [CI] 0.035–0.528) and PFS ($P = 0.004$; 95% CI 0.165–0.717) in multivariate analysis. Eastern Cooperative Oncology Group performance status (ECOG-PS) was the other independent prognostic factor for OS ($P = 0.001$, 95% CI 0.001–0.351). Acute grade 3 toxicity was observed in two patients, and late grade 3 toxicity in one patient. No grade 4 or 5 toxicity was observed.

Conclusion

Combined treatment with TT or immunotherapy and concurrent SRT was safe, without signals of increased severe toxicity. As we observed no signal of excess toxicity, full-dose SRT should be considered to achieve optimal metastasis control in patients receiving TT or immunotherapy. Favourable PFS and OS were observed for patients with oligometastatic RCC with a good ECOG-PS, which should form the basis for prospective testing of this treatment strategy in properly designed clinical trials.

Keywords

stereotactic, immunotherapy, targeted therapy, concurrent, oligometastases, renal cell carcinoma, #KidneyCancer, #kcsm, #urooncc

Introduction

Approximately a third of patients with RCC have metastatic disease at first diagnosis and another third may develop metastatic disease [1]. Historically, patients with metastatic RCC (mRCC) were characterized by a poor prognosis, but, with the development of targeted therapy (TT) and immune checkpoint inhibitors (ICIs), patient outcomes have improved significantly [2,3]. Nevertheless, complete responses remain rare and failure of TT or ICI treatment is regularly observed. While second-line options unfortunately achieve mostly only low response rates, a multidisciplinary approach including localized metastasis-directed therapy (MDT) of mRCC is increasingly performed.

One established method for localized treatment of mRCC is metastasectomy [4]. However, a surgical approach is not possible for all patients or all metastases locations for technical or clinical reasons. Although RCC was historically thought to be radioresistant, with the development of stereotactic radiotherapy (SRT) which delivers a very high localized dose, very promising local response rates have been described [5,6], such that SRT has recently been included in the National Comprehensive Cancer Network guidelines for mRCC patients [7]. Although the role of SRT in mRCC is increasing, the evidence on using this local treatment option in patients receiving TT or immunotherapy is very limited. The aim of the present study was to analyse the safety and efficacy of SRT in mRCC patients treated with concurrent TT or immunotherapy.

Patients and Methods

An international multicentre registry study was established by the German Society for Radiation Oncology (DEGRO) working group for radiosurgery and SRT, to collect data retrospectively on patients receiving SRT concurrent to TT/ICI (TOaSTT database). This study was approved by the ethics committees at all participating sites (BASEC-Nr. 2016-01807). For the present sub-analysis, all patients with a diagnosis of mRCC were extracted for the database. Patients were treated with SRT between April 2011 and March 2018. Inclusion criteria were: age ≥18 years; diagnosis of stage IV synchronous or metachronous metastatic disease; histological confirmation of RCC; SRT of any cranial or extracranial metastasis; and concurrent (≤30 days) treatment with TT or ICIs. Cranial SRT was defined as delivery of a maximum of five radiotherapy fractions; for single-fraction radiosurgery, the minimum dose for inclusion was 16 Gy. Stereotactic body radiotherapy was defined as delivery of a maximum of 10 fractions with a minimum total dose of 50 Gy (2 Gy equivalent, α/β of 10 Gy). Oligometastatic disease (OMD) was defined as five or fewer synchronous or metachronous metastases and included oligoprogressive disease defined as five or fewer metastases while on TT or ICI therapy [8,9].

Endpoints were overall survival (OS), time to systemic therapy switch, progression-free survival (PFS), local metastases control (LC), and toxicity. OS was defined as time from SRT to time of death; living patients were censored at the date of last follow-up. PFS and LC were defined as time from SRT to time of cancer progression per SRT-treated lesion, and were determined by positron-emission tomography CT or MRI, MRI, CT, ultrasonography or X-ray imaging. PFS and LC were evaluated by censoring patients at their most recent imaging. Time to systemic therapy switch was defined as time from SRT to time of start of a new systemic therapy. Acute severe toxicity within the irradiated area certainly, probably or possibly related to SRT (<3 months after SRT, grade ≥3 events) was analysed using the Common Terminology Criteria for Adverse Events v.4.03. Late severe toxicity was evaluated in patients with a follow-up of ≥3 months.

Descriptive statistical analysis was performed with the SPSS v.25.0 statistics software package (IBM Corp., Armonk, NY, USA). Kaplan–Meier survival curves with log-rank analysis for comparison of subgroups were used to evaluate OS, PFS, TT and LC. Fisher's exact and chi-squared tests were used to compare differences between groups. Univariate and backward multivariate Cox regression analyses were performed to identify independent variables for OS, PFS, LC and TT. The Pearson correlation test was performed on the dose response histogram. A P value of <0.05 was taken to indicate statistical significance.

Results

Patient Characteristics

Data on 53 patients from 12 participating centres were included. Baseline patient characteristics are summarized in Table 1. The median (range) patient age was 61 (38–84) years, 89% of patients had an Eastern Cooperative Oncology

Table 1 Patient characteristics of metastatic RCC patients treated with stereotactic radiotherapy concurrent to targeted therapy/immune checkpoint inhibitors ($N = 53$).

Patient characteristics at time of SRT	
Age, years	61 (38–84)
Sex, *n* (%)	
Male	39 (76.5)
Female	12 (23.5)
ECOG-PS, *n* (%)	
0	26 (49)
1	20 (38)
2	5 (9)
3	1 (2)
Goal of SRT, *n* (%)	
Oligometastatic disease	31 (58)
Palliative	22 (42)
Involved organs	2 (1–6)
Status of primary tumour, *n* (%)	
Controlled	40 (76)
Progressive	9 (17)
Unknown	4 (7.5)
SRT-treated lesions, *n*	
Brain	77
Lymph nodes	3
Lung	23
Liver	3
Bone	20
Soft tissue	2
SRT-treated lesions per patient	
Cranial	2 (1–5)
Extracranial	1 (1–4)
Previous systemic treatment lines	1 (1–5)
Type of systemic therapy, *n* (%)	
TKIs	32 (60)
PD-(L)1 inhibitors	17 (32)
mTOR inhibitors	4 (8)
Prescribed BED_{10}, Gy	
Cranial	63.3 (45.1–125.4)
Extracranial	67.6 (40.8–129.4)
Total GTV volume, mL	
Cranial	0.84 (0.1–20.2)
Extracranial	13.2 (0.4–150.5)

BED_{10}, biologically effective dose; ECOG-PS, Eastern Cooperative Oncology Group performance status; SRT, stereotactic radiotherapy; TKI, tyrosine kinase inhibitor; GTV, gross tumor volume. Data are median (range), unless otherwise indicated.

Group performance score (ECOG-PS) of ≤1, 72% had minimal comorbidities (age-adjusted Charlson Comorbidity Index ≤3). At the time of SRT, multi-organ metastatic disease was present in 65% of patients, with a median (range) of 2 (1–6) involved organs per patient. In terms of metastatic status, 31 patients (58%) had OMD, defined as five or fewer new or progressive lesions present and treated with MDT. In 42% of patients (22/53), SRT was performed with palliative intent at the discretion of the local treating physician.

Systemic Therapy

Overall, 77.4% of patients were receiving first-line systemic therapy, while 22.6% were receiving at least second-line therapy (Table 1). Of all patients, 32% received ICIs, consisting of nivolumab, pembrolizumab or avelumab. All other patients (68%) received TT, consisting of sunitinib, sorafenib, axitinib, erlotinib, pazopanib, temsirolimus or everolimus. ICI/TT were started before SRT in 76% of patients, with a median (range) start of 126 (5–1480) days before SRT. The remaining 24% of patients started their ICI/TT during SRT or at a median (range) of 5 (range 1–29) days after SRT. In 37% of cases, TT was paused during SRT, for a median (range) of 14 (2–21) days. ICI therapy was paused in none of the included patients during SRT.

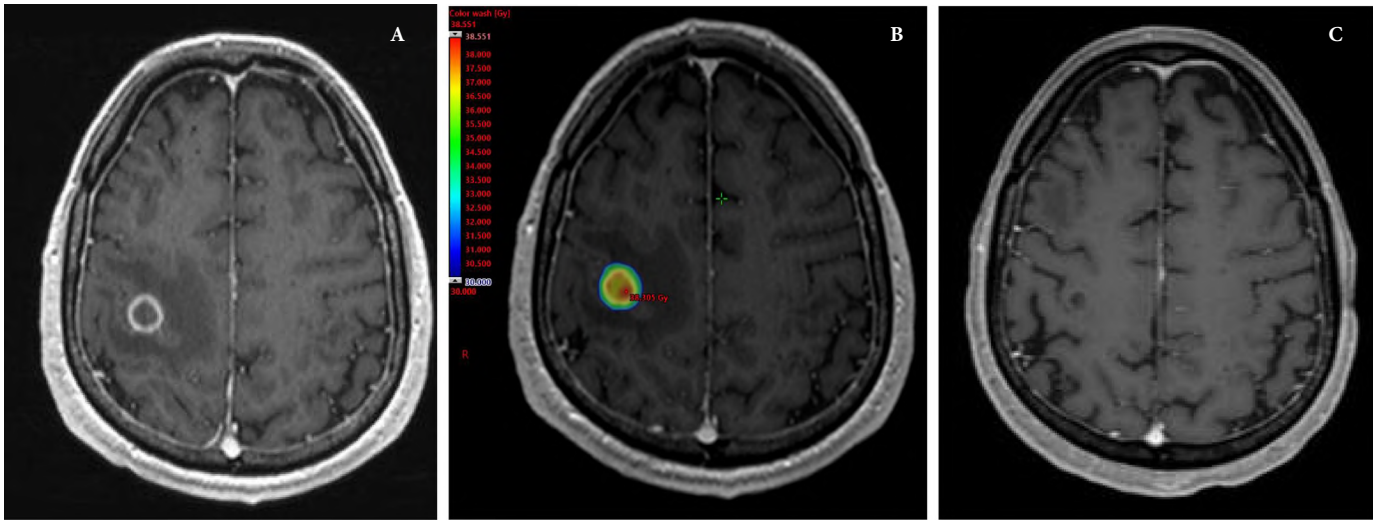
Stereotactic Radiotherapy

In total, 128 lesions were treated with SRT in 71 SRT sessions. Brain metastases were the most frequent location (52%), with a median (range) of 2 (1–5) brain metastases treated per patient (example shown in Fig. 1). The median (range) gross tumor volume (GTV) of brain metastases was 0.84 (0.07–20.2) mL. The median (range) prescribed physical dose and biologically effective dose (BED_{10}) for brain metastases was 20 (18–30) Gy and 63.3 (45–125) Gy in a median (range) of 1 (1–6) fraction. SRT of extracranial lesions was performed in 48% of patients. Treated lesions were located in lymph nodes ($n = 3$), lung ($n = 23$), liver ($n = 3$), bone ($n = 20$) or soft tissue ($n = 2$). In patients receiving ICIs specifically, SRT-treated lesions were located in the lymph nodes ($n = 2$), lung ($n = 8$), liver ($n = 1$), bones ($n = 4$) and brain ($n = 11$). A median (range) of 1 (1–4) extracranial lesion was treated per patient, with a median (range) prescribed physical dose of 24 (20–54) Gy and a BED_{10} of 67.6 (40.8–129.4) Gy in a median (range) of 3 (1–10) fractions. The median (range) GTV volume of stereotactic body radiotherapy was 13.2 (0.42–150.50) cc. The reported reasons for SRT were palliation of symptoms (38%), prevention of future complications (54%), attempt to prolong treatment with current systemic therapy (31%) and to induce a possible immunomodulation effect (17%).

Effectivity and Factors Influencing Survival

The median (range) follow-up was 12 (1–37) months. Local metastasis control of SRT-treated lesions after 1 year was 75% (Fig. 2). A higher radiation dose resulted in a better LC rate (Pearson correlation, $P = 0.0110$; Fig. 3). Patients receiving a BED_{10} of <60 Gy had worse LC rates after 1 year. No abscopal effects were observed. Overall, PFS after 1 year was 25%. The presence of OMD treated with SRT resulted in a significantly better PFS than presence of more than five lesions ($P = 0.003$; hazard ratio 0.34, 95% CI 0.165–0.708), with a median (range) of 11.6 (0.3–18) months compared to 3.3 (1.1–12.2) months. There was a trend towards better PFS for patients receiving ICI therapy compared to TT (median 11.6 vs 5.4 months; $P = 0.10$). This was not the case for LC (20.1 vs 14.5 months; $P = 0.476$) or OS (median 19.5 vs 18.3 months; $P = 0.329$). When progression developed,

Fig 1 Example of stereotactic radiotherapy (SRT)-treated metastases of the brain. **A**, Brain metastases of the left hemisphere with surrounding cerebral edema (T1 contrast-enhanced MRI). **B**, Delivered SRT to the cerebral metastases. **C**, T1 contrast-enhanced MRI 6 months after SRT showing tumour response as well as complete recovery of the cerebral oedema.



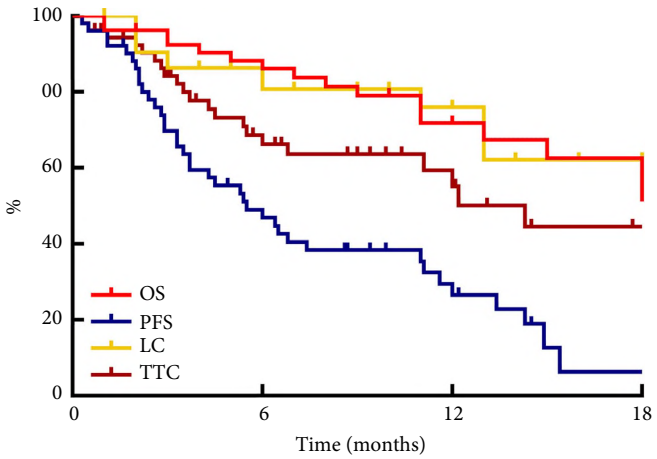
approximately half of patients (54%) progressed with five or fewer new lesions, mostly in more than one organ (59%). Progressing patients were treated with a second course of radiotherapy in 46% of cases and with surgical resection in 5.7% of new lesions. After 1 year, 62% of patients were still being treated with the same systemic therapy as at the time of SRT. This was significantly more common for ICI therapy compared to TT (83% vs 36%; $P = 0.035$). A median (range) time to systemic therapy switch of 14 (1–32) months for OMD and 8.1 (1–22 months) for palliative cases was observed ($P = 0.685$). When patients switched systemic treatment, the next line of treatment was most frequently another TT: 36% (14/39). Patients receiving TT switched to another TT (14%) or chemotherapy (10%), patients receiving ICI most commonly switched to TT (20%). After 1 year, the OS rate was 52% for palliative SRT (median [range] 13.1 [0.7–22] months) and 84% for patients with OMD (median [range] 23.3 [3–32] months). The cause of death was tumour-related in 94% of patients and never therapy-related.

The results of the univariate analysis are presented in Table 2. Independently prognostic variables for longer OS were OMD and an ECOG-PS of 0 at time of SRT (Fig. 4). Only OMD treated with SRT remained an independent prognostic variable for longer PFS. The time to systemic therapy switch was longer in the scenario of metastases confined to only one organ, and when the primary tumour was controlled at time of SRT.

Toxicity

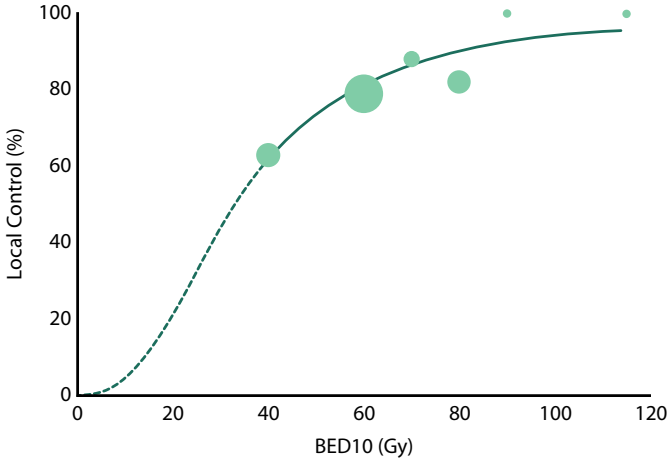
Acute severe toxicity possibly or probably caused or worsened by SRT was observed in two patients during the total of 71

Fig 2 Kaplan–Meier curve. LC, local metastasis control; OS, overall survival; PFS, progression-free survival; TTS, time to systemic therapy switch.



SRT sessions (2.8%). Both toxicities developed after SRT of brain metastases and consisted of grade 3 dysarthria and grade 3 incomplete paresis of both arms in one patient and grade 3 headache as well as grade 3 vertigo in another patient. Both were caused by cerebral oedema after SRT, as evaluated with MRI. The cerebral edema was regression after steroid treatment. One patient received SRT of three brain metastases with 21 Gy in 1 fraction while receiving therapy with sunitinib. The second patient received SRT of five brain metastases after whole-brain irradiation 4 years earlier. This patient was receiving everolimus, which was paused for 4 days during SRT with 20 Gy in 1 fraction. Late grade 3 toxicity was observed in one patient receiving SRT of a single brain metastases in the left frontal lobe while receiving

Fig 3 Dose volume histogram of local control rates after stereotactic radiotherapy of RCC metastases.



therapy with temsirolimus, and consisted of dysphasia caused by radiation necrosis, with no complete recovery after steroid treatment. Temsirolimus was not paused during treatment, and the applied radiation dose was 20 Gy in 1 fraction. No grade 4 or 5 toxicity was observed.

Discussion

Although SRT is now included as an option for local ablative treatment of mRCC lesions in international guidelines, there is only little evidence on the effects of SRT in patients who are simultaneously being treated with modern systemic therapy options such as TT or ICIs [6,10–20]. The limited available literature on this topic is disproportionate to the numerous mRCC patients receiving TT or ICIs that are increasingly treated with SRT in a multimodality approach, and is despite the observation that pausing these systemic therapies during SRT might pose a risk of disease flare [21].

The present study therefore focused on the safety and efficacy of metastasis-directed SRT concurrent with TT or ICI treatment in mRCC patients. Our data showed that concurrent treatment was characterized by a favourable safety profile, with a low risk of additional severe toxicity caused by SRT. Simultaneously, LC 1 year after SRT-treated lesions was promising. Patients with OMD, defined as a maximum of five metastases, all treated with SRT, had a significantly longer OS and PFS compared to patients with polymetastatic disease, defined as more than five metastases.

Although several retrospective studies have evaluated MDT in patients with oligometastatic RCC, the role of MDT in patients receiving simultaneous TT or ICI treatment is currently less well investigated. Over the last years, a few small retrospective studies proposed a benefit in tumour control of performing metastasectomy in patients receiving TT [22–25]. For SRT concurrent with TT, eight retrospective studies and one prospective study have been published since 2011 (Table 3). Most focused on brain metastases [5,10,12,16,19,26,27], but some also included extracranial lesions [5,13,14,17,19]. The combination of ICIs with SRT is a new approach in mRCC. In addition to our data, the currently available data consist of four retrospective studies [11,14,16,18] with small patient numbers published in the last 2 years, and the recently published first prospective study on concurrent SRT and ICI that included five patients [13] (Table 3). All available data, including the present study, describe a limited risk of severe toxicity by MDT, ranging from 0% to 3%, as well as 1-year LC ranging between 74% and 98%.

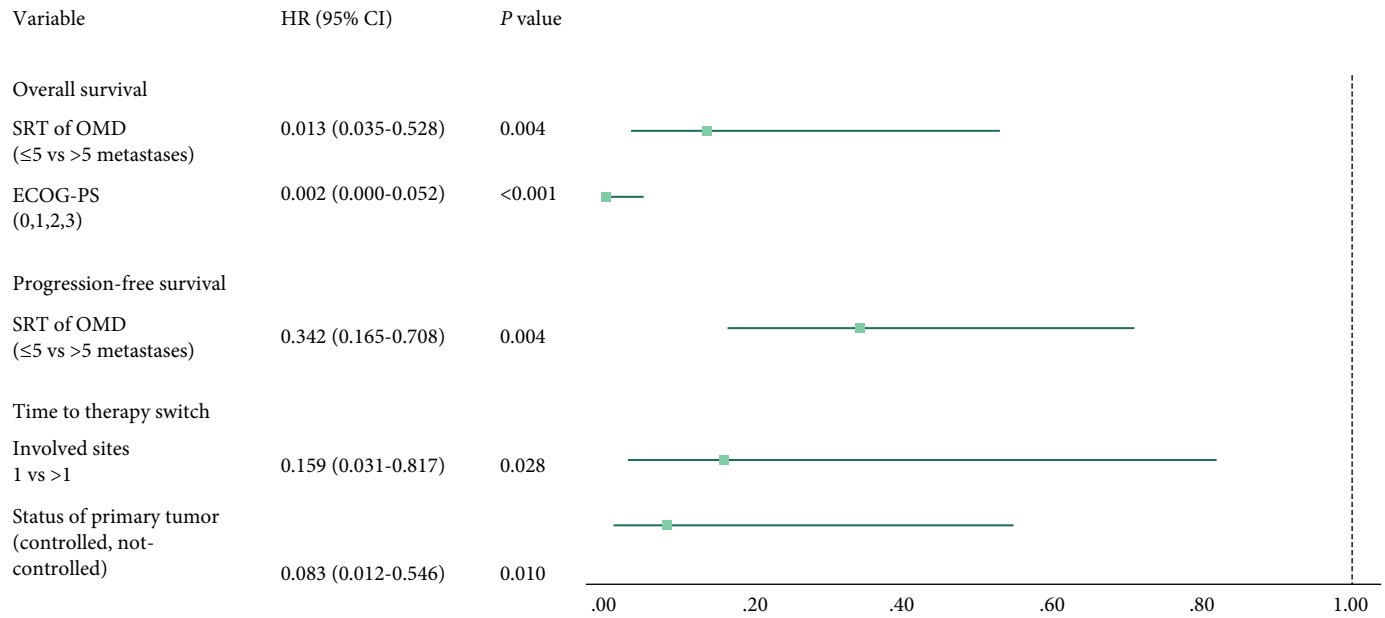
The major aim of MDT is to improve patient outcome by achieving durable LC or ablation of all metastatic lesions. MDT as monotherapy without concurrent TT or ICI has been reported to achieve local metastases control rates of approximately 90% in mRCC, especially for patients with

Table 2 Univariate Cox regression analysis.

Variables	Univariate analysis		
	OS *P*	PFS *P*	Time to systemic therapy switch *P*
Goal of MDT (OMD, palliative SRT)	0.006	0.058	0.338
Metastatic development (synchronous vs metachronous)	0.966	0.432	0.981
Previous lines of systemic treatment (1 vs >1)	0.087	0.26	0.343
Metastatic burden (≤5, >5 lesions)	0.004	0.003	0.041
Involved sites (1 vs >1)	0.026	0.166	0.064
Location of metastases (cranial vs extracranial)	0.29	0.267	0.751
ECOG-PS (0–3)	<0.001	0.627	0.133
Status of primary tumour (controlled vs progressive)	0.275	0.146	0.184
Systemic therapy (TT, ICIs)	0.329	0.1	0.157
SRT location (cranial, extracranial)	0.25	0.11	0.496
Start TT (before, during, after SRT)	0.279	0.131	0.176
TT paused during SRT (yes vs no)	0.852	0.409	0.339

P < 0.05 is significant. ECOG-PS, Eastern Cooperative Oncology Group performance status; ICI, immune checkpoint inhibitor; MDT, metastasis-directed therapy; OMD, oligometastatic disease; OS, overall survival; PFS, progression-free survival; SRT, stereotactic radiotherapy ; TT, targeted therapy.

Fig 4 Multivariate Cox regression analysis. $P < 0.05$ is significant. ECOG-PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; OMD, oligometastatic disease; SRT, stereotactic radiotherapy.



oligometastatic disease [20,28]. In the present study, LC of SRT-treated lesions after 1 year was lower, at approximately 75%. This finding needs to be interpreted in the context of our retrospective multi-institutional study, where lower SRT doses were used, potentially because of concerns regarding unexpected toxicity due to concurrent treatment with TT or ICIs. In the present study, we did not observe a signal of increased rates of severe toxicity after combined treatment methods. Concurrent treatment with TT or ICI also did not compensate for the lower SRT doses, indicating that full-dose and not reduced-dose SRT is required for such combined modality treatment concepts in order to achieve optimal LC rates [14,29,30].

Patients with OMD, defined as maximum of five metastases, all treated with SRT, had favourable survival rates in the present study. This was the case for patients receiving TT or ICIs. Completeness of MDT appears to be an important factor influencing survival in mRCC [14,24,25,28]. Although the biological background of local therapy in OMD is largely unknown, the first prospective studies in other tumour types have shown that MDT does play an important role in delaying disease progression and improving survival in the oligometastatic setting [31,32]. This lack of prospective data on MDT for oligometastatic mRCC was one motivation for the present study, where we have observed promising PFS and OS rates for OMD patients. This is in accordance with the retrospective study by Meyer et al. [5], where a PFS of 7.6 vs 8.6 months and an OS of 23.2 vs 33.9 months was obtained after SRT of OMD and oligoprogressive disease, respectively. In the present study, the median PFS and OS were 11.6 and 23.3 months, respectively, for OMD patients. These favourable survival data indicate that OMD patients do benefit from optimal local MDT and optimal systemic therapy, which was concurrent TT or ICI treatment in all patients in the present study. A further observation was that a good ECOG-PS influenced OS in these patients, which is known from other studies [26,32]. Therefore, based on the current retrospective data, patients with OMD with a good ECOG-PS appear to be most promising candidates for MDT.

Both TT and ICIs have become standard treatment options in mRCC and have significantly improved PFS and OS [33]. However, when resistance occurs, patients face limited systemic treatment options and the prognosis is poor. We showed that local SRT of oligoprogressive metastases, in some cases even repeat irradiations, could postpone time to systemic therapy switch by approximately 1 year, with a low risk of toxicity by local radiotherapy. In the study by Meyer et al. [5], a similar time to systemic therapy switch, a median of 10.5 months, was observed. These results indicate the potential of a multidisciplinary approach in these challenging patients.

Limitations of the present study include a possible selection bias attributable to the retrospective nature of the study and the inclusion of patients who might have had a favourable prognosis due to an initial good response to TT and ICIs, good ECOG-PS and a slow tumour progression. Furthermore,

Table 3 Overview of currently published literature on metastatic RCC concurrent to targeted therapy (tyrosine kinase inhibitors, mTOR inhibitors or immune checkpoint inhibitors).

Author	Year	Study type	Cohort	Patients receiving concurrent SRT + TT, *n*	Number treated lesions, median (range)	SRT region	TT	Start of TT	Median KPS	LC at 1 year, %	OS at 1 year, %	Acute severe (≤G3) toxicity, %	Late severe (≤G3) toxicity, %
Staehler et al. [19]	2011	Retrospective	NR	106	1.2 (1–2)	Brain, body	TKI	Concurrent	≥70	98	NR	0	0
Cochran et al. [12]	2012	Retrospective	Oligometastases, extensive metastatic disease	24	NR	Brain	TKI, mTORi, bevacizumab	NR	80	74	38	0	0
Verma et al. [26]	2013	Retrospective	NR	40	1 (1–19)	Brain	TKI, mTOR inhibitor	NR	NR	75		NR	2.5
Vickers et al. [27]	2013	Retrospective	NR	63	1 (1–NR)	Brain	TKI, mTOR inhibitor, bevacizumab	NR	≥80	NR	NR	NR	NR
Bates et al. [10]	2015	Retrospective	NR	2	1 (1–17)	Brain	TKI	Concurrent	≥90	NR	NR	NR	NR
Miller et al. [17]	2016	Retrospective	Oligometastases, extensive metastatic disease	70	1 (1–≥3)	Body (Spine)	TKI	Concurrent	80	96	NR	0	0
Hoerner-Rieber et al. [14]	2017	Retrospective	Oligometastases, extensive metastatic disease	20	1 (1–7)	Body (lung)	TKI ($n = 15$), ICI ($n = 5$)	NR	90	98	84	0	0
Chen et al. [11]	2018	Retrospective	NR	3	2 (1–13)	Brain	ICI	Within 2 weeks before/after SRT	≥80	88	NR	3	1
Meyer et al. [5]	2018	Retrospective	Oligometastases, oligoprogression, residual tumor	124	1 (1–5)	Brain, body	TKI, mTOR inhibitor, others	Paused during SRT	NR	83	NR	2.6	2.6
Mohamad et al. [18]	2018	Retrospective	Oligometastases, extensive metastatic disease	27	NR	Body	ICI	During or 8 weeks before/after SRT	≥80	NR	NR	5.4	NR
Klausner et al. [16]	2019	Retrospective	NR	35	1 (1–≥3)	Brain	TKI, mTOR inhibitor, ICI	Within 5 biological half-lives before SRT, not paused	NR	94	52	NR	NR
Juloori et al. [15]	2019	Retrospective	NR	231	1 (1–≥3)	Brain	TKI, mTOR inhibitor, cytokine therapy	Within 30 days before/after SRS	80	87	60	NR	NR
Dengina et al. [13]	2019	Prospective phase 1B	Oligometastases	17	NR	Body	TKI ($n = 12$), ICI ($n = 5$)	≥4 months before SBRT, not paused	NR	NR	NR	0	NR

ICI, immune checkpoint inhibitor; LC, local metastasis control; NR, xxx;OS, overall survival; SBRT, stereotactic body radiotherapy SRT, stereotactic radiotherapy; TKI, tyrosine kinase inhibitor; TT, targeted therapy; NR, not reported.

as all patients received combined modality treatment, this study does not allow the definitive influence of SRT on outcome to be evaluated. However, the available studies examining local therapy of metastases in RCC patients have consistently shown a positive effect on PFS, OS and time to systemic therapy. Prospective trials are under way (NCT03575611, NCT03256981). We decided to include both patients receiving ICI treatment and those receiving TT. Although we realize that the biology and tumour response differ for these different systemic therapies, it is of paramount importance to increase our knowledge on SRT in the metastatic setting for patients receiving modern targeted agents. Other limitations could be the small number of included patients and the heterogeneity in SRT treatment characteristics. However, the variations in applied radiation dose allowed us to evaluate the effectiveness with regard to LC and highlighted the importance of administration of higher SRT doses to obtain good LC.

In conclusion, combined treatment with TT or immunotherapy and concurrent SRT was safe, without signals of increased severe toxicity. As we observed no signal of excess toxicity, full-dose SRT should be considered to achieve optimal metastasis control in patients receiving TT or immunotherapy. Favourable PFS and OS was observed for patients with oligometastatic RCC, which should form the basis for prospective testing of this treatment strategy in properly designed clinical trials.

Conflicts of Interest

N. Sundahl reports non-financial support from Bayer, MSD, Bristol-Myers Squibb and Astellas, outside the submitted work. S. Siva reports personal fees from the National Health and Medical Research Council and Cancer Council Victoria Colebatch Fellowship outside the submitted work. G. Skazikis reports grants from the University of Zurich, during the conduct of the study. M. Geier reports personal fees from Roche and Bristol-Myers Squibb outside the submitted work. D. Kaul reports personal fees from Novocure outside the submitted work. S. Adebahr reports personal fees from the German Consortium of Translational Cancer Research (DKTK), during the conduct of the study. K. H. Kahl reports personal fees from Bristol Myers Squibb, MSD, Merck, AstraZeneca, Varian, Elekta and Zeiss Meditec, outside the submitted work. J. J. C. Verhoeff, O. Blanck, M. Guckenberger, J. Schaule, F. Roeder, F. Eckert and C. Fritz declare no conflicts of interest.

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Abbreviations: ECOG-PS, Eastern Cooperative Oncology Group performance status; ICI, immune checkpoint inhibitor; LC, local metastasis control; MDT, metastasis-directed therapy; mRCC, metastatic RCC; OMD, oligometastatic disease; OS, overall survival; PFS, progression-free survival; SRT, stereotactic radiotherapy; TT, targeted therapy.