Stereotactic radiotherapy combined with immune- or targeted therapy for metastatic renal cell carcinoma.

S.G.C. Kroeze¹, C. Fritz¹, J. Schaule¹, S. Siva², K.H. Kahl³, N. Sundahl⁴, O. Blanck⁵, D. Kaul⁶, S. Adebahr⁷, J.J.C. Verhoeff⁸, G. Skazikis⁹, F. Roeder¹⁰, M. Geier¹¹, F. Eckert¹², M. Guckenberger¹

¹Department of Radiation Oncology, University Hospital Zürich, University of Zurich, Zurich, Switzerland

²Department of Radiation Oncology, Peter MacCallum Cancer Centre, Melbourne, Australia

³Department of Radiation Oncology, University Hospital Augsburg, Augsburg, Germany

⁴Department of Radiation Oncology, University Hospital Ghent, Belgium

⁵Department of Radiation Oncology, University Medical Center Schleswig-Holstein, Kiel, Germany, Kiel, Germany

⁶Department of Radiation Oncology, Charité-University Hospital Berlin, Berlin, Germany

⁷Department of Radiation Oncology, Medical Center, Faculty of Medicine, University of Freiburg, German Cancer Consortium (DKTK), Partner Site Freiburg, Germany

⁸Department of Radiation Oncology, University Medical Center Utrecht, Utrecht, the Netherlands

⁹Department of Radiation Oncology, Schwarzwald-Baar Klinikum, Villingen-Schwenningen, Germany

¹⁰Department of Radiation Oncology, University Hospital Munich, Munich, Germany

¹¹Department of Radiation Oncology, Ordensklinikum Linz, Linz, Austria

¹²Department of Radiation Oncology, University Hospital Tübingen, Tübingen, Germany

Corresponding author:

Stephanie Kroeze

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as doi: [10.1111/BJU.15284](https://doi.org/10.1111/BJU.15284)

This article is protected by copyright. All rights reserved

University Hospital Zurich
Department of Radiotherapy
Rämistrasse 100
CH 8091 Zürich
Switzerland
Phone: +41 (0) 44 255 1111
E-Mail: Stephanie.kroeze@usz.ch

Keywords: Stereotactic, immunotherapy, targeted therapy, concurrent, oligometastases, Renal cell carcinoma

Article type : Original Article

Abstract

Objectives To evaluate the safety and efficacy of stereotactic radiotherapy (SRT) in metastatic RCC (mRCC) patients concurrently receiving targeted therapy or immunotherapy.

Patients and Methods Data on mRCC patients was extracted from a retrospective international multicenter register study (TOaSTT) investigating SRT concurrent (≤ 30 d) to TT/ICI. Overall survival (OS), progression free survival (PFS), local control (LC) and time to systemic therapy switch (TTS) were analyzed using Kaplan-Meier curves and log rank testing. Clinical and treatment factors influencing survival were analyzed using multivariate cox regression. Acute and late SRT-induced toxicity was defined by the CTCAE v4.03 criteria.

Results Fifty-three patients that underwent 128 SRTs were included, of which 58% of patients presented with oligometastatic disease (OMD). 32% and 68% of patients received ICI and TT, respectively. Twenty (37%) patients paused TT for median of 14 (range 2-21) days, ICI was not paused in any patient. A median of 1 (range 1-5) metastasis was treated per patient, with a median SRT dose of 65Gy BED₁₀ (range 40-129.4Gy). OS, LC and PFS at 1y were 71%, 75% and 25%, respectively. Median OS and PFS was not significantly different among patients receiving TT vs. ICI ($p=0.329$). New lesions were treated with a repeat-radiotherapy course in 46% of patients. After 1y, 62% of patients remained on the same systemic therapy as at the time of SRT; this was more frequent for ICI compared to TT (83% vs. 36%, $p=0.035$). OMD was an independent factor for OS ($p=0.004$, 95% CI 0.035-0.528) and PFS ($p=0.004$, 95% CI 0.165-0.717) in multivariate analysis. ECOG-PS was the other independent factor for OS ($p=0.001$,

95% CI 0.001-0.351). Acute grade 3 toxicity was observed in 2 patients, late grade 3 toxicity in 1 patient. No grade 4 or 5 toxicity was observed.

Conclusion Combined modality treatment with targeted therapy 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 targeted-, or immunotherapy. Favorable PFS and OS was observed for oligometastatic RCC patients with a good ECOG-PS, which should form the basis for prospective testing of this treatment strategy in properly designed clinical trials.

Introduction

Approximately a third of renal cell carcinoma (RCC) patients are metastatic at first diagnosis and another third may develop metastatic disease [1]. Historically, metastatic RCC (mRCC) patients were characterized by a poor prognosis. With the development of targeted therapy (TT) and immune checkpoint inhibitors (ICI) patient outcome has improved significantly [2, 3]. Still, 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 a localized metastatic directed treatment (MDT) of mRCC is increasingly performed.

One established modality for localized treatment of mRCC is metastasectomy [4]. However, a surgical approach is not possible for all patients and all metastases locations due to technical or clinical reasons. Although RCC was historically thought to be radioresistant, with the development of stereotactic radiotherapy (SRT) that 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 NCCN guidelines for metastatic RCC patients [7]. Although the role of SRT in mRCC is increasing, the evidence on using this local treatment option in patients receiving targeted- or immunotherapy is very limited. The aim of this study was to analyze safety and efficacy of stereotactic radiotherapy (SRT) in mRCC patients treated with concurrent targeted- or immunotherapy.

Patients and Methods

An international multicenter registry study was established by the German Society for Radiation Oncology (DEGRO) working group for radiosurgery and stereotactic radiotherapy, to retrospectively collect data 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 this 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: ≥ 18 years of age, diagnosis of stage IV synchronous or metachronous metastatic disease, histological confirmation of RCC, SRT of any cranial or extracranial metastasis, concurrent (≤ 30 days) treatment with TT or ICI. Cranial SRT was defined as delivery of maximum 5 radiotherapy fractions; for single fraction radiosurgery, the minimum dose for inclusion was 16Gy. Stereotactic body radiotherapy

(SBRT) was defined as delivery of maximum 10 fractions with a minimum total dose of 50 Gy (2 Gy equivalent, α/β of 10 Gy). Oligometastatic disease was defined as ≤ 5 synchronous or metachronous metastases and included oligoprogressive disease as ≤ 5 metastases under TT or ICI [8, 9].

Endpoints were overall survival (OS), time to systemic therapy switch (TTS), 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 PET-CT- or MRI, MRI, CT, ultrasound or X-ray imaging. PFS and LC were evaluated by censoring patients at their most recent imaging. TTS was defined as time from SRT to time of start of a new systemic therapy. Acute severe toxicity **within the irradiated area certainly, likely or possibly related to SRT** (< 3 months post-SRT, grade ≥ 3 events) was analyzed using the Common Terminology Criteria for Adverse Events (CTCAE) v4.03. Late severe toxicity was evaluated in patients with a follow-up of ≥ 3 months.

Descriptive statistical analysis was performed with SPSS v25.0 statistic software package (IBM Corp., Armonk, NY, USA). Kaplan-Meier survival curves with log-rank analysis for comparison of subgroups was used to evaluate OS, PFS, TT and LC. The Fisher's exact and Chi-square test was used to compare differences between groups. Univariate and backward multivariate Cox regression analysis was 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 less than 0.05 was regarded statistically significant.

Results

Patient characteristics

Data of 53 patients from 12 participating centers was included. Baseline patient characteristics are summarized in Table 1. Median patient age was 61 (range 38-84) years, 89% of patients had ECOG performance score of ≤ 1 , 72% had minimal co-morbidities (age-adjusted Charlson Comorbidity Index ≤ 3). At the time of SRT, multiorgan metastatic disease was present in 65% of patients, with a median of 2 (range 1-6) involved organs per patient. In terms of metastatic status, 31 patients (58%) had oligometastatic disease (OMD), defined as

≤5 new or progressive lesions present and treated with MDT. In 42% (22/53) of patients, SRT was performed in 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 in second-line therapy or more (Table 1). Of all patients, 32% received ICI, 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 of 126 (range 5-1480) days. The remaining 24% of patients started their ICI/TT during or a median of 5 (range 1-29) days after SRT. In 37% of cases, TT were paused during SRT, for a median of 14 (range 2-21) days. ICI 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 number of 2 (range 1-5) brain metastases treated per patient (example shown in Figure 2). Median GTV volume of brain metastases was 0.84cc (0.07-20.2). Median prescribed physical dose and BED₁₀ dose for brain metastases was 20 Gy (range 18-30Gy) and 63.3 Gy (range 45-125Gy) in median 1 fraction (range 1-6 fractions). 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 ICI 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 of 1 (range 1-4) extracranial lesion was treated per patient, with a median prescribed physical dose of 24 (range 20-54Gy) and BED₁₀ of 67.6 Gy (range 40.8-129.4Gy) in median 3 fractions (range 1-10). Median GTV volume of SBRT was 13.2cc (range 0.42-150.50cc). 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

Median follow-up was 12 (range 1-37) months. Local metastasis control of SRT-treated lesions after 1 year was 75% (Figure 1). A higher radiation dose resulted in a better local control rate (Pearson correlation, $p=0.0110$) (Figure 3). Patients receiving a BED_{10} of $<60\text{Gy}$ showed the worse local control rates after one 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 patients with >5 lesions ($p=0.003$) (HR 0.34, 95% CI 0.165-0.708), with a median of 11.6 months (range 0.3-18 months) compared to 3.3 months (range 1.1-12.2 months). There was a trend towards better PFS for patients receiving ICI 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, $p=0.476$) and OS (median 19.5 vs. 18.3 months, $p=0.329$). When progression developed, approximately half of patients (54%) progressed with ≤ 5 new lesions, mostly in >1 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 treated with the same systemic therapy as at the time of SRT. This was significantly more often for ICI compared to TT (83% vs. 36%, $p=0.035$). A median TTS of 14 (range 1-32) months for OMD and 8.1 (range 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, OS was 52% for palliative SRT (median 13.1 months (range 0.7-22 months)) and 84% for patients with OMD (median 23.3 months (range 3-32 months)). The cause of death was tumor-related in 94% and never therapy-related.

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 (Figure 4). Only OMD treated with SRT, remained an independent 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 tumor was controlled at time of SRT.

Toxicity

Acute severe toxicity possibly or likely caused or worsened by SRT was observed in two patients during the total of 71 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 edema after SRS, as evaluated with MRI, and regredient after steroid treatment. One patient received SRT of 3 brain metastases with 21 Gy in 1 fraction while under therapy with sunitinib. The second patient received SRT of 5 brain metastases after whole brain irradiation four year earlier. This patient was under therapy with everolimus, which was paused for 4 days during SRT with 20Gy 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 under therapy with temsirolimus, and consisted of dysphasia caused by radiation necrosis, with no complete recovery after steroid treatment. Temsirolimus was not paused during treatment, the applied radiation dose was 20Gy 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 metastatic RCC 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 ICI [6, 10-20]. The limited available literature on this topic is not in relation to the numerous mRCC patients receiving TT or ICI that are increasingly treated with SRT in a multimodality approach, and despite the observation that pausing these systemic therapies during SRT might pose a risk of disease flare [21]. This study therefore focused on the safety and efficacy of metastasis directed SRT concurrent with TT or ICI in mRCC patients. Our data showed that a concurrent treatment was characterized by a favorable safety profile, with a low risk of additional severe toxicity caused by SRT. Simultaneously, local control one year after SRT-treated lesions was promising. Patients with OMD defined as maximum 5 metastases, all treated with SRT, showed a significantly longer OS and PFS compared to patients with polymetastatic disease defined as more than 5 metastases.

Although several retrospective studies have evaluated MDT in oligometastatic RCC patients, the role of MDT in patients under simultaneous TT- or ICI-treatment is currently less well investigated. Over the last years, few and small retrospective studies proposed a benefit in tumor control of performing metastasectomy in patients receiving TT [22-25]. For SRT concurrent with targeted therapy, 8 retrospective studies and 1 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 ICI with SRT is a new approach in mRCC. Besides our data, the currently available data consists of 4 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 5 patients [13] (Table 3). All available data, including our study, describe a limited risk of severe toxicity by MDT, ranging from 0 to 3%, as well as 1-year local control ranging between 74% and 98%.

The major aim of MDT is to improve patient outcome by achieving durable local control or ablation of all metastatic lesions. MDT as monotherapy without concurrent TT or ICI has been reported to achieve local metastases control rates of about 90% in mRCC, especially for oligometastatic patients [20, 28]. In our study, local control of SRT-treated lesions after 1 year was lower with 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 of unexpected toxicity due to concurrent treatment with TT or ICI. Based on the results of our study, we did not observe a signal of increased rates of severe toxicity by combined modality treatment. Simultaneously, 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 in such combined modality treatment concepts in order to achieve optimal local metastases control rates [14, 29, 30].

Patients with OMD defined as maximum of 5 metastases, all treated with SRT, showed favorable survival in our study. This was both the case for patients receiving TT or ICI. 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 oligometastatic disease is largely unknown, first prospective studies in other tumor types have shown that MDT does play an important role in delaying disease progression and improving survival in the oligometastatic situation [31, 32]. This lack of prospective data on MDT for oligometastatic mRCC was one motivation for the current study, where we have observed promising PFS and OS for OMD patients. This is in accordance with the retrospective study of Meyer et al. [5], where a PFS of 7.6 vs. 8.6 months and OS of 23.2 vs. 33.9 months was obtained after SRT of OMD and OPD, respectively. In our study, median PFS and OS was 11.6 months and 23.3 months for oligometastatic patients, respectively. These favorable survival data indicate that

OMD patients do benefit from optimal local metastasis-directed therapy and optimal systemic therapy, which was concurrent TT or ICI in all patients in our 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, oligometastatic patients with a good performance status appear to be most promising candidates for MDT.

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

Limitations of our study are a possible selection bias by the retrospective nature of the study and the inclusion of patients who might have had a favorable prognosis due to an initial good response to TT and ICIs, good performance status and a slow tumor progression. Furthermore, as all patients received a combined modality treatment, our study does not allow to evaluate the definitive influence of SRT on outcome. 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 underway (NCT03575611, NCT03256981). We decided to include both patients receiving ICI and TT. Although we realize that the biology and tumor response is different to these different systemic therapies, it is of paramount importance to increase our knowledge on SRT in the metastatic situation of patients receiving modern targeting agents. Other limitations may 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 effectivity on local control and highlighted the importance of administration of higher SRT doses to obtain a good local control.

Conclusions

Combined modality treatment with targeted therapy 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 targeted-, or immunotherapy. Favorable PFS and OS was observed for oligometastatic RCC patients, which should form the basis for prospective testing of this treatment strategy in properly designed clinical trials.

Conflicts of Interest

S.G.C. Kroeze reports grants from Varian Medical Systems outside the submitted work. N. Sundahl reports non-financial support from Bayer, MSD, Bristol-Myers Squibb, and Astellas, outside the submitted work. S. Siva reports personal fees from National Health and Medical Research Council and Cancer Council Victoria Colebatch Fellowship outside the submitted work. G. Skazikis reports grants from 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 German consortium of translational cancer research (DKTK), during the conduct of the study. K.H. Kahl reports personal fees from Bristol Myers Squibb, personal fees from MSD, personal fees from Merck, personal fees from AstraZeneca, personal fees from Varian, personal fees from Elekta, personal fees from 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.

References

- [1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin*. 2018;68:7-30.
- [2] Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Oudard S, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. *J Clin Oncol*. 2009;27:3584-90.
- [3] Motzer RJ, Tannir NM, McDermott DF, Aren Frontera O, Melichar B, Choueiri TK, et al. Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. *N Engl J Med*. 2018;378:1277-90.
- [4] Capitanio U, Montorsi F. Renal cancer. *Lancet*. 2016;387:894-906.
- [5] Meyer E, Pasquier D, Bernadou G, Calais G, Maroun P, Bossi A, et al. Stereotactic radiation therapy in the strategy of treatment of metastatic renal cell carcinoma: A study of the Getug group. *Eur J Cancer*. 2018;98:38-47.
- [6] Siva S, Kothari G, Muacevic A, Louie AV, Slotman BJ, Teh BS, et al. Radiotherapy for renal cell carcinoma: renaissance of an overlooked approach. *Nat Rev Urol*. 2017;14:549-63.
- [7] NCCN. Kidney Cancer Version 2 2020 25/09/2020.
- [8] Guckenberger M, Lievens Y, Bouma AB, Collette L, Dekker A, deSouza NM, et al. Characterisation and classification of oligometastatic disease: a European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus recommendation. *Lancet Oncol*. 2020;21:e18-e28.
- [9] Lievens Y, Guckenberger M, Gomez D, Hoyer M, Iyengar P, Kindts I, et al. Defining oligometastatic disease from a radiation oncology perspective: An ESTRO-ASTRO consensus document. *Radiother Oncol*. 2020;148:157-66.
- [10] Bates JE, Youn P, Peterson CR, 3rd, Usuki KY, Walter KA, Okunieff P, et al. Radiotherapy for Brain Metastases From Renal Cell Carcinoma in the Targeted Therapy Era: The University of Rochester Experience. *Am J Clin Oncol*. 2017;40:439-43.
- [11] Chen L, Douglass J, Kleinberg L, Ye X, Marciscano AE, Forde PM, et al. Concurrent Immune Checkpoint Inhibitors and Stereotactic Radiosurgery for Brain Metastases in Non-Small Cell Lung Cancer, Melanoma, and Renal Cell Carcinoma. *Int J Radiat Oncol Biol Phys*. 2018;100:916-25.

- [12] Cochran DC, Chan MD, Aklilu M, Lovato JF, Alphonse NK, Bourland JD, et al. The effect of targeted agents on outcomes in patients with brain metastases from renal cell carcinoma treated with Gamma Knife surgery. *J Neurosurg.* 2012;116:978-83.
- [13] Dengina N, Mitin T, Gamayunov S, Safina S, Kreinina Y, Tsimafeyeu I. Stereotactic body radiation therapy in combination with systemic therapy for metastatic renal cell carcinoma: a prospective multicentre study. *ESMO Open.* 2019;4:e000535.
- [14] Hoerner-Rieber J, Duma M, Blanck O, Hildebrandt G, Wittig A, Lohaus F, et al. Stereotactic body radiotherapy (SBRT) for pulmonary metastases from renal cell carcinoma-a multicenter analysis of the German working group "Stereotactic Radiotherapy". *J Thorac Dis.* 2017;9:4512-22.
- [15] Juloori A, Miller JA, Parsai S, Kotecha R, Ahluwalia MS, Mohammadi AM, et al. Overall survival and response to radiation and targeted therapies among patients with renal cell carcinoma brain metastases. *J Neurosurg.* 2019;1-9.
- [16] Klausner G, Troussier I, Biau J, Jacob J, Schernberg A, Canova CH, et al. Stereotactic Radiation Therapy for Renal Cell Carcinoma Brain Metastases in the Tyrosine Kinase Inhibitors Era: Outcomes of 120 Patients. *Clin Genitourin Cancer.* 2019;17:191-200.
- [17] Miller JA, Balagamwala EH, Angelov L, Suh JH, Rini B, Garcia JA, et al. Spine stereotactic radiosurgery with concurrent tyrosine kinase inhibitors for metastatic renal cell carcinoma. *J Neurosurg Spine.* 2016;25:766-74.
- [18] Mohamad O, Diaz de Leon A, Schroeder S, Leiker A, Christie A, Zhang-Velten E, et al. Safety and efficacy of concurrent immune checkpoint inhibitors and hypofractionated body radiotherapy. *Oncoimmunology.* 2018;7:e1440168.
- [19] Staehler M, Haseke N, Nuhn P, Tullmann C, Karl A, Siebels M, et al. Simultaneous anti-angiogenic therapy and single-fraction radiosurgery in clinically relevant metastases from renal cell carcinoma. *BJU Int.* 2011;108:673-8.
- [20] Zaorsky NG, Lehrer EJ, Kothari G, Louie AV, Siva S. Stereotactic ablative radiation therapy for oligometastatic renal cell carcinoma (SABR ORCA): a meta-analysis of 28 studies. *Eur Urol Oncol.* 2019;2:515-23.
- [21] Chaft JE, Oxnard GR, Sima CS, Kris MG, Miller VA, Riely GJ. Disease flare after tyrosine kinase inhibitor discontinuation in patients with EGFR-mutant lung cancer and acquired resistance to erlotinib or gefitinib: implications for clinical trial design. *Clin Cancer Res.* 2011;17:6298-303.
- [22] Karam JA, Rini BI, Varella L, Garcia JA, Dreicer R, Choueiri TK, et al. Metastasectomy after targeted therapy in patients with advanced renal cell carcinoma. *J Urol.* 2011;185:439-44.
- [23] Park YH, Jung JW, Lee BK, Lee S, Jeong SJ, Byun SS, et al. Targeted therapy after complete resection of metastatic lesions in metastatic renal cell carcinoma. *Int J Urol.* 2015;22:153-7.

- [24] You D, Lee C, Jeong IG, Song C, Lee JL, Hong B, et al. Impact of metastasectomy on prognosis in patients treated with targeted therapy for metastatic renal cell carcinoma. *J Cancer Res Clin Oncol*. 2016;142:2331-8.
- [25] Yu X, Wang B, Li X, Lin G, Zhang C, Yang Y, 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.
- [26] Verma J, Jonasch E, Allen PK, Weinberg JS, Tannir N, Chang EL, et al. The impact of tyrosine kinase inhibitors on the multimodality treatment of brain metastases from renal cell carcinoma. *Am J Clin Oncol*. 2013;36:620-4.
- [27] Vickers MM, Al-Harbi H, Choueiri TK, Kollmannsberger C, North S, MacKenzie M, et al. Prognostic factors of survival for patients with metastatic renal cell carcinoma with brain metastases treated with targeted therapy: results from the international metastatic renal cell carcinoma database consortium. *Clin Genitourin Cancer*. 2013;11:311-5.
- [28] Dabestani S, Marconi L, Hofmann F, Stewart F, Lam TB, Canfield SE, et al. Local treatments for metastases of renal cell carcinoma: a systematic review. *Lancet Oncol*. 2014;15:e549-61.
- [29] Kano H, Iyer A, Kondziolka D, Niranjan A, Flickinger JC, Lunsford LD. Outcome predictors of gamma knife radiosurgery for renal cell carcinoma metastases. *Neurosurgery*. 2011;69:1232-9.
- [30] Ruhle A, Andratschke N, Siva S, Guckenberger M. Is there a role for stereotactic radiotherapy in the treatment of renal cell carcinoma? *Clin Transl Radiat Oncol*. 2019;18:104-12.
- [31] Palma DA, Olson R, Harrow S, Gaede S, Louie AV, Haasbeek C, et al. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. *Lancet*. 2019;393:2051-8.
- [32] Stenman M, Sinclair G, Paavola P, Wersall P, Harmenberg U, Lindskog M. Overall survival after stereotactic radiotherapy or surgical metastasectomy in oligometastatic renal cell carcinoma patients treated at two Swedish centres 2005-2014. *Radiother Oncol*. 2018;127:501-6.
- [33] Albiges L, Powles T, Staehler M, Bensalah K, Giles RH, Hora M, et al. Updated European Association of Urology Guidelines on Renal Cell Carcinoma: Immune Checkpoint Inhibition Is the New Backbone in First-line Treatment of Metastatic Clear-cell Renal Cell Carcinoma. *Eur Urol*. 2019;76:151-6.

Legends

Figure 1: Kaplan-Meier curve. OS = overall survival, PFS = progression-free survival, LC = local control, TTS = time to systemic therapy switch.

Figure 2: Example of a 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 tumor response as well as complete recovery of the cerebral edema.

Figure 3: Dose volume histogram of local control rates after SRT of RCC metastases.

Figure 4: Multivariate Cox regression analysis. $p < 0.05$ is significant. HR = hazard ratio, 95% CI = 95% confidence interval, ECOG-PS = Eastern Cooperative Oncology Group Performance Status.

Table 1: Patient characteristics of mRCC patients treated with SRT concurrent to TT/ICI.

Table 2: Univariate Cox regression analysis. $p < 0.05$ is significant. TT=targeted agents, ICI=immune checkpoint inhibitors. OS=overall survival, PFS=progression free survival, TTS=time to systemic therapy switch

Table 3: Overview of currently published literature on metastatic renal cell carcinoma (mRCC) concurrent to targeted therapy (tyrosine kinase inhibitors (TKI), mTOR-inhibitors (mTORi) or immune checkpoint inhibitors (ICI).

Role of the funding source: This work was financially supported by Varian Medical Systems. Varian Medical Systems was not involved in the study design, collection, analysis and interpretation of data, the writing of the report or in the decision to submit the article for publication. SA is supported by the German Cancer Consortium (DKTK), M Geier received a speaker fee from Roche and a speaker fee from Bristol-Myers-Squibb. FE receives research and educational grants from Elekta, Philips, Siemens, Sennewald. SS is supported by a National Health and Medical Research Council (NHMRC) fellowship, and Cancer Council Victoria (CCV) Colebatch Fellowship.

bju_15284_f1.jpg

bj_u_15284_f2.jpg

bju_15284_f3.jpg

bjv_15284_f4.jpg

Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:

Kroeze, SGC;Fritz, C;Schaule, J;Siva, S;Kahl, KH;Sundahl, N;Blanck, O;Kaul, D;Adebahr, S;Verhoeff, JJC;Skazikis, G;Roeder, F;Geier, M;Eckert, F;Guckenberger, M

Title:

Stereotactic radiotherapy combined with immunotherapy or targeted therapy for metastatic renal cell carcinoma

Date:

2020-11-19

Citation:

Kroeze, S. G. C., Fritz, C., Schaule, J., Siva, S., Kahl, K. H., Sundahl, N., Blanck, O., Kaul, D., Adebahr, S., Verhoeff, J. J. C., Skazikis, G., Roeder, F., Geier, M., Eckert, F. & Guckenberger, M. (2020). Stereotactic radiotherapy combined with immunotherapy or targeted therapy for metastatic renal cell carcinoma. *BJU INTERNATIONAL*, 127 (6), pp.703-711. <https://doi.org/10.1111/bju.15284>.

Persistent Link:

<http://hdl.handle.net/11343/286994>