Original Article

Stereotactic body radiotherapy (SBRT) for pulmonary metastases from renal cell carcinoma—a multicenter analysis of the German working group "Stereotactic Radiotherapy"

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Background: Renal cell carcinoma (RCC) is traditionally considered to be radioresistant. Radiotherapy response rates are believed to improve with hypofractionated, high dose stereotactic body radiotherapy (SBRT). However, limited data exist regarding the role of SBRT in the treatment of pulmonary metastases.

Methods: The working group "Stereotactic Radiotherapy" of the German Society of Radiation Oncology analyzed its multi-institutional database of more than 700 patients who received SBRT for pulmonary metastases. Treatment was performed at 10 centers between 2001 and 2016. Patients with metastatic RCC were included in the study. Tumor characteristics, treatment details, and follow-up data including survival, local control (LC), distant metastases, and toxicity were evaluated.

Results: A total of 46 RCC patients treated with SBRT for 67 lung metastases were identified, who received a median total biologically effective dose (BED_{iso}) at planning target volume (PTV) isocenter of 117.0 Gy (range, 48.0–189.0 Gy). A median fractional dose of 20.8 Gy at isocenter (range, 6.0–37.9 Gy) was administered in a median number of 3 fractions (1–8 fractions). After a median follow-up time of 28.3 months for all patients, 1- and 3-year LC rates were 98.1% and 91.9%, with corresponding 1- and 3-year overall survival (OS) of 84.3% and 43.8%, respectively. Pulmonary metastases treated with BEDiso ≥130 Gy showed a trend for superior LC (P=0.054). OS was significantly improved in both uni- and multivariate analysis for patients with higher Karnofsky performance scale, lower maximum pulmonary metastasis diameter and lack of post-SBRT systemic therapy due to progression (P=0.014; P=0.049; P=0.006). Only mild acute and late toxicity was reported.

Conclusions: SBRT for pulmonary metastases from RCC was associated with low treatment-associated toxicity, promising survival, and excellent LC, especially in those patients receiving a BED_{iso} ≥130 Gy.

Keywords: Renal cell carcinoma (RCC); lung metastases; stereotactic body radiotherapy (SBRT); radioresistance; extracranial stereotactic radiotherapy

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Introduction

Renal cell carcinoma (RCC) represents 2–3% of adult cancers in the European Union and accounts for approximately 34,700 deaths per year (1,2). Although 5-year survival for all patients is approximately 74%, survival rates are highly dependent on disease stage, declining to 67% when locoregional disease (stage III) is detected and 12% in patients with distant metastases (3,4). Most patients are diagnosed at an early stage, yet nearly one third of these patients will suffer from local or distant relapse in the course of their disease, and a similar proportion of patients present with metastatic spread at first diagnosis (5,6). Lung metastases are the most common presentation of distant disease, comprising 11–75% of cases, while hepatic metastases occur in 20–40% of patients (7-12).

When distant metastases are diagnosed, systemic treatment with targeted agents is usually administered (3). However, an oligo-metastatic state has been hypothesized, where systemic therapy and potential toxicity might be postponed by applying local treatment strategies to all evident tumor lesions (13). Furthermore, an objective response has been reported in 20–40% of patients, but complete response was only detected in 1–3% of cases with current targeted drugs (13-16). Consequently, in cases of oligoprogression, local ablative treatment to all synchronous and metachronous metastases, when technically feasible and clinically appropriate, might represent a potentially curative approach (13).

Surgical series for pulmonary metastasectomy as a local treatment method of RCC patients report excellent local control (LC) in case of complete resection and promising 3- and 5-year survival rates of 49–66% and 31–58%, respectively (17-27). However, some RCC patients are medically inoperable due to reduced performance status or comorbidities and some pulmonary metastases are technically not accessible or resectable. For these patients, stereotactic body radiotherapy (SBRT) which utilizes highly conformal ablative local doses to the tumor while sparing surrounding organs, has shown encouraging results (5,28-30). However, available reports concerning SBRT for RCC metastases have pooled heterogeneous data from various tumor locations (lung, bone, lymph node, brain, liver, etc.) with different sensitivities to high-dose radiation (5,6,28-33). This multi-institutional study reports the feasibility, safety, and efficacy of SBRT for pulmonary RCC metastases.

Methods

The working group "Stereotactic Radiotherapy" of the German Society of Radiation Oncology (DEGRO) analyzed its retrospective multi-institutional database including more than 700 patients treated with SBRT for more than 900 pulmonary metastases. Detailed description of the database has been previously published (34-36). For the current study, an update of the database was performed in April 2017. Patient data from institutions that did not participate in this database update were excluded from this study. In total, 46 patients with histologically confirmed RCC treated with SBRT for 67 pulmonary metastases at 10 different German centers between 2001 and 2016 were analyzed. Each center compiled patient characteristics, treatment details, and outcome data in an anonymized electronic file and delivered it to the coordinating center, where a pooled database was created. The analysis was approved by the Ethics committee of the University Hospital Heidelberg (S-280/2014).

Pulmonary SBRT was utilized if patients were classified medically inoperable, diagnosed with unresectable lung metastases or refused surgical resection. Fluoro-deoxy-glucose positron emission tomography (FDG-PET) imaging was only performed in five patients and biopsy confirmation was performed when the origin of the pulmonary lesion was in question (n=7). All centers used risk-adapted fractionation schemes adjusting the number

of fractions and single-fraction doses to tumor size and location (peripheral *vs.* central). Metastases were classified to be "peripheral" or "central" according to the Radiation Therapy Oncology Group (RTOG) definition (37,38). Treatment-related toxicity was categorized according to CTCAE v4.0.

For correlating radiation doses with clinical results, the biological effective dose (BED) was determined assuming: an α/β ratio of 10 Gy for the pulmonary metastases. BED was calculated using the linear-quadratic model (39):

$$\text{BED (Gy)} = \text{fractional dose} \times \text{number of fractions} \left(1+\frac{\text{fractional dose}}{\alpha/\beta}\right)$$

LC, overall survival (OS) and distant control (DC) were estimated using the Kaplan-Meier method. While LC was calculated for each individual pulmonary metastasis, OS and DC were determined following SBRT for the first, index pulmonary lesion if several pulmonary metastases were treated. LC was defined as no progressive disease within the high-dose area. Recurrences distant to the treated pulmonary metastasis in the same lobe were not classified as local but as distant failure.

Survival curves were compared between groups in univariate analysis applying the log-rank test or cox regression analysis. Receiver operating characteristics (ROC) curves and the Youden's index were applied to determine the optimal cut-off for BED at planning target volume (PTV) isocenter (BED_{ISO}). Multivariate cox models were performed including all variables which were statistically significant in univariate analysis. Multivariate analysis was not performed for LC, as no significant prognostic factor was identified in univariate analysis. LC, OS and DC were analyzed from the start of SBRT until the event of interest or the last follow-up visit. A $P \leq 0.05$ was considered statistically significant. All statistical analyses were performed with SPSS software (version 20.0).

Results

Patient and treatment characteristics

This multi-institutional analysis included data from 10 centers with extensive lung SBRT experience, of which seven were university hospitals. In total, data were collected from 46 patients treated with SBRT for 67 pulmonary metastases. Most patients were treated for one lung metastasis (median: 1 metastasis, range, 1–7 metastases). All patients were diagnosed with biopsy-proven metastatic RCC and had in median one additional metastasis (range, 0–15) besides the treated pulmonary lesion(s). Additional metastases were located in 77.1% in the lung. Of these 48.6% were treated with resection and 31.4% underwent additional SBRT. Overall, 83% of patients received definitive treatment with curative intent (SBRT, definitive radiotherapy or surgery, sometimes in combination with systemic therapy) to all known sites of metastasis, while the remaining 17% were treated with systemic therapy including chemotherapy, immunotherapy, or targeted agents. In total, 22 patients received systemic therapy prior to SBRT. Of these, chemotherapy was administered in two patients, followed by immunotherapy in five patients and tyrosine kinase inhibitors in 15 patients. SBRT to pulmonary metastases was applied at a median 73.8 months (range, 3.2 months–28.8 years) following diagnosis of the primary tumor. The time interval between diagnosis of the pulmonary metastasis and SBRT treatment was found to be 2.7 months (0.2–83.1 months) in median. Detailed patient and treatment characteristics are illustrated in *Tables 1* and *2*.

OS, LC and systemic progression

Median follow-up time for all patients was 28.3 months (range, 0.8–133.8 months) with 1- and 3-year LC rates of 98.1% and 91.9%, respectively (*Figure 1A*). Only 3 local relapses (4.5%) were detected during the follow-up period with a median time to local failure of 26.2 months (range, 10.5–27.7 months). Univariate analysis revealed a trend for increased LC when the $BED_{ISO} \geq 130$ Gy (P=0.054) (*Figure 1B*) (*Table 3*). Pulmonary metastases treated with a $BED_{ISO} < 130$ Gy resulted in a 3-year LC of 83.9%, while receipt of a $BED_{ISO} \geq 130$ Gy was associated with a 3-year LC of 100%.

One- and 3-year distant metastases free survival was found to be 45.7%, and 17.0%. Distant disease progression was the most common pattern of failure, with 69.6% of patients (n=32) developing new, out-of-field metastases. Distant metastases were mostly detected in the lung (n=26), the bone (n=4), the liver (n=4), the brain (n=4), and other locations (n=4).

One- and 3-year OS was 84.3% and 43.8% respectively (*Figure 2*). Karnofsky performance score, maximum pulmonary metastasis diameter and the lack of admission of systemic therapy after SBRT due to disease progression were identified as prognostic factors for OS in univariate analysis (P=0.010; P=0.011, P=0.001) (*Table 3*). Furthermore, the presence of metachronous metastases was associated with a trend towards improved OS compared to synchronous

Table 1 Baseline patient and lesion characteristics for 46 patients treated with SBRT for 67 pulmonary metastases

Factors	No. of patients/lesions	%	Median	Minimum	Maximum
Persons					
Age (yr)	46		68.5	35.4	85.1
Sex	46				
Male	34	73.9			
Female	12	26.1			
Pretreatment performance scale (Karnofsky index) (%)	46		90	60	100
Cancer stage at first diagnosis	46				
Stage I	10	21.8			
Stage II	7	15.2			
Stage III	15	32.6			
Stage IV (M+)	14	30.4			
Histology	46				
Clear cell	33	71.7			
Other	8	17.4			
Unavailable	5	10.9			
Grade	46				
Grade 1	7	15.2			
Grade 2	24	52.2			
Grade 3	5	10.9			
Unavailable	10	21.7			
Pulmonary lesions					
Metastasis diameter (cm)	67		2.1	0.6	7.6
Metastasis location	67				
Central	13	19.4			
Peripheral	54	80.6			
Number of metastases	67				
Single	12	17.9			
Multiple	55	82.1			
Time to metastasis	67				
Synchronous	3				
Metachronous	64				
Time interval between SBRT and first tumor diagnosis (years)	67		6.15	0.27	28.8
Systemic therapy before SBRT	67				
Yes	35	52.2			
No	32	47.8			

Table 1 *(continued)*

Table 1 *(continued)*

Factors	No. of patients/lesions	%	Median	Minimum	Maximum
Systemic therapy 4 weeks before SBRT	67				
Yes	13	19.4			
No	54	89.6			
Systemic therapy after SBRT	67				
Yes	27	40.3			
No	40	59.7			

SBRT, stereotactic body radiotherapy.

Table 2 SBRT treatment patterns for 67 lung metastases

Dose prescription parameters	No. of Lesions	%	Median	Minimum	Maximum
Fractional dose at PTV isocenter (Gy)	67		20.8	6.0	37.9
Number of fractions	67		3	1	8
BED_{PTV} (PTV periphery) (Gy)	67		84.4	35.7	180.0
BED_{ISO} (PTV isocenter) (Gy)	67		117.0	48.0	189.0
Dose inhomogeneity (PTV periphery dose/maximum dose) (%)	67		75	60	100.0
Fractionation					
1×20–24 Gy	11	16.4			
1×25–30 Gy	12	17.9			
3–4×7–8 Gy	6	9.0			
3×10–15 Gy	23	34.3			
3×16–18 Gy	5	7.4			
5×6–10 Gy	6	9.0			
8×5–7.5 Gy	4	6.0			

SBRT, stereotactic body radiotherapy; PTV, planning target volume; BED, biological effective dose.

lesions (P=0.055). Patients receiving definitive treatment to all metastatic lesions had non-significantly improved survival compared to patients who were treated with systemic therapy and SBRT-debulking of disease with 3-year OS-rates of 50.5% and 14.6%, respectively (P=0.077). Multivariate analysis revealed higher Karnofsky performance score, lower maximum pulmonary metastasis diameter as well as no admission of systemic therapy after SBRT as independent prognostic factors for OS (P=0.014; P=0.049; P=0.006).

Toxicity

Acute toxicity was mild with only four patients developing radiation induced common terminology criteria for adverse events (CTCAE) grade II pneumonitis. Three of these four patients were treated with a second course of SBRT to another pulmonary metastasis within 14 days of initial SBRT. No grade III–V pneumonitis was reported. One patient died 0.9 months following SBRT; consequently 30- and 60-day death rates were 1.5%. The death of this patient was not attributable to SBRT treatment, as it was secondary to perforated diverticulitis with peritonitis. Three patients developed further grade II+ toxicity: pulmonary fibrosis (1 patient), atelectasis (1 patient) and pleural effusion (1 patient). Higher toxicity rates were not observed in patients who received systemic therapy before SBRT.

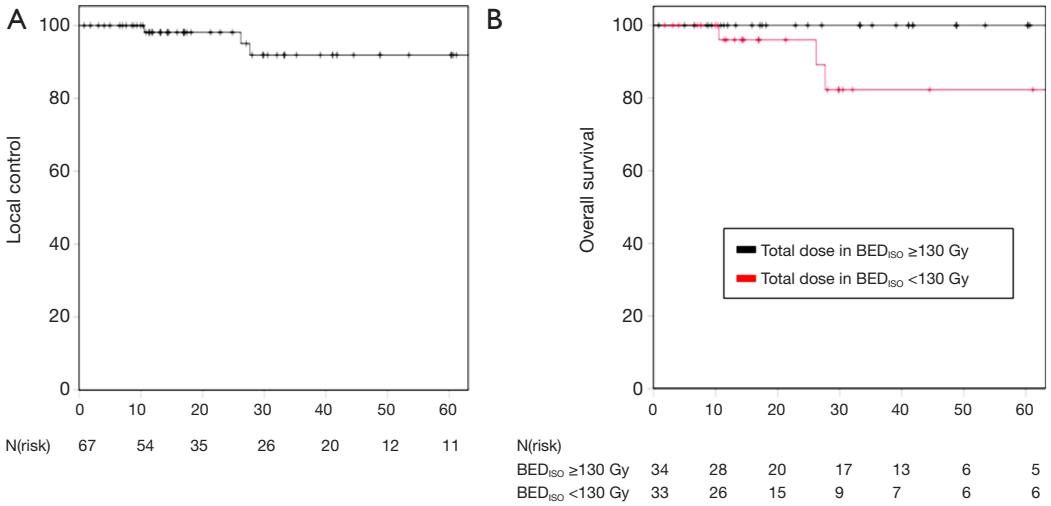

Figure 1 Outcome analysis. (A) Local control (LC) following SBRT for 67 lung metastases from RCC; (B) metastases treated with BED_{ISO} ≥130 Gy showed a tendency for superior LC (P=0.054). SBRT, stereotactic body radiotherapy; RCC, renal cell carcinoma.

Table 3 Univariate analysis of prognostic factors influencing LC and OS

Factors	LC			OS		
	HR	95% CI	P	HR	95% CI	P
Sex (female *vs.* Male)	0.281	(0.025, 3.107)	0.130	0.622	(0.233, 1.659)	0.343
Age	1.094	(0.920, 1.303)	0.310	1.002	(0.953, 1.053)	0.946
Karnofsky performance scale	0.977	(0.879, 1.087)	0.673	0.962	(0.933, 0.991)	0.010
Histology (clear cell *vs.* other *vs.* unavailable)	0.523	(0.015, 18.071)	0.720	0.963	(0.837, 1.109)	0.603
Grade (1 *vs.* 2 *vs.* 3 *vs.* unknown)	0.564	(0.045, 7.124)	0.658	0.906	(0.787, 1.043)	0.169
Time to metastasis (synchronous *vs.* Metachronous)	0.542	(0.049, 5.998)	0.618	0.425	(0.177, 0.999)	0.055
Number of metastases (solitary *vs.* multiple)	3.343	(0.303, 36.876)	0.325	1.044	(0.431, 2.525)	0.924
Maximum pulmonary metastasis diameter	1.276	(0.588, 2.767)	0.537	1.339	(1.068, 1.677)	0.011
Tumor location (peripheral *vs.* central)	1.971	(0.178, 21.770)	0.580	0.433	(0.146, 1.287)	0.123
BED_{PTV} (PTV periphery)	0.997	(0.955, 1.041)	0.896	0.998	(0.986, 1.011)	0.795
BED_{ISO} (PTV isocenter)	0.986	(0.962, 1.010)	0.250	1.000	(0.992, 1.007)	0.960
Total dose in BED_{ISO}: <130 Gy; ≥130 Gy	0.012	(0.001, 37.987)	0.054	1.259	(0.583, 2.746)	0.553
Definitive treatment to all further metastases (yes *vs.* No)	n	n	n	2.334	(0.911, 5.977)	0.077
Systemic therapy in general (no *vs.* yes)	0.666	(0.060, 7.352)	0.740	0.557	(0.252, 1.233)	0.149
Systemic therapy before SBRT (no *vs.* yes)	2.133	(0.193, 23.574)	0.537	0.673	(0.314, 1.444)	0.309
Systemic therapy 4 weeks before SBRT (no *vs.* yes)	3.641	(0.161, 36.767)	0.727	0.392	(0.139, 1.100)	0.075
Systemic therapy after SBRT (no *vs.* yes)	0.155	(0.013, 1.771)	0.133	0.190	(0.069, 0.527)	0.001
Systemic therapy 4 weeks after SBRT (no *vs.* yes)	0.721	(0.293, 1.322)	0.290	0.803	(0.622, 1.038)	0.094

The variables sex, histology, grade, time of metastasis, number of metastases; tumor location and total dose in BED_{ISO} </≥ 130 Gy were analyzed as categorical variables, while the other variables were taken as continuous variables for analysis. n, calculation of confidence intervals was not possible due to too few cases and events in each single group. OS, overall survival; LC, local control; HR, hazard ratio; BED, biological effective dose; PTV, planning target volume; SBRT, stereotactic body radiotherapy.

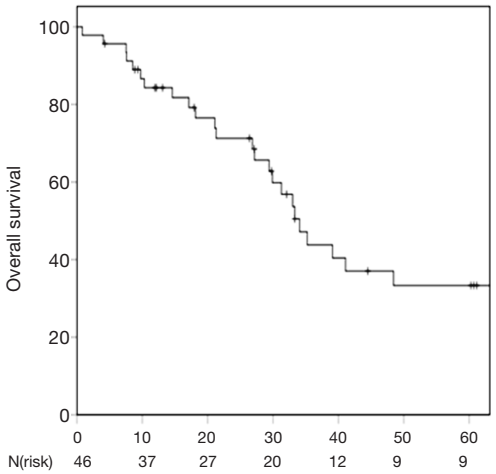

Figure 2 Overall survival (OS) after SBRT of 67 pulmonary metastases in 46 RCC patients. SBRT, stereotactic body radiotherapy; RCC, renal cell carcinoma.

Discussion

RCC is traditionally perceived to be a radioresistant malignancy with a limited role for radiotherapy in the management of localized disease (1). Although prospective trials investigating the role of radiotherapy in the neoadjuvant and adjuvant settings demonstrated improved LC, these findings have not translated into increased survival (40,41). Contrarily, smaller retrospective studies have suggested a potential advantage for adjuvant radiotherapy with larger tumors (pT3) or positive resection margins (40,42,43). Nevertheless, currently radiotherapy is primarily used for palliation of symptoms in metastatic RCC (3).

The efficacy of radiotherapy is highly dependent on applied doses and fractionation schemes. While RCC tumors appear to be radioresistant using conventionally fractionated radiotherapy, preclinical data suggest increased radiosensitivity of human RCC xenografts in nude mice when applying ablative, hypofractionated radiotherapy (44). In the clinical setting, dose escalation has also been shown to overcome radioresistance in RCC tumors: Zelefsky and colleagues reported 3-year LC of 88% following SBRT with high fractional doses for extracranial RCC metastases, while LC dropped to only about 20% when lower doses were used (30). A few other reports have also revealed LC rates of about 80–90% for extracranial SBRT in RCC patients (5,6,28,29,31,33). However, due to the limited number of RCC patients treated with SBRT, these reports combined data form different metastatic sites of including lung, bone, liver, lymph nodes or even primary RCC tumors (5,6,28,29,31,33).

As LC and treatment-related toxicity following SBRT are known to be highly dependent on treatment location, it is essential to analyze different SBRT treatment locations separately. To our knowledge, this analysis is the first study focusing on SBRT for solely pulmonary metastases from RCC. We observed excellent 1- and 3-year LC rates of 98.1% and 91.9% following SBRT of these metastases with low rates of treatment-associated toxicity.

In general, the most important factor for achieving optimal LC following SBRT is a sufficiently high BED. For lung and liver SBRT, doses above 100 Gy BED_{PTV} (PTV minimum dose) are recommended, while lower doses seem sufficient for spinal metastases (35,36,45-47). A recently published report by Wang *et al.* investigated SBRT for a wide variety of extracranial RCC metastases, including bone (38.8%), abdominal (28.0%) and thoracic (20%) lesions, demonstrating significantly improved LC if a BED_{PTV} of 98.7 Gy or higher was applied (28). Altoos *et al.* compared SBRT (n=36) and conventionally fractionated radiotherapy (n=17) for the treatment of thoracic, abdominal or soft tissue RCC metastases and also reported a BED_{PTV} ≥100 Gy to be associated with significantly superior LC. In our study, excellent LC rates exceeding 90% after 3 years for RCC pulmonary metastases were detected, despite a median BED_{PTV} of 84.4 Gy. As in other studies, we also observed a dose-response relationship: if pulmonary metastases received a BED_{ISO} ≥130 Gy at PTV isocenter, there was a strong trend for improved LC (P=0.054). Notably, only three local recurrences were identified in our cohort and hence this result has to be interpreted with caution. Due to the very low number of local relapses detected in this study, consequently analysis of further potential prognostic factors regarding LC was highly limited (*Table 3*) and results have to be regarded as preliminary. Clearly, larger, multi-center studies are needed to further clarify the impact of suspected prognostic factors.

To date, only smaller and retrospective surgical series for pulmonary metastasectomy in RCC patients have reported good 3- and 5-year survival rates of 49–66% and 31–58%, respectively (*Table 4*) (17-27). In this study, estimated 3- and 5-year OS rates with 44% and 33% were slightly lower compared to these surgical series. However, comparison between these studies is limited, as nearly all patients in this study were classified as medically inoperable due to comorbidities or higher age. While median age was 68.5 years in this study, reported median

Table 4 Surgical series for pulmonary metastasectomy in RCC patients

Study	Year	Treatment years	Number of patients (n)	3-year OS (%)	5-year OS (%)
Piltz *et al.* (20)	2002	1980–2000	105	54	40
Pfannschmidt *et al.* (19)	2002	1985–1999	191	–	37
Murthy *et al.* (18)	2005	1986–2001	92	49	31
Hofmann *et al.* (17)	2005	1975–2003	64	–	33
Assouad *et al.* (21)	2007	1984–2005	65	–	34
Kanzaki *et al.* (22)	2010	1973–2008	48	60	47
Meimarakis *et al.* (23)	2011	1986–2006	202	–	39
Kawashima *et al.* (25)	2011	1998–2008	25	53	36
Bölükbas *et al.* (24)	2012	1999–2008	107	–	47
Kudelin *et al.* (26)	2013	1999–2009	116	–	49
Renaud *et al.* (27)	2014	1993–2011	122	66	58
Own data	2017	2001–2016	46	44	33

RCC, renal cell carcinoma; OS, overall survival.

ages were 6–11 years lower in the surgical series, ranging from 57.7–62.0 years, potentially explaining the marginally lower OS rates observed in our study (17-19,21-23,25-27). Hence, SBRT for pulmonary metastases might be a valid alternative at least for patients in higher age and with comorbidities.

A survival benefit for patients with oligo-metastatic RCC has been suggested when complete metastasectomy in parenchymal organs is performed compared to no surgical resection (10,13). However, patient selection for this treatment approach is critical. A recent review of local treatments for metastases of RCC recommended the following criteria for suitable patients for a curative approach: good performance status, solitary or oligo-metastatic lesions, single organ sites, metachronous metastases, disease-free interval of over 2 years, absence of progression to treatment, and pulmonary metastasis size less than 4 cm in diameter in addition to several other, organ-specific factors (13). Corresponding to these recommendations, Karnofsky performance score and pulmonary metastasis diameter were identified as independent prognostic factors for superior OS in our study (P=0.010; P=0.009). Furthermore, a trend towards improved OS was detected for metachronous lesions when compared to synchronous metastases (P=0.055). Patients analyzed in the current study were mainly treated with pulmonary SBRT in a potentially curable oligo-metastatic tumor state. Thirty-six patients (83%) received definitive treatment including SBRT, surgery or radiotherapy with curative doses often in combination with systemic therapy to all detectable tumor lesions. However, 8 patients (17%) were treated with SBRT for debulking and palliation of disease in combination with systemic therapy. This group of patients experienced a worse median survival of 19.6 months following SBRT compared to those patients treated with curative intent with 29.8 months (P=0.077; *Table 3*). This finding may be explained by two mechanisms: (I) whether or not all lesions are radically treated maybe co-correlated with the overall metastatic tumor load, which is a known prognostic factor; (II) radical treatment of all imaging-defined metastases does indeed improve OS compared to debulking SBRT only.

RCC is considered to be an immunogenic tumor. Until 10 years ago, interferon alpha and high-dose interleukin-2 were the mainstays of treatment for patients with metastatic RCC (3). Although these systemic agents have been replaced by molecular, targeted therapies during the last years, the immunogenic potential of RCC remains an exciting avenue for future study. Immunotherapy with antibodies against the programmed cell death protein 1 (PD-1) or its ligand 1 (PD-L1) have demonstrated excellent preliminary results (48-50). Interestingly, SBRT might also be applied to enhance immunogenic the anti-tumor response via the abscopal effect: clinical studies have described regression of non-irradiated distant lesions following SBRT to an RCC metastasis (51-53). This effect is hypothesized to be immune

mediated (40,53). However, the abscopal effect occurs rarely after SBRT alone and might be fostered by simultaneous treatment with synergistic immunomodulatory agents (40,53). Hence, a potential future application of SBRT in patients with metastatic RCC might include the addition of systemic immunomodulatory therapy by inducing persistent anti-tumor immunity and potentially improving long-term survival (40,53).

Limitations of this study were mainly caused by the retrospective nature of this analysis. Despite the extensive study timespan and multi-institutional approach, patient numbers were quite low as only few RCC patients are treated with SBRT to pulmonary metastases. The median follow-up time of 28.3 months for all patients was too short to assess long-term LC, survival and potentially late toxicity. Furthermore, systemic treatments have drastically changed over the course of this study, and their improved efficacy may have influenced LC and survival following SBRT.

Conclusions

SBRT especially with BED_{iso} ≥130 Gy for pulmonary RCC metastases resulted in excellent LC with only minimal acute and late toxicity. Survival was favorable for metastatic RCC patients. Future studies are needed to evaluate the potential of SBRT in combination with target molecular agents and/or immunotherapy in the treatment of oligo-metastatic RCC patients.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The analysis was approved by the Ethics committee of the University Hospital Heidelberg (S-280/2014).

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