Cancer Treatment and Research Communications 22 (2020) 100161

Contents lists available at ScienceDirect

Cancer Treatment and Research Communications

journal homepage: www.elsevier.com/locate/ctarc

Treatment Outcome of metastatic lesions from renal cell carcinoma underGoing Extra-cranial stereotactic body radioTHERapy: The together retrospective study

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ARTICLE INFO

Keywords:
SBRT
Extra-cranial
Metastatic renal cell carcinoma
RCC
Stereotactic radiotherapy
Oligoprogressive
Oligometastatic

ABSTRACT

Objectives: stereotactic body radiation therapy (SBRT) use has increased overtime for the management of metastatic renal cell carcinoma (mRCC) patients, with a likely good control of irradiated lesions. We planned a retrospective multicenter Italian study, with the aim of investigating the outcome of treatment with SBRT for non-brain secondary lesions in mRCC patients.

Methods: all consecutive metastatic non-brain lesions from mRCC that underwent SBRT at nine Italian institutions from January 2015 to June 2017 were considered. The primary endpoint of the study was the lesion-PFS, calculated from SBRT initiation to the local progression of the irradiated lesion.

Results: 57 extracranial metastatic lesions from 48 patients with primary mRCC were treated with SBRT. At the median follow-up of 26.4 months, the median lesion-PFS was not reached (43 censored); 72.4% of lesions were progression-free at 40 months, with significantly better lesion-PFS for small metastatic lesions (< 14 mm). SBRT was safe and the 1-year local disease control was 87.7%. After SBRT, 18 patients (37.5%) permanently interrupted systemic therapy.

Conclusions: consistently with the previous literature, our findings support the use of SBRT in selected mRCC patients.

Introduction

Renal cell carcinoma accounts for more than 330,000 new cases worldwide and around 20% of patients have metastatic disease at diagnosis [1,2]. Systemic treatment currently represents the standard of care for metastatic renal cell carcinoma (mRCC) [3]. The recent

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https://doi.org/10.1016/j.ctarc.2019.100161

advances in the treatment of this tumor, from the introduction of antiangiogenic tyrosine kinase inhibitors (TKIs) to the most recent approval of immune checkpoint inhibitors (CKI), allowed to prolong overall survival (OS) of mRCC patients [4]. Considering this new treatment landscape, a multidisciplinary approach appears to be crucial for the management of long-survivors, in order to offer them a tailored strategy to tackle the disease overtime.

In this context, stereotactic body radiation therapy (SBRT) demonstrated good local control with a favorable toxicity profile for mRCC when an adequate dose and coverage were applied, suggesting the utility of a local approach especially in the case of oligometastatic disease [5]. *Per se*, an oligometastatic state is an independent favorable prognostic factor for OS, increasing the likeliness to benefit from locoregional approaches when used in addition to systemic therapies [6].

Despite renal cancer was historically considered to be radioresistant, the new SBRT techniques with hypofractionated radiation therapy and high-precision irradiation have the potential to maximize the treatment effect and minimize the adverse effect on the surrounding tissues [7]. As a consequence, SBRT use has increased overtime for the management of mRCC patients, with a likely good control of irradiated lesions. Recently, a wide range of retrospective reports and only one prospective study contributed to configure the landscape of the current clinical practice in this field [5,8–20].

To add further knowledge to this setting, unavoidably prevented from prospective clinical trials due to the really tailored strategy of application, we planned a retrospective multicenter Italian study, with the aim of investigating the outcome of treatment with SBRT for non-brain secondary lesions in mRCC patients.

Methods

In this observational retrospective multicenter study, we considered all consecutive metastatic lesions from mRCC that underwent SBRT at nine Italian institutions from January 2015 to June 2017. The inclusion criteria were represented by: (a) any histologic subtype of renal cancer; (b) SBRT of non-brain and not-only-bone lesions (namely with the inclusion of bone lesions only in the case of soft-tissue component with bone infiltration); (c) oligometastatic (defined as five or less metastatic lesions) OR oligoprogressive (defined as the appearance or dimensional increase of one to three metastatic sites) disease (d) adequate imaging acquired before treatment with computed tomography (CT) scan or magnetic resonance imaging (MRI); (e) availability of at least one radiological assessment after SBRT (including CT and/or MRI scan); (f) availability of clinical records of patients. Radiotherapy with only palliative/antalgic aim, surgical resection of metastases or previous radiotherapy of the target lesion were exclusion criteria. The decision about SBRT regimen (dose, duration and fractioning) was made at the discretion of the treating radiation oncologist.

The Local Ethical Committees of the participating centers gave the approval for the study and patients signed informed consent forms where applicable.

The primary endpoint of the study was the progression free survival of the irradiated lesions (lesion-PFS), calculated from SBRT initiation to the local progression of the irradiated lesion. The local progression event was defined as a minimum 20% increase in the major diameter, in the case of parenchymal lesions, and a minimum 20% increase in the minor diameter for nodal lesions, compared to baseline diameters. Data were considered as censored for lesion-PFS when progression did not occur at the time of the last follow-up. The local response to treatment was classified as increasing size, stable size, decreasing size or complete response, at each time-point compared to baseline, considering a maximum of four radiological assessments for each lesion (T1 vs. T0, T2 vs. T0, T3 vs. T0, T4 vs. T0). The imaging was obtained by CT scan every 3–4 months from radiotherapy, according to the usual clinical practice in the participating centers. The overall disease response assessment was defined according to RECIST 1.1 [21].

The secondary endpoints were overall response rate, progression free survival (PFS, per patient analysis), OS and SBRT-related toxicity. The latter was scored according to CTCAE V.5 [22].

Treatment planning and SBRT technique

The techniques used for treatment planning and delivery of SBRT at the nine treating institutions were quite homogeneous, according to the local clinical practice of each center. Treatment simulation was performed through a patient-customized cradle in the setup position, using specific personalized immobilization systems. Patient position was evaluated daily with cone beam CT before each treatment session. CT scan was performed using 2 mm slice thickness, with or without intravenous contrast. The contouring phase was performed by a radiation oncologist with delineation of gross tumor volume (GTV), its planning target volume (PTV) and the principal organs at risk. GTV was defined using simulation CT scan with or without rigid registration with MRI and/or PET-CT. PTV was created with an expansion around the GTV depending on the characteristic of each lesion (site and dimension) and the patient compliance. A 5 to 10 mm margin (isotropic or not) was added to the GTV. The planning phase was performed using an in-house treatment planning system software. The dose was prescribed according to the PTV or to an isodose line (mainly 95%, rarely 80% or 70%, making an inhomogeneity inside the target). The radiation technique was intensity modulated radiotherapy, mainly Arc therapy.

Statistical analysis

The characteristics of patients and of the irradiated lesions were summarized using descriptive statistics. The t-test for paired data was used to compare mean variation of the lesions' diameters. Lesion-PFS curves were obtained using the Kaplan–Meier method. The Log-rank test was performed to determine the differences in terms of lesion-PFS between groups. Median follow-up was estimated using the inverse Kaplan–Meier method [23]. ROC (Receiver Operating Characteristic) curves were built to establish the best cut-off for dichotomizing continuous variables. Differences were considered as statistically significant with $p < 0.05$. The Holm method [24] was used to adjust p-values keeping α constant (0.05) for multiple comparisons with t-test. When appropriate 95% confidence intervals (95% CI) were calculated. Considering the limited number of lesions and events, we choose not to perform multivariate analyses.

Statistical analyses were performed using SPSS Statistics 25.0 software (IBM Corporation, NY, USA).

Results

Between January 2015 and June 2017, 57 extracranial metastatic lesions from 48 patients with mRCC were treated with SBRT. The clinical characteristics of the patients treated, the SBRT dose levels and fractioning schedules were summarized in **Table 1**. The median follow-up 26.4 months (95% CI 23.3–29.4) and no patients were lost to follow-up.

Outcome of metastatic lesions treated with SBRT

The first radiological assessment compared to baseline was performed at the median time of 3.7 months after SBRT treatment. Overall, CT scans were acquired at the median interval of 3.5 months to assess the disease overall and the local control of the irradiated metastases. The local response to treatment was scored as increasing size, stable size, decreasing size and complete response; the results of the first two reassessments (T1 and T2) were summarized in Table 2.

The mean of the lesions' diameters decreased overtime after SBRT (**Fig. 1**). The dimensional change of the irradiated metastatic lesions from baseline to each radiological reassessment after treatment with

Table 1
Characteristics of advanced renal cancer patients and of their metastatic lesions treated with stereotactic body radiotherapy.

	Patients		Metastatic lesions
N° of patients	48 (100%)	N° of lesions	57 (100%)
Age (years)		**Site**	
Median	69	Lymph nodes	16 (28.1%)
Range	29–87	Lung	15 (26.3%)
		Bone lesions with soft tissue component	11 (19.3%)
		Adrenal gland	3 (5.25%)
		Pancreas	3 (5.25%)
		Other	9 (15.8%)
MSKCC score*		**Size at SBRT baseline**	
Favorable risk	19 (39.6%)	4–20 mm	30 (52.6%)
Intermediate risk	22 (45.8%)	21–40 mm	16 (28.1%)
Poor risk	7 (14.6%)	> 40 mm	11 (19.3%)
IMDC score*		**SBRT total dose**	
Favorable risk	18 (37.5%)	15–20 Gy	4 (7.0%)
Intermediate risk	26 (54.2%)	24–42 Gy	35 (61.4%)
Poor risk	4 (8.3%)	45–60 Gy	18 (31.6%)
Concurrent systemic therapy		**SBRT duration**	
		1–2 days	11 (19.3%)
Yes	26 (54.2%)	3–5 days	17 (29.8%)
No	22 (45.8%)	6–10 days	22 (38.6%)
		>10 days	7 (12.3%)
Treatment line		**Status at SBRT baseline**	
None	2 (4.2%)	Increasing size (*aim of control of oligoprogression*)	40 (70.2%)
I line	27 (56.2%)	Stable size (*aim of response consolidation*)	5 (8.8%)
II line	7 (14.6%)	Decreasing size (*aim of response consolidation with the purpose of systemic therapy holiday*)	12 (21.0%)
≥ III line	12 (25%)		
Systemic therapy after SBRT[§]		**Presence of necrosis at SBRT baseline (radiologically assessed)**	
Yes	30 (62.5%)	Yes	7 (12.3%)
No	18 (37.5%)	No	50 (87.7%)
Histology		**SBRT fractions (days)**	
Clear cell	45 (93.7%)	Median	5
Papillary	3 (6.3%)	Range	1–10

N° = number; MSKCC = Memorial Sloan-Kettering Cancer Center; SBRT = stereotactic body radiotherapy; IMDC = International Metastatic RCC Database Consortium; *assessed at the time of SBRT; [§]resumed after the first radiologic reassessment following SBRT.

SBRT, at the respective time-points, was statistically significant (respectively, with Holm correction: T1 vs. T0, $p = 0.025$; T2 vs. T0, $p = 0.018$; T3 vs. T0, $p = 0.004$; T4 vs. T0; $p < 0.0036$). The percentage change of the diameter of each lesion from baseline size is represented in Fig. 2.

Overall, the median lesion-PFS was not reached (43 lesions censored for progression) and 72.4% of lesions were progression-free at 40 months (**Supplementary Fig. 3a**). The local control rates at 1-year and 2-year were 83.6%, 72.4% respectively. The lesion-PFS was related to the first response of the irradiated lesion, defined as decrease in size at the first radiological evaluation and this finding was statistically significant ($p < 0.0001$; **Supplementary Fig. 3b**). The baseline size of the lesion, with the cut-off of 14 mm (14 mm or more vs. less than 14 mm, defined according to the ROC curve), was related to the outcome of SBRT, with significantly better lesion-PFS for small metastatic lesions ($p = 0.010$; **Supplementary Fig. 3c**).

Table 2
Change from baseline of the metastatic lesions after treatment with stereotactic body radiotherapy at the first two time-points.

Irradiated metastatic lesions	Baseline (T0)	First evaluation after SBRT (T1)	Second evaluation after SBRT (T2)
Presence of necrosis[§]			
Yes	7 (12.3%)	10 (17.5%)	11 (19.3%)
No	50 (87.7%)	47 (82.5%)	45 (78.9%)
Not evaluable	–	–	1 (1.8%)
Clinical benefit (improvement of local symptoms)			
Yes		14 (24.6%)	9 (15.8%)
No		9 (15.8%)	13 (22.8%)
Not applicable (asymptomatic) or not evaluable		34 (59.6%)	35 (61.4%)
Dimensional status[§]			
Increasing size	40 (70.2%)	7 (12.3%)	7 (12.3%)
Stable size	5 (8.8%)	33 (57.9%)	36 (63.1%)
Decreasing size	12 (21.0%)	17 (28.8%)	13 (22.8%)
Complete response	–	–	–
Not evaluable	–	–	1 (1.8%)
Local disease control	**17 (29.8%)**	**50 (87.7%)**	**49 (85.9%)**

SBRT = stereotactic body radiotherapy; [§]radiologic assessment.

The IMDC and the MSKCC score status of the patients at baseline did not have any impact on the SBRT outcome. Neither the site of the irradiated lesion (bone, lymph node, lung, other), nor the status of the lesion at the time of SBRT (increasing, stable or decreasing size), nor the presence of necrosis (radiological assessment) at baseline influenced the lesion-PFS to SBRT. Moreover, the improvement of local symptoms (defined as clinical benefit from SBRT) and the presence of necrosis at the subsequent reassessments were independent from the lesion-PFS.

Finally, the SBRT dose per fraction, using the cut-off of 6 Gy per dose (6 Gy or more vs less than 6 Gy, defined according to the ROC curve), was not significantly related to the lesion-PFS ($p = 0.052$; **Supplementary Fig. 3d**).

SBRT resulted to be safe, with 6% of grade (G) 1–2 SBRT-related toxicity (1 case G2, 2 cases G1; only one of them was receiving concurrent systemic therapy) and any severe toxicity (0% G3-4).

Outcome of patients and systemic therapy

The median PFS was 28.9 months (95% CI 16.3–41.7). The median OS was 49.2 months (95% CI 27.8–70.6), with 93.7% of patient alive at 12 months and 84.9% at 24 months.

Before the starting of SBRT, 46 patients (95.8%) were receiving systemic therapy (TKIs or other drugs).

The concurrent continuation of targeted therapy during SBRT was performed for 28 patients, while 29 patients interrupted systemic therapy to undergo SBRT, with no statistically significant different lesion-PFS between the two groups ($p = 0.213$). At the time of the first radiological evaluation (T1), 10 (21.7%) patients had partial response (PR), 31 (67.4%) had stable disease (SD), 6 (13.0%) had progressive disease (PD) and one was not evaluable. At T2, 12 (26.0%) patients had PR, 25 (54.3%) had SD and 8 (17.4%) had PD (3 not evaluable).

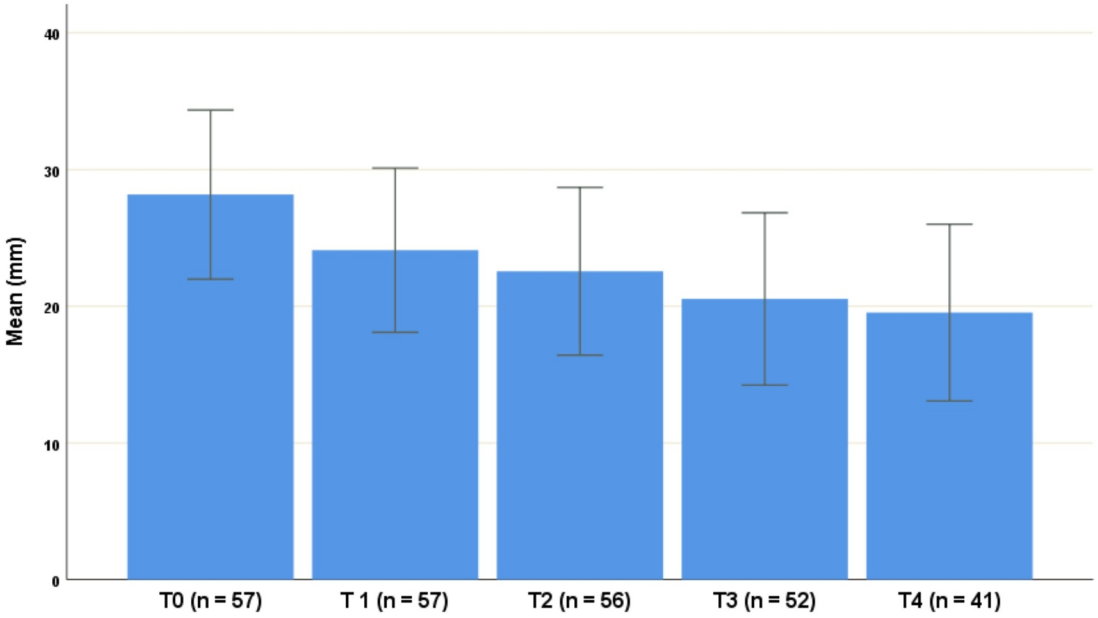

Fig. 1. Histogram representing the dimensional change of the lesions from baseline to each radiological reassessment after treatment with stereotactic body radiotherapy (SBRT), from baseline (T0) to four time-points (T1, T2, T3, T4). The whiskers show the 95% confidence intervals.

Finally, the reintroduction of systemic therapy after SBRT, occurred for 30 patients (62.5%), and this event did not influence the lesion-PFS overtime when compared to those of the 18 patients (37.5%) who permanently interrupted systemic therapy.

Discussion

In the era of the "embarrassment of riches" for the systemic therapy of mRCC, with several new treatment options enticing to easily change treatment line even in the case of oligoprogression, the importance of extending the clinical benefit from each single treatment line seems to be underestimated. Nevertheless, saving resources for the patient is still a crucial point, even considering the opportunity of "treatment holidays" in order to improve the quality of life without worsening the course of the disease. In this light, the use of loco-regional approaches could aid to improve the clinical management, allowing the temporary discontinuation of systemic therapy or recovering the disease control in oligoprogressive and/or oligometastatic cases. Despite limited prospective data, a meta-analysis addressed the issue of surgical metastasectomy in mRCC, showing good outcomes for this radical local approach [25]. Nevertheless, not all patients can be surgical candidates and alternative local approaches, such as SBRT, could be considered in this setting. The retrospective population presented herein, similarly to other previous case series reported by the literature (**Table 3**) [5,8–20], clearly represents such purposes, and furtherly supports the utility of SBRT approach for extra-cranial lesions.

According to our results, the local disease control was high after SBRT administration, reaching more than 87% of cases at first imaging assessment, with continuous benefit overtime, and this was consistent with the previous literature (see **Tables 2** and **Table 3**). The median lesion-PFS was not reached at 26.4 months of follow-up. Considering the high rate of progression-free lesions (72.4% at 40 months), the benefit from SBRT seems clinically relevant. Interestingly, the lesion-PFS was significantly related to the first local response, suggesting that lesions with an early response to radiotherapy have high probability of extended duration of response.

The reduction of lesions was significant overtime, and SBRT was effective regardless of any clinical element other than the size of the irradiated lesions, with a trend towards a better response in small lesions (baseline size smaller than 14 mm). Other clinical characteristics such as IMDC or MSKCC score of the patient, the site of the lesion, the status of the lesion at the time of SBRT (increasing or decreasing or stable size) and the radiological finding of necrosis did not affect the outcome of SBRT. Therefore, these findings support the use of SBRT in customized cases, irrespective of such characteristics.

From a clinical point of view, the improvement of symptoms was achieved in more than 60% of patients (14 out of 23 with local symptoms, see **Table 2**), despite the palliation of symptoms was not the primary intent of SBRT. Curiously, it was not related to the local objective response.

Finally, the dose of radiotherapy seemed not to be influent (despite a trend was noticed with the cut-off of 6 Gy) and SBRT was definitely safe, with a low rate of treatment-related mild toxicity (G1-2) and no severe toxicities, irrespective of the concurrent administration of TKIs in most patients.

The present study unavoidably considers a well-selected patient population, including oligometastatic patients at diagnosis, cases with indication to response consolidation after good outcome to systemic treatments and, in the case of progressing diseases, only patients with oligoprogression, thus allowing local approaches. This positive selection bias does not allow to draw definitive conclusions about the issue. As further limitations, the analysis is retrospective, with relatively limited number of patients (similarly to those already reported by the literature [5, 8–20], see **Table 3**), and the patient population is distributed in 9 centers. Furthermore, this population does not clarify the possible role of different systemic therapies administered previously or during SBRT, since data about specific drugs are lacking.

On the other hand, the present study has some strengths. The relatively short time of enrollment (18 months) was planned in order to minimize the impact of the evolving landscape of the systemic treatments, thus rendering the results consistent within the clinical context of TKI and CKI treatments. This is not always true for the previous literature, often lowered in more aged contexts. Moreover, the 57 lesions considered in the present work are visceral or nodal, excluding central nervous system and purely bone metastases.

A further novelty of our work is represented by the evaluation of size modifications of the treated lesions overtime, at several time-points after SBRT administration. Thanks to the adequate follow-up of 26.4 months, the consistency of the size reduction across the subsequent assessments demonstrated the long-lasting effect of radiotherapy, with

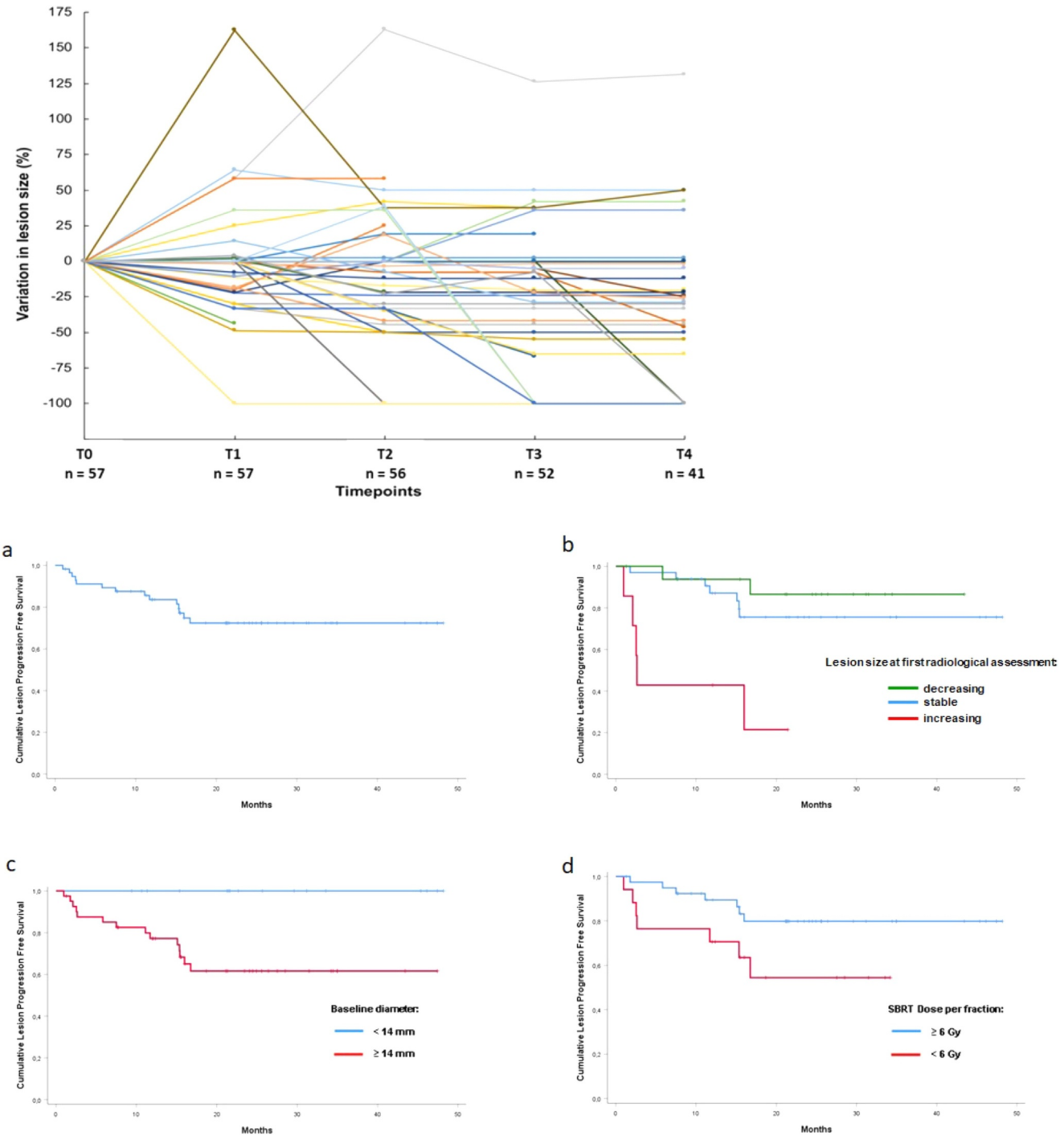

Fig. 2. Spider plot representing the dimensional change of the lesions from baseline to each radiological reassessment after treatment with stereotactic body radiotherapy (SBRT), at four time-points (T0-T4). The median time interval among each radiological assessment and the subsequent was of 3.5 months. The median overall time interval from baseline to the fourth radiological assessment after SBRT (T0-T4) was of 15 months. Lines are overlapping where different lesions had the same dimensional change.

persistent significant responses shown overtime at four time-points compared to baseline. Such persistence of benefit could be exerted throughout slow mechanisms, like those involving the immune system and possibly the abscopal effect [26–27].

Considering the primary purpose of SBRT, represented by the intent to either consolidate response or disease control, or obtain otherwise to restore the control in an oligoprogressive disease, the usefulness of the approach is suggested by the 37.5% of patients who did not need to restart the systemic therapy 3.7 months after their SBRT. Remembering that such patients are affected by metastatic cancer, the possibility to offer a treatment holiday may positively influence the history of the disease, both in terms of quality of life and recovering from toxicities from previous treatments, and this may also impact on survival. Moreover, considering the recent advances in the field of the new immunotherapy with immune checkpoint inhibitors, their synergism with radiotherapy is being explored and exploited across all cancer types, with several evidence in favor of their combination [28].

In conclusion, our findings are consistent with the previous literature and further support the use of SBRT in selected mRCC patients within the context of tailored approaches. SBRT seems to be definitely

Table 3
Summary of reports describing activity of stereotactic body radiotherapy in metastatic renal cell carcinoma. Only the study by Svedman et al. [18] is a prospective phase II trial, being all the others retrospective studies.

Study reference	Number of mRCC patients	Number of treated metastatic lesions	Most common metastatic site	Median SBRT dose and number of fractions	Median follow-up	1-y LCR	2-y LCR	3-y LCR	PFS	OS
Present study	48	57	Lymph nodes: 28% Lung: 26% Bone 19%[#]	Most common fractionation schedules: - 5 Gy x 5 fr - 6 Gy x 5 fr - 8 Gy x 3-5 fr - 10 Gy x 3-5 fr - 15 Gy x 3 fr	26 months	84%	72%	-	Median: 28.9 months	Median: 32.0 months - 1-y OS rate: 93.7% - 2-y OS rate: 84.9%
Franzese et al, 2019 [9]	58	73	Lung: 53%	45 Gy in 5 fr	16 months	90%	-	-	Median: 11.1 months	Median: 28.4 months
Wang et al, 2017 [5]	84	175	Abdomen: 28%	Median BED: 134.5 Gy	17 months	91%	-	-	-	-
Hoerner-Rieber et al, 2017 [8]	46	67	Lung: 100%	20.8 Gy in 3 fr	28 months	98%	-	92%	-	- 1-y OS rate: 84.3% - 3-y OS rate: 43.8%
Amini et al, 2015 [10]	46	95	Bone: 100%	27 Gy in 3 fr	10 months	74%	61%	-	-	-
Altoos et al, 2015 [11]	34	53	Lung: 43%	50 Gy in 5 fr	16 months	100%[*]	93%[*]	93%[*]	-	-
Grossman et al, 2015 [12]	16	67	Lung: 63%	50 Gy Median fractional dose: 5 Gy	-	95%[°]	-	-	Median: 6.0 months	Median: 50.2 months
Ranck et al, 2013 [13]	18	39	Bone: 28%	39.0 Gy	16 months	-	91%	-	- 2-year PFS rate: 35.7% - Median DFS: 12.7 months	2-year OS rate: 85%
Zelefsky et al, 2012 [14]	58	105	Bone: 99%	- 44%: SD-IGRT (18-24 Gy, median 24 Gy) - 56%: Hypofractionation (20-30 Gy x 3-5 fr)	12 months	-	-	44%	-	-
Stinauer et al, 2011 [15]	13	25	Lung: 74%	40-60 Gy in 3-5 fr	28 months	95%	-	-	-	Median: NR
Nguyen et al, 2010 [16]	48	55	Spinal metastases: 100%	24-30 Gy in 1-5 fr	13 months	82%	-	-	-	- 1-year OS rate: 72% - Median: 22 months
Teh et al, 2007 [17]	14	23	Extracranial sites: 100%	24-40 Gy in 3-6 fr	9 months	87%[§]	-	-	-	
Svedman et al, 2006 [18]	25	82	Lung/mediastinum: 70%	Most common fractionation schedules: - 8 Gy x 4 fr - 10 Gy x 4 fr - 15 Gy x 2 fr - 15 Gy x 3 fr	- 52 months for censored patients - 18 months for uncensored patients	79%[§]	-	-	-	Median: 32.0 months
Wersäll et al, 2005 [19]	50	162	Lung: 72%	Most common fractionation schedules: - 8 Gy x 3-4 fr - 10 Gy x 3-5 fr - 15 Gy x 2-3 fr	- 37 months for censored patients - 13 months for uncensored patients	90%[§]	-	-	-	- Median (oligometastatic patients): 37 months - Median: (patients with > 3 metastases): 19 months
Zhang et al, 2019 [20]	47	65	Bone: 43% Lung: 15%	22.1 ± 4.0 Gy x 1 fraction 14 (21.5%) 12.8 ± 2.2 Gy x 3 fractions 21 (32.3%) 8.0 ± 1.4 Gy x 5 fraction 30 (46.2%)	30 months	-	91%	-	-	Median OS not reached 1-y OS rate: 93.1% 2-y OS rate: 84.8%

Abbreviations: y, year; BED, biologically effective dose; DFS, disease-free survival; fr, fractions; LCR, local control rate; NR, not reached; OS, overall survival; PFS, progression-free survival; mRCC, metastatic renal cell carcinoma; SBRT, stereotactic body radiation therapy; SD-IGRT, single-dose image-guided intensity-modulated radiotherapy.

[*] percentage referred only to lesions treated with SBRT.

[°] including melanoma patients enrolled in the study.

[#] only bone lesions with soft tissue component were included.

[§] not better defined.

safe and useful to both improve the local control of the disease and delay the systemic treatment. SBRT use could be more effective on small lesions, thus suggesting considering SBRT as an early treatment option in the clinical course of the metastatic disease. In the light of these elements and of the current use of immunotherapy in clinical practice, prospective studies exploiting the possible synergy between CKI and SBRT are currently ongoing in this setting [29].

Declaration of Competing Interest

M. Bersanelli received research funding from Seqirus, Pfizer, Bristol-Myers Squibb (BMS) and Novartis and honoraria for advisory role and as speaker at scientific events from BMS, Novartis, Pierre-Fabre and Pfizer. S. Buti received research funding from Novartis and honoraria for advisory role and as speaker at scientific events from Pfizer, BMS, IPSEN, Pierre-Fabre, Merck Sharp & Dohme (MSD), AstraZeneca. G. Procopio received honoraria for advisory role from Bayer, BMS, Ipsen, MSD, Novartis, Pfizer. All other authors declared no conflict of interest.

Acknowledgment

None.

Ethical considerations

The protocol for the research project has been approved by the Ethics Committees of the participating institutions within which the work was undertaken and that it conforms to the provisions of the Declaration of Helsinki (as revised in Fortaleza, Brazil, October 2013).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ctarc.2019.100161.

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