Editorial Commentary

Role of stereotactic body radiation therapy for the management of renal cell carcinoma: tailoring treatment in the era of the "embarrassment of riches"

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The recent advances in the treatment of metastatic renal cell carcinoma (mRCC), from the introduction of the first antiangiogenic tyrosine kinase inhibitor (TKI) sorafenib in 2005 to the most recent approval of the first immune checkpoint inhibitor (CKI) nivolumab in 2015, allowed to improve the management of the disease and most importantly to prolong overall survival (OS) (1,2). In this era, especially after the publication of recent pivotal trials introducing three new therapeutic combinations in the first-line treatment setting (3-5), we can properly talk about the "embarrassment of riches" for the systemic therapy for clear-cell mRCC.

With such new treatment options, one could be enticed to rapidly switch treatment line in the case of oligoprogression, underestimating the importance of extending clinical benefit from each single treatment line. Nevertheless, saving resources is still a crucial point, also considering multidisciplinary approaches, potentially becoming relevant in the management of long-surviving patients.

Despite renal cancer was historically considered radioresistant, it is reported to have a lower α per β coefficient of the linear-quadratic model (6). Thus, irradiations with high dose per fraction are more likely to obtain good local control (LC). In the stereotactic body radiotherapy (SBRT) era, thanks to high-precision irradiation with image guided systems and lesion tracking, the dose per fraction can be increased, offering the possibility to maximize the effectiveness on the target lesion while minimizing the adverse effects on the surrounding healthy tissues (6). In the case of mRCC, SBRT may contribute to tackle the disease overtime, sometimes recovering the control of an oligoprogressive disease, or otherwise allowing the temporary discontinuation of systemic therapy, offering "treatment holidays" to responding oligometastatic patients, improving their quality of life without compromising the history of the disease.

Recently, an interesting report about the role of SBRT for the management of oligometastatic mRCC was published by Franzese *et al.* in *The Journal of Urology* (7), retrospectively describing the outcome of 73 irradiated extra-cranial metastases from 58 mRCC patients. The irradiated sites were mostly lung (53%), nodes (26%) and bone (10%).

The authors described the outcome of a mono-institutional population treated between 2004 and 2016, with contraindications to secondary surgery after previous nephrectomy, underwent SBRT for progression of isolated disease sites or to consolidate the response to systemic treatment. Endpoints of the study were the infield LC, progression free survival (PFS) of patients and OS. Acute and late SBRT-related toxicity was also explored (7).

The clinical target volume (CTV) was delineated by computed tomography (CT) scan. The radiotherapy

technique was not specified (probably constituted by the intensity modulated arc therapy). Treatment was guided by daily Cone Beam CT. Median CTV diameter was 26 mm and planning target volume diameter 39 mm. Median total prescribed dose was 45 Gy in a median number of 5 fractions (7).

At the median follow-up of 16.1 months, the LC rate at 12 and 18 months was 90.2% in both time-points with PFS rate 46.2% and 35.0% respectively at 12 and 18 months. Such data are consistent with those of other similar reports from the literature (7-19).

Two further relevant data to be noticed among the results of this study are represented by the long median time to distant metastases, of 32.7 months, and by the median interval between diagnosis and the onset of systemic therapy, of 37.5 months, undoubtedly configuring a positively selected population, as then demonstrated by the 100% of surviving patients at 2-year (7). Anyhow, one could argue about those 5 months of metastatic disease without systemic therapy, strongly suggesting the possible utility of SBRT to delay the initiation of the systemic treatment. Indeed, since the authors clearly reported the timing of systemic therapies, we can conclude that only 65.5% of patients received systemic treatment before SBRT, whilst 20 patients (34.5%) didn't receive any drug before the irradiation of the metastases. Notably, the median interval between SBRT and the subsequent systemic treatment onset was 9.7 (range, 3.1 to 18.9) months. In this setting, SBRT successfully controlled the disease at its onset, delaying the beginning of systemic drugs, thus preserving patient quality of life.

The safety of SBRT in the study population was also investigated. In the acute setting, no grade 3 or 4 (G3–4) adverse events were observed, whilst 1.7% of patients had G2 toxicity and 12% had G1 side effects (fatigue, pain, nausea/vomiting). Late toxicities were rare, but maybe less manageable, with G1–2 pneumonitis in 6.8% of cases (7). The authors did not report whether such toxicities occurred in patients undergoing systemic therapy during SBRT, not allowing to hypothesize a radiosensitizing effect possibly impacting also on tolerability. Nevertheless, the evidence about treatment with radiotherapy during systemic therapy with TKI is wide across several tumor types (20-22) and the safety of administrating TKI at the standard dose for renal cancer patients concurrently with radiotherapy was demonstrated in early phase trials (21).

Another interesting highlight from this study is represented by the reporting of a non-clear cell histology subgroup (10 patients) (7). Despite being only a case series, it addresses the literature lack about the issue of applying SBRT in such minor histotype of mRCC, which radiosensitivity is still largely unknown. At our knowledge, this is the first report published about the issue. Moreover, the authors performed a stratified analysis of patients with clear-cell histology, demonstrating that only for such subgroup the control of irradiated metastases positively correlated with the use of systemic therapies before SBRT [hazard ratio (HR) of 0.15; 95% CI, 0.026–0.85, P=0.032]. This element could suggest that the radiosensitising activity of TKI could be true for clear-cell mRCC, but unlikely when considering non-clear cell histologies (papillary and chromophobe cell carcinoma). Indeed, in the overall population, no benefit from receiving prior systemic therapy emerged in terms of PFS. On the other hand, other clinical elements with a positive impact of PFS were represented by the presence of metachronous *vs.* synchronous metastases (HR 0.20; 95% CI, 0.08–0.51, P=0.001) and of single *vs.* multiple metastases (HR 0.35; 95% CI, 0.18–0.69, P=0.002). Unexpectedly, OS was influenced only by the lesion diameter (HR 1.8; 95% CI, 1.06–3.06, P=0.028), but this was not confirmed at the multivariate analysis (7).

This work has nevertheless several limitations. The enrollment time is quite extended, from 2004 to 2016, including a likely heterogeneous population, up today already anachronistic, considering the rapidly evolving paradigm of treatment already cited for mRCC. Indeed, on a hand 46.5% received TKI, whilst 13.8% of patients only received unspecified intraosseous therapies and even 6.9% received only chemotherapy, creating a legitimate doubt of undertreatment for this study population (23). Therefore, the reliability of such results can be still feasible for TKI treated populations, but it suffers from lacking data about CKI treatment options, currently representing the mainstay of advanced renal cancer therapy.

Eventually, this study is retrospective, with consequent selection bias. It cannot be clarified whether the prolonged survival observed in this group is a result of a selected patient population with indolent tumors, or whether it is due to the treatment intervention with SBRT. These elements should be considered as both accountable for the possible survival improvement, because oligometastatic patients usually have more time to receive local therapies aside from systemic approaches, thus increasing their likeliness to improve survival. Once again, we have no real need to wonder if the chicken or the egg came first: the crucial point of the issue is the translation of these data

into clinical practice, identifying the best candidates for integrated therapies among mRCC patients. A further step will necessarily be represented by the identification of the best sequence or combination of such local treatments with the novel immunotherapies. The combination of systemic immunotherapy and SBRT on metastatic sites could represent the best approach to oligometastatic mRCC in the next future, due to a possible abscopal effect (24). Moreover, combining CKI with SBRT could enhance the local and systemic efficacy of both treatments and overcome the radioresistance of certain tumors (25). Some trials are currently ongoing to address this hypothesis, investigating the feasibility and the activity of the combination of radiotherapy and immunotherapy for mRCC patients (26).

As already cited, further several reports from the literature, summarized by *Table 1* (8-19), also demonstrated a high LC with SBRT, overall confirming the feasibility of such local approach for mRCC patients, especially in the case of oligometastatic disease. Probably, the more effective the systemic therapy, the more useful the loco-regional approach in the history of the disease (27), now opening the door on a golden era in which the treatment for oligometastatic or oligoprogressing mRCC will be really patient-tailored.

Table 1 Current evidence about the role of extracranial stereotactic body radiation therapy (SBRT) for the treatment of distant lesions from metastatic renal cell carcinoma (mRCC)

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-year LCR	2-year LCR	3-year LCR	PFS	OS
Franzese *et al.*, 2019 (7)	58	73	Lung: 53%	45 Gy in 5 fr	16.1 months	90.2%	–	–	Median: 11.1 months	Median: 28.4 months
Wang *et al.*, 2017 (8)	84	175	Abdomen: 28%	Median BED: 134.5 Gy	16.7 months	91.2%	–	–	–	–
Hoerner-Rieber *et al.*, 2017 (9)	46	67	Lung: 100%	20.8 Gy in 3 fr	28.3 months	98.1%	–	91.9%	–	1-year OS rate: 84.3%; 3-year OS rate: 43.8%
Amini *et al.*, 2015 (10)	46	95	Bone: 100%	27 Gy in 3 fr	10 months	74.1%	61.4%	–	–	–
Altoos *et al.*, 2015 (11)	34	53	Lung: 43%	50 Gy in 5 fr	16 months	100%*	93.4%*	93.4%*	–	–
Grossman *et al.*, 2015 (12)	16	67	Lung: 63%	50 Gy; median fractional dose: 5 Gy	–	94.7%°	–	–	Median: 6.0 months	Median: 50.2 months
Ranck *et al.*, 2013 (13)	18	39	Bone: 28%	39.0 Gy	16.2 months	–	91.4%	–	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 ×3–5 fr)	12 months	–	–	44%	–	–

Table 1 (*continued*)

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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-year LCR	2-year LCR	3-year LCR	PFS	OS
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	13.1 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	LCR: 87%[§]	–	–	–	
Svedman *et al.*, 2006 (18)	25	82	Lung/ mediastinum: 70%	Most common fractionation schedules: 8 Gy ×4 fr; 10 Gy ×4 fr; 15 Gy ×2 fr; 15 Gy ×3 fr	52 months for censored patients; 18 months for uncensored patients	LCR: 79%[§]	–	–	–	Median: 32.0 months
Wersäll *et al.*, 2005 (19)	50	162	Lung: 72%	Most common fractionation schedules: 8 Gy ×3–4 fr; 10 Gy ×3–5 fr; 15 Gy ×2–3 fr	37 months for censored patients; 13 months for uncensored patients	LCR: 90%[§]	–	–	–	Median (oligometastatic patients): 37 months; median: (patients with >3 metastases): 19 months

Only retrospective studies have been published. Their characteristics were reported, and the outcomes were summarized, showing high rates of local control. *, percentage referred only to lesions treated with SBRT; °, including melanoma patients enrolled in the study; [§], not better defined. 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-IG-RT, single-dose image-guided intensity-modulated radiotherapy.

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Footnote

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

References

1. Cancer Progress Timeline. Kidney Cancer. Available online: https://www.asco.org/research-progress/cancer-progress-timeline/kidney-cancer
2. Choueiri TK, Motzer RJ. Systemic Therapy for Metastatic Renal-Cell Carcinoma. N Engl J Med 2017;376:354-66.
3. Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. N Engl J Med 2018;378:1277-90.
4. Rini BI, Plimack ER, Stus V, et al. Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. N Engl J Med 2019;380:1116-27.
5. Motzer RJ, Penkov K, Haanen J, et al. Avelumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. N Engl J Med 2019;380:1103-15.
6. Funayama S, Onishi H, Kuriyama K, et al. Renal Cancer is Not Radioresistant: Slowly but Continuing Shrinkage of the Tumor After Stereotactic Body Radiation Therapy. Technol Cancer Res Treat 2019;18:1533033818822329.
7. Franzese C, Franceschini D, Di Brina L, et al. Role of

Stereotactic Body Radiation Therapy for the Management of Oligometastatic Renal Cell Carcinoma. J Urol 2019;201:70-5.
8. Wang CJ, Christie A, Lin MH, et al. Safety and Efficacy of Stereotactic Ablative Radiation Therapy for Renal Cell Carcinoma Extracranial Metastases. Int J Radiat Oncol Biol Phys 2017;98:91-100.
9. Hoerner-Rieber J, Duma M, Blanck O, 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.
10. Amini A, Altoos B, Bourlon MT, et al. Local control rates of metastatic renal cell carcinoma (RCC) to the bone using stereotactic body radiation therapy: Is RCC truly radioresistant? Pract Radiat Oncol 2015;5:e589-96.
11. Altoos B, Amini A, Yacoub M, et al. Local Control Rates of Metastatic Renal Cell Carcinoma (RCC) to Thoracic, Abdominal, and Soft Tissue Lesions Using Stereotactic Body Radiotherapy (SBRT). Radiat Oncol 2015;10:218.
12. Grossman CE, Okunieff P, Brasacchio RA, et al. Stereotactic Body Radiation Therapy for Oligometastatic Renal Cell Carcinoma or Melanoma: Prognostic Factors and Outcomes. Int J Radiat Oncol 2015;93:E202.
13. Ranck MC, Golden DW, Corbin KS, et al. Stereotactic body radiotherapy for the treatment of oligometastatic renal cell carcinoma. Am J Clin Oncol 2013;36:589-95.
14. Zelefsky MJ, Greco C, Motzer R, et al. Tumor Control Outcomes After Hypofractionated and Single-Dose Stereotactic Image-Guided Intensity-Modulated Radiotherapy for Extracranial Metastases From Renal Cell Carcinoma. Int J Radiat Oncol Biol Phys 2012;82:1744-8.
15. Stinauer MA, Kavanagh BD, Schefter TE, et al. Stereotactic body radiation therapy for melanoma and renal cell carcinoma: impact of single fraction equivalent dose on local control. Radiat Oncol 2011;6:34.
16. Nguyen QN, Shiu AS, Rhines LD, et al. Management of spinal metastases from renal cell carcinoma using stereotactic body radiotherapy. Int J Radiat Oncol Biol Phys 2010;76:1185-92.
17. Teh B, Bloch C, Galli-Guevara M, et al. The treatment of primary and metastatic renal cell carcinoma (RCC) with image-guided stereotactic body radiation therapy (SBRT). Biomed Imaging Interv J 2007;3:e6.
18. Svedman C, Sandström P, Pisa P, et al. A prospective Phase II trial of using extracranial stereotactic radiotherapy in primary and metastatic renal cell carcinoma. Acta Oncol 2006;45:870-5.
19. Wersäll PJ, Blomgren H, Lax I, et al. Extracranial stereotactic radiotherapy for primary and metastatic renal cell carcinoma. Radiother Oncol 2005;77:88-95.
20. Jakob J, Simeonova A, Kasper B, et al. Combined sunitinib and radiation therapy for preoperative treatment of soft tissue sarcoma: results of a phase I trial of the German interdisciplinary sarcoma group (GISG-03). Radiat Oncol 2016;11:77.
21. Kao J, Chen CT, Tong CC, et al. Concurrent sunitinib and stereotactic body radiotherapy for patients with oligometastases: final report of a prospective clinical trial. Target Oncol 2014;9:145-53.
22. Tong CC, Ko EC, Sung MW, et al. Phase II trial of concurrent sunitinib and image-guided radiotherapy for oligometastases. PLoS One 2012;7:e36979.
23. Buti S, Bersanelli M, Sikokis A, et al. Chemotherapy in metastatic renal cell carcinoma today? A systematic review. Anticancer Drugs 2013; 24:535-54.
24. Formenti SC, Demaria S. Combining radiotherapy and cancer immunotherapy: a paradigm shift. J Natl Cancer Inst 2013;105:256-65.
25. Dovedi SJ, Adlard AL, Lipowska-Bhalla G, et al. Acquired resistance to fractionated radiotherapy can be overcome by concurrent PD-L1 blockade. Cancer Res 2014;74:5458-68.
26. Masini C, Iotti C, Ciammella P, et al. NIVES study: A phase II trial of nivolumab (NIVO) plus stereotactic body radiotherapy (SBRT) in II and III line of patients (pts) with metastatic renal cell carcinoma (mRCC). J Clin Oncol 2018;36:abstr TPS4602.
27. Conti A, D'Elia C, Cheng M, et al. Oligometastases in Genitourinary Tumors: Recent Insights and Future Molecular Diagnostic Approach. Eur Urol 2017;16:309-15.

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