Editorial Commentary

Stereotactic body radiation therapy for oligometastatic renal cell carcinoma: improving outcomes in an otherwise radioresistant malignancy

Thomas H. Beckham[1], Brandon S. Imber[1], Charles B. Simone II[1,2]

[1]Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [2]New York Proton Center, New York, NY, USA

Correspondence to: Charles B. Simone II, MD, FACRO. New York Proton Center, 225 East 126th Street, New York, NY 10035, USA.
Email: csimone@nyproton.com.

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Franzese *et al.* recently analyzed the outcomes of patients treated at their institution with stereotactic body radiation therapy (SBRT) for oligometastatic renal cell carcinoma (RCC) (1). They reported a 2-year survival rate from SBRT of 100% and excellent local control with very few toxicities. As we place their findings into the context of overall management of metastatic RCC (mRCC), a number of points warrant discussion.

A commonly held belief about RCC is that radiotherapy is of limited benefit due to inherent radioresistance. This belief is rooted in *in vitro* studies that demonstrated relatively higher radiation doses are required for equivalent cell kill effects (2). A meta-analysis of conventionally fractionated radiation (1.8–2.5 Gy per fraction) in the high-risk adjuvant setting, however, revealed a clear locoregional control benefit to radiotherapy, suggesting that RCC is responsive to radiotherapy (3).

Advances in imaging and precision of modern radiation delivery has enabled the development and widespread adoption of SBRT as a treatment modality for many primary cancers as well as metastatic sites (4). SBRT permits the delivery of significantly higher irradiation doses per fraction and thus takes advantage of different mechanisms of radiation-induced tumor cell killing. In tumors that are otherwise thought to be radioresistant to conventionally fractionated radiotherapy, SBRT should help to overcome this challenge via direct tumor ablation (5).

SBRT has been shown to result in high rates of local control for primary RCC as well as renal metastases (6). The largest prospective study treated 45 primary renal tumors (30 RCCs and 15 transitional cell carcinomas) with SBRT to 25 Gy in a single fraction and found 98% local control at 9 months (7). Numerous additional reports, both prospective and retrospective, show generally impressive rates of local control with SBRT for primary RCC and are highlighted in a recent review by Siva *et al.* (8).

Focusing on metastatic lesions, Franzese *et al.* report a high local control rate of 90.2% at 18 months (1). This is consistent with other series reporting local control for RCC metastases. From 170 RCC spine metastases, Yamada *et al.* (9) reported a crude local failure rate of only 1% using single fraction SBRT (median dose 24 Gy). In a prospective study of SBRT to primary and metastatic RCC, local control was achieved in 98% of lesions using several dose regimens (8 Gy ×4, 10 Gy ×4, 15 Gy ×2 or 15 Gy ×3) tailored to the site of disease with respect to irradiation dose constraints of adjacent organs at risk (10). Thus, with the infrequent exception of metastases whose location limits the feasibility of SBRT, the available literature demonstrates that mRCC lesions have high rates of local control with modern dose-escalated SBRT.

As a retrospective single institutional experience, there are some important limitations to consider when interpreting the study by Franzese *et al.* Reported patients were treated

over the course of 14 years, a time period during which multiple new systemic therapies were introduced for mRCC and imaging and delivery of SBRT evolved considerably. This heterogeneity and lack of an internal era-matched cohort treated without SBRT limits interpretation of the report. Additionally, the median reported follow-up of 16 months is too short to gain an appreciation for the presence of durable responses on the progression free survival (PFS) and overall survival (OS) curves. This is of relevance as it would be quite noteworthy if there is the presence of a tail on the survival curves following SBRT, indicating a group of patients who are cured or enjoy long-term disease free survival after metastasis directed therapy (MDT).

Franzese *et al.* review the literature on MDT for RCC, evaluating both SBRT and metastasectomy, and they revealed some common findings for prognosis after MDT. First, a solitary metastasis portends a better prognosis than multiple metastases. Second, metachronous development of metastases (i.e., diagnosis of metastasis after the diagnosis and perhaps treatment of the primary site) is associated with better outcomes. Both features intuitively associate with biologically more indolent metastatic behavior and should be kept in mind when considering MDT in mRCC. When interpreting retrospective analyses of the outcomes of MDT, particularly when a comparison is offered between those who receive and do not receive MDT such as the series of metastasectomy patients reported by Kavolius *et al.* (11), it is important to understand the selection biases underlying the decision for MDT. Such patients are typically more likely to be young and fit with a more indolent disease course. These biases are challenging to control for using multivariable analyses, which is why randomized data from carefully designed studies are needed.

Fortunately, randomized evidence of SBRT in treating oligometastatic and oligoprogressive disease is emerging. SABR-COMET randomized patients with up to five metastases from various histologies, including RCC, to standard of care with or without SBRT to all metastatic foci (12). The addition of SBRT resulted in a doubling of the PFS and an improvement in OS. Similarly, a multi-center phase II trial (13,14) randomized patients with non-small cell lung cancer with up to five metastases at diagnosis who did not progress after first line chemotherapy to consolidative chemotherapy with or without SBRT to all sites of distant disease and showed a tripling of PFS and an improvement in OS. Additionally, a University of Texas Southwestern Medical Center randomized trial showed that the addition of SBRT to maintenance chemotherapy for patients with limited metastatic NSCLC (primary plus up to 5 metastatic sites) also achieved a tripling of PFS (15) These finding are promising, and the outcomes of larger, confirmatory studies are eagerly anticipated.

The potential utility of SBRT must also be interpreted with the consideration that contemporary management of mRCC is evolving. RCC was one of the first cancers in which a clinical benefit for cytoreductive surgical management for both primary or distant sites of disease was shown. A pooled analysis of 331 patients from two Phase III trials randomizing interferon *vs.* cytoreductive nephrectomy (CN) found an OS advantage of nearly 6 months for CN (16). Regarding MDT, a recent meta-analysis of over 2,000 patients found that complete metastasectomy was strongly associated with improved OS compared with incomplete or no metastasectomy (pooled HR 2.4, P<0.001) (17). The findings of that meta-analysis were in keeping with those of an earlier systematic review that included both surgery and radiotherapy and suggested comparability between the two MDT approaches (18).

Despite promising data from these and other studies, the role of upfront surgery in metastatic disease is now being questioned. One of the main reasons is improved systemic therapy. The multi-kinase inhibitor sunitinib is a standard of care option for mRCC (19), and two recent phase III trials investigated the incremental utility of CN. The SURTIME trial (20) randomized patients receiving sunitinib to immediate or deferred CN. The study was terminated early due to poor accrual but did signal that OS might be improved with delayed CN. The CARMENA trial (21) also terminated early but showed that sunitinib alone was noninferior to CN followed by sunitinib. Both studies were challenged by questions of investigator equipoise, biological heterogeneity and high rates of surgical complications (22) that may theoretically be improved by less invasive SBRT. SBRT as cytoreduction of primary disease has been studied but, to date, has not been established as a routine aspect of mRCC care (23). These studies offer an important lesson for modern oligometastatic trials, namely that patient selection remains critical for multimodality treatment to identify those who may gain incremental utility from local therapies. This will remain particularly salient in RCC as systemic options expand and improve including introduction of immunotherapy agents against the PD-1 and CTLA-4 pathways (24). An updated systematic review of CN, including these two recent trials, advocates for aggressive upfront management for oligometastatic disease and those with favorable responses following systemic

therapy (25). The optimal sequencing of all MDT options, including SBRT, in the context of better systemic options remains an open question.

SBRT has dramatically widened the scope of what metastatic lesions are feasible to definitively control locally without the need for invasive surgical procedures. In select oligorecurrent or oligometastatic patients, SBRT offers the potential to delay the onset of new lines of systemic therapy, preserve patient quality of life, improve PFS, and even prolong OS. Early randomized data have validated this concept and demonstrated clear benefits, and larger studies are underway. Even as these reports, questions will remain. Chiefly, can we identify not only a clinically oligometastatic phenotype, but also understand from the wide array of obtainable genomic and epigenomic data which patients disease will manifest truly oligometastatic biology? This is likely to be critical in determining which patients will benefit most from MDT and gaining a better understanding of how to incorporate local therapies for metastatic disease into the broader management of mRCC patients. Intensive analysis of colorectal metastases has demonstrated that a multi-omics approach can reliably predict long-term survivors after metastasectomy (26). Thoughtful application of existing and emerging tools to understand metastatic biology may help us identify metastatic patients who may even be curable with SBRT and MDT.

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Footnote

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

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