Editorial Commentary

# Stereotactic ablative radiotherapy: a game-changer in primary renal cancer therapy

**Francesco Mosè Castronovo[1]^, Thomas Zilli[1,2,3]^, Antonio Angrisani[1]^, Davide Giovanni Bosetti[1]^**

[1]Radiation Oncology Clinic, Oncology Institute of Southern Switzerland, Ente Ospedaliero Cantonale (EOC), Bellinzona, Switzerland; [2]Faculty of Biomedical Sciences, University of Southern Switzerland, Lugano, Switzerland; [3]Faculty of Medicine, University of Geneva, Geneva, Switzerland

*Correspondence to:* Thomas Zilli, MD. Radiation Oncology Clinic, Oncology Institute of Southern Switzerland, Ente Ospedaliero Cantonale (EOC), Via Ospedale, 6500 Bellinzona, Switzerland; Faculty of Biomedical Sciences, University of Southern Switzerland, Lugano, Switzerland; Faculty of Medicine, University of Geneva, Geneva, Switzerland. Email: Thomas.Zilli@eoc.ch.

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Renal cell carcinoma (RCC) ranks as the eighth most common cancer globally. Although surgical resection remains the optimal treatment for localized RCC, a notable subset of patients, predominantly elderly with concurrent medical comorbidities, faces challenges including the risk of renal dysfunction (1).

In the setting of non-surgical patients, active surveillance or ablative techniques, such as cryotherapy or radiofrequency ablation, are currently proposed as therapeutic alternatives by the current international guidelines. In the last decade, stereotactic ablative body radiotherapy (SABR) has been integrated into the therapeutic armamentarium as a treatment option for non-operable RCC patients or for patients refusing surgery. The findings from the prospective phase 2 trial (NCT02141919) conducted by Hannan *et al.* undoubtedly mark a significant stride in advancing the expanding knowledge base concerning SABR for RCC (2). In analogy with the data from the IROCK meta-analysis (the International Radiosurgery Consortium of the Kidney) (3), SABR confirms even in this trial its safety and impressive local disease control rate (94% at 1 year) with minimal acute and late toxicity.

While the authors should be congratulated for conducting this important trial and the results are undoubtedly of great interest, this study offers several points for discussion.

First, although no consensus exists regarding the optimal dose and fractionation, this trial implemented two SABR schedules: either 36 Gy delivered in 3 fractions or 40 Gy in 5 fractions. Compared to the Focal Ablative Stereotactic Radiotherapy for Cancers of the Kidney (FASTRACK II) trial using 26 Gy in one fraction for tumors ≤4 cm and 42 Gy in 3 fractions for larger tumors (4), the SABR doses used in this trial by Hannan *et al.* had a lower biological effective dose (BED). Using a α/β ratio of 2.6 Gy for RCC tumor control (5), the calculated BED was 286 Gy for the single fraction (26 Gy) and 268 Gy for three fractions (42 Gy) schedule of the FASTRACK II trial compared with a BED of 202 Gy and 163 Gy for the three (36 Gy/3 fx) and five fractions (40 Gy/5 fx) regimen used in the present study. This difference can probably explain the higher local control rate observed in the FASTRACK II study, 100% at a median follow-up of 43 months, with only one patient developing a distant failure (freedom from distant failure of 99%), compared to a 94% rate at a median follow-up of 36 months observed in the trial by Hannan et al., using comparable RECIST (Response Evaluation Criteria in Solid Tumors) criteria (5).

The second question regards the impact of SABR on tumor growth as evaluated through radiographic assessments. Evaluating the tumor response to SABR using computed

^ ORCID: Francesco Mosè Castronovo, 0009-0003-0448-0195; Thomas Zilli, 0000-0002-4784-9883; Antonio Angrisani, 0000-0003-4470-7561; Davide Giovanni Bosetti, 0000-0002-2654-1281.

 

tomography (CT) criteria poses several challenges. The time course of response after SABR in RCC revealed two primary patterns: a slow, but continuous shrinkage of tumor size or a transient dimensional increase during the initial short-term follow-up followed by a second decrease in size (6). Careful identification of this pseudo-progression remains crucial. In a retrospective study of twenty-four patients treated with SABR, five tumors (20%) presented an initial growth before ultimately shrinking in volume below their original size. These tumors increased their volume by an average of 24% (range, 13–32%), reaching their peak volume around an average of 8.6 months (range, 5–19 months) after SABR (7).

Based on these data, we have concerns regarding the reliability of the per-protocol radiographic criteria suggested by the authors to evaluate local control, wherein a radiographic local failure was defined as a dimensional increase of >4 mm/year based on average growth rates of biopsy-proven RCC under active surveillance. Particularly, we find these criteria unreliable for evaluating response post-SABR, especially within a short follow-up period, in the light of newer evidence. Notably, among the sixteen patients included in the trial, one developed a radiographic local failure according to the per protocol criteria, despite presenting histologic evidence of response at 1-year.

Hence, it is likely that a period of cellular deceleration and response to necrosis spanning several months or potentially even years precedes any radiographically visible change in size (7), potentially explaining the transient growth observed early after SABR. We thank the authors for evaluating pathologic changes after SABR at the 1-year endpoint; this is one of the first studies to demonstrate this late state of radiation-induced terminal replicative arrest in a prospective clinical trial. Nevertheless, performing a biopsy at one year is probably a too brief timeframe, limiting correct discrimination between treatment response and disease progression. The determination of an optimal timeline for performing histopathological assessments to define local failure remains an open challenge. Use of angiogenic imaging markers like prostate-specific membrane antigen (PSMA) positron emission tomography (PET)/CT may represent an interesting non-invasive diagnostic tool to evaluate tumor response in RCC after SABR that requires further investigation (8).

In conclusion, this prospective study undoubtedly represents another milestone in confirming the high rates of local control and minimal toxicity of SABR, making this treatment a valuable strategy to consider in the management of primary RCC.

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