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EDITORIAL

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The investigational role of cytoreductive stereotactic ablative radiation therapy (SABR) to the primary tumor in metastatic kidney cancer

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1. Introduction

Renal cell carcinoma (RCC) represents around 3% of all cancers in the world, being the 14th most common and its incidence is higher in the older population [1]. It has been estimated that in Europe there will be a 40.5% increase in the incidence in the next 20 years for people older than 75 [2]. In elderly patients, it is difficult to offer always an invasive therapeutic approach (i.e. radical nephrectomy or thermal ablation) because of advanced age or medical comorbidities, so it may happen to under-treat them in clinical practice [3]. Moreover, nephrectomy might cause an important renal function decline delaying or impairing systemic therapy. Thus, in recent years great interest has grown in nonsurgical therapies such as stereotactic ablative radiation therapy (SABR) based on the results of several retrospective studies on primary and metastatic RCC [4,5], and these results have led to prospective trials [6,7]. More specifically, SABR has been investigated in a phase II non-randomized trial (Fastrack) for the curative treatment of primary RCC in 70 patients judged unfit for surgery, with excellent oncologic and renal function outcomes [6]. From the radiobiological point of view, SABR allows high-dose radiation leading to direct neoplastic cell killing, and tumor microenvironment remodeling with caspases-mediated endothelial apoptosis and immune response activation through the expression of tumor-associated antigens (TAAs) and the production of pro-apoptotic circulating cytokines [8]. In the metastatic setting, these effects on the tumor microenvironment can be enhanced by Tyrosine Kinase Inhibitors (TKIs) and immune checkpoint inhibitors (ICIs) which have revolutionized the therapeutic landscape of RCC [9,10]. Although concerns have been raised about the efficacy of SABR compared with nephrectomy or thermal ablation based on the presence of viable tumor cells in post-SABR kidney biopsies [11], recently Hannan et al. demonstrated that cytoreductive SABR is effective for the treatment of primary kidney cancer [12]. They conducted a phase II trial enrolling 16 patients with biopsy-confirmed RCC (maximum diameter ≤5 cm) who underwent SABR (36 Gy in 3 fractions, or 40 Gy in 5 fractions) with local control (LC) and pathologic evidence of tumor response at 1 year as primary endpoints. LC was obtained in 94% of the patients with pathologic evidence of tumor response, and the median renal function loss 1 year after SABR, assessed as the estimated glomerular filtration rate (eGFR), was 4.5 ml/min. The most innovative result of the study by Hannan et al. was that post-SABR kidney biopsies demonstrated a significant decrease in cellularity and proliferative state of remaining scant viable tumor cells (reduction of Ki-67 positivity compared with pre-SABR specimens, $p = 0.0078$). Moreover, there was microenvironment remodeling with increased fibrosis, and dense hyalinization with remaining scant tumor cells expressing p16, a marker for cellular senescence, reflecting a permanently non-replicative state. Therefore, based on clinical and translational data elderly metastatic RCC (mRCC) patients in need of cytoreductive therapy of the primary unfit or refusing surgery might receive SABR because it is a safe and effective noninvasive treatment that triggers the immune response, in such an immunogenic tumor, and can be combined with current systemic options (TKIs and ICIs) without delaying their initiation.

2. SABR as a cytoreductive option in mRCC

In the era of TKIs and immune checkpoint inhibitors, several studies have demonstrated that cytoreductive nephrectomy (CN) might have an important role in the favorable and intermediate IMDC (International Metastatic RCC Database Consortium) prognostic categories [11]. SABR as an alternative in elderly unfit mRCC patients may be used for early ablation to prevent further metastatic seeding resulting in long-term freedom from disease, for the immune-response trigger, the disruption of metastatic cross-talk, and the induction of an 'abscopal effect.' Cytoreductive SABR in combination with ICIs is under investigation in a phase II randomized CYTOSHRINK (NCT04090710) trial enrolling mRCC patients with IMDC intermediate or poor-risk disease. The study randomizes untreated metastatic kidney cancer patients who decline or are unsuitable for CN in a 2:1 fashion to ipilimumab and nivolumab plus SABR (30–40 Gy in 5 fractions) to the primary kidney tumor (max diameter, 20 cm) between cycles 1 and 2 (experimental arm), versus standard of care ipilimumab and nivolumab alone (standard arm), with the primary endpoint of progression-free

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Table 1. Ongoing trials on cytoreductive SABR to the primary tumor in metastatic kidney cancer.

Study	Ref.	Phase	SABR schedule	Primary tumor staging
CYTOSHRINK	[13]	II	30–40 Gy (5 × 6 Gy; 5 × 8 Gy)	T1-T3, max diameter 20 cm
SAMURAI	[14]	II	42 Gy (3 × 14 Gy)	Treatable with SABR, no diameter cutoff
NAPSTER	[15]	II	42 Gy (3 × 14 Gy)	T1-T3, no diameter cutoff

survival (PFS) [13]. The phase II randomized trial SAMURAI (NCT05327686) will evaluate cytoreductive SABR in 240 patients with mRCC receiving immunotherapy, who are not recommended for surgery, or who decline surgery. Patients with intermediate or poor IMDC risk will be randomized in a 2:1 ratio to receive SABR plus standard systemic therapy vs standard systemic therapy alone including the doublet immunotherapy or immunotherapy + TKI based on the physician's choice. SABR will be delivered in 3 fractions of 14 Gy (total dose, 42 Gy) to the primary kidney tumor. The primary endpoint is nephrectomy and radiographic progression-free survival [14]. In the NAPSTER trial (NCT05024318), cytoreductive SABR combined with pembrolizumab will be used as a neoadjuvant therapy in treatment-naive mRCC patients planned for CN [15]. A total of 26 patients will be randomized to receive SABR (42 Gy in 3 fractions) plus pembrolizumab (3 cycles) vs SABR (42 Gy in 3 fractions) only. All patients will undergo CN at 9 weeks after completion of neoadjuvant treatment. The primary endpoints are: to evaluate major pathological response (defined as <10% viable cells) and to study tumoral microenvironment inflammation modifications (more specifically, changes in tumor-responsive T-cells, resident memory CD8+ T-cells and/or transcription factor T cell factor-1 (TCF-1+) T-cells from baseline pretreatment biopsy to post-nephrectomy). Safety of immunotherapy + SABR, the association between immune response and major pathological response, and changes in PD-L1/PD-L2 expression in tumors will be studied as secondary endpoints.

3. Expert opinion

Due to advancements in radiation oncology and radiobiology, we can precisely deliver high-dose radiation to the primary kidney tumor and metastases with ablative intent while minimally impacting surrounding healthy tissues, and evidence of the efficacy of ablative radiotherapy in RCC is based on several meta-analyses and prospective clinical trials. The results of these studies in the localized RCC setting have generated great interest in cytoreductive SABR for mRCC, with several trials currently ongoing (Table 1). Soon, new radiotracers in molecular imaging for diagnosis and response assessment (e.g. 68 Ga-PSMA or radiolabeled girentuximab) and novel treatment modalities such as biology-guided radiotherapy will be available in this area of active investigation.

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Declaration of interest

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