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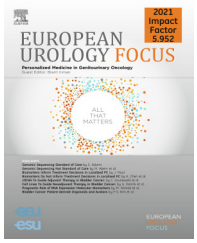

Review – Kidney Cancer

The Emerging Role of Extracranial Stereotactic Ablative Radiotherapy for Metastatic Renal Cell Carcinoma: A Systematic Review

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Abstract

Context: Although the management of metastatic renal cell carcinoma (mRCC) has been revolutionized by the advent of new systemic agents, still few patients experience a long-term durable response. Stereotactic ablative radiotherapy (SABR) is nowadays commonly used as metastasis-directed therapy (MDT), but limited data exist on how best to implement this strategy as part of a multimodal approach.

Objective: To evaluate the potential role of extracranial SABR in mRCC and to identify future therapeutic developments of SABR in different disease settings.

Evidence acquisition: A systematic review was conducted in May 2022 according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement on the PubMed database. Thirty-four studies were selected for inclusion in this systematic review.

Evidence synthesis: SABR has been used with four main goals: (1) eradication of the whole metastatic burden in synchronous and metachronous oligometastatic patients, resulting in a long-term local control (LC) rate of >90% and median progression-free survival (PFS) ranging between 8 and 15 mo; (2) eradication of oligoprogressive lesions, enabling an extension of the duration of the systemic therapy by approximately 9 mo; (3) improvement of the response to systemic therapy in polymetastatic patients, resulting in an overall response rate ranging from 17% to 56%; and (4) cytoreduction in polymetastatic mRCC patients, with LC rates ranging between 71% and 100%, and preservation of the renal function, but unclear PFS and overall survival impact. Overall, the combination of SABR and systemic agents has been associated with overall good tolerance, with grade ≥3 toxicity ranging from 0% to 13%.

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Conclusions: Current data highlight the role of SABR as an emerging MDT treatment option in both oligometastatic and oligoprogressive extracranial mRCC, able to ensure long-term disease control and delay the use of next-line systemic therapies. The use of SABR for cytoreduction in the de novo metastatic disease and as an immunological booster in the polymetastatic setting remains investigational and warrants further investigations.

Patient summary: Radiotherapy delivered with ablative doses (>6 Gy per fraction) is a promising treatment strategy for patients diagnosed with metastatic renal cell carcinoma. Excellent outcome results have been observed in patients with a limited number of metastases, improving metastasis-free survival by several months. For patients with a few metastases progressing under systemic therapy, radiotherapy allows an extension of the duration of the ongoing therapy by several months.

1. Introduction

Metastatic renal cell carcinoma (mRCC) is a heterogeneous disease, with presentations ranging from an indolent evolution to a rapid and widespread progression. Large randomized clinical trials have focused on improving the outcomes of these patients through the use of combined and more efficient systemic therapies. Recently, management of mRCC has been revolutionized by the advent of immune checkpoint inhibitors (ICIs) replacing or being added to treatments with tyrosine kinase inhibitors (TKIs) alone. First-line TKIs and ICIs have shown a significant improvement in overall survival (OS) rates compared with sunitinib alone, becoming the standard of care treatment in both International Metastatic renal cell Database Consortium (IMDC) favorable- and IMDC intermediate/poor-prognosis mRCC patients [1–3]. Doublet ICI treatment combining nivolumab and ipilimumab has also shown a survival benefit among IMDC intermediate- and poor-prognosis mRCC patients [4]. Nevertheless, despite these considerable improvements in systemic therapies used for mRCC, few patients experience a durable clinical response, with the median progression-free survival (PFS) period ranging from 11.6 to 15.4 mo in the first-line treatment. Additional therapeutic strategies to improve the efficacy of systemic therapies are therefore eagerly needed, especially in patients with a limited disease burden.

In mRCC, the use of radiation therapy (RT) has long been restricted to palliative purposes only because of the perceived radioresistance of renal cell carcinoma (RCC) [5]. Technological advances in RT delivery, allowing targeted dose escalation with ultrahypofractionation (>6 Gy per fraction), have, in recent years, opened the door to the use of stereotactic ablative radiotherapy (SABR) in multiple clinical settings. In oligometastatic patients, metastasis-directed therapy (MDT) is able to achieve durable local control (LC), similar to that observed with surgical metastasectomy [6].

To date, the implementation of SABR with systemic therapies is increasingly being studied in different mRCC disease settings, but the long-term outcomes and toxicity of this strategy remain unclear. This systematic review aims to provide data on the current and future roles of SABR in patients with mRCC, with both synchronous and metachronous extracranial metastases.

2. Evidence acquisition

2.1. Protocol and registration

The protocol of this study was published on the online systematic review register PROSPERO (registration number: CRD42022338439).

2.2. Data sources and searches

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. The literature search was performed on May 8, 2022, on PubMed, using the following keywords: "stereotactic body radiation therapy (SBRT)" AND "renal cell carcinoma," and then "SABR" AND "renal cell carcinoma." We also searched ClinicalTrials.gov for ongoing or completed studies assessing SABR for mRCC patients.

2.3. Study selection

Eligible studies were those reporting both oncological and toxicity outcomes after SABR, for patients diagnosed with mRCC. There was no period restriction. Case report, preclinical data, protocols, and reviews were excluded from the review. Papers focusing on patients with intracranial metastases were also excluded from the analysis, as they are subjected to specific considerations in terms of therapeutic decisions. All abstracts and full-text articles were screened independently by two authors (J.L.G and T.Z.). Discrepancies were resolved through discussion between the authors. The selection process is summarized in the PRISMA flowchart (Fig. 1).

2.4. Search results

This search retrieved a total of 111 articles. After evaluation of the abstract content, 56 articles were assessed for eligibility. After full-text reading and removal of duplicates, 34 articles were finally included in this review. Prospective trials are detailed in Table 1. Retrospective data have been summarized in Supplementary Table 1.

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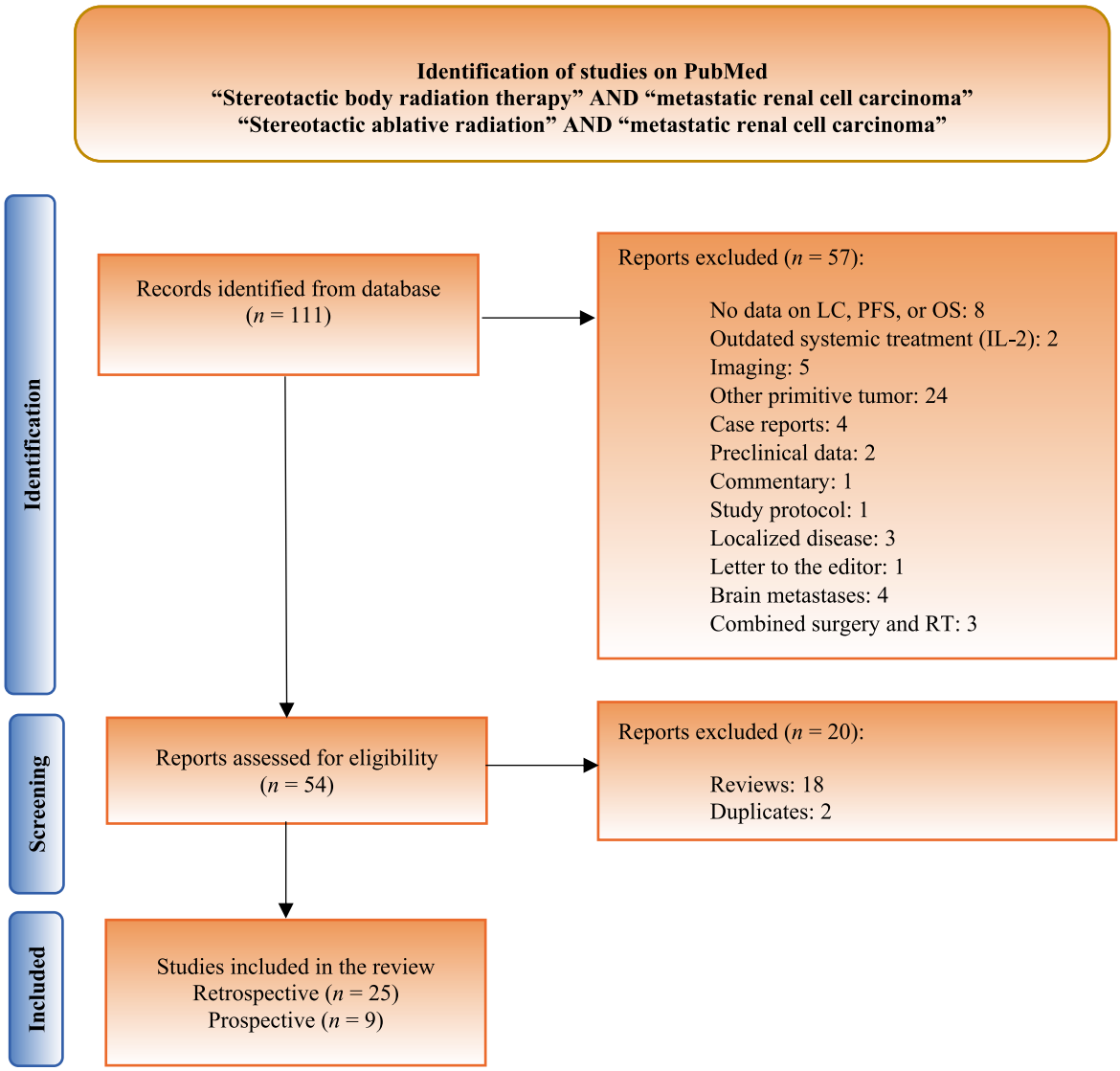

Fig. 1 – PRISMA study flowchart. IL-2 = interleukin-2; LC = local control; OS = overall survival; PFS= progression-free survival; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses; RT = radiotherapy.

2.5. Risk of bias

A full risk of bias assessment was undertaken using the ROBINS-1 tool as per the Cochrane Collaboration guidelines for the nine prospective studies (Table 2).

2.6. Data synthesis

A narrative synthesis of the data was performed. The articles have been classified in four major subgroups, including the role of SABR in the cytoreductive, oligometastatic, oligoprogressive, and polymetastatic settings. The primary focus of this review was oncological, with evaluation of LC, PFS, and OS rates. Toxicity of SABR and combined treatments was the secondary endpoint.

3. Evidence synthesis

3.1. Cytoreductive SABR

Cytoreductive nephrectomy (CN) has long been performed as frontline treatment in order to reduce the tumor burden and remove the source of new metastases (Fig. 2) [7]. Based on its OS benefit compared with interferon alpha-2b (IFNα) alone, CN has remained the standard of care for de novo mRCC for nearly 20 yr [8]. However, the results of the CARMENA and SURTIME randomized trials, conducted in the era of TKIs, have challenged this paradigm [9,10]. While patients with favorable-risk IMDC disease and a relatively low metastatic burden are still reasonably considered for CN, patients with poor-risk IMDC disease are more appropriately treated with systemic therapy in the first-line setting. Therefore, as the panel of systemic treatment options available is rapidly increasing, the actual role of CN remains unclear.

While the main disadvantage of CN was the significant morbidity of the intervention and the delay in the introduction of systemic treatments, SABR of the primary represents an alternative solution that offers a noninvasive cytoreductive approach. While little data are available regarding concomitant cytoreductive SABR and systemic treatment, at the very least SABR is likely to decrease the time between cytoreduction and first-line therapies. Outcome and toxicity results of a cytoreductive SABR approach were reported by

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Table 1 – Prospective trials in oligometastatic, oligoprogressive, and polymetastatic mRCC patients

Trial	Number of patients	Nephrectomy	Systemic therapy	Dose/fractionation	SABR toxicity	LC	PFS	OS
Cytoreductive SABR								
Correa et al (2018) [13]	12 patients (8% FR, 67% IR, 25% PR)	–	No systemic therapy (50%) Adjuvant TKI (41.7%) Adjuvant mTOR-I (16.7%)	25–30–35 Gy/5 fx	Grade 3: 25% Grade 4–5: 0%	Median tumor size reduction: 17.3% (range: +5.3% to −54.4%)	NS	1-yr OS: 38.1% 2-yr OS: 19.1%
Oligometastatic setting								
Siva et al (2022) [31] RAPPORT	30 patients (56% FR, 44% IR) 83 lesions	100%	ICI (pembrolizumab, 6 mo)	20 Gy/1 fx 30 Gy/3 fx	Grade 3: 13% Grade 4–5: 0%	2-yr LCR: 92%	1-yr PFS: 60% 2-yr PFS: 45%	1-yr OS: 90% 2-yr OS: 74%
Tang et al (2021) [30]	30 patients (47% FR, 50% IR, 3% PR)	100%	No systemic therapy	60–70 Gy/10 fx 52.5–67.5 Gy/15 fx	Grade 3: 6.6% Grade 4: 3.3%	At median follow-up of 17.5 mo: 97%	1-yr PFS: 64%	1-yr OS: 100%
Oligoprogressive setting								
Hannan et al (2022) [41]	20 patients (25% FR, 75% IR) 29 lesions	95%	TKI (40%) ICI (40%) ICI + TKI (15%) mTOR-I + TKI (5%)	≥25 Gy/1 fx (16.2%) ≥36 Gy/3 fx (56.8%) ≥40 Gy/5 fx	Grade 3: 5% Grade 4–5: 0%	NS	Median PFS: 11.1 mo	1-yr OS: 73.7%
Cheung et al (2021) [42]	37 patients (32% FR, 68% IR) 57 lesions	NS	TKI	Lung: 48–60 Gy/5 fx Liver: 30–60 Gy/3–6 fx Adrenal/kidney: 30–40 Gy/5 fx Brain: 15–30 Gy/1–5 fx Spine: 18–40 Gy/1–5 fx	Grade 3–5: 0%	1-yr LCR: 93%	Median PFS: 9.3 mo	1-yr OS: 92%
Polymetastatic setting								
Hammers et al (2020) [47] RADVAX	25 patients (8% FR, 80% IR, 12% PR)	NS	Dual ICI (nivolumab + pembrolizumab)	50 Gy/5 fx	Grade 2: 8%	NS	ORR: 56%	NS
Masini et al (2022) [48] NIVES	69 patients (26% FR, 65% IR, 9% PR)	77%	ICI (nivolumab)	30 Gy/3 fx	Grade 3–5: 0%	NS	Median PFS: 5.6 mo ORR: 17%	Median OS: 20 mo
Dengina et al (2019) [19]	17 patients	100%	TKI (47%) ICI (29%) mTOR-I (24%)	NS	Grade ≥2: 0%	Response rate: 76%	NS	NS
De Wolf et al (2017) [45]	13 patients	100%	TKI (pazopanib)	Dose escalation 24–36 Gy/3 fx	Grade 4: 7.7%	1-yr LCR: 83%	1-yr PFS: 28%	NS

FR = favorable risk; fx = fractions; ICI = immune checkpoint inhibitor; IR = intermediate risk; LC = local control; LCR = local control rate; mRCC = metastatic renal cell carcinoma; mTOR-I = mammalian target of rapamycin inhibitor; NS = nonspecified; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PR = poor risk; SABR = stereotactic ablative radiotherapy; TKI = tyrosine kinase inhibitor.

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Table 2 – Risk of bias assessment using the ROBINS-1 tool (as per the Cochrane Collaboration guidelines)

Study		Before intervention		At intervention	After intervention				Overall risk of bias
First author	Year	Bias due to confounding	Bias in selection of participants in the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Low/moderate/serious/critical
Correa et al [11,13]	2018	Serious	Moderate	Low	Low	Low	Moderate	Low	Serious
Siva et al [31]	2022	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Tang et al [30]	2021	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Hannan et al [41]	2022	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Cheung et al [42]	2021	Moderate	Moderate	Low	Moderate	Low	Low	Low	Moderate
Hammers et al [47]	2020	Moderate	Moderate	Low	No information	No information	No information	Low	Moderate
Masini et al [48]	2022	Moderate	Moderate	Low	Moderate	Low	Low	Low	Moderate
Dengina et al [19]	2019	Moderate	Moderate	Low	Low	Low	Moderate	Moderate	Moderate
De Wolf et al [45]	2017	Low	Moderate	Low	Low	Low	Low	Moderate	Moderate

Correa et al [11] in a retrospective series of 11 patients with IMDC intermediate-risk (55%) or poor-risk (45%) prognosis mRCC. Delivered SABR doses ranged from 25 to 40 Gy in five fractions, delivered either to the tumor (median diameter of the renal tumors, 9.5 cm) or the whole kidney. One patient received a concomitant TKI, which was discontinued early due to hematuria, and three patients received additional TKI treatment. SABR appeared well tolerated, with only one report of grade 2 diarrhea and grade 3 nausea. With respect to a radiographic response, SABR resulted in a stable disease for 71.4% of the patients. The median OS was 20.4 mo, which compares favorably with literature data at the time of the study (predicted OS for poor- and intermediate-risk IMDC patients of 8.8 and 27 mo, respectively [12]). Within a prospective phase I dose-escalation trial, the same team evaluated the role of cytoreductive SABR in 12 inoperable clear-cell mRCC patients, mostly diagnosed with IMDC intermediate-risk disease (66.7%) [13]. No patient received concomitant systemic therapy. SABR was found to be safe and tolerable, with three grade 3 events (fatigue and bone pain) reported at doses of 30 and 35 Gy, both schedules delivered in five fractions. Overall renal function was largely preserved, with no reduction in the glomerular filtration rate at 12 wk after SABR. SABR resulted in a median tumor size reduction of 17.3%, with no reports of local failure. Although these studies provide encouraging data in terms of toxicity and LC (similar to what has been published previously among patients with localized disease [14]), half of the patients did not receive further systemic treatment, and the median OS remained poor overall (median OS of 6.7 mo). Consistently with previous literature on CN in an unselected mRCC population [15], cytoreductive SABR is not associated with an OS benefit, but it can nevertheless be considered an alternative local strategy to CN. Another approach might be to implement deferred cytoreductive SABR for patients who achieve partial or near-complete response after first-line systemic therapy. The SURTIME trial demonstrated a survival benefit of 17.4 mo for patients undergoing deferred CN after first-line sunitinib compared with those receiving upfront CN [10]. In the CARMENA trial, deferred CN allowed discontinuation of systemic therapy for patients with a near complete response after sunitinib [9]. As this approach still remains experimental, it could represent an interesting research landscape to be studied prospectively with SABR (Fig. 3).

To date, no data are available on combined first-line cytoreductive SABR and ICIs, although this combination is supported by a strong biological rationale. While immunotherapy alone can be challenging for mRCC patients, as they demonstrate poor tumor-associated antigen (TAA) expression, SABR may be helpful for inducing TAA release, resulting in a synergistic response when combined with ICIs [16]. The combination of SABR and programmed cell death 1 (PD-1) agents has been shown to increase the frequency of abscopal (out-of-field) effects in mRCC mice models [17]. Singh et al [18] reported increased expression of both TAA and calreticulin, an immunomodulatory molecule, in primary renal tumor after a single 15 Gy SABR session. Both proliferating CD8+ and FOXP3+ T cells were identified in the close microenvironment, providing evidence of immunomodulation. As clinical evidence of abscopal effect remains scarce [19], the combined SABR and

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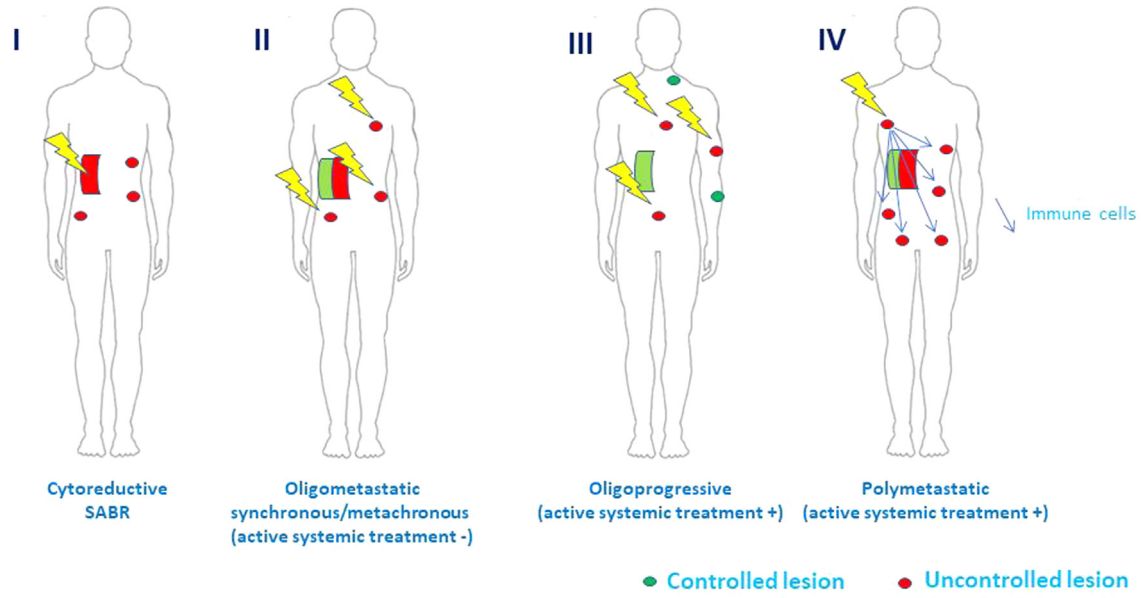

Fig. 2 – Graphical representation of implementation of stereotactic ablative radiotherapy (SABR) in the different metastatic renal cell carcinoma disease settings.

ICI approach is currently being investigated within two phase II trials, the CYTOSHRINK (NCT04090710) and the NRG-GU012 SAMURAI trials. Both trials randomize intermediate to poor IMDC prognosis mRCC patients to first-line dual ICIs or a combination of ICIs and TKIs, as per current guidelines, with or without cytoreductive SABR (30–40 Gy in five fractions). Results of these trials are eagerly awaited to provide high-level evidence on the role of upfront cytoreductive SABR for mRCC in the immunotherapy era.

3.2. *SABR in the oligometastatic setting*

The oligometastatic paradigm postulates that patients with a limited number of metastases can be treated with a curative intent on all metastatic sites, either by surgery or by SABR [20]. In this specific population (Fig. 2), a recently published meta-analysis confirmed the safety and excellent results in terms of LC of an MDT approach with SABR [21]. The phase II SABR-COMET trial, recruiting patients with var-

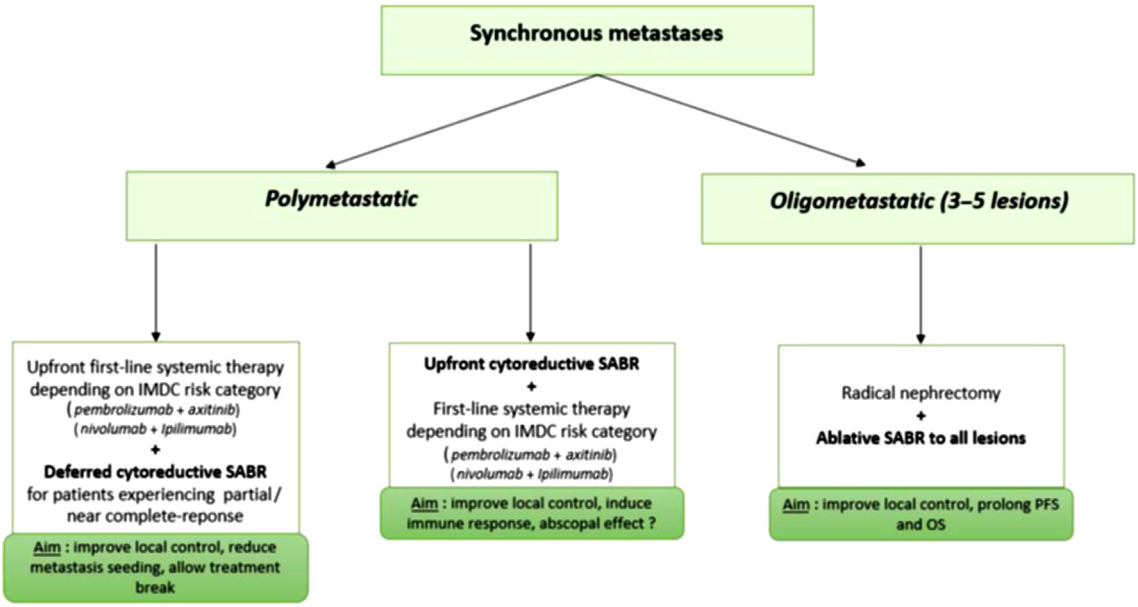

Fig. 3 – Implementation of SABR for metastatic renal cell carcinoma patients diagnosed with synchronous metastases. IMDC = International Metastatic renal cell Database Consortium; OS = overall survival; PFS= progression-free survival; SABR = stereotactic ablative radiotherapy.

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ious primary tumors (breast, colorectal, lung, and prostate), demonstrated an improvement in both PFS (8-yr PFS rate of 21.3% vs 0%, $p < 0.001$) and OS (8-yr OS rate of 27.2% vs 13.6%, $p = 0.008$) compared with the standard of care strategy [22].

Various retrospective data are available in mRCC, highlighting the relevance of SABR in the oligometastatic setting. The SABR-ORCA meta-analysis of 28 studies and 623 patients with 2733 extracranial lesions treated with SABR showed LC and OS rates at 1 yr of 89.1% and 86.8%, respectively. Treatment-related toxicities were minimal, with only a 0.7% rate of grade 3–4 side effects [23]. However, inclusion of both a heterogeneous population with oligometastatic, oligoprogressive, or polymetastatic patients and heterogeneous treatments, with SABR performed either alone or combined with systemic therapies, represents the major limitation of this study. Nevertheless, results of the SABR-ORCA meta-analysis highlight several points on the role of SABR in mRCC. First, SABR can achieve a long-term LC in >90% of the cases, even when it is delivered without concomitant systemic treatments [24–27]. Biologically effective doses of >100 Gy are required to achieve these control rates, similar to what has been observed at other disease sites [25,28]. Second, SABR can be used in mRCC as an effective strategy to delay the introduction of systemic treatments. In a series of 188 mRCC patients, Meyer et al [29] reported a median freedom from systemic therapy time of 14.2 mo, with 27.5% patients being disease free after a median follow-up of 22 mo. Similar results were published by Zhang et al [27] in a retrospective series of 47 mRCC patients with 88 metastases treated with SABR, with a median time to systemic therapy initiation of 15.2 mo. In the prospective phase II trial by Tang et al [30], SABR performed in place of systemic treatment resulted in 1-yr PFS and 1-yr systemic therapy–free survival rates of 64% and 82%, respectively. Sequential SABR can therefore allow sustained systemic therapy breaks for select patients with oligometastatic RCC.

Distant disease progression is the most common pattern of failure, and local therapy alone may provide long-term disease control but can rarely cure. As micrometastatic disease may already be present at the time when SABR is planned, these findings bring the rationale for performing SABR in combination with systemic therapies. To date, few studies provide data on SABR performed in combination with current first-line standard of care therapies. The RAPPORT phase I/II trial evaluated both safety and efficacy of total metastatic irradiation followed by a short-course of anti–PD-1 immunotherapy (pembrolizumab) [31]. Thirty patients were enrolled, 44% and 56% of whom were diagnosed with intermediate- and favorable-risk IMDC disease, respectively. The median time between the diagnosis of primary RCC and metastatic disease was 11 mo. The combination of SABR and ICIs was safe, with 13% of the patients experiencing treatment-related grade 3 toxicity, and there were no reports of grade 4 or 5 toxicity. This trial confirmed the excellent outcomes achieved with SABR, with a 2-yr LC rate of 92%. Durable antitumor efficacy was demonstrated in this subset of patients diagnosed with mRCC, as the 1- and 2-yr PFS estimates were 60% and 45%, respectively, while the corresponding OS rates were 90% and 74%, respectively. Interestingly, the 15.6-mo PFS rate of the RAPPORT trial compares favorably with the historical cohorts of patients treated with pembrolizumab alone (7.1 mo within the Keynote-427 trial [32]).

National Comprehensive Cancer Network guidelines consider to date both metastasectomy and SABR as standard of care strategies for patients with oligometastatic mRCC [33]. Based on the Keynote-564 trial [34], these same guidelines advocate adjuvant pembrolizumab after metastasectomy for synchronous or metachronous clear-cell lesions within 1 yr after nephrectomy. Still, this cutoff remains arbitrary, and other models can probably better predict the overall prognosis of oligometastatic mRCC patients. Franzese et al [35] designed a risk-group classification by a recursive partitioning analysis of 129 oligometastatic mRCC patients treated with SABR. Four prognostic classes were identified, the highest OS being in patients aged $\leq$65 yr treated for extracranial metastases. Models incorporating biological factors have also shown improved prediction of both metastatic potential and overall prognosis, compared with the IMDC categories [36]. Awaiting the implementation of these models within randomized trials, patients with favorable disease characteristics (time interval between diagnosis and metastatic state of >12 mo, age $\leq$65 yr, extracranial metastases, and so on) may probably be the best candidates for the SABR-alone approach (Fig. 4). Further evidence on the impact of the addition of SABR to the standard of care systemic treatment will be provided in the coming years by the OligoRARE (NCT04498767), SABR-COMET-3 (NCT03862911), and SABR-COMET-10 (NCT03721341) randomized phase III trials.

3.3. *SABR in the oligoprogressive setting*

Oligoprogression represents a clinical situation in which a limited number of metastases (five or fewer) have progressed, while other sites are controlled under systemic therapy [37]. The biology of oligoprogressive disease remains poorly understood to date, but most hypotheses on this status are based on a branching clonal evolution with genetic/epigenetic resistance patterns [38]. In clinical practice, the long validated approach has been to switch systemic therapy at progression, with no distinction between oligoprogression and multisite progression. However, successive lines of systemic therapies are usually associated with shorter PFS intervals and increased toxicity rates [39]. SABR has increasingly been considered in this setting, usually with the goal of prolonging ongoing systemic therapy and sparing a line of treatment (Fig. 2).

The first report on SABR for patients with oligoprogressive mRCC showed an extended duration of the systemic therapy of approximately 9 mo [29,40]. Meyer et al [29] published the largest cohort of oligoprogressive mRCC patients, with a sample size of 101 patients. As this retrospective study represents the first proof of concept for SABR in this setting, one of its major limitations relates to its conduct in the TKI era. More recently, Schoenhals et al [40] reported outcome results of 36 oligoprogressive patients diagnosed with favorable-risk (27.8%) or intermediate-risk (61.1%) IMDC mRCC. Of the patients, 91% received nephrectomy, performed either in nonmetastatic (75%) or in metastatic (16%) situations. SABR was delivered at all progression sites, with a median time from the start of systemic therapy to SABR of 11.4 mo. Based on these promising results, the same team designed a single-arm phase II trial

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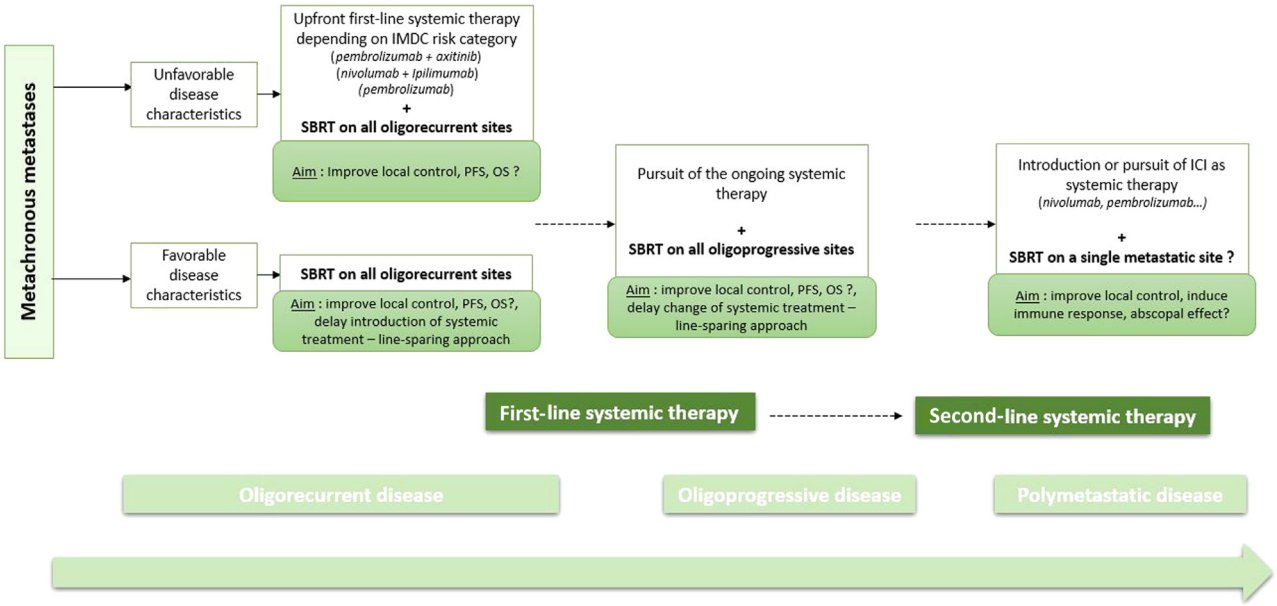

Fig. 4 – Implementation of SABR for metastatic renal cell carcinoma patients diagnosed with metachronous metastases. ICI = immune checkpoint inhibitor; IMDC = International Metastatic renal cell Database Consortium; OS = overall survival; PFS = progression-free survival; SABR = stereotactic ablative radiation; SBRT = stereotactic body radiation therapy.

that recruited 20 patients with mRCC on first to fourth lines of systemic therapy [41]. Most patients had synchronous metastases (60%), and among them all received CN. At enrollment, systemic therapy was represented by ICIs for eight patients, TKIs for eight patients, and a combination therapy for four patients. At 1 yr, 44.2% of patients remained on the same systemic therapy. The median time from SABR to initiation of new systemic therapy was 11.1 mo, demonstrating excellent results in terms of a line-sparing strategy. Cheung et al [42] reported similar results in a prospective trial of oligoprogressive patients on systemic TKI therapy. Thirty-seven mRCC patients were enrolled and treated for 57 oligoprogressive lesions. The majority (54%) of patients were diagnosed with metachronous metastases and intermediate-risk IMDC disease (68%). The median duration of TKI therapy before oligoprogression was 18.6 mo, which was longer than in the Checkmate-214 [4] and Keynote-426 [1] trials (8.4 and 11.1 mo, respectively). The 1-yr LC rate of irradiated lesions was 93%, and the estimated PFS was 9.3 mo. The use of next-line systemic therapy was delayed for a median of >1 yr. Although predictors of longer PFS remain unclear, patients with an indolent disease course (longer duration of systemic therapy before progression [42] and fewer metastases [five or fewer] at oligoprogression [41]) may benefit most from SABR in the oligoprogressive setting. Franzese et al [43] also suggested that outcomes after SABR are strongly correlated with the volume of the metastatic burden. While a cutoff was not established in their retrospective study, a higher total number of metastases was the only predictor of worse LC, PFS, and OS.

Schoenhals et al [40] showed that conducting SABR during ICI treatment was associated with longer PFS (>28.4 mo, $p = 0.0001$), although these data have not been confirmed prospectively [41]. Further data on combined SABR and ICI therapies will be provided by the NCT04974671 single-arm phase II trial, currently opened but not yet recruiting. The GETUG-StORM-01 trial (NCT04299646) is currently recruiting patients under either TKIs or ICIs with one to three oligoprogressive sites, randomizing patients to continuation of ongoing systemic therapies with or without SABR on all progressive metastatic lesions. Although the continuation of ongoing treatment in oligoprogressive patients does not represent a current standard of care, addition of SABR for oligoprogressive lesions can represent an attractive opportunity to modify the disease evolution (Fig. 4).

3.4. *SABR as an adjunct to systemic therapy*

The response rate of systemic treatments prescribed as second or third line falls drastically, reaching at best only 25% [44], raising the need for identifying further strategies to enhance their efficacy. It has long been hypothesized that SABR has the potential to improve the effects of immune therapy in the polymetastatic setting, prompting increasing interest in patients with mRCC [45]. Liu et al [46] retrospectively reviewed 74 patients treated either with ICIs and TKIs, or with ICIs and TKIs combined with SABR. Most patients (78.4%) were classified into IMDC intermediate- or poor-risk category, and 85.1% of the patients underwent nephrectomy. All patients received first-line TKIs, as per guidelines at the time the study was performed, and the median duration of first-line therapy was 8.6 mo. Among patients treated with systemic therapy alone, the median PFS was 5.0 mo, while it reached 13.2 mo in the combined systemic therapy and SABR group. Patients who received the combined treatment demonstrated a significant improvement in OS compared with patients treated with systemic therapy alone (38.5 vs 15.4 mo). Encouraging results were also provided in the prospective RADVAX trial, which enrolled a population of patients diagnosed with polymetastatic clear cell mRCC [47]. SABR was delivered to one to two disease sites with a dose of 50 Gy in five fractions, between the first and second doses of nivolumab and

ipilimumab. Most patients were diagnosed with IMDC intermediate-risk disease (80%). A high percentage of patients (40%) required immune suppressive therapy with prednisone for immune-related adverse events. Among the 25 patients included, the overall response rate (ORR) was 56%, with six of the 14 patients continuing to have no progressive disease after a median follow-up of 24 mo. As this trial demonstrated considerable antitumor activity after the combination of an ICI and SABR, it is unclear whether these results represent a true abscopal effect compared with the disease control achieved by either of or both the treatment modalities. On the contrary, conflicting findings were found within the phase II single-arm NIVES trial combining SABR and nivolumab for patients progressing after first-line TKI therapy [48]. Of the 69 patients included in the study, only one patient achieved a complete response and 11 patients a partial response, resulting in an ORR of 17% and median PFS of 4.1 mo. In this trial, a 26% rate of grade 3–4 immune events was observed, while no grade 3–4 SABR-related events were reported. In clinical practice, this trial did not provide evidence in favor of an added benefit of SABR in combination with nivolumab for patients with a polymetastatic disease.

The discrepancies between the results of the RADVAX and NIVES studies raise the question of appropriate systemic treatment and timing of SABR in the polymetastatic setting. In addition, patient selection remains a crucial issue. Masini et al [48] suggested that the relatively high proportion of patients diagnosed with non–clear cell mRCC within the NIVES trial (17%) may have contributed to the low ORR, as this histology is known to have a worse prognosis. Currently, no data are available for mRCC patients on predictive factors associated with a response to combined therapy. In head and neck cancers, low PD-L1 expression has been associated with a greater benefit from the addition of SABR to nivolumab, suggesting that less inflamed tumors may preferentially benefit from increased antigen presentation resulting from SABR [49]. While the combined therapy of SABR and ICIs may have synergistic local effects, data from prospective studies suggest that the abscopal effect is relatively rare and probably should not be considered the primary endpoint in the design of future trials. Instead, some authors advocate for a comprehensive irradiation of all metastatic sites even in the polymetastatic setting, rather than performing irradiation of a single site [50]. Further data are warranted before implementing this approach in clinical practice (Fig. 4).

4. Conclusions

In the rapidly evolving management of mRCC, SABR is increasingly being implemented in the therapeutic algorithm, and represents an attractive and safe treatment option in different disease scenarios. In de novo or metachronous oligometastatic mRCC patients, SABR has been associated with LC rates of >90% and a PFS benefit ranging between 8 and 15 mo, although its role in association with systemic therapies has not yet been defined clearly. While in oligoprogressive mRCC patients, SABR enables an extension of the duration of the ongoing therapy by approximately 9 mo, in the polymetastatic setting, the use of SABR to enhance the response to systemic therapies has been associated with conflicting results and remains investigational. As cytoreductive treatment, SABR showed excellent LC rates and good preservation of the renal function, even if its impact on PFS and OS remains unclear. Results of ongoing and future prospective studies will certainly help better define the role of SABR in the different disease settings, particularly in combination with immunotherapy.

***Author contributions*:** Thomas Zilli had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Zilli, Le Guevelou.
Acquisition of data: Zilli, Le Guevelou.
Analysis and interpretation of data: Le Guevelou, Sargos, Siva, Ploussard, Ost, Gillessen, Zilli.
Drafting of the manuscript: Zilli, Le Guevelou.
Critical revision of the manuscript for important intellectual content: Le Guevelou, Sargos, Siva, Ploussard, Ost, Gillessen, Zilli.
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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euf.2022.08.016.

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