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Original Research Article

SABR for oligometastatic renal cell carcinoma

Chang David [a,b,*], Ali Muhammad [a,b], Udovicich Cristian [a,b], Tran Ben [b,c], Azad Arun [b,c], Au Lewis [b,c], Spain Lavinia [b,c], Perera Marlon [d], Siva Shankar [a,b]

[a] Department of Radiation Oncology, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia
[b] Sir Peter MacCallum Department of Oncology, The University of Melbourne, Melbourne, Victoria, Australia
[c] Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia
[d] Division of Surgical Oncology, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia

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ABSTRACT

Stereotactic ablative body radiotherapy (SABR) aims to accurately deliver a higher than conventional dose of radiotherapy to a well-defined target tumour incorporating advanced immobilisation and imaging techniques. SABR is an emerging treatment option for primary kidney cancer especially when surgery is contraindicated. Increasingly, SABR is being incorporated into the management of low-volume stage IV kidney cancers to delay the need for systemic therapy or to prolong the duration of ongoing systemic treatment. This review will evaluate the evidence and limitations of SABR for oligometastatic renal cell carcinoma.

Introduction

Each year more than 350,000 people are diagnosed with renal cell carcinoma (RCC) globally [1]. The incidence of RCC has more than doubled in the USA from 1975, likely due to improved accessibility and quality of cross-sectional imaging [2]. Historically, RCC with distant metastases has been associated with poor survival due to a lack of effective treatment options [2,3]. Approximately 15 % of patients with RCC present with de novo metastatic disease and a further 20 % of patients with localised disease treated with curative-intent nephrectomy will develop subsequent metastatic disease [4].

Over the past decade, there have been significant advances in treatment with angiogenesis-directed therapies and immunotherapy, resulting in a RECIST objective response rates of up to 42 % [5].

With the increasing incidence of RCC, earlier detection and better systemic treatment options, there will likely be an increasing role for oligometastatic-directed surgery and stereotactic ablative body radiotherapy (SABR). The role of metastatesectomy has been addressed previously in literature with suggestion of potential oncologic benefit. Though, these benefits must be considered in the context of substantial morbidity associated with such resections [6].

Oligometastatic-directed SABR may provide benefit over metastasectomy. SABR involves the precise delivery of ablative doses of radiotherapy over one to five fractions. The most obvious advantage of SABR is that it is non-invasive; it is also well tolerated. It can be an effective treatment option for the primary tumour, brain metastases, oligometastatic and oligoprogressive RCCs. This review will focus on the current evidence and role of SABR for oligometastases and oligoprogression in advanced RCC.

RCC oligometastases

In 1995, Hellman and Weichselbaum first described Oligometastases as a clinical state in which “tumours early in the progression may have metastases limited in number and location because the facility for metastatic growth has not been fully developed and the site for such growth is restricted” [8]. ESTRO-ASTRO consensus document defines oligometastatic disease as 1–5 metastatic lesions, whereby all metastatic sites must be safely treatable (Fig. 1) [9]. RCC can metastasize to the lungs, bones, lymph nodes, liver, brain and many other organs [10]. However, the incidence of RCC oligometastatic disease is currently not well understood.

Diagnosing RCC oligometastases

When diagnosing oligometastatic disease, the ESTRO-ASTRO consensus document recommends utilizing the most accurate and accepted staging scans available [9]. Currently, standard staging of RCC includes a CT and bone scan. PET (positron emission tomography) imaging using various tracers have increasing roles in the accurate diagnosis of oligometastatic RCC (Fig. 2). FDG PET/CT has become a standard imaging modality for several cancers. However, it has limited

* Corresponding author at: Department of Radiation Oncology, Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia.

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specificity and sensitivity for RCC except for more advanced disease and a high nuclear grade [11,12]. An imaging modality that has demonstrated promise is prostate-specific membrane antigen (PSMA) PET/CT. PSMA PET/CT has vastly improved the staging accuracy of prostate cancer compared to conventional CT and bone scan [13]. Despite the name, PSMA is also frequently expressed by the neovasculature of several non-prostatic tumours, including RCC [14]. Several small prospective studies have demonstrated superior sensitivity of PSMA PET for the detection of RCC metastases compared to conventional imaging [15–18]. For example, Meyer et al. prospectively evaluated PSMA PET/CT for 14 patients with oligometastatic RCC as detected on conventional imaging [18]. In 4 patients, PSMA PET/CT was able to detect more lesions than conventional imaging and of those, 3 patients were no longer considered oligometastatic. When compared to FDG PET/CT, PSMA PET/CT has superior sensitivity for local recurrence and bone metastases though similar for detection of soft tissue metastases [19]. In a retrospective analysis of 61 patients with RCC by Udovicich et al. PSMA PET/CT led to a change in management of approximately 50 % of patients by detecting additional metastases [20].

Another PET tracer with the potential to better define an oligometastatic RCC is Zr-DFO-girentuximab that targets carbonic anhydrase IX, widely over-expressed by majority of clear cell RCC tumours [21]. The IMPACT-RCC study prospectively compared Zr-DFO-girentuximab and FDG PET/CT for 42 patients newly diagnosed with metastatic clear cell RCC. Zr-DFO-girentuximab PET/CT was able to detect 91 % of lesions versus 84 % for FDG PET/CT and 56 % for CT alone [22]. As more sensitive scans become available, oligometastasic-directed therapies will likely become more effective as smaller metastases will be detected and amenable to SABR. Furthermore, considering the tracer's specificity towards RCC, an area that is being explored is targeted radionuclide therapy. A phase 2 study of Lutetium 177-labeled anti CAIX antibody, 177Lu-girentuximab, has demonstrated acceptable safety profiles [23]. Of the 14 patients recruited to the trial, 9 demonstrated disease stabilization after only 1 or 2 cycles. The STARLITE 2 phase 2 study (NCT05239533) is currently exploring the safety and efficacy of combining 177Lu-girentuximab with nivolumab for patients with advanced ccRCC. If proven to be safe and effective, radionuclide therapy has the potential to improve the outcomes of patients with oligometastatic or oligoprogressive RCC in combination with systemic therapy and SABR.

SABR in lieu of systemic therapy

There are currently two published prospective phase 2 trials (Table 1) and several retrospective studies evaluating SABR for RCC oligometastases. A single institution trial conducted at the MD Anderson Cancer Centre recruited 30 patients with up to five clear cell RCC metastases [24]. All participants previously had nephrectomy, and most were in the International Metastatic RCC Database Consortium (IMDC) favourable (47 %) or intermediate (50 %) risk groups. Only 30 % of the participants had received first line systemic treatment in the past. During the first round of SABR, 94 % had 1 (67 %) or 2 (27 %) sites treated. If there was progression in three or fewer metastases (existing or new), patients could receive salvage radiotherapy to these sites in order to delay commencement of systemic therapy. Thirteen participants (43 %) received a second round of radiotherapy. The most common targets were lung (40.8 %), bone (16.3 %) and lymph nodes (14.3 %). At a median follow up of 17.5 months, 1-year progression-free survival (PFS) of 64 % (95 % CI 48–85) was achieved and 10 % of patients developed grade 3 or 4 toxicity. The 1-year adjusted systemic therapy-free survival probability was 86 % and as expected local control (LC) rates were excellent at 97 % (95 % CI 90–100).

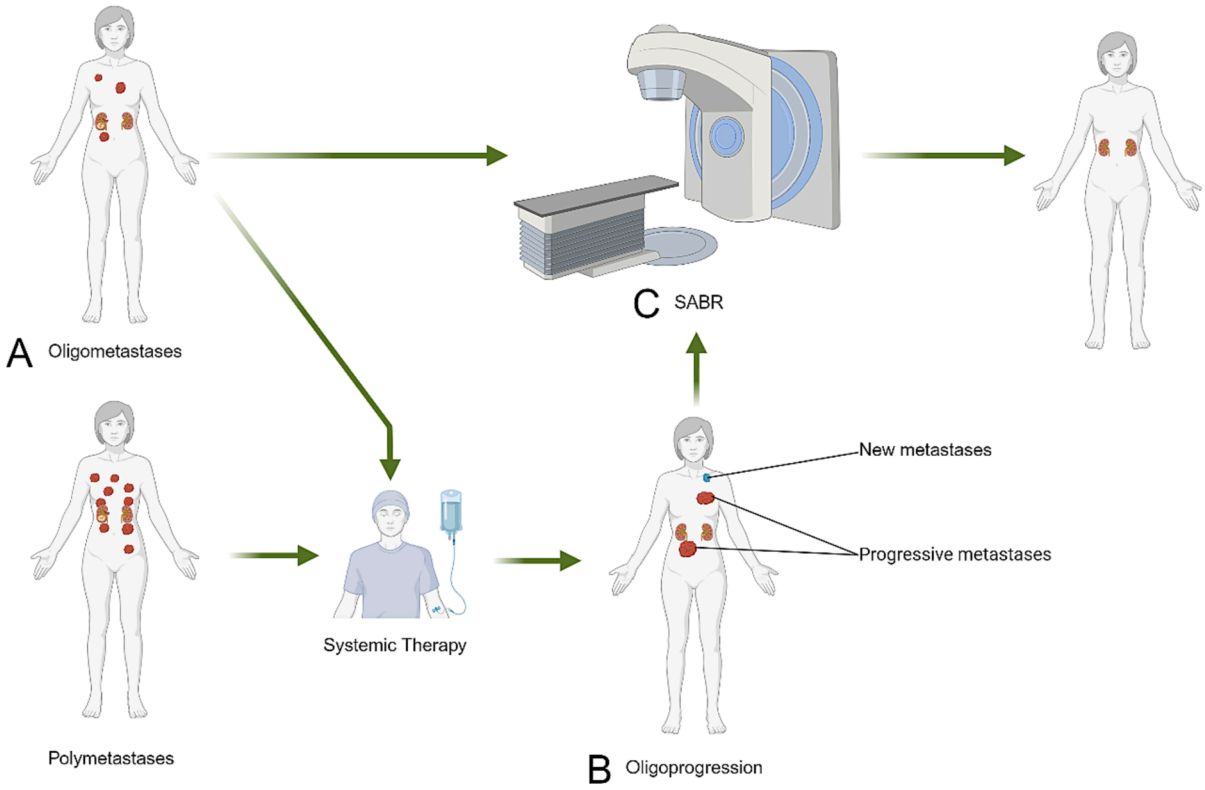

Fig. 1. Role of SABR for RCC oligometastases and oligoprogression. A) De-novo oligometastatic disease is defined as the first presentation with 1–5 metastatic lesions, where all sites must be safely treatable. B) Oligoprogression occurs when polymetastatic disease (>5 metastases) is treated with systemic treatment (with or without local treatment) and subsequently 1–5 new and/or growing metastases develop during systemic therapy. C) Both situations and several other disease states as defined by The European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus recommendation can be managed with SABR to delay or prevent the need for systemic therapy.[7].

Another prospective phase 2 single arm trial at the University of Texas Southwestern Medical Centre, evaluated SABR for 23 patients with ≤3 extracranial metastasis [25]. Most had a previous nephrectomy (95.7 %) though one patient did have the primary tumour treated with SABR (4.3 %). All patients were either in the favourable (73.9 %) or intermediate (26.1 %) IMDC risk groups. The majority (82.6 %) were clear cell RCC but participants with chromophobe (8.7 %) and papillary RCC (8.7 %) were also included. With a median follow up of 21.7 months, 1- year freedom from systemic therapy rate was 91.3 % and 1-year PFS was 82.6 %. There were no grade 3 or 4 toxicities and LC was excellent at 100 %.

A multi-centre prospective, registry-based, single-arm, observational trial conducted in the UK evaluated the outcomes of SABR for patients with 1–3 extracranial metastatic sites [26]. Patients had a disease-free interval from primary tumour development to metastases of longer than 6 months, WHO performance status of 2 or lower and a life expectancy of at least 6 months. The registry included 1422 patients overall, including 143 with renal cancer. For this subset of patients, excellent outcomes were observed. The 1-year and 2-year outcomes for overall survival were 95.3 % and 82.4 % respectively, metastases-free survival was 89.1 % (95 % CI 81.5–93.7 %) and 45.0 % (95 % CI 30.3–50.8 %), respectively, and local control were 94.9 % (95 % CI 88.8–97.7 %) and 78.0 % (95 % CI 65.5–86.4 %) respectively.

There are several retrospective studies that corroborate the positive findings of the prospective studies. Zhang et al. investigated the outcomes of 41 patients with clear cell and 6 patients with non-clear cell metastatic RCC [27]. Majority were in the favourable (42.6 %) or intermediate prognosis (34 %) groups with the remainder of participants having unknown risk prognosis. Most (74.5 %) had only 1 oligometastasis. Eleven of 47 patients (23.4 %) received a second subsequent SABR and another 3 patients (6.3 %) received a third round of SABR to subsequent area of oligometastases. The 2-year LC was 91.5 % and there was no grade 3 or 4 toxicity. Patients with single metastasis at initial presentation demonstrated better freedom from systemic treatment of 25.5 months versus 4.8 months. Non-clear cell histology was associated with worse outcomes however, the publication did not specify the non-clear cell histology types of which there are several of with highly variable prognosis.

A larger single institution retrospective analysis by Marvaso et al. included 61 patients with up to 5 intracranial and extracranial metastases [28]. Seventy four percent of patients were treated for a solitary oligometastasis. The study was not solely focused on oligometastases and included patients with oligoprogressive metastasis (18 %). Unlike in forementioned studies, patient had a far lower median dose of 25 Gy in 5–10 fractions which would not be considered ablative. Not surprisingly, the 2 year in-field progression free survival was relatively low at 55 %, highlighting the importance of delivering adequate doses of radiotherapy.

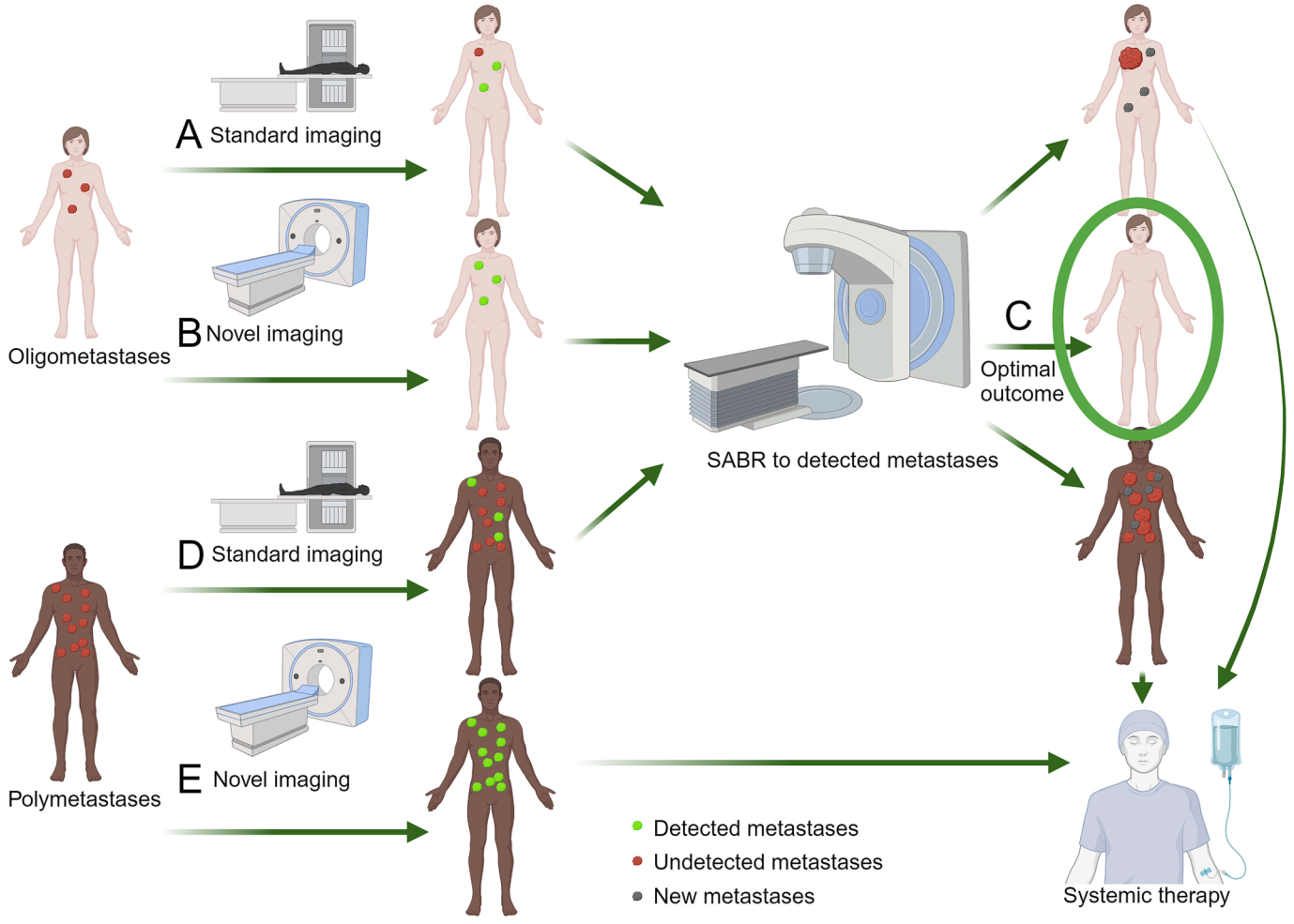

Fig. 2. Novel imaging modalities with higher sensitivity and specificity may lead to improved patient selection and outcomes for patients with RCC oligometastases. A) Standard imaging such as CT and bone scan may miss smaller oligometastases. B) In the future, novel imaging modalities may be able to detect smaller oligometastases for targeting with SABR. C) This can reduce the rates of local and distant progression after SABR. D) With standard imaging, polymetastases are more likely to be falsely diagnosed as oligometastases resulting in suboptimal patient selection for SABR. E) Novel imaging modalities with superior sensitivity may lead to improved accuracy in diagnosis and improved management.

Table 1
SABR for RCC oligometastases and oligoprogression prospective clinical trials.

Author (year)	Patient (n)	Radiation Dose	Toxicity	Primary endpoint and Local Control
SABR in lieu of systemic treatment				
Tang et al. (2021) [24]	30	50 Gy/4 fractions (most common, 39.3 % of treatments), BED10 112.5 Gy Lowest BED10 59.5 Gy EQD2 = 49.58 Gy (α/β = 10)	G2 10 % G3 6.7 % G4 3.3 %	Coprimary endpoints: 1. Feasibility of definitive radiotherapy as treatment strategy - Yes 2. Median PFS 22.7 months LC: 1 year 97 % (95 % CI 90–100)
Hannan et al. (2021) [25]	23	20–25 Gy/1 36–39 Gy/3 35–40 Gy/5 Lowest BED10, 59.5 Gy EQD2 = 49.58 Gy (α/β = 10)	G2 4.3 % No G3/4 toxicities G5 4.3 % 1 death due to immune-related colitis 3 months after SABR while on subsequent checkpoint inhibitor.	Primary endpoint: Freedom from systemic therapy for >1 year in >60 % of patients One-year PFS was 82.6 % LC: 1 year 100 %
SABR at time of oligoprogression				
Hannan et al. (2022) [40]	20	≥ 25 Gy/1 ≥ 36 Gy/3 ≥ 40 Gy/5 Lowest BED10 72 Gy EQD2 = 60 Gy (α/β = 10)	G2 15 % G3 5 %	Primary endpoint: Extend ongoing systemic therapy by >6 months in >40 % of patients SABR extended the duration of ongoing systemic therapy by >6 months in 70 % of patients LC: 100 % with median follow up of 10.4 months
Cheung et al. (2021) [41]	37	Median BED10 72 Gy corresponding to 40 Gy/5	Acute G1-2 fatigue 19 % Acute G1 nausea/ vomiting 16 % Acute G1-2 dyspnoea or cough 14 % Late G1-2 dyspnoea and pneumonitis 11 % Acute or late G1-2 bone/ chest wall pain 11 % No G3 or higher toxicities	Primary endpoint: Determine the local control of the irradiated oligoprogressive tumours at 1 year LC: 1 year 93 % (95 % CI 71–98 %)

PFS = progression free survival, LC = local control rate.

Several older studies on both oligorecurrence, oligometastases and oligoprogressive disease states have been evaluated in a meta-analysis in 2019 [29]. Zaorsky et al. analysed 28 studies and showed excellent 1-year LC rates of 90 % and Grade 3–4 toxicity rates of 1 %. Despite excellent LC, the 1-year overall survival for extracranial disease was superior (86.8 %) to intracranial disease (49.7 %). This may reflect the poor penetrance of systemic treatment agents through the blood brain barrier. For example, a phase 2 trial of sunitinib for untreated RCC brain metastases demonstrated no objective intracranial response and phase 2 trial of Nivolumab was associated with an intracranial response rate of only 12 % [30,31].

Taken together, the evidence suggests that SABR is a relatively safe treatment for RCC oligometastases and is associated with ≥G3 or higher toxicity when compared to systemic therapy. Prospective SABR trials for RCC oligometastases is associated with G3+ toxicity of 0–10 % compared to 47 % for ipilimumab/nivolumab and 64 % for sunitinib [32]. However, if patients are likely to require systemic treatment soon after SABR, then alternative strategies should be considered. In the future, the SOAR study (NCT05863351), a phase III randomised controlled trial, will compare SABR versus standard of care systemic therapy for RCC oligometastases and compare the overall survival of both approaches. The ASTROs phase 2 trial (NCT06004336) will randomise patients with RCC oligometastases to SABR versus SABR plus 1 year of pembrolimzumab to determine the safety. Outcomes of such trials should better guide the clinician in determining best course of action in the management of RCC oligometastases.

Prognostic factors

When considering SABR for oligometastatic RCC, several factors may be considered in determining suitability. The IMDC Prognostic Model stratifies patients with metastatic RCC into favourable, intermediate and poor risk groups based on a number of risk factors including Karnofsky performance status <80 %, <1 year from diagnosis to treatment, anaemia, thrombocytosis, neutrophilia and hypercalcaemia [33]. In the era of immunotherapy, 18-month overall survival can vary from 50 % for the poor risk group to 78 % for intermediate risk and 90 % for favourable risk groups [34,35]. As a result, the majority of studies evaluating SABR for RCC oligometastases included only IMDC favourable and intermediate risk groups. Furthermore, most patients had 1–2 metastases although patients with up to 5 metastases were often eligible. In addition, retrospective study by Zhang et al. showed superior outcomes for those with a single metastasis [27]. Therefore, it is important to appreciate the limited data in the setting of IMDC poor risk groups and those with more numerous oligometastases.

Synchronous metastatic RCC is associated with worse outcomes than metachronous oligometastatic RCC, especially with longer interval between initial diagnosis and development of metastases [36]. Analysis by IMDC showed that metachronous disease occurring >7 years after the initial diagnosis was associated with the best overall survival and time to treatment failure, followed by metachronous oligometastasis being diagnosed after >2–7 years, >12–24 months, >3–12 months and 0–3 months. This is supported by the findings of retrospective analysis on SABR for RCC oligometastases that demonstrated superior freedom from systemic therapy duration for those presenting with metachronous oligometastases [27]. Other poor prognostic factors to consider include sarcomatoid and collecting duct RCCs, aggressive variants of kidney

cancer for which there is very limited experience with SABR [37,38].

There have been specific attempts at prognostic stratification when considering SABR for oligometastatic RCC. Franzese et al. evaluated 129 patients with 242 RCC oligometastases treated with SABR and performed a recursive partitioning analysis identifying 4 prognostic classes [39]. Patients aged ≤65 years treated on extracranial metastases had the best 3-year overall survival of 82.6 % (95 % CI 65.3–91.8 %) followed by patients aged >65 years, without a history of metastatic bone disease, treated on extracranial metastases (67.9 %, 95 % CI 45.6–82.7 %) and patients >65 years, with a history of metastatic bone disease, treated on extracranial metastases (37.5 %, 95 % CI 5.6–71.7 %). Patients who had brain metastases treated with stereotactic radiosurgery had the poorest 3-year overall survival of 9.7 % (95 % CI 1.8–25.8 %). Further prognostic strategies should be developed in the future so that ideal candidates can be treated with SABR whilst potentially poor responders should consider upfront systemic therapy.

SABR to primary kidney tumour in the presence of metastases

For de novo oligometastatic RCC, SABR can be delivered to the renal primary if the patient is not a surgical candidate. When patients present with polymetastatic RCC, upfront cytoreductive nephrectomies may not provide a benefit except for select cases including patients with symptoms related to the primary tumour [42,43]. The role of SABR to the renal primary in the setting of polymetastatic disease remains investigational with at least 2 prospective clinical trials, CYTOSHRINK (NCT04090710) and NRG-GU012 SAMURAI trials (NCT05327686), currently evaluating the role of SABR in combination with immunotherapy.

SABR at oligoprogression of metastatic disease

The European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus recommendation defines oligoprogressive disease as few growing or newly developed metastases under active systemic treatment (Fig. 1) [7]. Oligorecurrent disease states are when there are limited number of recurrent metastases after a systemic therapy-free interval. This differs from oligopersistent disease states, which is the presence of few persistent metastases during active systemic treatment. Several past studies have not differentiated these categories and often grouped them together for analysis. However, with improved consensus on nomenclature, future studies are more likely to differentiate these groups.

Clinical Trials on SABR for RCC Oligoprogression

Several prospective (Table 1) and retrospective studies have evaluated SABR for RCC oligoprogression. A Canadian phase 2 prospective multicentre trial assessed 37 patients with metastatic RCC who had initial stability or response to ≥3 months of treatment with tyrosine kinase inhibitors (TKI) followed by oligoprogressive metastases treated with SABR [41]. Only patients with Karnofsky performance ≥80, clear cell RCC and IMDC favourable or intermediate risk disease were recruited. Though up to five oligoprogressive metastases were allowed, 92 % involved either one or two oligoprogressive metastases. SABR was associated with 1-year local control rates of 93 % with no Grade ≥3 toxicities but 21 of 37 patients progressed outside the irradiated region with a median PFS of 9.3 months.

In the only other published phase 2 prospective trial, 20 patients receiving up to 4th line systemic therapy with 1–3 RCC oligoprogressive metastases were enrolled [40]. Patients with IMDC high risk disease and poor performance status (ECOG 3–5) were excluded. The primary endpoint was to assess whether SABR could extend current systemic therapy by 6 months or more in greater than 40 % of patients. With a median follow up of 10.4 months, one patient developed G3 colitis with small bowel perforation and this was in the setting of concurrent Everolimus and Lenvatinib. No other G3 or G4 toxicities occurred. Subsequent SABR was allowed to new sites of oligoprogression if it was safe to do so to prolong systemic therapy. Seventy percent of patients were able to extend their systemic therapy for >6 months and at 1 year 44.2 % of patients were still on the same systemic therapy. The 6 months modified PFS (time from SABR to the onset of new systemic therapy or death) for participants with 5 or fewer metastases at the time of SABR was 100 % compared to 50 % for those with six or more metastases. This difference was statistically significant in an exploratory, unspecified, univariate analyses suggesting that the number of existing metastases, even if not progressive, is a poor prognostic factor.

A number of retrospective studies have evaluated the role of SABR for RCC oligoprogressive metastases. A retrospective study investigated the outcomes of 72 patients with IMDC favourable to intermediate risk disease and with up to 3 extracranial oligoprogressive sites after at least 3 months of disease control on systemic treatment [44]. Most subjects (82 %) had either 1 or 2 oligoprogressive sites. With a median follow-up of 21.7 months, PFS of 12.1 months and freedom from subsequent escalation of systemic therapy of 19.2 months was achieved. Grade 3 or higher toxicities were uncommon. Another retrospective analysis identified 36 patients with mostly 1 oligoprogressive metastasis (83.3 %) and clear cell RCC (97.2 %) [45]. Only 5.6 % of participants had IMDC poor risk disease. With a median follow-up of 20.4 months, SABR resulted in median modified PFS (SABR to the start of a subsequent systemic therapy, death or loss to follow-up) of 9.2 months. Although treatment was well tolerated in most, one patient developed grade 5 haemoptysis possibly related to SABR. On a univariate analysis, patients receiving immunotherapy at time of SABR exhibited a significantly longer median PFS (not reached by 28.4 months) compared to those receiving VEGF inhibitor (9.2 months) or mTOR inhibitor (2.2 months).

An Italian retrospective study assessed the outcomes of 28 patients with RCC oligoprogression whilst on first-line oral pazopanib [46]. Majority of patients had clear cell histology (93 %), ECOG 0–1 performance status (100 %) and 1–2 oligoprogressive sites (86 %). SABR was associated with a relatively short PFS of 4.55 months compared to other similar studies and this may be partly attributable to the lack of immunotherapy noting that SABR was delivered between 2010 and 2016 before immunotherapy was widely available for metastatic RCC.

The largest multi-centre retrospective study on the topic included 207 patients who had up to 5 oligorecurrent (42.9 %) or oligoprogressive (57.1 %) RCC metastases treated with SABR [47]. Approximately a third of patients received concurrent systemic therapy. With a median follow-up of 18.6 months, 3-year local control rates of 69.8 % and 3-year PFS of 50.8 % were achieved. On a multivariate analysis for both RCC oligorecurrent and oligoprogressive sites, total number of metastases was significantly associated with PFS, with >5 metastases resulting in lower PFS than 1–5 total metastases. In a separate retrospective single centre investigation by the same author, 44 patients with 74 RCC oligoprogressions were treated with SABR [48]. Approximately 90 % of patients had 1 or 2 sites treated with SABR. Median PFS was 9.8 months and higher number of treated metastasis (2–4 versus 1) was associated with worse PFS. Long disease-free interval of >60 months was associated with better outcomes than those with shorter intervals. Both studies indicate that the number of oligoprogressive and non-oligoprogressive metastases at time of SABR are potentially poor prognostic factors.

There are several other retrospective studies that included various states of metastatic RCC including oligometastases, oligorecurrent and oligoprogressive disease states [49–51]. They included mix of different clinical situations but did demonstrate an excellent LC and safety profiles. In addition, number of older retrospective studies of patients receiving SABR for oligoprogressive disease have been evaluated in a meta-analysis by Zaorsky et al. demonstrating excellent local control with minimal toxicity [29].

In summary, SABR for RCC oligoprogression can be well tolerated and can delay the need to alter systemic therapy. However, it is important to highlight that majority of the studies included patients with

only favourable or intermediate risk IMDC disease and the number of oligoprogressive diseases tended to be low at mostly 1–2. Most of the data is on clear cell metastatic RCC and so it is difficult to extrapolate the outcomes to non-clear cell RCC, especially sarcomatoid and collecting duct variants that are generally associated with worse outcomes. A retrospective analysis by Schoenhals et al. does suggest a better response with immunotherapy but further confirmation is required with larger prospective studies in the future [45]. In the setting of polymetastatic disease, prospective trials of immunotherapy and SABR combinations have shown mixed results with no strong indication of synergism [52,53].

Prognostic factors

In the future, more novel prognostic markers or tests may be developed to guide the clinician in determining who would benefit from SABR the most. Zengin et al. collected the genomic and/or transcriptomic sequencing data of 30 patients undergoing SABR for oligoprogressive RCC to identify prognostic markers [54]. In this preliminary study, genes related to antioxidant systems were significantly overexpressed in patients who demonstrated worse outcomes after SABR and genes associated with G2/M checkpoint, mitotic spindle and E2F targets were overrepresented in patients with better outcomes. The authors postulated that over-representation of the antioxidative system in the poor responders may be due to the reliance of radiotherapy on reactive oxygen species for effectiveness. However, considering that SABR is associated with excellent LC, other mechanisms may be involved.

SABR combined with short-course systemic therapy

SABR is associated with excellent rates of local control for RCC oligometastases. However, most progress outside irradiated regions and the addition of a short-course systemic therapy may potentially improve outcomes. To evaluate the safety of this concept, the RAPPORT single-arm multi-institutional phase 1/2 trial recruited patients with either favourable risk (56 %) or intermediate risk (44 %) with up to 5 RCC oligometastases after 2 or fewer lines of prior systemic therapy [55]. Seventy-seven percent of lesions were treated with 20 Gy in 1 fraction SABR whilst the rest received 30 Gy in 10 fractions (where 20 Gy in 1 fraction SABR was not feasible). This was followed by 8 cycles of Q3W pembrolizumab 200 mg. With a median follow-up of 28 months for 30 evaluable patients, 4 patients (13 %) developed grade 3 toxicity and there was no grade 4 or 5 toxicity. Freedom from local progression at 2-yr was 92 % and 2-yr PFS was 45 %. Though encouraging, larger trials are required to further study the role of SABR and short-course systemic therapy for RCC oligometastases.

There are several prospective studies that evaluated the safety of SABR in combination of systemic therapy for RCC polymetastases, whereby not all lesions were irradiated (Table 2). The rationale for such approach is to investigate the potential synergism between SABR and systemic therapy. However, there is no evidence yet that SABR enhances outcomes in metastatic renal cell carcinoma and further investigation is warranted.

Dose and fractionation

When SABR is delivered as the primary treatment modality for localised RCC, common dose fractionation schedules include 26 Gy in a single fraction and 30–45 Gy in 3 to 5 fractions [57]. In the RCC oligometastases and oligoprogression settings, various dose fractionations have been utilised in prospective clinical trials (Table 1), all with excellent local control. Most patients in these trials had dose fractionations with BED10 of at least 59.5 Gy and EQD2 = 49.58 Gy ($\alpha/\beta = 10$) though often higher doses were delivered. In comparison, retrospective study by Marveso et al. applied a lower median dose of 25 Gy in 5–10 fractions, with the most frequent schedule being 25 Gy in 5 (18 %,

Table 2
Prospective trials on SABR combined with systemic therapy.

Author (year)	Patient (n)	Systemic therapy	Toxicity	Outcomes
Oligometastases combined with systemic therapy				
Siva et al. (2022) [55]	30	Pembrolizumab	G1-2 63 % G3 13 % No G4-5 toxicity	Primary endpoint: Safety Well-tolerated overall Median follow-up 28 months 1-yr FFLP 94 % 2-yr FFLP 92 % 1-yr DPFS 63 % 2-yr DPFS 52 % 1-yr OS 90 % 2-yr OS 74 %
Oligometastases and Polymetastases combined with systemic therapy				
Dengina et al. (2019) [56]	17	Sunitinib (35 %) Nivolumab (29 %) Everolimus (18 %) Lenvatinib + Everolimus (6 %) Temsirolimus (6 %) Sorafenib (6 %)	G1 12 % No G2 or higher toxicity	Primary endpoint: Rate of any adverse events related to SBRT No G2 or higher toxicity Median follow-up 8 months Metastases treated with SABR: Complete response (29 %) Partial response (47 %) Stable (24 %) Non-irradiated control metastases: Stable (94 %) Progression (6 %)
Hannan et al. (2022) [52]	30	IL-2	22 grade ≥3 toxicity mostly or all related to IL-2 treatment No grade 5 toxicity	Primary endpoint: ORR 16 % 8 % complete response LC for SABR treated metastases 96.7 % Median PFS 2 months Median OS 37 months
Masini et al. (2022) [53]	69	Nivolumab	G3-4 26 % No G3-4 toxicity related to SABR	Primary endpoint: ORR 17 % (29 % for irradiated lesions and 12 % for non-irradiated lesions) Median follow-up 26 months Median PFS 5.6 months

FFLP = freedom from local progression, DPFS = distant progression free survival, ORR = overall response rate, OS = overall survival, PFS = progression free survival, LC = local control rate.

BED10 37.5 Gy), 45 Gy in 3 (14 %, BED10 112.5 Gy), 21 Gy in 1 (8 %, BED10 65.1 Gy) and 36 Gy in 3 (6 %, BED10 79.2 Gy) [28]. Perhaps, as a result of the lower BED10, 18 % of patients failed locally at 1 year, higher than reported on prospective clinical trials. Lesions with early progression were associated with lower EQD2 ($\alpha/\beta = 10$)(median EQD2 = 31.25) than those with partial response/complete response (median EQD2 = 36 Gy) or stable disease (median EQD2 = 54.3 Gy). Outside the oligometastases and oligoprogression setting, there have been several studies that evaluated dose fractionation for RCC. In a retrospective study of 46 patients with 95 RCC bone metastases treated with either SABR (50 metastases) or conventional external beam radiotherapy (45 metastases), control rates were significantly higher at 12 months for SABR (74.9 % versus 44.1 %) [58]. BED7 of at least 80 Gy was associated with superior clinical local control under multivariate analysis though not for radiographic local control. On a secondary analysis of 2 prospective studies on SABR for spinal RCC metastases, various dose fractionations of 30 Gy in 5, 27 Gy in 3 or 24 Gy in 1 fraction, were analysed [59]. Local control was superior for 24 Gy in 1 (BED10 81.60 Gy, $\alpha/\beta =$ 10 EQD2 68 Gy) when compared to 30 Gy in 5 (BED10 48 Gy, $\alpha/\beta = 10$ EQD2 40 Gy) and 27 Gy in 3 (BED10 51.3 Gy, $\alpha/\beta = 10$ EQD2 42.8 Gy). Zelefsky et al. retrospectively evaluated the outcomes of administering various dose fractionations for 105 RCC lesions [60]. The overall 3-year actuarial local progression-free survival was superior (88 %) for >24 Gy in single fraction SABR versus <24 Gy in single fraction SABR (21 %) and hypofractionation regimens of 20–30 Gy in 3 or 5 fractions (17 %).

Though further data is required to guide the optimal dose fractionation for RCC oligometastases and oligoprogression, at least a BED10 of 59.5 Gy (equivalent to ≥20 Gy in 1 fraction) would be advisable based on available prospective studies though higher doses (preferably BED10 >81.6 Gy, $\alpha/\beta = 10$ EQD2 >68 Gy, equivalent to ≥24 Gy in 1 fraction) should be delivered if safe to do so.

Conclusion

SABR for oligoprogressive and oligometastatic RCC is effective and generally well tolerated. In carefully selected patient groups, SABR has the potential to delay the commencement of or prolong current systemic therapy or in some situations, avoid it altogether. Larger prospective trials are required to further define its benefits and improve the identification of patients who would benefit the most from this promising treatment.

CRediT authorship contribution statement

Chang David: Writing – original draft. **Ali Muhammad:** Writing – review & editing. **Udovicich Cristian:** Writing – review & editing. **Tran Ben:** Writing – review & editing. **Azad Arun:** Writing – review & editing. **Au Lewis:** Writing – review & editing. **Spain Lavinia:** Writing – review & editing. **Perera Marlon:** Writing – review & editing. **Siva Shankar:** Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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