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Radiotherapy for renal cell carcinoma: renaissance of an overlooked approach

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Abstract | Conventional radiotherapy previously had a limited role in the definitive treatment of renal cell carcinoma (RCC), owing to the disappointing outcomes of several trials and the perceived radioresistance of this type of cancer. In this context, radiotherapy has been relegated largely to the palliation of symptoms in patients with metastatic disease, with variable rates of response. Following the availability of newer technologies that enable safe delivery of high-dose radiotherapy, stereotactic ablative radiotherapy (SABR) has become increasingly used in patients with RCC. Preclinical evidence demonstrates that RCC cells are sensitive to ablative doses of radiotherapy (≥8–10 Gy). Trials in the setting of intracranial and extracranial oligometastases, as well as primary RCC, have demonstrated excellent tumour control using this approach. Additionally, an awareness of the capacity of high-dose radiation to stimulate antitumour immunity has resulted in novel combinations of SABR with immunotherapies. Here we describe the historical application of conventional radiotherapy, the current biological understanding of the effects of radiation, and the clinical evidence supporting the use of ablative radiotherapy in RCC. We also explore emerging opportunities to combine systemic targeted agents or immunotherapies with radiation. Radiotherapy, although once an overlooked approach, is moving towards the forefront of RCC treatment.

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Radiotherapy is an important and effective modality that is widely used in the treatment of many of the commonest malignancies. However, the use of radiotherapy is currently limited in patients with kidney cancer, with estimates of the current level of use, relative to the potential optimal level of use, being approximately 27% based on a review of evidence-based guidelines[1]. The long-standing preconception that renal cell carcinoma (RCC) is biologically radioresistant was entrenched following reports from early preclinical studies indicating that isolated RCC cells were among the most radioresistant of all cell types to conventional doses of radiotherapy *in vitro*[2]. However, more than 30 years ago, radiotherapy was also proven to be highly effective in the palliation of symptoms in patients with advanced-stage RCC, particularly when higher doses of radiation are used[3,4]. With the advent of technologies enabling the precise delivery of ultra-high-dose stereotactic 'ablative' radiation (SABR)[5], local antitumour efficacy comparable to that of surgery has been consistently observed in other types of cancer[6,7]. These observations raise an important question as to why radiotherapy remains an overlooked approach for the treatment of patients with RCC. In this Review we describe the historical application of conventional radiotherapy for the treatment of RCC and the current biological understanding of the effects of radiation, in addition to the available clinical evidence supporting the use of ablative radiation for the treatment of patients with primary and/or metastatic RCC. We also provide an overview of the evidence supporting the combination of ablative radiotherapy with systemic targeted therapies and explore emerging opportunities, such as the combination of immunomodulation with radiotherapy.

Conventional radiotherapy in RCC

Preoperative (neoadjuvant) radiotherapy for primary disease. The application of conventionally fractionated radiotherapy in patients with RCC has been investigated for >50 years. The use of conventionally fractionated radiotherapy in the setting of RCC, defined as doses per fraction of ≤2 Gy, has been impeded by preclinical evidence[2] suggesting a high level of inherent radioresistance, in addition to a lack of any demonstrable benefit of radiotherapy in clinical studies[8]. In one of the earliest randomized studies to evaluate the use of preoperative radiotherapy followed by radical nephrectomy, compared with radical nephrectomy alone, in patients

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Key points

- Conventional radiotherapy has a limited role in the treatment of renal cell carcinoma (RCC), and is largely limited to the palliation of symptoms of metastatic disease
- Evolving technology has facilitated the safe delivery of ablative doses of radiotherapy, in fewer fractions, and has been increasingly adopted in the clinical management of patients
- Preclinical and clinical evidence demonstrates that RCC is sensitive to ablative doses of radiation (typically ≥8 Gy per fraction), with tumour control rates of approximately 90%
- High-dose radiation seems to have an immunogenic effect in patients with RCC, and might explain the abscopal effects sometimes observed with this approach
- Combinations of ablative radiotherapy with systemic targeted therapies or immunotherapies are promising approaches that might improve outcomes

with primary RCC, investigators reported the outcomes of a total of 126 patients[9]. The preoperative radiotherapy group received a 30-Gy dose of radiation in 15 fractions at 2 Gy per fraction. This low dose of radiation, relative to that used in patients with other types of cancer, was selected owing to concerns regarding the risk of liver damage in patients with right-sided tumours. The primary end point of this study was 5-year overall survival and no significant benefit of preoperative radiotherapy was observed compared with radical nephrectomy alone; although, the authors noted the improved overall survival duration of patients in the subgroup with tumour-infiltrating intrarenal or extrarenal veins and/or lymph vessels. A further analysis of the outcomes of patients in this cohort revealed that the rate of complete resection was significantly better among patients in the radiotherapy arm, and this resulted in a reduced frequency of metastases, delayed onset of metastases, and an improved short-term prognosis. Ultimately, this study failed to provide evidence supporting the use of radiotherapy in patients with localized RCC. The results of a second randomized trial were published a few years later[10]. This trial had a cohort of 88 patients in total, with patients in the preoperative radiotherapy arm receiving 33 Gy over a 3-week period, which is also considered a relatively low dose. The 5-year overall survival duration of patients in this study was found to be unexpectedly lower among those in the preoperative radiotherapy arm (47% versus 63% among those in the radical nephrectomy only arm, although no statistically significant differences were observed). Furthermore, subgroup analysis failed to reveal any specific group of patients that benefited from preoperative radiotherapy. Accordingly, interest in the use of preoperative radiotherapy waned following these results.

Postoperative (adjuvant) radiotherapy for primary disease. Around the same time that data from trials investigating preoperative use of radiotherapy[9,10] were published, similar randomized trials were being conducted in the postoperative setting. Finney and colleagues[11] published data from a randomized group of patients with high-risk disease who had either positive surgical margins or inferior vena cava involvement that underwent radical nephrectomy either with ($n = 52$) or without ($n = 48$) subsequent radiotherapy. No improvement in

overall survival was observed with use of radiotherapy. In another randomized study the efficacy of postoperative radiotherapy was investigated using a dose of 50 Gy in 20 fractions delivered to the tumour bed and nodal regions in patients with stage 2 or 3 RCC[12]. The overall (crude) relapse rate was 48% and this rate did not differ significantly between patients in either arm. In addition, high rates (44%) of gastrointestinal toxicities affecting the stomach, duodenum and liver were observed, as well as unacceptable mortality rates (20%) among patients in the radiotherapy arm. A 2010 meta-analysis that included data from seven studies revealed an improvement in the extent of local control with use of postoperative radiotherapy, albeit without any significant survival benefit; however, five of the seven studies included were retrospective in design[8]. Overall, the analysis highlighted the substantial limitations of the various studies including the use of non-conformal radiotherapy techniques, inappropriate dosing, and outdated technology, thus highlighting the need for more contemporary randomized series in order to better inform the future management of patients with RCC.

Intraoperative radiotherapy for primary disease. The use of intraoperative radiotherapy in patients with primary RCC, particularly in those with locally recurrent and/or advanced-stage disease, has also been reported. Data from one of the largest series with outcomes currently available, consisting of 98 patients from nine different institutions, revealed that the 5-year disease-specific and disease-free survival rates compare favourably to those of patients in surgical series without use of intraoperative radiotherapy[13]. Also, of the approximately 70% of patients whose disease eventually relapsed, only 11% of these were in-field relapses. However, given the paucity of data available on the outcomes following this approach, intraoperative radiotherapy for RCC should still be considered experimental. When assessing the overall body of evidence for use of conventionally fractionated radiotherapy in the definitive management of patients with primary RCC, intraoperative use of radiotherapy seems to have only limited utility.

Conventional palliative radiotherapy

In the palliative setting, conventional radiotherapy can be used to alleviate pain, control the severity of neurological symptoms or to ameliorate haematuria. The outcomes of a number of retrospective studies[3,4,14–17] and a few prospective trials[18–21] generally indicate response rates of >50% among patients with metastatic RCC receiving conventionally fractionated radiotherapy. However, a high level of heterogeneity in response rates of patients in the various studies is apparent, with rates >80% and <20% reported from different cohorts. Lee and colleagues[20] reported the outcomes of a multicentre phase II trial, in which 83% of patients had site-specific pain relief after receiving conventional radiotherapy at a dose of 30 Gy in 10 fractions, with a median response duration of 3 months. Global quality of life (QOL) was also found to improve in 33% of patients. However, the outcomes of other

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SABR
Stereotactic ablative radiotherapy, refers to high-dose per fraction, conformal radiotherapy, typically delivered in one or a few sessions.

Gy
Gray, the unit of radiation, used in the International System of Units, defined in joules per kilogram.

α-subunit of hypoxia inducible factor
(HIF-1α). A subunit of the transcription factor hypoxia inducible factor-1, which has a critical role in the management of the cellular response to hypoxia, and can stimulate transcription of a number of genes that are responsible for various functions, including angiogenesis, cell proliferation and survival.

von Hippel Lindau (VHL) tumour suppressor gene
A regulator of tumorigenesis located on chromosome 3, which is subject to dominant inheritance and associated with cancer growth when lost or mutated.

E3 ubiquitin ligase
A protein that is involved in the regulation of cell trafficking, DNA repair, and signalling, as well as cell-cycle control.

Gap 2 (G2) phase
G2 phase is a phase of the cell cycle that directly precedes mitosis, during which the cell undergoes rapid growth and protein synthesis. The checkpoint between G2 and mitosis results in cell-cycle arrest during the G2 phase in response to stressors such as oxidative stress or radiation.

studies in this setting are less impressive. A prospective study with a larger cohort of patients, albeit with either RCC or melanoma, revealed a 57% improvement in reported levels of pain following the delivery of radiotherapy to symptomatic bony metastases, with a shorter median response duration of 2.4 months[21]. Data published by Onufrey and colleagues[3] revealed an apparent dose–response relationship, demonstrating increasing efficacy with dose escalation from 20 Gy to 60 Gy. This finding is supported by data from another retrospective study, in which 86% of patients derived palliative benefit from radiation therapy delivered to metastatic lesions at various locations (including bone, soft tissue, spinal cord, brain and lungs), with complete response rates improving significantly with increased doses of radiation[4]. Reports from these studies did not contain any descriptions of adverse events associated with radiotherapy or whether the risk of adverse events increased with higher radiation doses. Wilson and colleagues[15] reported that patients with bone metastases have the longest responses durations, and those with brain metastases have the shortest. Thus, palliative radiotherapy, delivered to either primary or metastatic lesions, has a well-defined role in controlling the localized symptoms of advanced-stage RCC.

Changing paradigm: ablative radiation
Biological rationale for ablative approaches. With the consistently unimpressive rates of effective tumour control using conventional radiotherapy, attention turned to the evaluation of ablative regimens. These modern radiotherapy approaches have gained traction in the treatment of various other malignancies, such as those of the lung, liver and spine[5]. SABR refers to the delivery of radiation doses typically in excess of 8–10 Gy per fraction[22]. While requiring greater precision to deliver safely than low-dose radiotherapy, this approach might

overcome several of the molecular mechanisms that might be responsible for the inherent radioresistance of RCC cells observed *in vitro* (BOX 1)[2,23].

Hypoxia-inducible factor-1 (HIF-1α) in RCC. The expression of the α-subunits of the hypoxia-inducible factors (HIF-1α) is increased under hypoxic conditions and might be associated with hypoxia-related radiation resistance in patients with RCC. Loss of function of the von Hippel–Lindau tumour suppressor gene (*VHL*), which regulates the expression of HIF-1α, is one of the commonest characteristics of patients with RCC[24]. *VHL* has been found to be mutated or methylated in >90% of patients with clear cell RCC. VHL is the E3 ubiquitin ligase for HIF-1α, which, when functional, promotes the regulated degradation of HIF-1α protein. Thus, loss of VHL function leads to high levels of HIF-1α and the consequent activation of HIF-1α-dependent signalling. Conversely, decreased HIF-1α levels have been shown to lead to significant increases in radiosensitivity and G2 cell-cycle arrest in RCC cell lines[25]. Moeller and colleagues[26] demonstrated that activation of HIF-1α signalling during the course of fractionated radiation therapy initiates 'pleotropic adaptive responses' in both tumour cells and in the microvascular network. These adaptive responses, as well as the stimulation of endothelial cell survival by HIF-1α[26], promote resistance to conventionally fractionated radiotherapy in patients with RCC.

Ablative-doses of radiation might overcome inherent radiation resistance. Patients with RCC generally have a low response rate to conventional radiotherapy but have a high response rate to high dose-per-fraction schedules, suggesting that the dose/fractionation sensitivity of RCC cells (the so called α/β ratio) might be lower than that of other tumour types. Generally, cell lines with an α/β ratio >10 are considered radiosensitive. Ning and colleagues[27] conducted a study in which the survival of two widely used human RCC cell lines, Caki-1 and A498, was investigated using clonogenic assays. When cells were irradiated using 2-Gy conventional fractions, only a small proportion of cell death was noted, compared with an exponentially higher rate of cell death at >6 Gy per fraction. In this study, the α/β ratios of Caki-1 and A498 cells were 6.9 and 2.6 respectively. However, several factors such as the dose rate, and other interlaboratory variations might affect the estimated α/β ratio. Additionally, the findings of *in vitro* studies do not always reflect the *in vivo* or clinical situation. Ablative doses of radiotherapy are theoretically an attractive approach for RCC as they are more likely to induce cell death through alternative mechanisms, rather than creating a mitotic catastrophe as a result of DNA damage. These alternative mechanisms include activation of ceramide-mediated apoptosis as well as damage to vascular endothelial cells, resulting in tumour hypoxia[4,28]. Fuks and Kolesnick[29] showed that when high-dose single-fraction radiotherapy (≥8 Gy) is used, endothelial cell apoptosis contributes to tumour cell death. Furthermore, sphingomyelin phosphodiesterase (SMPD1; also known as acid

Box 1 | Advantages and disadvantages of SABR in patients with primary RCC

Advantages
- Can be adminsitered as an outpatient treatment
- Safe and minimally toxic
- Provides promising local control rates
- No definite size limitations
- Not limited by tumour location
- Might stimulate or promote antitumour immunity
- Suitable for patients with surgically unresectable tumours
- Feasible in patients with a functionally solitary kidney

Disadvantages
- Does not enable tissue sampling for histological confirmation
- Limited prospective evidence for outcomes
- Safe lower limit of renal function pre-SABR remains undefined
- Optimal dose and fractionation regimen remains undefined
- Ideal treatment response assessment modality not yet established
- Very stringent technical and quality assurance requirements
- Requirement of intensive training of the whole radiotherapy team

SABR, Stereotactic ablative radiotherapy

sphyngo-myelinase) has an important role in the generation of the proapoptotic second messenger ceramide. This membrane phospholipid component initiates the transmembrane signalling cascades that result in apoptosis. By contrast, when low-dose fractionated radiotherapy (1.8–3.0 Gy per fraction) is used, endothelial cell damage does not increase the extent of tumour cell death because the signalling pathway activated at this dose is inhibited by activated HIF-1α[29]. This mechanism might partially explain the increased efficacy provided by, and, therefore, interest in, ablative-dose radiotherapy as a treatment for RCC.

Signal transducers and activators of transcription (STATs). STAT transcription factors, of which a total of seven have been identified, can be activated by various extracellular stimuli, including epidermal growth factor receptor signalling, and cytokines[30]. Hui and colleagues[31] first reported the overexpression of STAT1 in human RCC tumour tissue samples and demonstrated that inhibition of STAT1 signalling by fludarabine or siRNA increases the radiosensitivity of RCC cells. Zhu and colleagues[32] also demonstrated that overexpression of STAT1 in human RCC cells is associated with chemoradioresistance. These findings indicate that targeted inhibition of STAT1 might sensitize RCC cells to chemotherapy and/or radiotherapy. Similar results were observed in another study, which demonstrated that zoledronic acid has a direct *in vitro* radiosensitizing effect on RCC cells by enhancing radiotherapy-induced caspase-3 activation[33]. This effect is achieved by downregulation of STAT1 expression, thereby potentiating the caspase-3-mediated apoptosis pathway[33]. The molecular mechanisms by which STAT1 can influence cellular responses to radiation are currently not well understood; however, targeting STAT1 might be a promising future strategy for optimizing the efficacy of radiotherapy in patients with RCC.

Delivery of ablative radiation
In the past, the delivery of high doses of radiation per fraction was avoided owing to the risks of late-onset adverse effects. However, in the modern era, the introduction of precision techniques such as intracranial stereotactic radiosurgery (SRS) and SABR (FIG. 1) have enabled the safe delivery of much higher doses per fraction than conventional techniques. These techniques rely on robust image-guided selection of the radiation field, tumour visualization, patient immobilization, and advanced planning techniques that use a higher number of beam entry points than conventional techniques. These modifications result in highly conformal dose delivery that sculpts around the tumour, with steep dose gradients that limit the radiation dose delivered to the surrounding organs at risk.

Efficacy of stereotactic radiotherapy in patients with metastatic RCC. Intracranial SRS has a well-established role in the treatment of brain metastases in patients with RCC. Following the development of intracranial and extracranial stereotactic techniques, increasingly impressive outcomes have been reported. In the context of RCC, rates of local control are typically exceptional compared with those provided by conventionally fractionated radiotherapy. The findings of a systematic review and meta-analysis published in 2015 (REF. 34) indicate that intracranial SRS provides a weighted local control rate of 92%, with median overall survival durations ranging from 6.7 to 25.6 months (TABLE 1). These data encompass 1,301 patients with >3,433 treated metastases. The reported incidences of grade 3–4 toxicities ranged from 0% to 6% of patients. Similarly, for patients with extracranial RCC metastases treated using SABR, the conclusions of this systematic review[34] indicate a weighted local control rate of 89%, with median overall survival durations ranging from 11.7 to 22 months. The available published data include 807 patients with RCC with a total of 1,326 treated metastases. Reported rates of grade 3–4 toxicities range from 0% to 4% (TABLE 2).

The use of stereotactic radiotherapy to treat patients with oligometastatic RCC is attracting increasing levels of interest. Oligometastatic RCC is variably defined in the literature as having up to three or five metastases[34–37]. In these patients, the use of metastasis-directed therapy is postulated to not only improve the level of local disease control and control of symptoms, but might also translate to durable systemic control, improved overall survival outcomes and, in some patients, even cure. Ranck and colleagues[35] reported the outcomes of 18 patients, of whom 33% had oligometastatic disease and were treated 'radically' with stereotactic body radiotherapy (SBRT) targeting all known sites of disease. These patients had an impressive 2-year overall survival rate of 85%. Wersall and colleagues[38] reported the survival outcomes of patients treated with SABR for oligometastatic disease to be superior to those of patients receiving the same treatment for more-widespread disease (37 versus 19 months, respectively). However, further prospective research is still required, to determine the possibility of defining and identifying a subgroup of patients in whom aggressive local control with SABR can lead to long-term survival.

Overall, intracranial SRS and extracranial SABR seem to be highly effective and safe approaches for the control of metastases in patients with RCC. However, patient selection is paramount in order to justify the resources currently required to deliver stereotactic radiotherapy safely. These techniques are likely to be of limited utility in patients with widely disseminated disease with inadequate responses to systemic therapy, as these patients are unlikely to survive long enough to benefit from the more durable local control provided by irradiation of the metastases. Similarly, patients with severely symptomatic disease might instead benefit from conventional radiotherapy or use of extirpative approaches, as stereotactic approaches often require additional time for planning and/or quality assurance. Additionally, large doses-per-fraction might result in initial oedema or worsening of pre-existing inflammation. However, in selected patients with limited metastases, SRS and SABR are effective, convenient and safe approaches that enable durable control of RCC to be achieved.

α/β ratio
A measure of a tissue or tumour response to a specific radiation dose.

Caki-1
A human clear cell RCC cell line derived from a patient of white ethnicity. This cell line has an epithelial morphology and provides a useful model for the study of kidney cancer.

A498
A commonly used renal cell carcinoma cell line typically used to model the behaviour of clear cell RCC.

SMPD1
Sphingomyelin phosphodiesterase 1, an enzyme that is found in lysosomes and has a role in the conversion of sphingomyelin to ceramide, and in maintaining the normal structure and function of the cell.

SRS
Stereotactic radiosurgery, describes a high, single-fraction, ablative dose of radiotherapy, delivered in a very conformal, precise manner.

SBRT
Stereotactic body radiotherapy, high dose-per-fraction ablative and highly conformal radiotherapy typically delivered as a single, or small number of fractions to an extracranial site. Often used interchangeably with SABR.
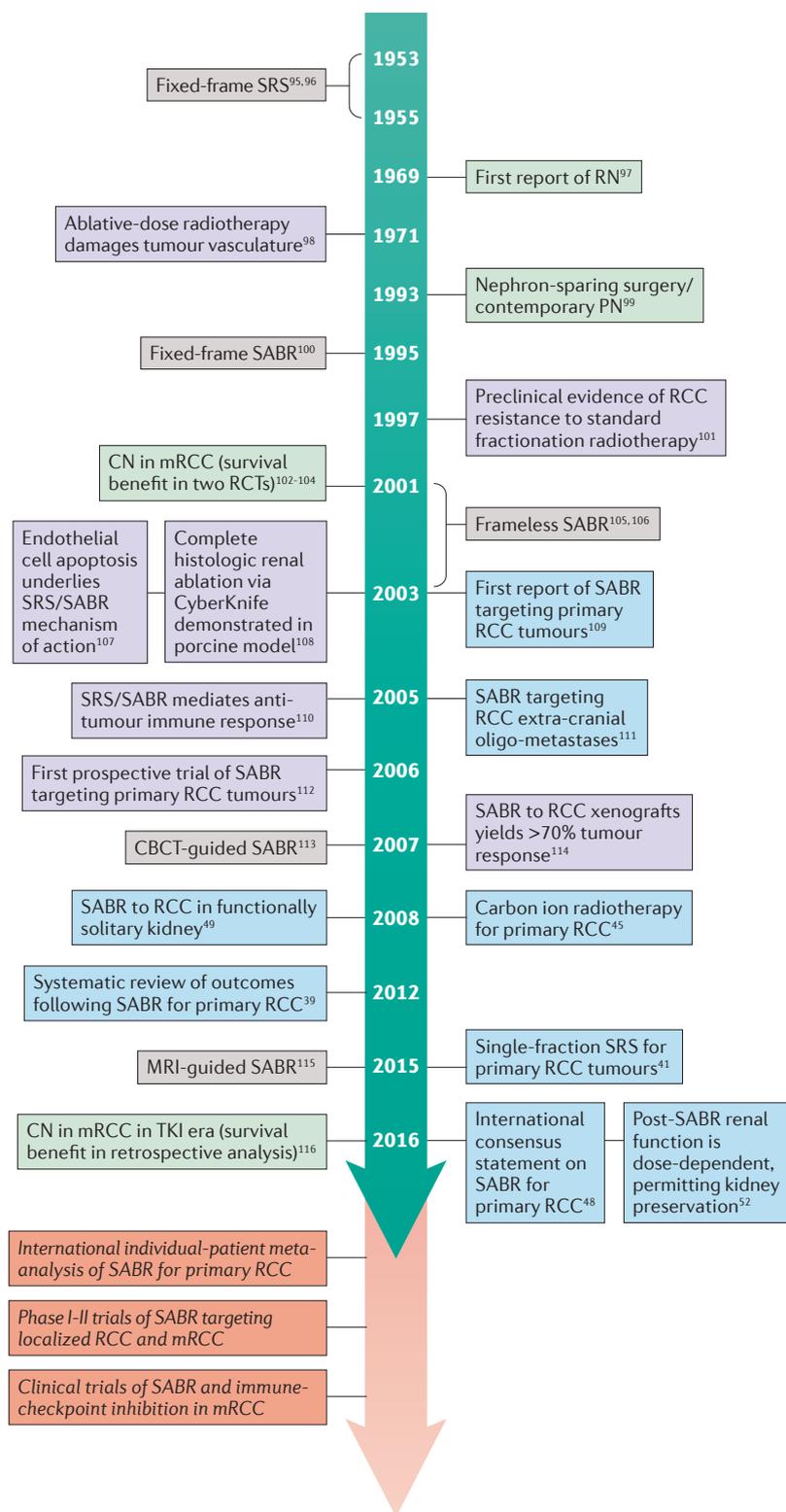
Figure 1 Timeline (left column)

1953 — Fixed-frame SRS[95,96]

1955

1969 — First report of RN[97]

1971 — Ablative-dose radiotherapy damages tumour vasculature[98]

1993 — Nephron-sparing surgery/ contemporary PN[99]

1995 — Fixed-frame SABR[100]

1997 — Preclinical evidence of RCC resistance to standard fractionation radiotherapy[101]

2001 — CN in mRCC (survival benefit in two RCTs)[102-104]

— Frameless SABR[105,106]

2003 — Endothelial cell apoptosis underlies SRS/SABR mechanism of action[107] — Complete histologic renal ablation via CyberKnife demonstrated in porcine model[108] — First report of SABR targeting primary RCC tumours[109]

2005 — SRS/SABR mediates anti-tumour immune response[110] — SABR targeting RCC extra-cranial oligo-metastases[111]

2006 — First prospective trial of SABR targeting primary RCC tumours[112]

2007 — CBCT-guided SABR[113] — SABR to RCC xenografts yields >70% tumour response[114]

2008 — SABR to RCC in functionally solitary kidney[49] — Carbon ion radiotherapy for primary RCC[45]

2012 — Systematic review of outcomes following SABR for primary RCC[39]

2015 — MRI-guided SABR[115] — Single-fraction SRS for primary RCC tumours[41]

2016 — CN in mRCC in TKI era (survival benefit in retrospective analysis)[116] — International consensus statement on SABR for primary RCC[48] — Post-SABR renal function is dose-dependent, permitting kidney preservation[52]

International individual-patient meta-analysis of SABR for primary RCC

Phase I–II trials of SABR targeting localized RCC and mRCC

Clinical trials of SABR and immune-checkpoint inhibition in mRCC

Figure 1 | **Timeline of advances in radiotherapy for the management of RCC.** Reports of SABR targeting primary RCC tumours are shown in blue, developments in radiotherapy technology are shown in grey, advances in surgery are shown in green, and discoveries in basic science are shown in purple. Future and/or ongoing studies are shown in red. CBCT, cone-beam computerized tomography; CN, cytoreductive nephrectomy; PN, partial nephrectomy; RCTs, randomized controlled trials; RN, radical nephrectomy; SABR, stereotactic ablative radiotherapy; SRS, stereotactic radiosurgery; TKI, tyrosine-kinase inhibitor.

Efficacy of SABR in primary RCC. Technological advances in image guidance and motion management in patients receiving radiotherapy have facilitated the application of SABR to the treatment of patients with primary RCC. The use of SABR in these patients is an exciting and rapidly developing aspect of radiotherapy. Specific challenges exist, given that delineation of the tumour mass from the surrounding nonmalignant kidney tissue is often difficult at the time of treatment delivery, and the insertion of fiducials as surrogates for tumour position is complicated by the risks of haemorrhage in patients with highly vascular tumours. No data from randomized trials evaluating the efficacy of SBRT in patients with primary RCC are currently available. The majority of reported studies are retrospective, with data from a few prospective trials beginning to emerge (TABLE 3). A systematic review was published in 2012, consisting of 10 studies comprising 126 patients with inoperable RCC treated with SBRT[39]. Three studies were prospective in design and seven were retrospective. The weighted local control rate obtained across all studies was 92.9% with a weighted rate of grade ≥3 toxicities of 3.8%, although most studies had a limited follow-up duration (median 2–3 years). More recent prospective studies[40–43] have continued to indicate high short-term and medium-term rates of local control that are typically >90%, with low toxicity rates, as seen in previous studies. The main acute toxicities reported in the literature are self-limiting acute nausea and fatigue, followed by radiation dermatitis and enteritis. Reported severe toxicities include renal toxicities, duodenal ulceration and skin toxicities, although the overall rates of all of these toxities were low (in <5% of patients)[42,44,45].

The noninvasive approach enabled by SABR provides distinct advantages compared with alternative thermal ablation techniques. These include a lack of specific size limitations for the primary tumour, the capacity to treat tumours located in close proximity to the collecting vessels and ureter, and the ability to treat tumours at any location within the affected kidney. SABR is inherently tissue sparing and is, therefore, an attractive approach in patients with complex renal lesions, in which total nephrectomy might otherwise be required in patients whose suitability for such invasive surgery is borderline (FIG. 2).

Preservation of renal function and response assessment after SABR for primary RCC. Post-treatment response assessment and preservation of renal function are two key areas of ongoing investigation. The kinetics of tumour growth are particularly variable after SABR and are often dependent on the growth rate of the tumour before treatment[46]. Many lesions remain stable or partially sensitive according to conventional CT-based criteria, such as Response Evaluation Criteria In Solid Tumours (RECIST)[47]. Contrast enhancement, a feature associated with treatment failure in patients undergoing thermal ablation, is persistent after SABR and typically accumulates over time[46]. In contrast to direct thermal ablation, SABR does not immediately disrupt tumour and stromal architecture, but instead

Table 1 | **Intracranial stereotactic radiation surgery in patients with metastatic RCC**

Study (*n* = number of patients)	Metastases (% of patients)	Marginal dose (Gy)	Outcomes	Toxicities
Amendola *et al.* (2000)[117] *n* = 22	Brain:18%; extracranial: 91%	Mean 18 (15–22): unknown if marginal dose	Crude local control 91%; median OS 8 months	Radiation necrosis in 5% of patients
Bates *et al.* (2015)[118] *n* = 14	Brain: 52%; extracranial: 76%	NR (14.5–20 isocentre)	Crude local control 79%, median OS 8.3 months versus 8.5 months in patients receiving SRS or SRS plus WBRT	NR
Cochran *et al.* (2012)[119] *n* = 61	Brain: 46%; extracranial: 90%	Median 20 (13–24)	1-year local control 93%; median OS duration 9 months; 1-year OS rate 38%, after a median follow-up duration 9 months*	Radiation-induced oedema or necrosis in 10% of patients; haemorrhage in 3% of patients
Fokas *et al.* (2010)[120] *n* = 68	Brain: 62%; extracranial: 32%	Median 19 (15–22)	Crude local control 75%[‡]; 1-year local control 83%*	Grade ≥3 acute toxicities in 3% of patients receiving SRS only; in 3% of patients receiving SRS + WBRT; grade 3 late-onset toxicities in 4% of patients receiving SRS only, 5% (2/68) with SRS + WBRT, overall 6% late-onset toxicities
Goyal *et al.* (2000)[121] *n* = 29	Brain: 62%; extracranial: 86%	Median 18 (7–24)	Crude local control 92%; 1-year local control 85%; median OS duration 7 months; 1-year OS rate 36% after a median follow-up duration of 7 months	Radiation necrosis in 14% of patients
Hernandez *et al.* (2002)[122] *n* = 29	Brain: 55%; extracranial: 100%	Median 17 (13–30)	Crude local control 100%; 1-year local control 100%; median OS duration 7 months after a median follow-up duration 7 months	NR
Hoshi *et al.* (2002)[123] *n* = 42	Brain: 52%; extracranial: 98%	Median 25 (20–30)	Crude local control 93%[‡]; 1-year local control 91%; median OS duration 13 months;1-year OS rate 45% after a median follow-up duration of 10 months	1 mortality secondary to tumour haemorrhage
Ikushima *et al.* (2000)[124] *n* = 10	Brain: 90%; extracranial: 90%	All 42 in 7 fractions, to isocentre	Crude local control 88%; 1-year local control 90%; median OS duration 26 months; 1-year OS rate 90% after a median follow-up duration of 5 months	0% of patients had acute or late-onset toxicities
Ippen *et al.* (2015)[90] *n* = 66	Brain: 59%; extracranial: 96%	22 in 1 fraction (12–30 Gy in 1–5 fractions)	Crude local control 93% in SRS group, 94% in SRS + surgery group, 88% in SRS + WBRT group; 1-year local control 84% in SRS group; median OS duration 13.9 months; 1-year OS rate 55% after a median follow-up duration of 10 months	Acute grade ≥3 toxicities in 4.5% of patients; late-onset grade ≥3 toxicities in 1.5% of patients
Janssen *et al.* (2015)[125] *n* = 36	Brain: 56%; extracranial: 61%	Range from 16–23	NR	NR
Kano *et al.* (2011)[93] *n* = 158	Brain: 51%; extracranial: 77%	Median 18 (10–22)	Crude local control 91%; 1-year local control 87%; median OS duration 8 months; 1-year OS duration 38% after a median follow-up duration of 8 months*	Symptomatic adverse effects observed in 7% of patients; tumour haemorrhage observed in 6% of patients; of note, clinical follow up data were only available from 108/158 patients
Kim *et al.* (2012)[126] *n* = 46	Brain: 57%; extracranial: 83%	Mean 21 (12–25)	Crude local control 85%; median OS duration 10 months; 1-year OS rate 41%	Symptomatic tumour haemorrhage in 2% of patients; hydrocephalus in 2% of patients
Majewski *et al.* (2015)[127] *n* = 51	NR	NR	Crude local control 94%; median OS duration 9.4 months; 1-year OS rate 40%	NR

Table 1 (cont.) | **Intracranial stereotactic radiation surgery in patients with metastatic RCC**

Study (n = number of patients)	Metastases (% of patients)	Marginal dose (Gy)	Outcomes	Toxicities
Muacevic et al. (2004)[128] n = 85	Brain: 35%; extracranial: 67%	Median 21 (15–35)	Crude local control 94%; 1-year local control 94%; median OS duration 11 months; 1-year OS rate 50% after a median follow-up duration of 11 months	Mortality secondary to tumour haemorrhage in 4% of patients; symptomatic radiation-associated toxicities in 13% of patients
Nicolato et al. (2013)[129] (abstract) n = 130	NR	Mean 21 (13–26)	Crude local control rate 88%; median OS duration 25 months; OS rate 64% at 18 months	Permanent complications seen in 3.4% of treated lesions (2 owing to perilesional oedema, 4 owing to post-radiosurgical imaging changes)
Noel et al. (2004)[94] n = 28	Brain: 43%; extracranial: 100%	Median 17 (11–22) prescribed to isocentre	Crude local control rate 97%; 1-year local control rate 93%; median OS duration 11 months; 1-year OS rate 48% after a median follow-up duration of 14 months	Radionecrosis, seizure and tumour haemorrhage reported in 4% of patients
Payne et al. (2000)[130] n = 21	Brain: 81%; extracranial: 67%	Mean 20 (11–40)	Crude local control rate 100%; median OS duration 8 months	No radiation-associated toxicities reported
Rades et al. (2015)[131] n = 28	Brain: 57%; extracranial: 61%	Modal 20 Gy in 1 fraction (16–20)	1-year local control 50% (for 16–18 Gy doses) and 81% (for 20 Gy doses); 1-year OS rate 16% (16–18 Gy); 56% (20 Gy)	NR
Samlowski et al. (2008)[36] n = 32	Brain: 44%; extracranial: 100%	NR (15–24)	Crude local control 86%; 1-year local control 86%; median OS duration 10 months; 1-year OS rate 43%	6% of patients had symptomatic radiation necrosis
Schlöggl et al. (1998)[89] n = 23	Brain: 57%; extracranial: 57%	Median 18 (8–30)	Crude local control 98%; median OS duration 11 months; 1-year OS rate 48%	9% of patients had an increase in the severity of perifocal oedema; 4% of patients had radionecrosis
Seastone et al. (2014)[91] n = 166	Brain: 76%; extracranial: NR	Modal 24 (12–35)	Crude local control 90%; 1-year local control 75%	NR
Shuto et al. (2010)[132] n = 105	NR	Mean 22 (8–30)	Crude local control 84%; 1-year local control 71%*; median OS duration 12 months after a median follow-up duration of 7 months*	2% of patients had haemorrhage requiring surgery; 5% of patients had peritumoural oedema
Staehler et al. (2010)[65] n = 51	NR	Median 20 (20–20)	1-year local control 100%; median OS duration 11 months; 1-year OS rate 51% after a median follow-up duration of 16 months	4% of patients had grade 2 tumour haemorrhage; 6% of patients had grade 2 convulsions

NR, not reported; OS, overall survival; RCC, renal cell carcinoma; SRS, stereotactic radiation surgery; WBRT, whole-body radiation therapy. *Information obtained via personal correspondence; ‡according to number of patients rather than targets.

CKD
Chronic kidney disease, usually a progressive irreversible decline in kidney function, typically over a period of months to years

relies on ongoing and often prolonged evolution of cell death. Ongoing tumour shrinkage can be observed for years following SABR[42,46]. As such, routine analysis of post-treatment biopsy samples can give misleading indications of the extent of tumour shrinkage and is not a recommended approach[48]. SABR seems to be effective, with reports indicating that this approach is well tolerated without the need for renal replacement therapy in patients with single functional kidneys[49,50]. However, patients undergoing SABR who also have pre-existing stage 4–5 chronic kidney disease (CKD) are at risk of considerable renal impairment following treatment, with a report published in 2016 describing two patients with severe baseline CKD, both of

whom required post-SABR dialysis[51]. A predictive model has been proposed to enable the prediction of the extent of renal preservation, based on the dose of SABR delivered to nonmalignant kidney tissues, which might provide a practical tool for treatment planning[52].

Current status and future directions of SABR for primary RCC. Further investigations of the efficacy and safety of SABR in patients with primary RCC are warranted before this approach can be considered a standard treatment option alongside surgery for patients with primary RCC. However, the findings of prospective clinical trials, albeit those involving small

Table 2 | **Review of extracranial SABR literature for metastatic RCC**

Study (n = number of patients)	Locations of metastases	Marginal dose (Gy)	Outcomes	Toxicities
Altoos et al. (2015)[133] n = 34	27 thorax, 3 skin and soft tissue, 6 abdomen	Modal 50 Gy in 5 fractions	1-year local control 100%; median follow-up duration of 16 months	Fatigue was the commonest grade 1 toxicity (in 48% of patients); pneumonitis and mucositis were the commonest grade 2 toxicities (in 6% of patients); only 1 patient had a grade ≥3 toxicity as defined by NCI CTCAEv4 criteria; these data include toxicities at sites treated with conventional EBRT
Amini et al. (2015)[134] n = 46	16 spine, 15 bony pelvis, 10 bony thorax, 5 bony lower extremity, 3 bony upper extremity, 1 skull	Modal 27 Gy in 3 fractions	Crude local control 88%; 1-year local control 74% after a median follow-up duration of 10 months	Fatigue, dermatitis and nausea were the commonest grade 1 toxicities (in 7% of patients); pain, dermatitis, nausea amd fatigue were the commonest grade 2 toxicities (in 2% of patients); only one patient had a grade 3 toxicity – dermatitis, and no grade ≥4 toxicities were observed
Balagamwala et al. (2012)[135] n = 57	Spine	Median 15 Gy in a single fraction, unknown if marginal	Crude local control 77%; 1-year local control 50%; median OS duration of 12 months after a median follow-up duration of 5 months	33% of patients had toxicities of any grade: 10.5% had grade 1 fatigue; 2% had grade 3 nausea and vomiting and no grade 4 toxicities were observed; 8% of patients had pain flares (not graded)
Gerszten et al. (2005)[136] n = 48	Spine	Mean 16 Gy in a single fraction	Crude local control 88%*; 1-year local control 96% after a median follow-up duration of 37 months	No radiation-related toxicities were reported
Ghia et al. (2016)[92] n = 43	20 thoracic spine, 20 lumbar spine, 4 cervical spine, 3 thoracolumbar junction	Modal 24 Gy in 1 fraction	1-year local control 82%; median OS duration 22.8 months after a median follow-up duration of 23 months	Pain flare (in 33% of patients); post-treatment fracture (in 29% of patients); grade 3 late-onset radiculopathy/foot drop in one patient
Hannan et al. (2016)[137] n = 16	NR	Median 24.5 Gy for single fraction, 30 Gy for 3 fractions	Crude local control 95% after a median follow-up duration of 9 months	Two grade 1 toxicities reported
Jhaveri et al. (2012)[138] n = 18	14 spine, 6 pelvis, 4 ribs/clavicle	Modal 40 Gy in 5 fractions	Median follow-up duration of 10 months	Grade 1 toxicity in one patient
Majewski et al. (2015)[109] n = 34	Intracranial, extracranial	NR	1-year local control 70% after a median follow-up duration of 9.4 months	NR
Nguyen et al. (2010)[139] n = 48	Spine	Modal 27 Gy in 3 fractions	Crude local control 78%; 1-year local control 80%; median OS duration 22 months after a median follow-up duration of 13 months	No grade 3 or 4 neurological toxicity (McCormick and associates scheme); grade 1 fatigue in 23% of patients. grade 2 fatigue in 13% of patients; grade 2 nausea in 11% of patients; grade 2 vomiting in 7% of patients; grade 3 pain in one patient; grade 3 anaemia in one patient
Ranck et al. (2013)[35] n = 18	11 bone, 10 abdominal lymph node, 7 mediastinum/hilum, 4 lung, 2 kidney, 2 adrenal, 2 liver, 1 soft tissue	Modal 50 Gy in 10 fractions, unknown if marginal dose	Crude local control 95%; 1-year local control 96% after a median follow-up duration of 16 months	Grade 1 fatigue in 61% of patients; grade 1 rib fracture in 12% of patients; grade 2 radiculitis in 6% of patients; grade 2 bone pain in 6% of patients; no grade ≥3 acute or late-onset toxicities reported
Staehler et al. (2010)[65] n = 55	Spine	Median 20 Gy in a single fraction	Crude local control 98%; 1-year local control 94%; median OS duration 17 months after a median follow-up duration of 33 months	Grade 1 abdominal pain in one patient
Svedman et al. (2006)[112] n = 26	63 lung or mediastinum, 5 kidney, 5 adrenal, 4 thoracic wall, 3 abdominal glands, 3 liver, 1 pelvis, 1 spleen	40 Gy in 4 fractions‡	Crude local control 99%; 1-year local control 100%; median OS duration of 32 months; after a median follow-up duration of 52 months‡	Grade 1–2 toxicities reported in 58% of patients; grade 5 toxicity reported in one patient

Table 2 (cont.) | **Review of extracranial SABR literature for metastatic RCC**

Study (n = number of patients)	Locations of metastases	Marginal dose (Gy)	Outcomes	Toxicities
Teh et al. (2007)[140] n = 14	Orbits, head and neck, lung, mediastinum, sternum, clavicle, scapula, humerus, rib, spine, abdominal wall (23 metastases in total)	Modal 24 Gy in 3 fractions[‡]	Crude local control 86%*; 1-year local control 81% after a median follow-up duration of 9 months[‡]	No grade ≥2 toxicities reported
Thibault et al. (2015)[141] n = 116	187 osteolytic spine (15 cervical, 89 thoracic, 66 lumbar, 17 sacrum)	Median 16 Gy in 1 fraction	Median OS duration of 11 months after a median follow-up duration of 8 months	Vertebral compression fractures in 34/187 (18%) of metastases following stereotactic radiotherapy
Tinkle et al. (2015)[142] (abstract) n = 38	Primary RCC, locally recurrent RCC, bone, soft tissue	Median BED_{10} 48 Gy	1-year local control 88%; 1-year OS rate 82% after a median follow-up duration of 19.7 months	No grade 3 or 4 toxicities
Wang et al. (2016)[143] (abstract) n = 91	75 bone, 28 lung, 18 liver, 22 lymph nodes, 45 other	8–60 Gy in 1–5 fractions	1-year local control 91%; 1-year OS 76.5% after a median follow-up duration of 10.7 months	NR
Wersäll et al. (2005)[144] n = 50	117 lung, 12 kidney metastases, 6 adrenal gland, 5 thoracic wall, 4 bone, 3 mediastinum, 3 abdominal lymph gland, 2 liver, 1 spleen, 1 pancreas	Modal 32 Gy in 4 fractions, 40 Gy in 4 fractions and 45 Gy in 3 fractions[‡]	Crude local control 98%; 1-year local control 99% after a median follow-up duration of 37 months[‡]	Any grade toxicities reported in 40% of patients, one incidence of mortality[‡]
Zelefsky et al. (2012)[145] n = 55	59 spine, 22 pelvic bones, 14 other, 9 femur, 1 lymph node	Modal 24 Gy in a single fraction	Crude local control 72%; 1-year local control 72% after a median follow-up duration of 12 months	Fractures in 7% of patients; grade 2 dermatitis in 4%; grade 4 erythema in 2%

BED_{10}, biologically effective dose. EBRT, external-beam radiation therapy; NCI–CTCAEv4, National institute for cancer research Common Terminology Criteria for Adverse Events, version 4; NR, not reported; OS, overall survival. SABR, stereotactic ablative radiotherapy. *According to number of patients rather than targets; [‡]includes patients with metastatic and primary RCC

cohorts of patients, have demonstrated considerable promise thus far. By comparison other ablative techniques such as radiofrequency or microwave ablation, or indeed cryotherapy, have relatively fewer prospective clinical trial data available to support their use; however, despite this paucity of evidence, these techniques have become established in the management of patients with RCC whose tumours are largely deemed inoperable. Multicentre, prospective clinical trials investigating the efficacy of SABR must be completed if this approach is to be considered a future standard-of-care treatment of RCC. Eligible patients are currently being recruited to three such studies in Australia[53], Japan[54] and Canada[55].

Combination with targeted therapies
With the introduction of targeted anticancer therapies (such as sunitinib, sorafenib and pazopanib), patients with metastatic disease are having increasingly prolonged survival durations. A new, favourable subgroup of patients receiving targeted agents can increasingly be identified, in whom locally directed treatments such as SABR might also be effective[56]. In this context, treatment with SABR might delay the need to switch an otherwise effective targeted agent when targeted to a single lesion containing a clonal tumour population that has escaped systemic control[57], a concept termed 'oligoprogressive' disease[58]. Targeted therapies are also, theoretically, attractive adjuvant interventions after local treatment of the primary disease. A strong rationale, therefore, exists for the combination of SABR, either targeting the primary tumour or symptomatic metastatic lesions, with targeted therapies; however, such an approach necessitates careful consideration of the potential adverse interactions between SABR and targeted therapies in both nonmalignant and tumour tissues.

Vascular targeted therapies in combination with SABR.
High-dose radiation, in particular in the form of SABR, has the potential to affect terminally differentiated

Table 3 | **Review of available data on SABR for primary RCC**

Study (n = number of patients)	Marginal dose (Gy)	Outcomes	Toxicities
Chang et al. (2016)[51] n = 16	30–40 Gy in 5 fractions	Crude local control 100%; median follow-up duration of 19 months	1 grade 2 acute toxicity and 2 grade-4 late-onset toxicities
Gilson et al. (2006)[146] n = 33	Median 40 Gy in 5 fractions	Crude local control 94%; estimated 2-year local control rate 92%; mean follow-up duration 17 months	NR
Lo et al. (2014)[147] n = 3	40 Gy in 5 fractions using Cyberknife technology	Crude local control 100%; mean follow-up duration of 21.7 months	1 grade 1 acute toxicity (nausea)
McBride et al. (2013)[148] n = 15*‡	Median 33 Gy in 3 fractions	Crude local control 87%: 1 failure at 30.7 months; 1 failure at 31.2 months; median follow-up duration of 36.7 months	1 grade 3 toxicity (renal); 7 acute grade 1 toxicites (5 fatigue, 2 nausea)
Nair et al. (2013)[149] n = 3	39 Gy in 3 fractions	Crude local control 100%, mean follow-up duration of 13.3 months	1 acute grade 1 toxicity (nausea)
Nomiya et al. (2008)[87] n = 10	Median 72 Gy E in 16 fractions	Crude local control 100%; estimated 2-year local control 100%; 5-year OS rate 74%; median OS duration of 57.5 months	Grade 4 toxicities in 10% of patients; no other toxicities > grade 1
Qian et al. (2003)[109] n = 20*	40 Gy in 5 fractions	Crude local control 93%; estimated 2-year local control 86%; mean OS duration 12 months	NR
Pham et al. (2014)[40] n = 20‡	26 Gy in 1 fraction 42 Gy in 3 fractions	Follow-up duration for toxicity reporting of 6 months	Grade 1–2 toxicities in 60% of patients; no grade ≥3 toxicities
Ponksy et al. (2015)[42] n = 19‡	Maximum dose of 48 Gy in 4 fractions	Median follow-up duration of 13.7 months	Grade 2 toxicities in 5.2% of patients; grade 3–4 toxicities in 15.8% of patients
Siva et al. (2016)[43] n = 33*‡	26 Gy in 1 fraction; 42 Gy in 3 fractions	Crude local control 97%; 2-year local control 100%; 2 year OS duration 92% after a median follow-up duration of 24 months	Grade 1–2 toxicities in 78% of patients; grade 3 toxicities in 3% of patients
Svedman et al. (2006)[112] n = 5*	40 Gy in 4 or 5 fractions, 45 Gy in 3 fractions	Crude local control 80%; 2-year local control 91%; median survival duration of 32 months after a mean follow-up duration of 52 months	Grade 1–2 toxicities in 89% of patients, grade 3 toxicities in 4%
Svedman et al. (2008)[49] n = 7	40 Gy in 4 fractions	Crude local control 86%; 2-year local control 91% after a mean follow-up duration of 39 months	Grade 1–2 toxicities in 58% of patients
Teh et al. (2007)[140] n = 2	1 patient received 24 Gy in 3 fractions; dose for second patient not reported	Crude local control 100%; 2-year local control 100% after a median follow-up duration of 9 months (median follow-up data are for all 16 patients in the study, and not provided separately on the 2 patients with primary RCC)	No grade ≥2 toxicities reported, as defined by RTOG/EORTC criteria; no deterioration in renal function
Staehler et al. (2015)[41‡§] n = 30	25 Gy in 1 fraction using Cyberknife technology	Crude local control 98% at >9 months; median OS duration unknown after a median follow-up duration of 28.1 months	Grade 1–2 toxicities in 13% of patients
Wang et al. (2014)[88] n = 9	36–51 Gy to 50% isodose line at 3–5 Gy per fraction	5-Year local control 43%; 5-year OS rate 35%	Acute grade 1 toxicities in 44% of patients; late-onset grade 2 toxicities in 22% of patients
Wersall et al. (2005)[123] n = 8	40 Gy in 4 or 5 fractions; 45 Gy in 3 fractions	Crude local control 100%; 2-year local control 100%; median OS duration >58 months; median follow-up duration of 37 months	Grade 1–2 toxicities in 20% of patients; grade 3 toxicities in 19%

NR, not reported; OS, overall survival; SABR, stereotactic ablative radiotherapy. *Data presented in an abstract; ‡Data are prospective; §Data are pooled with results obtained from 15 patients with transitional cell carcinoma.

late-reacting nonmalignant tissues such as the great vessels, spinal cord, and penetrating microvasculature that supply luminal structures such as the airways and bowels. These late-reacting nonmalignant tissues are also affected directly by targeted therapies; thus, toxicity levels could escalate when these drugs are combined with exposure to high-dose radiation[56]. For example, concurrent use of thoracic radiotherapy with bevacizumab resulted in a high incidence of trachea-oesophageal fistulae, prompting the early termination of a trial involving patients with non-small-cell lung cancer[59]. Similar complications have been reported with the use of vascular endothelial growth factor (VEGF)-receptor tyrosine-kinase inhibitors (TKIs), such as sunitinib[60]. Radiation-recall pneumonitis has also been reported with the administration of such agents soon after radiotherapy[61]. Similarly, ischaemic bowel complications, including perforation, have been reported with concurrent use of VEGF-targeted therapies and SABR[62,63]. The occurrence of these complications indicates the need for careful assessment of the radiation schedule and doses delivered to vital organs when combining high-dose radiotherapy with biologically targeted agents. In 2014, the authors of a review[64] on the combination of targeted agents with radiotherapy in patients with soft-tissue sarcomas stated that, theoretically, angiogenesis inhibitors might improve the efficacy of radiotherapy. These effects were attributed to either the normalization of tumour blood vessels, therefore improving tumour oxygenation levels and reducing intratumoural pressure, or by increasing the rate of tumour apoptosis through direct inhibition of cellular survival signals.

Combining high-dose radiotherapy with systemic targeted agents. Data are available from several studies investigating the outcomes of patients receiving TKIs in combination with SRS. In a study conducted by Staehler and colleagues[65], 106 patients with spinal ($n = 55$) or cerebral ($n = 51$) metastatic lesions and an Eastern Cooperative Oncology Group status of 0 or 1 were treated with either sorafenib or sunitinib and simultaneous SRS. No skin toxicities, neurotoxicities or myelopathies occurred after SRS, and undergoing SRS did not alter the risk of adverse effects of sorafenib or sunitinib. The authors concluded that simultaneous treatment with systemic targeted anti-angiogenic agents and SRS for selected patients with RCC with spinal and/ or cerebral metastases is safe and effective[65]. In a further study by Miller and colleagues[66] the outcomes of 151 patients with spinal metastases from primary RCC receiving SRS alone or variably receiving TKIs before or concurrently with radiotherapy were compared. No grade ≥3 toxicities occurred following SRS with concurrent TKI treatment, and the incidences of post-SRS vertebral fracture (21% of any grade) and pain flare (17% of any grade) were similar across cohorts.

Recommendations for drug–radiotherapy combinations. Preclinical data suggest that VEGF–TKIs are effective in combination with radiotherapy, although no data have been published in the past 5 years on the use

of sorafenib, pazopanib or temsirolimus in combination with radiotherapy in patients with RCC. In the absence of sufficient data supporting use of the combination of SABR and targeted therapies for RCC, caution must be used when combining these two approaches. At present, insufficient evidence is available to recommend any specific duration of interruption of the delivery of systemic agents when combining with SABR. Instead, we suggest that attention should be focused on constraining the radiation doses delivered to the organs at risk, particularly to luminal structures. Several prospective trials[67–74] are currently underway, and are intended to provide further information on the interactions of targeted therapies or immunotherapies with SABR in patients with RCC.

Immune-stimulating effects

Radiotherapy is recognized to have the capacity to prime the immune system for an adaptive antitumour response. The abscopal effect, which refers to distant tumour regression after localized irradiation, is postulated to be an immune-mediated effect, although other putative biological mechanisms also exist[75,76]. Direct ionizing radiation elicits innate immune recognition of the tumour following the release of danger signals from tumour cells[77]. Such signals include antigenic peptides generated by radiation-induced cell death, which enhance the antigen repertoire presented by immune-presenting cells, as well as the subsequent production of cytokines and peptides that can augment antitumour immune responses. Three molecular signals are required for the danger response: dendritic-cell-mediated phagocytosis of dying tumour cells, cross-presentation of tumour-derived antigens to T cells and the activation of tumour-specific T cells. Translocation of calreticulin to the surface of dying irradiated cancer cells provides an 'eat-me' signal, which is important for recognition and engulfment of dying tumour cells by dendritic cells[78]. The release of inflammatory molecules from irradiated tumour cells, such as high mobility group protein B1 and ATP, which bind to toll-like receptor 4 (TLR4) or the purinergic receptor $P2X_7$, respectively, also promote antigen processing and cross-presentation by dendritic cells, in addition to T-cell priming[79]. All of these molecules provide the tools for improved recognition and killing by tumour-specific T cells. The intense, localized radiation provided by SABR would also drive the release of antigens by tumours, which are taken up by resident dendritic cells, which then mature and migrate to the draining lymph nodes, where they induce a tumour-specific T-cell response (both $CD4^+$ and $CD8^+$)[79]. Effector T cells then traffic to the tumour microenvironment where they release effector molecules and induce tumour cell apoptosis.

The ablative dose fractionation spectrum employed by SABR has the potential for even greater augmentation of the antitumour immune response than conventional radiotherapy[28]. Ablative doses of radiotherapy result in a greater degree of both stromal and/or vascular damage and ceramide-induced endothelial cell damage, in addition to increased apoptosis of tumour cells[80]. This approach results in a tumour microenvironment that is

High mobility group protein B1
A chromatin protein that is secreted by immune cells and acts as a mediator of inflammation
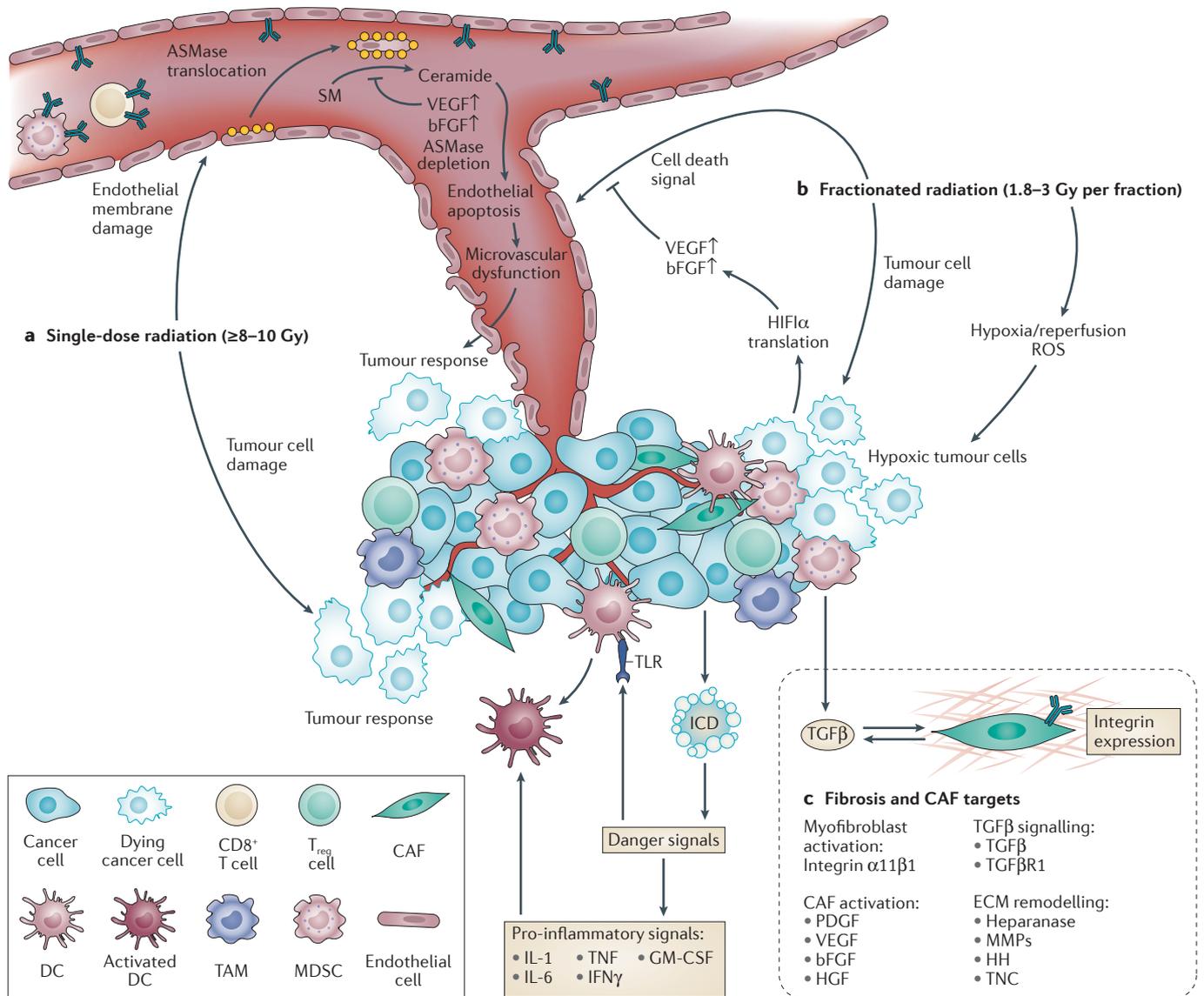
a | Single-dose radiation (≥8–10 Gy)

b | Fractionated radiation (1.8–3 Gy per fraction)

c | Fibrosis and CAF targets

Myofibroblast activation:
Integrin α11β1

CAF activation:
• PDGF
• VEGF
• bFGF
• HGF

TGFβ signalling:
• TGFβ
• TGFβR1

ECM remodelling:
• Heparanase
• MMPs
• HH
• TNC

Pro-inflammatory signals:
• IL-1   • TNF   • GM-CSF
• IL-6   • IFNγ

Figure 2 | **Models of microvascular endothelial engagement in tumour responses to radiotherapy.** Endothelial damage can be induced by both **a** | High single-dose radiotherapy (≥8–10 Gy) and **b** | Low-dose (1.8–3 Gy) fractionated radiotherapy. The resulting microvascular dysfunction enables the conversion of sublethal doses of radiation in tumour cells into lethal lesions via an as yet unknown mechanism. Endothelial apoptosis and microvascular dysfunction contribute substantially to tumour cell lethality and tumour cure in the single-dose approach. Radiation induces translocation of endothelial cell ASMase into glycosphingolipid-enriched and cholesterol-enriched plasma membrane rafts, where it hydrolyses sphingomyelin (SM) to generate the proapoptotic second messenger ceramide, thus initiating transmembrane signalling and apoptosis. Inhibition of this process by ASMase depletion or by proangiogenic growth factors markedly attenuates the lethal response of tumour cells to this type of radiotherapy. By contrast, the endothelial cell damage induced by exposures to low-dose fractionated radiotherapy does not enhance tumour cell death effectively, as the death signalling pathway in endothelium is repressed by concomitant activation of tumour cell HIF-1α. Reactive oxygen species (ROS) generated by waves of hypoxia and reoxygenation occurring after each radiation exposure lead to translation of HIF-1α mRNA transcripts stored in specialized cytosolic stress granules of hypoxic tumour cells. This adaptive response generates

VEGF and other proangiogenic factors that attenuate radiation-induced apoptosis in endothelial cells. Genetic inhibition of the HIF-1α response leads to extensive endothelial apoptosis, microvascular dysfunction, enhanced tumour cell death and delayed tumour growth. The mechanism of endothelial damage in this response remains unknown, and a possible involvement of the ASMase pathway has not as yet been assessed. This observation indicates the potential for pharmacological targeting of HIF-1α to improve the outcome of fractionated radiotherapy via engagement of the endothelial apoptosis component. **c** | Fibrosis targets can be subcategorized into those that affect stromal activation, those that affect extracellular matrix (ECM) remodelling, and those that affect transforming growth factor β (TGFβ) signalling. bFGF, basic fibroblast growth factor; CAF, cancer-associated fibroblast; DC, dendritic cell; GM–CSF, granulocyte-macrophage–colony-stimulating factor; HGF, hepatocyte growth factor; HH, Hedgehog; ICD, immunogenic cell death; IFNγ, interferon gamma; MDSC, myeloid-derived supressor cell; MMP, matrix metalloproteinase; PDGF, platelet-derived growth factor; TAM, tumour-associated macrophage; TGFβR1, transforming growth factor β receptor 1; TLR, toll-like receptor; TNC, tenascin C; TNF, tumour necrosis factor; VEGF, Vascular-endothelial growth factor. Modified with permission obtained from SpringerNature © Barker, H.E. et al. The tumour microenvironment after radiotherapy: mechanisms of resistance and recurrence. Nat. Rev. Cancer 15, 409–425 (2015)

enriched with tumour-derived antigens, with coexisting activation of dendritic cells, antigen cross-presentation and tumour-specific T-cell responses. While the optimal radiotherapy dose and fractionation required to elicit the most effective antitumour immune responses is not yet known[81], these factors are highly likely to be dependent upon tumour histology, location and the tumour micro-environment[82]. In a preclinical study, involving mouse models of melanoma and RCC, single-fraction 15-Gy doses of radiation delivered using SABR in combination with PD-1 blockade generated an additive antitumour immune response at both the irradiated and distant tumour locations[83]. The feasibility of single-fraction SABR in combination with PD-1 blockade is currently being investigated in an early phase clinical trial[67].

Histological subtypes

RCC is a heterogenous entity with a number of distinct histological variants. The most common subtype is clear cell RCC (ccRCC) (comprising 75–90% of tumours), followed by papillary RCC (10–15%) and chromophobe RCC (4–5%), each of which have distinct molecular and clinical characteristics[84,85]. Historically, clinical studies have combined patients with clear cell and those with non clear cell carcinoma subtypes; however, evidence is emerging that the various subtypes respond differently to systemic therapies[85]. Currently, very limited data are available regarding the differential responsiveness of these different RCC subtypes to radiotherapy.

In the adjuvant setting, Eminaga and colleagues[86] assessed the outcomes of patients receiving post-operative radiotherapy for sarcomatoid RCC. This study included 408 patients with localized disease from the Surveillance, Epidemiology and End Results (SEER) database, and found no differences in disease-specific survival or overall survival outcomes in patients who received postoperative adjuvant radiotherapy versus those who did not[86]. In the setting of definitive treatment, only three studies provide information regarding histological disease subtypes[51,87,88] (TABLE 3) with the majority of patients having ccRCC. Of these, one study provided data on the individual level of local control, with local control obtained in a patient with granular cell RCC for 6 months, in a patient with papillary RCC for 12 months, and varying between 3 months and 122 months in patients with ccRCC.

Equally limited data are available on the differential responses to radiotherapy of patients with metastatic RCC. In analyses of the outcomes following stereotactic radiotherapy in patients with RCC, only 12 studies provided information regarding the histological subtypes of RCC[35,36,89–98] (TABLES 1,2). Again, the majority of patients in all studies had ccRCC, with the exception of one study, in which papillary cell RCC was more common[94]. Three of these studies assessed the effect of histological subtype on the extent of local control and on survival outcomes; however, no significant differences were observed[92–94]. Ongoing radiotherapy studies should aim to report the histological subtypes of patients and any differences in outcomes seen, to guide the delivery of personalized radiotherapy in the future.

Conclusions

Owing to the historical perceptions of radioresistance, conventionally fractionated radiotherapy has a limited role in the definitive or adjuvant treatment of patients with primary RCC and has not been adopted into the definitive management algorithm of oligometastatic disease. However, conventional radiotherapy retains a clinically relevant role in the palliation of symptomatic primary and metastatic RCC, in particular for those with bleeding, pain or neurological symptoms. With the evolution of newer technologies enabling the safe application of high-dose ablative radiotherapy, SRS and SABR have been increasingly used in patients with RCC. Clinical trials in the setting of intracranial and extracranial oligometastases, as well as primary RCC, have demonstrated the excellent local efficacy of this approach. Additionally, an emerging awareness of the capacity of high-dose radiation to stimulate an immune response has resulted in novel combinations of SRS and SABR with immunotherapy-based approaches. Scanning the horizon, future advances in the field will likely result from the integration of systemic targeted agents and immunotherapies with high-dose radiation. This approach might take the form of either synergistic combinations to enhance drug efficacy or localized ablation approaches targeting escaped subpopulations of oligoprogressive metastases in the context of disease that is otherwise controlled by systemic therapies. Once an overlooked approach, radiotherapy is undergoing a renaissance in the mainstream management of RCC.

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Author contributions

Competing interests statement