Stereotactic body radiotherapy for primary renal cell carcinoma: a systematic review and practice guideline from the International Society of Stereotactic Radiosurgery (ISRS)

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Surgery is the standard of care for patients with primary renal cell carcinoma. Stereotactic body radiotherapy (SBRT) is a novel alternative for patients who are medically inoperable, technically high risk, or who decline surgery. Evidence for using SBRT in the primary renal cell carcinoma setting is growing, including several rigorously conducted prospective clinical trials. This systematic review was performed to assess the safety and efficacy of SBRT for primary renal cell carcinoma. Review results then formed the basis for the practice guidelines described, on behalf of the International Stereotactic Radiosurgery Society. 3972 publications were screened and 36 studies (822 patients) were included in the analysis. Median local control rate was 94·1% (range 70·0–100), 5-year progression-free survival was 80·5% (95% CI 72–92), and 5-year overall survival was 77·2% (95% CI 65–89). These practice guidelines addressed four key clinical questions. First, the optimal dose fractionation was 25–26 Gy in one fraction, or 42–48 Gy in three fractions for larger tumours. Second, routine post-treatment biopsy is not recommended as it is not predictive of patient outcome. Third, SBRT for primary renal cell carcinoma in a solitary kidney is safe and effective. Finally, guidelines for post-treatment follow-up are described, which include cross-axial imaging of the abdomen including both kidneys, adrenals, and surveillance of the chest initially every 6 months. This systematic review and practice guideline support the practice of SBRT for primary renal cell carcinoma as a safe and effective standard treatment option. Randomised trials with surgery and invasive ablative therapies are needed to further define best practice.

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Introduction

The standard of care for operable patients presenting with primary renal cell carcinoma is surgical extirpation. As the European Organisation for Research and Treatment of Cancer Genito-Urinary Group (EORTC-GU) non-inferiority phase 3 trial 30904 by Van Poppel and colleagues[1] did not show the superiority of partial nephrectomy over radical nephrectomy for overall survival, both approaches are considered reasonable standards. Partial nephrectomy has the advantage of being a nephron-sparing approach; however, increased rates of local recurrence have been observed.[1] Currently, the American Urological Association,[2] American Society of Clinical Oncology,[3] and National Comprehensive Cancer Network[4] prioritise partial nephrectomy over radical nephrectomy when intervention is needed for small renal masses. However, not all patients are suitable for surgery. Another established option for inoperable patients is thermal ablation, but there are several notable limitations to this modality. Thermal ablation is an invasive approach with reduced local control and increased potential morbidity for centrally located tumours abutting the renal hilum or proximal ureter, and with tumour sizes greater than 3–3·5 cm.[5] Furthermore, as of yet there is no prospective clinical trial evidence to support thermal ablation for primary renal cell carcinoma.

It is in this context that stereotactic body radiotherapy (SBRT, also referred to as stereotactic ablative body radiotherapy [SABR]) has emerged as a non-invasive nephron-sparing option in patients who are medically inoperable, technically high risk, or who have declined surgery.[6] By contrast, SBRT has the advantage that it is non-invasive and can treat both complex and centrally located tumours and larger tumours. There are also reports on the use of SBRT for tumour thrombi, selected for patients with thrombus extending below the level of the atrium.[7] Few data are available informing the eligibility of these indications; however, general principles apply, including respecting dose tolerance of surrounding organs and treatment at high-volume centres. In 2022, published outcome data from 190 patients in the International Radiosurgery Oncology Consortium for Kidney (IROCK) showed that despite a median tumour diameter of 4·0 cm, the cumulative incidence of local failure at 5 years was only 5·5%.[8] These outcomes are concordant with a previous meta-analysis published in 2019, which included 26 studies (11 prospective trials) and 372 patients.[9]

The purpose of this systematic review is to summarise the current literature on SBRT for primary renal cell carcinoma and to provide recommendations for treatment within specific scenarios of interest relevant to the management of this disease entity. This guideline was conducted on behalf of the International Stereotactic Radiosurgery Society (ISRS) guidelines committee.

Methods

Search strategy and selection criteria

This systematic review summarises the current literature specific to SBRT for primary renal cell carcinoma. The inclusion criteria were defined using the PICOS study design method (table 1), and the search strategy and screening approach was compliant with PRISMA guidelines, involving two independent reviewers (SSL

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and SS). Disagreements regarding the eligibility of studies were resolved through discussion to reach a consensus with involvement of a third author (MA) if necessary. Key questions to inform the ISRS guideline were selected through panel selection and recommendations were formulated through consensus agreement on the formulated questions. Medical literature including clinical trials, cohort studies (retrospective and prospective), case series (more than two patients), and published abstracts reported in English from Jan 1, 1995 to April 5, 2023 were searched in PubMed and Embase. SBRT was defined as greater than 5 Gy per fraction to the primary renal tumour and we excluded studies treating only extrarenal renal cell carcinoma metastases. We also excluded reviews, meta-analyses, case reports (fewer than two patients); and dosimetric, motion-management, or radiotherapy planning studies. A broad search strategy was used, using MeSH and text word approaches and with the following search string: "Radiotherapy[MH] or radiation therapy or stereotactic[tiab] or cyberknife or sabr or sbrt" AND "Kidney neoplasms[MH] or kidney neoplasm[tiab] or renal neoplasms[tiab] or kidney cancer[tiab] or renal cell carcinoma[tiab] or "Carcinoma, Renal Cell"[Mesh] or renal cell cancer[tiab] or renal adenocarcinoma[tiab]" AND "english[Filter]". This systematic review was registered with PROSPERO (CRD42021292050).

Data extraction

Extracted data included the number of patients, number of treated lesions, tumour size and stage, median patient age, median follow-up duration, toxicities (using the Common Terminology Criteria for Adverse Event criteria, grades 2–5), renal function, local control, progression-free survival, and overall survival. We applied distinct descriptive approaches to summarise different types of outcomes. For variables such as age, we reported the mean (range) across all studies. Conversely, for variables such as follow-up duration, tumour size, biopsy confirmation, local control, progression-free survival, and overall survival we used the median and confidence interval as a robust measure of central tendency. The primary outcomes were local control, progression-free survival, and overall survival. We also assessed treatment-related toxicity, renal function, and radiotherapy treatment details.

Results

3258 citations were identified from the MEDLINE search and 1080 from other sources, including Embase. Removal of duplicates resulted in 3972 records, and initial screening of titles and abstracts led to the exclusion of 3806 records. 166 studies were further assessed for eligibility, leading to the exclusion of 130 studies. This search yielded 36 eligible studies that met all criteria and were included in the analysis (figure). The publications (30 articles and six abstracts) included both retrospective series (n=23) and prospective trials (n=13; table 2). The total number of eligible patients was 822. The weighted age was 71·69 years (range 62–83), with 598 (72·8%) of 822 patients who were male and 224 (27·2%) female. The weighted median follow-up was 31·2 months and the weighted median maximum tumour size was 4·4 cm. From 20 studies, biopsy confirmation occurred in a median of 98%. The median weighted baseline estimated glomerular filtration rate was 55 mL/min (range 28·7–82). Median reported local control rates were 94·1% (range 70·0–100). In the six studies that reported 5-year PFS, the median PFS was 80·5% (95% CI 0·72–0·92) and in the 12 studies that reported 5-year OS, the median was 77·2% (95% CI 0·65–0·89%). A total of 45 (3·9%) patients from 25 studies were reported to undergo post-treatment dialysis. Treatment-related toxicities at grade 2 intensity were reported in 31 (5·3%), grade 3 in 15 (2·7%), and grade 4 in four (0·7%).

Discussion

Optimal dose regimens for SBRT and SABR in patients with primary renal cell carcinoma

SBRT has been administered at different doses for primary renal cell carcinoma in different trials, pooled analyses, and institutional studies, resulting in similar treatment outcomes when high biologically effective doses, defined as 72 or more Gy_{10}, were used. The reported regimens delivering higher biologically effective doses assuming a low alpha to beta ratio of 10 for renal

	Inclusion criteria	Exclusion criteria
Patient or study population, or problem	Adults >18 years; renal cell carcinoma stage I–IV disease	Paediatric patients; non-renal cell carcinoma histology
Intervention	SABR targeting primary renal tumour; dose per fraction (≥5 Gy)	SABR targeting metastatic sites
Comparison or control	NA	NA; no comparative-effectiveness or randomised studies published
Outcomes	Local control; progression-free survival; overall survival; assess treatment-related toxicity, renal function, and radiotherapy treatment details	NA
Study design	Reports at least one of the above-listed outcomes; prospective clinical trials; cohort studies (retrospective and prospective); case series (≥two patients); published abstracts	Reviews, meta-analyses, and guidelines; case reports (<two patients); dosimetric, motion-management, or radiotherapy planning studies; basic science or preclinical studies

SABR=stereotactic ablative body radiotherapy. NA=not applicable.

Table 1: **Population, intervention, comparison, outcomes, and study design criteria for study selection**

cell carcinoma include 26 Gy in one fraction (biologically effective doses 93·6 Gy_{10}), 36–60 Gy in three fractions (79·2–180 Gy_{10}), 48 Gy in four fractions (105·6 Gy_{10}), and 40 Gy in 5 fractions (72 Gy_{10}). All schedules were prescribed with heterogeneous distributions and with high peak doses within the target. In a meta-analysis by Correa and colleagues,[9] the reported local control using mostly one, three, or five fractions (biologically effective doses 37·5–151·2 Gy_{10}) ranged from 70–100% (mostly 90–100%) with varying follow-up times (range 9–48·3 months) and tumour sizes. Grade 3–4 toxicities ranged from 0% to 25% (mostly <10%). Given the considerable variations in the regimens used, tumour size, follow-up times, and the absence of individual patient data in this study, the optimal regimen could not be established.

There were reported trials on SBRT for primary renal cell carcinoma that used standardised regimens. McBride and colleagues[20] reported the results of a phase 1 dose escalation trial of SBRT for inoperable primary renal cell carcinomas in 15 patients. The radiation dose was escalated from 21 Gy in three fractions to 48 Gy in three fractions. With a median follow-up of 36·7 months (range 24·2–72·2), there were no grade 4 toxicities and two patients in the low-dose groups (21 Gy in three fractions and 27 Gy in three fractions) developed recurrence at 30·7 months and 31·2 months, respectively. In a prospective clinical trial by Siva and colleagues,[29] 33 of the 37 enrolled patients with 34 inoperable primary renal cell carcinomas were treated with SBRT and one patient had a primary cancer in each kidney (two tumours). Patients with renal cell carcinoma smaller than 5 cm received a dose of 26 Gy in one fraction (n=17) and those with renal cell carcinomas larger than 5 cm received a dose of 42 Gy in three fractions (n=17). The 1-year and 2-year local control was 100% with a median follow-up of 24 months (range 11·8–36). No grade 4 toxicities were reported, but one patient developed local recurrence 28 months after SBRT. In a phase 1 dose-escalation trial of SBRT for medically inoperable stage T1-T3N0M0 renal cell carcinomas by Grubb and colleagues,[36] the radiation dose was escalated from 48 Gy in three fractions to 60 Gy in three fractions. With a median follow-up of 34·2 months (range 5·6–70·2), the 3-year local control rate was 90% according to RECIST 1.1 criteria. Unsuccessful treatment based on RECIST occurred in a patient who received 60 Gy in three fractions. None of the patients progressed to an estimated glomerular filtration rate less than 30 mL/min. Hannan and colleagues[44] reported the results of their phase 2 trial for SBRT on biopsy-confirmed radiographically enlarging primary renal cell carcinoma (≤5 cm). 16 patients received a dose of either 36 Gy in three fractions (n=10) or 40 Gy in five fractions (n=6). With a median follow-up of 36 months, the 1-year radiographic local control by RECIST was 100% and the disease control rate was 94%.

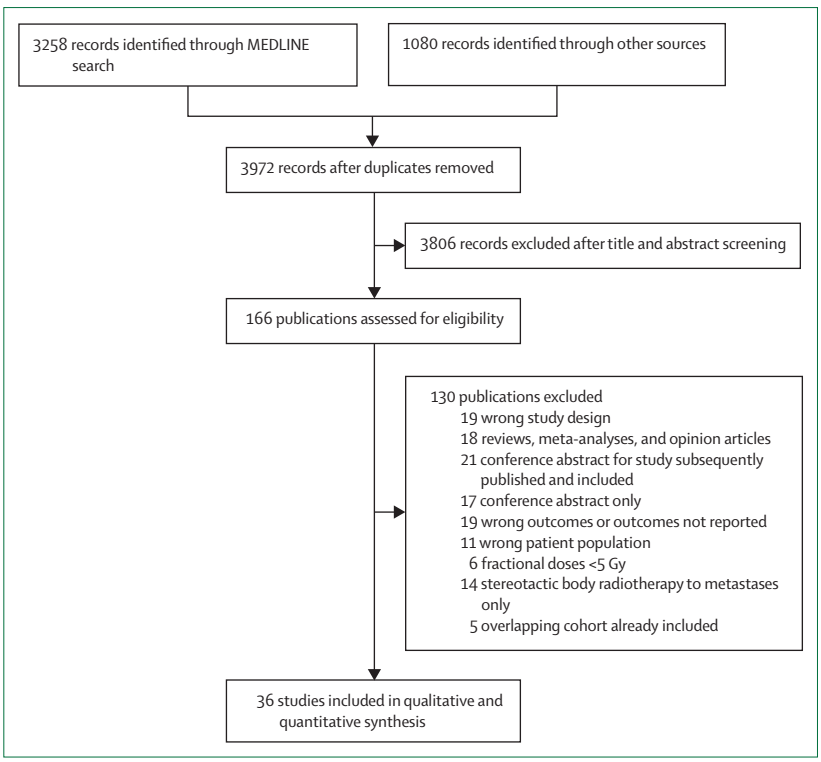

Figure: **Flow diagram of study selection**

The first report from IROCK[45] included 223 patients pooled from nine institutions. The median follow-up was 30 months. There was no difference in local control between patients receiving single-fraction SBRT at 25 Gy (range 14–26) and those receiving multiple fractions at a median of 40 Gy in four fractions (range 24–70); both exceeded 95%. There was also no difference in the mean renal function change or overall toxicity profile between the two cohorts. However, for unknown reasons, the patients in the single-dose cohort showed better PFS, cancer-specific survival, and distant control. On Nov 17, 2022, IROCK reported the 5-year outcomes of 190 patients with a median follow-up of 5 years (IQR 3·4–6·8). The 3-year cumulative local failure rate was 5·5%, the 5-year cumulative local failure rate was 5·5%, and the 7-year cumulative local failure rate was 8·4%.[8] Patients who received single-fraction SBRT had significantly lower local failure and higher progression-free survival than patients who received multifraction treatments. These improvements persisted even when the tumour size (<4 cm *vs* ≥4 cm) was accounted for. There were no differences in toxicities between the two cohorts.

Other studies of SBRT in renal cell carcinoma that used five fractions used variable doses, making it difficult to draw conclusions about dose response. A study by Wurzer and colleagues[17] (reported in abstract form) showed a local control of 87% in 23 patients treated with SBRT with a dose of 40 Gy in five fractions and a median

	Article type	Study design	SABR to primary RCC patients, n			Tumours treated, n	SABR platform	Confirmed via biopsy rate (%)	Patient age (mean years)	Tumour size (median cm unless stated otherwise)	Follow-up (mean months)	Dose in fractions (Gy, n)	OS (median)	PFS (median)	Local control (%)	Treatment related toxicity			Post-SABR change in renal function (eGFR change %)
			Total	Stage 1–2	Stage 3–4											Grade 1–2	Grade 3	Grade 4–5	
Qian et al (2003)[10]	Abs	Retro	20	20	NR	27	Ck	NR	62	367 cm³ (mean)	12	40 Gy in 5	NR	NR	93%	NR	NR	NR	NR
Beitler et al (2004)[11]	Art	Retro	9	7	2	11	L	82%	72	4·55	26·7	40 Gy in 5	57 months	NR	89%	22	11	0	NR
Wersäll et al (2005)[12]	Art	Retro	8	5	3	8	L	NR	NR	NR	37	40 Gy in 5	NR	NR	87·5%	43	45	0	Unchanged
Gilson et al (2006)[13]	Abs	Retro	14	33	NR	33	NR	NR	62	356 cm³ (mean)	17	40 Gy in 5 (median)	NR	NR	94%	NR	NR	NR	NR
Svedman et al 2006)[14]	Art	Pros	5	4	1	5	L	NR	64	NR	52	45 Gy in 3; 40 Gy in 4; 32 Gy in 4; 30 Gy in 2	NR	NR	80%	NR	0	0	NR
Teh et al (2007)[15]	Art	Retro	2	0	2	2	L	100%	NR	10–200 cm³	9	24–40 Gy in 3–6	NR	NR	100%	0	0	0	Unchanged
Svedman et al (2008)[16]	Art	Retro	7	1	6	7	L	NR	NR	5·5	49	30 Gy in 3; one patient had 40 Gy in 4	NR	NR	85·7%	57	0	0	Unchanged creatinine in 5, creatinine increased in 2
Wurzer et al (2012)[17]	Abs	Retro	23	23	0	23	L & Ck	NR	NR	NR	37	40 Gy in 5	NR	NR	87%	NR	0	0	NR
Chebotareva et al (2013)[18]	Abs	Retro	18	0	18	18	Ck	NR	NR	5–180 cm³	15·5	30–52 Gy in 3–4	NR	NR	100%	44·4	0	0	Unchanged creatinine in 17; creatinine increased in 1
Nair et al (2013)[19]	Art	Retro	2	2	0	2	Ck	NR	NR	21·3 cm³	13	39 Gy in 3	NA	NA	100%	33·3	0	0	6%
McBride et al (2013)[20]	Abs	Pros	15	15	0	15	Ck	NR	75	3·4	36·7	21–48 Gy in 3	NR	NR	80%	46·7	0	0	–18%
Lo et al (2014)[21]	Art	Retro	3	3	0	3	Ck	100%	83	5	13	40 Gy in 5	NR	NR	100%	33·3	0	0	–6·7%
Hanzly et al (2014)[22]	Art	Retro	4	4	0	4	L	NR	72·5	5·1	21·5	15 Gy in 1	NR	NR	75%	0	0	0	Unchanged
Staehler et al (2015)[23]	Art	Pros	29	29	0	30	Ck	100%	65·6	33·7 cm³	28·1	26 Gy in 1	2 year 84%	2 year 92%	100%	20	0	0	–6·5%
Ponsky et al (2015)[24]	Art	Pros	19	19	0	19	Ck	95%	77·6	57·9 cm³	13·7	24–48 Gy in 4	2 year 72%; 3 year 72%	NR	100%	11·5	10·5	5·3	NR
Chang et al (2016)[25]	Art	Retro	16	16	0	16	L	56%	73	4	19	30–40 Gy in 5	NR	NR	100%	6·25	0	Two grade 4 CKD events	–7·92%

(Table 2 continues on next page)

	Article type	Study design	SABR to primary RCC patients, n			Tumours treated, n	SABR platform	Confirmed via biopsy rate (%)	Patient age (mean years)	Tumour size (median cm unless stated otherwise)	Follow-up (mean months)	Dose in fractions (Gy, n)	OS (median)	PFS (median)	Local control (%)	Treatment related toxicity			Post-SABR change in renal function (eGFR change %)
			Total	Stage 1–2	Stage 3–4											Grade 1–2	Grade 3	Grade 4–5	
(Continued from previous page)																			
Correa et al (2018)[26]	Art	Retro	11	2	9	11	L	64%	79	9·5	46·8	25–40 Gy in 5	2 year 53%; 3 year 53%	NR	70%	54·5	9·1	0	−2·4%
Sun et al (2016)[27]	Art	Retro	32	32	0	32	Ck	NR	74·5	3·9	18·7	21–48 Gy in 3	NR	NR	92·7%	NR	NR	NR	NR
Kaidar-Person et al (2017)[28]	Art	Retro	6	6	0	6	Ck	NR	68·5	5	29·5	39 Gy in3	NR	NR	100%	50	0	0	Unchanged
Siva et al (2017)[29]	Art	Pros	33	33	0	34	L	92%	78	4·8	24	26 Gy in 1 or 42 Gy in 3	2 year 92%	NR	97%	79	3	0	−11%
Singh et al (2017)[30]	Art	Pros	14	0	14	14	L	100%	63·9	NR	1	15 Gy in 1	NR	NR	NR	62·5	6	0	NR
Correa et al (2018)[31]	Art	Pros	12	0	12	12	L	100%	66·8	8·7	5·8	25–35 Gy in 5	NR	NR	100%	66·7	25	0	−9·9 %
Kasuya et al (2018)[32]	Art	Retro	19	15	4	19	CIRT	42%	67	3·6	79·2	66–80 Gy in 12–16 (CIRT)	5 year 74%	5 year 68·9%	94·1 %	63	0	5·3	−9·6 %
Kasuya et al (2019)[33]	Art	Pros	8	7	1	8	CIRT	25%	71	4·3	43·1	66–72 Gy in 12 (CIRT)	NR	NR	100%	75	0	0	−10·8%
Funayama et al (2019)[34]	Arti	Pros	13	13	0	13	L	NR	72	2·28	48·3	60 or 70 Gy in 10	3 year 71·3%	NR	92·3 %	15·4	0	0	−16·7%
Blitzer et al (2021)[35]	Art	Retro	7	5	2	7	L (IMRT & MR guided)	100%	74	6·4	17	40 Gy in 5	NR	3–36 months 100%	100%	14	57	14	Unchanged
Grubb et al (2021)[36]	Art	Pros	11	11	0	11	Ck	100%	76·5	3·7	34·3	48, 54, or 60 Gy in 3	3 year 75·8%; 5 year 55·7%	NR	90%	63·6	9·1	0	−7%
Senger et al (2019)[37]	Art	Retro	10	7	3	13	Ck	100%	70·5	2·88	27	24 or 25 Gy in 1 or 36 Gy in 3	2 year 80%	NR	92·3%	20	0	0	0·3 %
Tetar et al (2020)[38]	Abs	Retro	38	0	0	38	MR Linac	55%	79	5·4	12·2	40 Gy in 5	NR	NR	95·7 %	3	0	0	NA
Staehler et al (2022)[39]	Art	Retro	99	NR	NR	NR	Ck	100%	65	2·8	28·1	25 Gy in 1	2 year 64%	NR	98%	NR	NR	NR	−6·5%
Freifeld et al (2022)[40]	Art	Retro	15	0	15	15	L	93%	72	3 (thrombus diameter)	19	40 Gy in 5	34 months	NR	..	NR	0	0	NR
Kirste et al (2022)[41]	Art	Pros	7	7	0	8	L	NR	44	2·8	43	50 Gy in 5; one patient had 60 Gy in 8	86%	86%	100%	43	0	0	−7·1%

(Table 2 continues on next page)

	Article type	Study design	SABR to primary RCC patients, n			Tumours treated, n	SABR platform	Confirmed via biopsy rate (%)	Patient age (mean years)	Tumour size (median cm unless stated otherwise)	Follow-up (mean months)	Dose in fractions (Gy, n)	OS (median)	PFS (median)	Local control (%)	Treatment related toxicity			Post-SABR change in renal function (eGFR change %)
			Total	Stage 1–2	Stage 3–4											Grade 1–2	Grade 3	Grade 4–5	
(Continued from previous page)																			
Siva et al (2022)[8]	Art	Retro	190	190	0	190	Various	83%	73·6	4	60	25–42 Gy in 1 to 5	NR	3 year 72·1%; 5 year 63·6%	96%	70	0	1	−14·2%
Lapierre et al (2023)[42]	Art	Pros	13	NR	NR	12	L	100%	78	3·3	23	32, 40, or 48 Gy in 4 or 40 Gy in 5	NR	NR	100%	41·7	0	0	−5·9%
Glicksman et al (2023)[43]	Art	Retro	74	68	6	74	L	49%	80	4·6	27·8	30–45 Gy in 5 or 42 Gy in 3	1 year 100%; 4 year 89·7%	89%	93%	NR	NR	NR	−14·0%
Hannan et al (2023)[44]	Art	Pros	16	16	0	16	L	100%	72	3·2	36	36 Gy in 3 or 40 Gy in 5	3 year 79%	NR	94%	50	0	0	−12·1%

Abs=abstract. Art=article. CIRT=carbon-ion radiotherapy. Ck=CyberKnife. CKD=chronic kidney disease. eGFR=estimated glomerular filtration rate. IMRT=intensely modulated radiotherapy. L=Linac. MR=magnetic resonance. NA=not applicable. NR=not reported. OS=overall survival. PFS=progression-free survival. Pros=prospective analysis. RCC=renal cell carcinoma. Retro=retrospective analysis. SABR=stereotactic ablative body radiotherapy.

Table 2: **Data tables of the included studies**

follow-up of 37 months. Studies that used lower doses ranging from 25 Gy to 40 Gy in five fractions had fewer patient numbers and many had shorter follow-up.[9] Correa and colleagues[26] reported a local control of 70% and a median follow-up of 3·9 years (IQR 0·6–4·9) with 25–40 Gy in five fractions. In this study, larger tumours were included, with treatment of the primary tumour in the metastatic setting in several patients.

Based on the best evidence available to date, single-fraction SBRT delivered at 25–26 Gy appears to be a favourable regimen provided that the organ-at-risk radiation dose tolerance can be met. The regimen of 26 Gy in one fraction has been tested in a prospective trial[29] with excellent local control and a favourable toxicity profile. Therefore, this regimen can be regarded as a standard regimen for tumours less than 5 cm if the dosimetric constraints can be met. For larger tumours, it is prudent to use multiple fractions. Three prospective trials have tested three fraction regimens. As local failure occurred in patients receiving lower doses (21 Gy and 27 Gy in three fractions)[20] and the highest dose (60 Gy in three fractions) in a prospective trial,[36] a dose higher than 48 Gy in three fractions might not be necessary. A dose of 42–48 Gy in three fractions appears to be reasonable given the high local control and favourable toxicity profile, as has been shown in prospective trials. If a five-fraction regimen is used due to issues with meeting organ-at-risk constraints, a regimen of 40 Gy in five fractions could be a reasonable alternative, although consideration should be given to increase the prescribed dose due to the reported lower long-term local control rate.[17] A recommendation of dose constraints is beyond the scope of this article; however, dose constraints adapted from TROG 15.03 FASTRACK II trial (NCT02613819) have been included in the appendix.

The role of kidney biopsy in patients who receive SBRT for primary renal cell carcinoma

Diagnostic imaging with CT or MRI and contrast constitutes the standard modality for response evaluation after SBRT for primary renal cell carcinoma. However, challenges exist in the interpretation of radiographic findings. The tumour mass and contrast enhancement commonly persist after SBRT, rendering response assessment difficult.[27]

Recognising the issues with response assessment after SBRT, the two phase 1 trials from Case Western Reserve University on SBRT for medically inoperable primary renal cell carcinomas incorporated post-treatment biopsies in the protocols. For the first phase 1 trial,[24] a post-treatment percutaneous biopsy was planned 6 months after SBRT. Among the 19 patients treated, 11 underwent a biopsy at a median of 9 months (range 5·8–21·7). Patients had negative (one patient), positive (seven), and atypical non-invasive (three) findings from biopsies. Two of the patients with a positive first biopsy underwent a second biopsy. One of these patients had

cryoablation before the second biopsy. Both second biopsies were negative for recurrent or residual disease. One of the two patients with a positive biopsy at 11 months, and a negative biopsy at 20·5 months, also had initial radiographic progression and did not undergo any salvage therapy, but the tumour subsequently shrank. In the second phase 1 trial,[36] 11 patients were enrolled, and an optional post-treatment biopsy was planned at 6–12 months for patients with residual masses. Standard haematoxylin and eosin staining protocols were used. A post-hoc analysis of post-treatment biopsy samples was done to identify whether major biomarkers of tumour viability post-SBRT could be established. Immunohistochemical analysis of Ki-67 and survivin (proliferation markers), CD34 (angiogenesis marker), mammalian target of rapamycin (mTOR), hypoxia-inducible factor 1, and hypoxia-inducible factor 2) expression were performed. Five of 11 patients consented to optional post-treatment biopsy at a median of 6 months and all biopsies were positive for tumour cells. Three received no therapy and were alive without local tumour or distant progression after 1·2–3·9 years. In the post-hoc pathological analysis, ten patients from the combined cohort from both phase 1 trials had matched pre-treatment and post-treatment biopsy tissue stained by immunohistochemistry for additional analysis. Only five patients had adequate tumour cells in both pre-SBRT and post-SBRT biopsy samples available for comparison. Ki-67 was negative and CD34 was positive in vessel staining for all specimens. Survivin and hypoxia-inducible factor 2 expression were more frequently absent in tumours after treatment compared with pre-treatment. However, there was no clear pattern of expression of these proteins.

Hannan and colleagues recently conducted a prospective, phase 2 clinical trial of SBRT for primary renal cell carcinoma.[44] Patients harbouring biopsy-proven, T1a–T1b tumours with established radiographic growth (median 0·8 cm per year) were treated with three-fraction (36 Gy) or five-fraction SBRT (40 Gy). A composite primary endpoint (radiographic with pathological response on post-treatment biopsy) was evaluated and showed 94% local control at a median follow-up of 36 months. Mean change in growth rate was –1·3 cm/year after SBRT. The authors also performed detailed histological and molecular analyses of post-treatment biopsies 1 year after SBRT: tumours showed decreased cellularity, increased fibrosis, increased hyalinisation (p=0·0039), and decreased Ki67 (p=0·0078). The remaining tumour cells were scarce and expressed p16 as an immunohistochemical marker of cellular senescence indicative of a terminal (permanently non-replicative) differentiation state. Transcriptomic and proteomic analysis also suggested differential regulation of gene sets involved in senescence and apoptotic pathways between pre-SBRT and post-SBRT specimens.

Overall, given that a positive biopsy does not predict subsequent local tumour and distant progression and there is no clear pattern of expression of biomarkers for tumour viability, a routine post-SBRT biopsy does not appear to contribute to response evaluation above diagnostic imaging alone and, therefore, is only recommended in patients with imaging findings concerning disease progression. In contrast, pre-treatment biopsy confirmation is recommended. As SBRT for primary renal cell carcinoma is an emerging treatment option, the burden of proof lies with this modality. Therefore, to establish robust evidence in comparison with surgery, biopsy confirmation is highly recommended. Of note, the biopsy confirmation rate of reported series is similar to that in the thermal ablation literature.

See **Online** for appendix

The role of SBRT and SABR in patients with a solitary kidney

A new primary renal cell carcinoma tumour in a solitary kidney is an uncommon, but challenging scenario for the management of primary renal cell carcinoma. This situation most commonly arises in the context of a previous nephrectomy for primary renal cell carcinoma in a contralateral kidney. Less commonly, the presence of a congenitally atrophic kidney or a non-functioning contralateral kidney can also manifest as a presentation. Surgical resection can increase the risk of end-stage renal dysfunction and subsequent dialysis, particularly when the new primary tumour has a complex morphology, which can preclude nephron-sparing approaches. Evidence for the treatment of a solitary kidney with SBRT was initially published in 2007, with a series of seven patients treated for a solitary kidney.[16] The authors reported local control in six of seven cases. Serum creatinine was normal pre-treatment and remained stable in six of the cases, with no cases of dialysis required.

Since this study,[16] several subsequent clinical reports have included patients with a solitary kidney. In 2019, Correa and colleagues reported outcomes for 81 patients with a solitary kidney treated with SBRT for primary renal cell carcinoma, with a median follow-up of 2·6 years.[46] After SBRT, the mean estimated glomerular filtration rate decrease was –5·8 mL/min (–9% from baseline). None of the patients required dialysis. This cohort had a mean baseline estimated glomerular filtration rate of 64·6 mL/min, and 14 patients (21·5%) had a decrease in estimated glomerular filtration rate of 15 mL/min or more.

A dose–response relationship exists between the irradiated kidney cortical parenchyma volume and functional decline. As part of a clinical trial, a patient with a solitary kidney and 3·8 cm primary renal cell carcinoma with pre-existing chronic kidney disease (estimated glomerular filtration rate 48 mL/min) underwent serial 99mTc–DMSA SPECT–CT imaging (200 MBq injected activity) and estimated glomerular

filtration rate was calculated by 51Cr-EDTA plasma clearance at baseline (1 month pre-treatment) at 2 weeks, 3 months, 12 months, and 18-months post-SBRT.[47] Imaging indicated that renal cortical function is spared to regions with absorbed radiation dose values below approximately 50% of the prescription dose (13 Gy of a single 26 Gy fraction). Therefore, maximising the conformality of SBRT delivery should be a high priority in this context.

To prevent kidney function decline, both patient selection and treatment factors should be considered. Referral to a renal medicine physician to minimise comorbidities and medications predisposing to further evolution of chronic kidney disease is recommended. Additionally, caution is advised when considering SBRT for patients with a solitary kidney and chronic kidney disease class 4 or 5–combined decision making regarding the risk of dialysis with any treatment intervention and involving a nephrologist is recommended irrespective of the treatment modality used. Finally, technical approaches should be considered to reduce the volume of irradiated kidney, particularly in the intermediate dose-wash region.

Optimal post-treatment follow-up schedule after SBRT or SABR for primary renal cell carcinoma

Post-treatment follow-up after SBRT should be consistent with surgical guidelines. Cross-axial imaging of the abdomen, including both kidneys and adrenals, should be performed. As a minimum, surveillance scans, including chest imaging, should be used to assess distant disease recurrence. A consensus statement issued by IROCK in 2016 was based on responses from eight institutions.[48] All institutions used CT (with contrast when renal function allowed) for response assessment of the treated primary tumour. In addition, five centres used MRI imaging. Follow-up frequency was 3–4 months for the first year, 3–6 months for the second year, and 3–12 months for the subsequent 3 years for all centres. Occasionally, however, tumours might be seen to initially enlarge in the immediate post-treatment period putatively due to post-therapy inflammation.[49,50] Based on these findings, the TransTasman Radiation Oncology Group 15.03 (FASTRACK II) study protocol specifies that the first post-treatment CT imaging occurs at 6 months.[51] Renal function tests, including urea, electrolytes, and estimated glomerular filtration rate should be performed at scheduled follow-up visits.

The RECIST criteria is the most common system for assessing response and tumour control after SBRT. It is important to note that primary renal cell carcinoma reduces in size over many years after SBRT.[27,50] Central necrosis is common within the renal cell carcinoma carcass, which is not captured by traditional size measurements. However, RECIST is a generalised system applied to all solid tumour measurements and does not necessarily consider the specificities of the tumour location or treatment modality. The American Urological Association have presented a definition more specific to the kidney, which might be relevant to thermal ablation or post-surgical changes. Although this is more site-specific than RECIST, it is problematic when applied to the post-SBRT setting.[52] In particular, the absence of enhancement, which might apply to surgery and thermal ablation[53] is not particularly useful following SBRT. Contrast enhancement changes often slowly evolve after radiotherapy. Contrast enhancement might initially increase post-therapy in primary clear cell renal cell carcinoma (potentially due to inflammatory effects on vasculature) and does not correlate to tumour control.[27]

Summary of recommendations

Taken together, the data for primary renal cell carcinoma suggests that a single fraction of 25–26 Gy is an attractive treatment strategy associated with optimal outcomes in smaller tumours. Ideal alternatives include 42–48 Gy in three fractions, and potentially 40 Gy in five fractions; however, control rates with this five-fraction schedule have yet to match 1–3-fraction regimens. Post-treatment biopsy should not be recommended in routine clinical practice, as conventional immunohistochemistry does not correlate to outcomes. For patients with a solitary kidney, SBRT is an approach associated with excellent

	Level of evidence	Strength of recommendation	Citation
Optimal dose regimens for SBRT in patients with primary renal cell carcinoma include 26 Gy in one fraction if the tumour is ≤4–5 cm and 42–48 Gy in three fractions if the tumour is >4–5 cm, or potentially 40 Gy in five fractions if the dose constraints for organs-at-risk cannot be met for three fractions	IV	Moderate	8, 9, 17, 20, 26, 29, 36, 44, 45
A routine post-SBRT biopsy should not be performed to evaluate response and is only recommended in patients with imaging findings concerning for disease progression	IIb	Strong	24, 36, 44
For patients with a solitary kidney, SBRT is an approach associated with both excellent local control and acceptable renal function preservation (except in patients with stages 4 and 5 chronic kidney disease); technical approaches to reduce the volume of irradiated kidney, particularly in the intermediate dose-wash region, is recommended	IIIa	Strong	16, 46, 47
Optimal post-treatment follow-up schedule after SBRT for primary renal cell carcinoma includes cross-axial imaging of the abdomen, including both kidneys and adrenals every 6 months and surveillance scans including chest imaging at a minimum	IIb	Moderate	48–52

Level of evidence derived using Oxford Centre for Evidence-Based Medicine: Levels of Evidence.[54] Strength of recommendation derived using GRADE consensus methodology.[55] RCC=renal cell carcinoma. SBRT=stereotactic body radiotherapy.

Table 3: **ISRS recommendations for patients with primary renal cell carcinoma receiving SBRT**

local control and acceptable renal function preservation. Although follow-up schedules are not completely standardised, early cross-axial imaging (ie, 3 months post-therapy) can be confounded by pseudo-progression, therefore, it might not be informative to eventual disease control. Imaging evaluating the chest and abdominal regions is required, and a suggested schedule is 6 monthly contrast-enhanced CT imaging. Renal function tests, including urea, electrolytes, and estimated glomerular filtration rat, should be performed at scheduled follow-up visits. Recommendations are summarised in table 3. The ideal candidates for SBRT are patients who are medically inoperable, technically not suited to surgery, or are at high risk of postoperative dialysis. There is no uniform consensus for medical inoperability, but it is assessed by multidisciplinary review and by a urologist considering medical comorbidities, such as poor cardiac function, bleeding diathesis, poor performance status, high risk for general anaesthesia.

Conclusions

SBRT for primary kidney cancer is an emerging modality, with reported outcomes to date being comparable to those of other local treatment modalities. Importantly, the evidence for SBRT in the primary renal cell carcinoma setting is buttressed by multiple rigorously conducted prospective clinical trials. By comparison, there are no prospective trials of thermal ablation yet. Surgical data are also restricted, with the pivotal study of surgery being the EORTC phase 3 trial, which in the purist interpretation, found that radical nephrectomy remains the standard of care over partial nephrectomy.[1] Future studies should focus on novel response assessment tools to optimise follow-up methods. Furthermore, SBRT for primary renal cell carcinoma in the context of metastases is an area of active investigation; two ongoing randomised trials investigating cytoreductive SBRT are actively recruiting—CYTOSHRINK (NCT04090710) and SAMURAI (NCT05327686). With the evolution of the current body of evidence, we suggest that the next iteration of studies should involve multicentre clinical trials with larger sample sizes and long-term follow-up. Comparative randomised trials with other treatment modalities are eagerly awaited.

Contributors

SS, SSL, AS, and RK were responsible for conceptualisation, development of the methodology, and supervision of the study. MA, MNB, SS, and SSL were responsible for data collection and curation, investigation, and project administration. ZZ conducted the formal analyses. SS, SSL, AVL, MNB, MA, ZZ, AS, and RK were responsible for writing the first draft of the systematic review. MG, M-SK, MS, ACT, and BJS were responsible for method, validation, and critical review and revision of the systematic review. SS and SSL directly accessed and verified the underlying data reported in the systematic review and all authors reviewed the final version and take responsibility for the decision to submit this systematic review for publication.

Declaration of interests

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