NHS England Evidence Review:

Stereotactic ablative body radiotherapy for primary kidney cancer

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Prepared by Solutions for Public Health (SPH) on behalf of NHS England Specialised Commissioning

Contents

1. Introduction

This evidence review examines the clinical effectiveness, safety and cost effectiveness of stereotactic ablative body radiotherapy (SABR) with or without supportive care compared to standard care alone for the treatment of medically inoperable localised primary kidney cancer (renal cell carcinoma).

The population covered by this review includes medically inoperable patients with localised T1[1] primary kidney cancer or renal cell carcinoma (RCC)[2]. For the purposes of this review, the term medically inoperable includes patients with comorbidities precluding surgery, including but not limited to patients unfit for a general anaesthetic, those with a solitary kidney or those using anticoagulants.

SABR is a highly targeted form of external radiation therapy which targets a tumour with radiation beams from different angles at the same time, enabling the tumour to receive a high dose of radiation while the tissues around the tumour receive a low dose. The treatment is delivered in fewer numbers of treatments (hypofractionation) than conventional radiotherapy using one to eight treatments, called 'fractions', which are delivered in outpatient day case settings.

Current standard care for patients who are medically inoperable includes ablation (such as cryotherapy, radiofrequency ablation and microwave ablation), watchful waiting and supportive care. Exclusion criteria for ablation include, for example, if the tumour is close to vessels or the renal pelvis.

In addition, the review scope included the identification of possible subgroups of patients within the included studies who might benefit from SABR more than others, and the dose, fractionation and duration of SABR that were used in the included studies.

[1] T1 renal cell carcinoma includes T1a tumours (tumours between 0cm and 4cm in maximum diameter) and T1b tumours (tumours between 4cm and 7cm in maximum diameter).
[2] The terms primary kidney cancer and renal cell carcinoma (RCC) are used interchangeably.

2. Executive summary of the review

This evidence review examines the clinical effectiveness, safety and cost effectiveness of stereotactic ablative body radiotherapy (SABR) with or without supportive care compared to standard care alone for the treatment of medically inoperable, localised primary kidney cancer (renal cell carcinoma (RCC)). The searches for evidence published since January 2013 were conducted on 15th September 2023 and identified 520 potential references. These were screened using their titles and abstracts and 34 full text papers potentially relating to the use of SABR for treating people with medically inoperable localised RCC were obtained and assessed for relevance.

Three prospective case series (Siva et al 2017 (n=37), Swaminath et al 2021 (n=32), Zarkar et al 2023 (n=19)) and three retrospective case series (Glicksman et al 2023 (n=74), Correa et al 2019 (n=81), Sun et al 2016 (n=40)), none of which included a comparator group, were identified for inclusion. The included studies ranged in follow-up duration from six months to a median of 2.57 years, with the latest time point reported being four years. Outcomes reported included the critical outcomes of local control (five studies), overall survival (four studies) and progression free survival (four studies) and the important outcomes of cancer specific survival (two studies), health related quality of life (one study), organ specific disease (four studies) and safety (two studies). No studies were identified that reported the important outcome of time to further intervention.

One cost effectiveness analysis (Donovan et al 2022) which compared SABR with radiofrequency ablation (RFA) over a five-year time horizon from the perspective of the Canadian public health care payer was identified for inclusion.

In terms of clinical effectiveness:

For all the clinical effectiveness outcome measures reported, because none of the studies included a comparator group of patients who did not receive SABR, it is not clear how the outcomes reported for patients treated with SABR compare with outcomes for people who receive other treatments or supportive care instead of SABR.

- **Local control (critical outcome)**
    - Five case series that included patients with medically inoperable, localised RCC provided very low certainty evidence relating to local control rates. Rates of failure of local control reported were under 10% up to four years after treatment with SABR. 61% of patients had an objective reduction in tumour size at one year in one study. *Statistically significant* reductions in mean tumour growth rates and tumour size were reported in another study.

- **Overall survival (critical outcome)**
    - Four case series that included patients with medically inoperable localised RCC provided very low certainty evidence relating to overall survival rates. Two of the studies reported overall survival rates of over 90%, with one study reporting results up to four years after SABR (overall survival rate 91.6%). A third study reported an overall survival rate of 78.3% at one year (six of the seven deaths in this study were not related to SABR or RCC), and a fourth study reported overall survival of 73.6% at four years. The relatively small size of the studies meant that confidence intervals for survival rates, where reported, were relatively wide (for example 81% to 100% at two years).

- **Progression free survival (critical outcome)**
    - Four case series that included patients with medically inoperable localised RCC provided very low certainty evidence relating to progression free survival rates, with two

studies reporting results up to four years after SABR treatment (progression free survival rate 89.7% and 68.3% respectively). Rates of close to 90% were reported at two years after SABR in two studies while the third study reported a progression free survival rate of 77.5% at 2 years. The relatively small size of the studies meant that confidence intervals for survival rates, where reported, were relatively wide (for example 78% to 100% at two years).

- **Cancer specific survival (important outcome)**
    - Two case series that included patients with medically inoperable localised RCC provided very low certainty evidence relating to cancer specific survival rates, reporting one death related to cancer over a median follow-up period of 17 months in one study and a cancer specific survival rate of 98.2% up to 4 years in the second study.

- **Time to further intervention (important outcome)**
    - No evidence was identified for this outcome.

- **Health related quality of life (QoL)**
    - One prospective case series that included patients with medically inoperable localised RCC provided very low certainty evidence relating to health related QoL outcomes over a six month follow-up period using three different tools that include a variety of QoL-related metrics. No statistically significant change in any QoL metric was reported over the 6 month period. Two of the many comparisons of individual time points to baseline for individual metrics resulted in p-values just below 0.05, but given the number of comparisons made, they do not reliably indicate statistical significance. The large amount of missing data at each time point further reduces the certainty of the results.

- **Organ specific disease response**
    - Four case series that included patients with medically inoperable localised RCC provided very low certainty evidence relating to changes in renal function, with one study reporting results up to four years after SABR treatment. The studies reported a *statistically significant* reduction in estimated glomerular filtration rate (eGFR) of -5.4ml/min at six months to a larger reduction (-14ml/min) at four years, although confidence intervals were relatively wide. One study also reported improvements in eGFR in 18.8% of patients at one year and 15% at two years reducing to 0% at four years and another study reported an increase in eGFR in 26.2% of patients with a solitary kidney at a median of 20.4 months. One study reported an increase in the number of patients on dialysis (5.4% increase) and the number with stage 3 chronic kidney disease, as well as a reduction in the proportion of renal function from the SABR-treated kidney over the course of the study (median follow-up 28 months). A second study (in patients with a solitary kidney) reported no patients on dialysis at a median of 20.4 months after SABR.

In terms of safety:

- **Adverse effects**
    - Two case series that included patients with medically inoperable localised RCC provided very low certainty evidence relating to adverse events following SABR. One study (n=33) reported that 58% of patients had at least one Grade 1 adverse event, 21% had at least one Grade 2 event and 3% had at least one Grade 3 event, with the Grade 3 event being fatigue in one patient more than 90 days after SABR. The second study (n=19) reported the worst Grade of each type of adverse event over each patient's follow-up period. Most types of adverse events listed were not reported at all by over 89% of patients, except for fatigue (63.3% of patients had Grade 1 fatigue and 15.8%

had Grade 2 fatigue) and nausea (5.3% of patients had Grade 1 nausea and 21.1% had Grade 2 nausea). Grade 3 adverse events (anaemia, colitis and haematuria) were experienced by single patients. Without a comparator group in either of the studies, it is not clear how many of these events are experienced by people who receive other treatments or supportive care instead of SABR.

In terms of cost effectiveness:

- One recent cost effectiveness analysis compared treatment of patients with inoperable early stage RCC with SABR compared to treatment with RFA over a 5-year time horizon based on the Canadian health care payer's perspective (including costs of personnel, supplies and capital but not rehabilitation and medication costs). This study reported that SABR was cost effective compared to RFA (incremental cost effectiveness ratio (ICER) of Canadian dollars (CAD) -4,490 per quality assured life year (QALY) gained). Sensitivity analyses suggested that the rate of distant metastasis had the greatest impact on calculated ICERs followed by utility values. The Canadian perspective of this study and any recent changes in treatment of metastatic RCC may limit its generalisability to the current NHS context in England.

In terms of subgroups:

- **T1a vs T1b tumours[3]**
  - One retrospective case series reported hazard ratios (HRs) for the critical outcomes of local control, overall survival and progression free survival for people with T1b vs T1a inoperable RCC who received treatment with SABR. No statistically significant differences were observed in these outcomes for T1b compared to T1a tumours. Another retrospective case study reported a *statistically significant* association between having a tumour of ≥4cm and having a 15ml/min or greater decrease in eGFR after SABR treatment. Without a comparator group included in these studies, it is not clear whether outcomes are significantly different for T1b vs T1a tumours in people who receive other treatments or supportive care instead of SABR. One recent cost effectiveness analysis reported a substantially higher cost effectiveness of SABR for people with T1b tumours (ICER per QALY gained CAD -22,904) compared to T1a tumours (ICER per QALY gained CAD 2,207).[4]

- **T1a tumours suitable for ablative procedures vs not suitable for ablative procedures**
  - No evidence was identified pertaining to these subgroups from the studies selected for inclusion in this review.

- **Solitary kidney vs two kidneys**
  - No evidence was identified pertaining to these subgroups from the studies selected for inclusion in this review.

- **Anticoagulant use vs no anticoagulant use**
  - No evidence was identified pertaining to these subgroups from the studies selected for inclusion in this review.

[3] The term T1a includes tumours between 0cm and 4cm in maximum diameter; the term T1b includes tumours between 4cm and 7cm in maximum diameter.
[4] These results were reported in the abstract and narrative; Table 3 of the paper reported slightly different results: ICER per QALY gained of CAD -29,905 for T1b tumours and CAD 2,208 for T1a tumours.

Dose, fractionation and duration of SABR used:

- The six included case series delivered SABR treatment (volumetric arc therapy, intensity modulated therapy, CyberKnife) at doses varying from 21Gy to 70Gy in different numbers of fractions ranging from one to ten. Different regimens tended to be used within individual studies. Where reasons for this were reported it was either based on physician decision, tumour size, location within the kidney, proximity to upper abdominal organs at risk or changes in practice over the duration of the study. Where multiple fractions were used, one study reported these being daily and four studies reported that fractions were delivered on alternate or non-consecutive days. None of the studies reported the duration of time required to deliver the SABR treatment.

Limitations

The most important limitation relating to the evidence included is the lack of a comparator group. This means that it is not clear whether the outcomes reported for patients with localised medically inoperable RCC after treatment with SABR are different from those after other treatments or supportive care instead of SABR. Other limitations that reduce the certainty in the outcomes reported include the retrospective nature of three of the studies; five of the studies not being UK based and most being single centre studies; the varying reasons for patient inclusion from being unfit for a general anaesthetic to high risk of post-surgical need for dialysis to patient refusal of surgery; unclear reporting about whether there was complete inclusion of patients; and missing data, particularly for the study of health related QoL.

Limitations introducing uncertainty to the cost effectiveness evidence in relation to its generalisability to the NHS in England include the Canadian perspective of the analysis, together with the variability reported in the sensitivity analyses and the use of relatively older literature relating to outcomes (particularly if newer treatments are now available for metastatic RCC).

Conclusion

This evidence review includes six case series reporting outcomes after treatment with SABR for patients with localised medically inoperable early stage RCC followed up for up to a median of 2.57 years, with one study reporting outcomes up to four years after SABR. With respect to critical outcomes, overall, these case series reported a relatively low rate of failure of local control (2% and 7.77% at four years in two studies respectively), overall survival rates of over 90% in most studies (91.6% at four years in one study, 73.6% at four years in a second study), and progression free survival rates of close to 90% at up to four years after SABR in one study and 68.3% in a second study. For the important outcomes, two studies reported cancer specific survival rates of over 90%; one study of health related QoL outcomes reported no statistically significant trends in a number of QoL measures over the 6 months after SABR treatment; and four of the studies reported renal function outcomes after SABR. These studies reported a statistically significant reduction in average eGFR up to four years after SABR, although some patients had in improved eGFR initially (15% of patients at 2 years in one study and 26.2% at a median of 20.4 months in a second study). One study reported that patients had a reduction in the proportion of renal function from the SABR-treated kidney.

Safety outcomes were reported by two case series. Most adverse events were Grade 1 or Grade 2. The most common adverse events reported were fatigue, nausea and chest wall pain. The only Grade 3 adverse events reported were fatigue (one patient) in one study (n=33) and anaemia, colitis and haematuria in another study (1 patient each, n=19). No Grade 4 adverse events were reported.

Subgroup analysis in one study did not show any statistically significant differences in outcomes for T1b tumours compared to T1a tumours, while another study reported a statistically significant association between a fall in eGFR after SABR and having a tumour of 4cm or greater. No subgroup results were reported by the included studies in relation to patients suitable vs unsuitable for ablative procedures, patients with one vs two kidneys or patients using vs not using anticoagulants.

The treatment schedules for SABR in the included studies varied from 21Gy to 70Gy delivered in one to ten fractions usually on alternate days, with decisions about treatment schedules based on a variety of reasons including physician decision, tumour characteristics and changes in clinical practice over time.

One recent cost effectiveness analysis from the Canadian public health care payer's perspective over a 5-year time horizon reported an ICER of CAD -4,490 per QALY gained for SABR compared to RFA, with the cost effectiveness being substantially higher for T1b tumours (ICER per QALY CAD -22,904) compared to T1a tumours (ICER per QALY CAD 2,207).

Overall, these case series reported relatively good outcomes following SABR in relation to local control, overall survival, progression free survival, other important outcomes and safety, but it is not clear how the reported outcomes compare with outcomes in the same patient group who do not receive SABR. In addition, SABR was assessed to be cost effective compared to RFA, although there may be limitations in the generalisability of the study to the NHS in England.

3. Methodology

Review questions

The review questions for this evidence review are:

1. In people with medically inoperable localised primary kidney cancer, what is the clinical effectiveness of SABR treatment +/- supportive care compared with current standard care alone?
2. In people with medically inoperable localised primary kidney cancer, what is the safety of SABR treatment +/- supportive care compared with current standard care alone?
3. In people with medically inoperable localised primary kidney cancer, what is the cost-effectiveness of SABR treatment +/- supportive care compared with current standard care alone?
4. From the evidence selected, are there any subgroups of patients that may benefit from SABR treatment +/- supportive care more than the wider population of interest?
5. From the evidence selected, what dose, fractionation and duration of SABR were used?

See Appendix A for the full review protocol.

Review process

The methodology to undertake this review is specified by NHS England in their *'Guidance on conducting evidence reviews for Specialised Services Commissioning Products'* (2020).

The searches for evidence were informed by the PICO document and were conducted on 15th September 2023.

See Appendix B for details of the search strategy.

Results from the literature searches were screened using their titles and abstracts for relevance against the criteria in the PICO document. Full text references of potentially relevant evidence were obtained and reviewed to determine whether they met the inclusion criteria for this evidence review.

See Appendix C for evidence selection details and Appendix D for the list of studies excluded from the review and the reasons for their exclusion.

Relevant details and outcomes were extracted from the included studies and were critically appraised using a checklist appropriate to the study design. See Appendices E and F for individual study and checklist details.

The available evidence was assessed by outcome for certainty using modified GRADE. See Appendix G for GRADE Profiles.

4. Summary of included studies

Three prospective case series (Siva et al 2017, Swaminath et al 2021, Zarkar et al 2023) and three retrospective case series (Glicksman et al 2023, Correa et al 2019, Sun et al 2016), none of which included a comparator group, were identified for inclusion. The included studies ranged in follow-up duration from six months to a median of 2.57 years, with the latest time point reported being four years. Between them, the study outcomes reported included the critical outcomes of local control (five studies), overall survival (four studies) and progression free survival (four studies) and the important outcomes of cancer specific survival (two studies), health related quality of life (one study), organ specific disease (four studies) and safety (two studies). No studies were identified that reported the important outcome of time to further intervention.

One cost effectiveness study (Donovan et al 2022) which compared SABR with radiofrequency ablation (RFA) over a five-year time horizon was identified for inclusion.

Table 1 provides a summary of the included studies and full details are given in Appendix E.

Table 1: Summary of included studies

Study	Population	Intervention and comparison	Outcomes reported

Correa et al 2019
 	
Retrospective case series
 	
Germany, Australia, USA, Canada, Japan; 9 institutions
	81 patients with RCC in a solitary kidney treated with SABR[a]
	
	Mean maximum tumour dimension (mm): 35.0, median 37.2 (IQR 25.0 to 42.9)
	
	Median age 66.5 years (range 42.2 to 93.3)
	
	Histology not available for 7 (8.6%); 91.4% clear cell RCC
	
	Subgroup analysis: decrease in eGFR for tumours ≥4cm vs <4cm
		Intervention
		
		SABR (no further detail reported)
		
		Mean total dose (Gy): 28.9 (SD ± 12.3), median 25.0 (range 14.0 to 70.0)
		
		Mean number of fractions: 1.9 (SD ± 2.5), range 1 to 10
		
		Single fraction only: 13 patients (16.1%)
		
		Mean fraction dose (Gy): 22.1 (SD ± 6.0), median 25.0 (range 6.0 to 26.0)
		
		Comparison
		No comparator group
			Median follow-up 2.57 years (95% CI 2.12 to 3.33)
			
			Critical outcomes
			• Local control (based on RECIST criteria[b]) at 2 and 4 years
			• Overall survival at 2 and 4 years
			• Progression free survival at 2 and 4 years
			
			Important outcomes
			• Cancer specific survival at 2 and 4 years
			• Organ specific disease at median of 20.4 months
			  • Change in eGFR from baseline
			  • % at each level of CKD based on eGFR
			  • % with decrease in eGFR of ≥15 ml/min
			  • % with increase in eGFR from baseline
			  • % on dialysis

Donovan et al 2022 Cost effectiveness study using outcome data from literature review Canadian public health care	Patients with early stage, node negative, kidney confined medically inoperable RCC Subgroup analysis included T1a vs T1b tumours Outcome data based on literature review; sample size not reported	**Intervention** SABR, 5 fractions **Comparison** RFA Included costs of supplies, personnel, capital costs and machinery	**Important outcomes** • Cost effectiveness • ICER per QALY gained over 5-year time horizon

Study	Population	Intervention and comparison	Outcomes reported
payer's perspective			

Glicksman et al 2023
 	
Retrospective case series
 	
Canada, single centre
	74 patients with localised RCC treated with curative-intent who were deemed medically inoperable or unresectable or declined surgery
	
	T1 to T4 tumours (T1 89%) with no evidence of lymph node or distant metastases
	
	Median age 80 years (IQR 73 to 86)
	
	Histology not available for 39 (52.7%)
	
	Subgroup analysis included T1a vs T1b tumours
		Intervention
		SABR using IMRT (2.7%) or VMAT (97.3%), 35 to 45Gy in 5 fractions or 42Gy in 3 fractions (physician's decision) delivered on alternate days
		
		30Gy in 5 fractions: 1 patient (1.4%)
		35Gy in 5 fractions: 22 patients (29.7%)
		40Gy in 5 fractions: 41 patients (55.4%)
		45Gy in 5 fractions: 6 patients (5.4%)[c]
		42Gy in 3 fractions: 4 patients (8.1%)[c]
		
		Comparison
		No comparator group
			Median follow-up 27.8 months (IQR 17.6 to 41.7)
			
			Critical outcomes
			• Local control
			  • Cumulative incidence of local failure (based on RECIST criteria) at 1, 2 and 4 years
			• Overall survival at 1, 2 and 4 years
			• Progression free survival at 1, 2 and 4 years
			
			Important outcomes
			• Organ specific disease
			  • Median change in eGFR from baseline to 1, 2 and 4 years
			  • % with improved eGFR compared to baseline at 1, 2 and 4 years
			  • % with stage 3+ chronic kidney disease
			  • Additional patients on dialysis
			  • Proportion of renal function from the ipsilateral (SABR-treated) kidney at 1, 2 and 4 years
			  • Change in proportion of renal function from the ipsilateral kidney over time

Siva et al 2017
 	
Prospective case series
 	
Australia, single centre
	37 patients with small RCC who were medically inoperable, high risk for surgery because of likelihood of post-surgical dialysis or refused surgery, and who had not received current or prior systemic therapy or previous high-dose radiotherapy to the upper abdomen
	
	T1 to T2 tumours (T1a 35%, T1b 62%, T2 3%)
	
	Median age 78 years (range 42 to 91)
	
	Histology not reported for 3 patients (9%)
		Intervention
		SABR using conventional c-arm linear accelerator
		
		RCCs <5cm maximum dimension: 26Gy, 1 fraction: n=17
		
		RCCs ≥5cm maximum dimension: 42 Gy in 3 fractions: n=17
		
		33/37 received all treatments (to 34 RCCs); 1 patient died prior to SABR (pulmonary embolus after international flight); 1 patient completed 2 of 3 planned fractions because of social difficulties; 2 patients could not meet planned dose constraints.
			Median follow-up 24 months, minimum 12 months
			
			Critical outcomes
			• Local control
			  • Objective tumour size reduction at 1 year
			  • Local control based on RECIST criteria at last follow-up
			• Overall survival at 1 and 2 years
			• Progression free survival at 1 and 2 years (freedom from local and distant progression)
			
			Important outcomes
			• Organ specific disease
			  • Mean change in eGFR from baseline to 1 and 2 years

Study	Population	Intervention and comparison	Outcomes reported
	No subgroup analysis reported	**Comparison** No comparator group	• Safety • Grade 1, 2 and 3 events at ≤90 days after SABR, >90 days after SABR and overall

Sun et al 2016
 	
Retrospective case series
 	
USA, single centre
	40 patients (41 tumours) with renal masses who were deemed to be poor candidates for surgery or minimally invasive tumour ablation who had had at least 2 imaging studies before SABR and 1 after SABR and had not had repeat cycles of SABR
	
	T1 to T2 tumours (T1a 53.7%, T1b 43.9%, T2a 2.4%)
	
	Median age 74.5 years (range 45 to 93)
	
	Histology not available for 8 (19.5%) and 1 (2.4%) had urothelial carcinoma; remainder had RCC
	
	No subgroup analysis reported
		Intervention
		SABR using CyberKnife system with Synchrony system (Accuracy) to track movement
		
		SABR dose (Gy): mean 38, range 21 to 48
		
		Delivered in daily fractions: Initially 21 Gy in 3 fractions. Gradually increased during the study period to 48 Gy in 3 fractions.
		
		Number of tumours:
		21Gy: 3
		24Gy: 1
		27Gy: 4
		30Gy: 5
		33Gy: 2
		36Gy: 2
		39Gy: 8
		45Gy: 1
		48Gy: 15
		
		Comparison
		No comparator group
			Median follow-up 561 days (range 83 to 1,366), median 489
			
			Critical outcomes
			• Local control
			  • Local control based on RECIST criteria
			  • % with <5mm growth
			  • Mean tumour growth rate (average of 3 linear dimensions)
			  • Mean tumour volume growth rate
			  • Change in size of tumours

Swaminath et al 2021
 	
Prospective case series
 	
Canada, 2 institutions
	32 patients with non-metastatic RCC who were medically inoperable, ineligible for other locally ablative treatments or refused surgery with ECOG performance status[d] of 2 or less
	
	T1 tumours (T1a 40.6%, T1b 59.4%)
	
	Median age not reported (<70 years: n=5; 71 to 80 years: n=9; 81 to 90 years: n=15; >90 years: n=3)
	
	Histology not available for 9 (28.1%)
	
	No subgroup analysis reported
		Intervention
		SABR using VMAT
		
		35Gy in 5 fractions: 16 patients, 50%
		40Gy in 5 fractions: 11 patients, 34.4%
		45Gy in 5 fractions: 1 patient, 3.1%
		42Gy in 3 fractions: 4 patients, 12.5%
		
		Fractions delivered every second day.
		
		Selected dose based on tumour size, location within kidney, and proximity to upper abdominal organs at risk
		
		Comparison
		No comparator group
			Median follow-up not reported
			
			Important outcomes
			• Health related QoL
			  • EQ-5D-3L[e] visual analogue scale and health utility score at 1 week, 1 month, 3 months and 6 months
			  • EORTC-QLQ-C15-PAL[f] global QoL score, physical functioning, emotional functioning, fatigue, nausea and vomiting, dyspnoea, pain, insomnia, appetite, and constipation at 1 week, 1 month, 3 months and 6 months
			  • FACT FKSI-19[g] overall converted score at 1 week, 1 month, 3 months and 6 months

Study	Population	Intervention and comparison	Outcomes reported

Zarkar et al 2023
 	
Prospective case series
 	
UK, single institution
	19 patients with T1 non-metastatic RCC who were non-surgical candidates (not fit for general anaesthetic or unsuitable for CA/RFA due to location of tumour) with consensus at urological MDT that radical treatment was appropriate
	
	T1 tumours (<4cm: n=5; ≥4cm: n=14)
	
	Median age 76 years (IQR 64 to 82)
	
	Histology: all 19 had biopsy confirmed RCC
	
	No subgroup analysis reported
		Intervention
		
		SABR using standard Linear Accelerator, using volumetric modulated arc therapy (VMAT) (n=11) or CyberKnife (n=8)
		
		26Gy in 1 fraction: 8 patients
		42Gy in 3 fractions on alternate days: 11 patients
		
		Comparison
		No comparator group
			Median follow-up 17 months (range 5 to 32 months)
			
			Critical outcomes
			• Local control
			  • Local control based on RECIST criteria at 6 months and 12 months
			  • Median reduction in tumour size from baseline to 6 months and 12 months
			  • Rate of local control at 6 months and 12 months
			• Overall survival at 6 months and 12 months
			• Progression free survival over whole follow-up period
			
			Important outcomes
			• Cancer specific survival
			  • Deaths related to cancer over whole follow-up period
			• Organ specific disease
			  • Mean change in eGFR from baseline to 6 months, 6 months to 12 months and baseline to 12 months
			• Safety
			  • Worst grade of each type of adverse event (grades 1, 2, 3 or 4) over each patient's follow-up period

Abbreviations
CA: cryoablation; CKD: chronic kidney disease; ECOG: Eastern Cooperative Oncology Group; eGFR: estimated glomerular filtration rate; EORTC QLQ-C15-PAL: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 15 Palliative Care; EQ-5D-3L: European Quality of Life 5 Dimensions 3 Level; FACT FKSI: Functional Assessment of Cancer Therapy – Kidney Specific Index; Gy: Gray; ICER: Incremental cost effectiveness ratio; IMRT: intensity modulated radiotherapy; IQR: Interquartile range; MDT: multi-disciplinary team; QoL: quality of life; QALY: Quality-adjusted life year; RCC: renal cell carcinoma; RECIST: Response Evaluation Criteria in Solid Tumours; RFA: radiofrequency ablation; SABR: stereotactic ablative body radiotherapy; T stage: tumour stage; UK: United Kingdom; USA: United States of America; VMAT: volumetric modulated arc therapy

a Correa et al (2019) also included a group of patients with 2 kidneys. However, as there was no indication that that group were medically inoperable, only data for the group with a single kidney are reported here (having only one kidney effectively means that the patient's RCC is medically inoperable).
b RECIST is a set of published rules that define when tumours in cancer patients improve ("respond"), stay the same ("stabilize"), or worsen ("progress") during treatment.
c These figures were reported in Table 2 of the paper. However, 6/74 is in fact 8.1% and 4/74 is 5.4%.
d The ECOG performance status score describes a patient's level of functioning in terms of their ability to care for themself, daily activity, and physical ability (walking, working, etc.). Higher score indicates greater disability
e EuroQol-5D-3L (EQ-5D-3L) is a standardised health questionnaire that provides a simple descriptive profile and a single value for health status. It is made up of five dimensions (mobility, self-care, usual activities, pain or discomfort and anxiety or depression), each of which are rated at one of three levels (no, some or severe problems).
f QLQ-C15-PAL is the abbreviated version of EORTC-QLQ-C30 (an established core cancer questionnaire). It consists of 15 categories, including functional scales (physical, emotional function), symptom scales (fatigue, pain, nausea, dyspnoea, insomnia, anxiety, depression, appetite loss, constipation) and a final question on global QoL.

Study	Population	Intervention and comparison	Outcomes reported
g FACT FKSI-19 is a 19-item questionnaire for the functional assessment of cancer therapy that includes disease-related symptoms specific to kidney cancer. It was developed with input from patients with kidney cancer and clinical experts.			

5. Results

In people with medically inoperable localised primary kidney cancer, what is the clinical effectiveness and safety of SABR treatment +/- supportive care compared with current standard care alone?

Outcome	Evidence statement
Clinical Effectiveness	
Critical outcomes	
Local control **Certainty of evidence:** Very low	Local control is important to patients because it reflects how effective the treatment is at preventing the cancer from growing or spreading. Local failure carries detrimental symptoms for the patient alongside the psychological burden of the recurrence of cancer. Two prospective and three retrospective case series provided evidence relating to local control measured at different time points up to four years. None of the studies included a comparator group. **At 6 months follow-up** • One prospective case series (Zarkar et al 2023) (n=15) (median follow-up 17 months, range 5 to 32 months) reported partial response for 3 patients and stable disease for 12 patients based on RECIST criteria[5]; a median reduction in tumour size of 16.67% (IQR 2.7 to 28.0) and a rate of local control of 94.4% (95% CI 66.6% to 99.2%). **(VERY LOW)** **At 12 months follow-up** • The same prospective case series (Zarkar et al 2023) (n=15) (median follow-up 17 months, range 5 to 32 months) reported partial response for 5 patients and stable disease for 9 patients based on RECIST criteria; a median reduction in tumour size of 26.5% (IQR 7.9 to 34.5) and a rate of local control of 94.4% (95% CI 66.6% to 99.2%). **(VERY LOW)** • One retrospective case series (Glicksman et al 2023) (n=74) (median follow-up 27.8 months, IQR 17.6 to 41.7) reported a cumulative incidence of local failure of 5.85%. **(VERY LOW)** • One prospective case series (Siva et al 2017) (n=33) (median follow-up 24 months, minimum 12 months) reported an objective tumour size reduction in 61% of RCCs. **(VERY LOW)** **At median follow-up of 16 months** • One retrospective case series (Sun et al 2016) (n=41 tumours) (mean follow-up 561 days, median 489 days) reported progressive disease for 1 tumour (2.4%), stable disease for 31 (75.6%), partial response for 8 (19.5%) and complete response 1 tumour (2.4%). This study also reported <5mm growth[6] for 38 tumours (92.7%) and *statistically significant reductions* in mean tumour growth rate (average of 3 linear dimensions) (before SABR 0.68 cm/year, after SABR -0.37 cm/year, p<0.0001 for each dimension) and in mean tumour volume growth rate (before SABR 21.21 cm^3/year, after SABR -5.35 cm^3/year, p=0.002). It reported narratively that there was a *"Statistically significant decrease of … the size of renal tumours"* after SABR (p-value not reported) and that no subsequent growth that met criteria for response to treatment subsequently did not meet criteria. **(VERY LOW)** **At 2 years follow-up or two years median follow-up** • One retrospective case series (Glicksman et al 2023) (n=74) (median follow-up 27.8 months, IQR 17.6 to 41.7) reported a cumulative incidence of local failure of 7.77%. **(VERY LOW)**

[5] RECIST is a set of published rules that define when tumours in cancer patients improve ("respond"), stay the same ("stabilize"), or worsen ("progress") during treatment.
[6] This figure included tumours that decreased in size or did not change in size

Outcome	Evidence statement
	• One retrospective case series (Correa et al 2019) (n=81) (median follow-up 2.57 years, 95% CI 2.12 to 3.33) reported local control rates, based on RECIST criteria, of 98.0% for patients with a solitary kidney. One patient had local disease recurrence. **(VERY LOW)** • One prospective case series (Siva et al 2017) (n=33) (median follow-up 24 months, minimum 12 months) reported partial response for 4 patients and stable disease for 28 patients at last follow-up based on RECIST criteria. **(VERY LOW)** **At 4 years follow-up** • One retrospective case series (Glicksman et al 2023) (n=74) (median follow-up 27.8 months, IQR 17.6 to 41.7) reported a cumulative incidence of local failure of 7.77%. **(VERY LOW)** • One retrospective case series (Correa et al 2019) (n=81) (median follow-up 2.57 years, 95% CI 2.12 to 3.33) reported local control rates, based on RECIST criteria, of 98.0% for patients with a solitary kidney. One patient had local disease recurrence. **(VERY LOW)** **Five case series that included patients with medically inoperable, localised RCC provided very low certainty evidence relating to local control rates. Rates of failure of local control reported were under 10% up to four years after treatment with SABR. 61% of patients had an objective reduction in tumour size at one year in one study. *Statistically significant* reductions in mean tumour growth rates and tumour size were reported in another study. However, without a comparator group in any of the studies, it is not clear how this compares with local control rates for people who receive other treatments or supportive care instead of SABR.**
Overall survival **Certainty of evidence:** Very low	Overall survival is important to patients because it reflects how long people live after treatment, although it does not take the cause of death into account, or provide information about their health and wellbeing during that time. Two prospective and two retrospective case series provided evidence relating to overall survival measured at different time points up to 4 years. None of the studies included a comparator group. **At 6 months follow-up** • One prospective case series (Zarkar et al 2023) (n=19) (median follow-up 17 months, range 5 to 32 months) reported an overall survival rate of 94.7% (95% CI 68.1% to 99.2%). **(VERY LOW)** **At 12 months follow-up** • The same prospective case series (Zarkar et al 2023) (n=19) (median follow-up 17 months, range 5 to 32 months) reported an overall survival rate of 78.3% (95% CI 51.9% to 91.3%). Of the 7 deaths, 6 were not related to SABR or RCC (cardiac arrest (1), sepsis (1), heart failure (1), left ventricular failure (1), pneumonia (2)) **(VERY LOW)** • One retrospective case series (Glicksman et al 2023) (n=74) (median follow-up 27.8 months, IQR 17.6 to 41.7) and a prospective case series (Siva et al 2017) (n=33) (median follow-up 24 months, minimum 12 months) both reported an overall survival rate of 100%. **(VERY LOW)** **At 2 years follow-up** • One retrospective case series (Glicksman et al 2023) (n=74) (median follow-up 27.8 months, IQR 17.6 to 41.7) reported an overall survival rate of 100%. **(VERY LOW)** • One retrospective case series (Correa et al 2019) (n=81) (median follow-up 2.57 years, 95% CI 2.12 to 3.33) reported an overall survival rate of 81.5% for patients with a solitary kidney. **(VERY LOW)** • One prospective case series (Siva et al 2017) (n=33) (median follow-up 24 months, minimum 12 months) reported an overall survival rate of 92% (95% CI 81% to 100%). **(VERY LOW)**

Outcome	Evidence statement
	At 4 years follow-up • One retrospective case series (Glicksman et al 2023) (n=74) (median follow-up 27.8 months, IQR 17.6 to 41.7) reported an overall survival rate of 91.6%. **(VERY LOW)** • One retrospective case series (Correa et al 2019) (n=81) (median follow-up 2.57 years, 95% CI 2.12 to 3.33) reported an overall survival rate of 73.6% for patients with a solitary kidney. **(VERY LOW)** **Four case series that included patients with medically inoperable localised RCC provided very low certainty evidence relating to overall survival rates. Two of the studies reported overall survival rates of over 90%, with one study reporting results up to four years after SABR (overall survival rate 91.6%). A third study reported an overall survival rate of 78.3% at one year (six of the seven deaths in this study were not related to SABR or RCC), and a fourth study reported overall survival of 73.6% at four years. The relatively small size of the studies meant that confidence intervals for survival rates, where reported, were relatively wide (for example 81% to 100% at two years). In addition, without a comparator group in any of the studies, it is not clear how these overall survival rates compare with overall survival rates for people who receive other treatments or supportive care instead of SABR.**
Progression free survival **Certainty of evidence:** Very low	Progression free survival is important to patients because it represents the time for which their disease is not progressing. Stable disease might represent longer survival and that patients experience less symptoms from the disease itself. It can be determined sooner than overall survival outcome measure and is therefore a useful outcome for studies with shorter follow-up periods. Two prospective and two retrospective case series provided evidence relating to progression free survival measured at different time points up to four years. None of the studies included a comparator group. **At 12 months follow-up** • One retrospective case series (Glicksman et al 2023) (n=74) (median follow-up 27.8 months, IQR 17.6 to 41.7) reported progression free survival of 91.4% (cumulative incidence of local progression 5.85%; cumulative incidence of distant metastasis 4.24%, 1 lung, 1 spine, 1 adrenal). **(VERY LOW)** • One prospective case series (Siva et al 2017) (n=33) (median follow-up 24 months, minimum 12 months) reported progression free survival of 97% (95% CI 91% to 100%) (freedom from distant progression 97%, 95% CI 91% to 100%; freedom from local progression 100%). **(VERY LOW)** **At median follow-up of 17 months** • One prospective case series (Zarkar et al 2023) (n=19) (median follow-up 17 months, range 5 to 32 months) reported that 1 patient had local progression and 2 had distant progression. **(VERY LOW)** **At 2 years follow-up** • One retrospective case series (Glicksman et al 2023) (n=74) (median follow-up 27.8 months, IQR 17.6 to 41.7) reported progression free survival of 89.7% (cumulative incidence of local progression 7.77%; cumulative incidence of distant metastasis 4.24%, 1 lung, 1 spine, 1 adrenal). **(VERY LOW)** • One retrospective case series (Correa et al 2019) (n=81) (median follow-up 2.57 years, 95% CI 2.12 to 3.33) reported a progression free survival rate of 77.5% for patients with a solitary kidney. **(VERY LOW)** • One prospective case series (Siva et al 2017) (n=33) (median follow-up 24 months, minimum 12 months) reported progression free survival of 89% (95% CI 78% to 100%) (freedom from distant progression 89%, 95% CI 78% to 100%; freedom from local progression 100%). **(VERY LOW)** **At 4 years follow-up**

Outcome	Evidence statement
	• One retrospective case series (Glicksman et al 2023) (n=74) (median follow-up 27.8 months, IQR 17.6 to 41.7) reported progression free survival of 89.7% (cumulative incidence of local progression 7.77%; cumulative incidence of distant metastasis 4.24%, 1 lung, 1 spine, 1 adrenal). **(VERY LOW)** • One retrospective case series (Correa et al 2019) (n=81) (median follow-up 2.57 years, 95% CI 2.12 to 3.33) reported a progression free survival rate of 68.3% for patients with a solitary kidney. **(VERY LOW)** **Four case series that included patients with medically inoperable localised RCC provided very low certainty evidence relating to progression free survival rates, with two studies reporting results up to four years after SABR treatment (progression free survival rate 89.7% and 68.3% respectively). Rates of close to 90% were reported at two years after SABR in two studies while the third study reported a progression free survival rate of 77.5% at 2 years. The relatively small size of the studies meant that confidence intervals for survival rates, where reported, were relatively wide (for example 78% to 100% at two years). In addition, without a comparator group in any of the studies, it is not clear how these progression free survival rates compare with progression free survival rates for people who receive other treatments or supportive care instead of SABR.**
Important outcomes	
Cancer specific survival **Certainty of evidence:** Very low	Cancer specific survival is important to patients because it reflects how long people live after treatment and excludes death due to causes unrelated to the cancer, although it does not provide information about their health and wellbeing during that time. One prospective case series and one retrospective case series provided evidence relating to cancer specific survival. The study did not include a comparator group. **At median follow-up of 17 months** • One prospective case series (Zarkar et al 2023) (n=19) (median follow-up 17 months, range 5 to 32 months) reported 1 death related to cancer. **(VERY LOW)** **At 2 years follow-up** • One retrospective case series (Correa et al 2019) (n=81) (median follow-up 2.57 years, 95% CI 2.12 to 3.33) reported a cancer specific survival rate of 98.2% for patients with a solitary kidney. **(VERY LOW)** **At 4 years follow-up** • One retrospective case series (Correa et al 2019) (n=81) (median follow-up 2.57 years, 95% CI 2.12 to 3.33) reported a cancer specific survival rate of 98.2% for patients with a solitary kidney. **(VERY LOW)** **Two case series that included patients with medically inoperable localised RCC provided very low certainty evidence relating to cancer specific survival rates, reporting one death related to cancer over a median follow-up period of 17 months in one study and a cancer specific survival rate of 98.2% up to 4 years in the second study. Without a comparator group in the study, it is not clear how this compares with cancer specific survival rates for people who receive other treatments or supportive care instead of SABR.**
Time to further intervention **Certainty of evidence:** Not applicable	Time to further intervention is important to patients because it is linked to disease progression, which carries detrimental symptoms for the patient alongside the psychological burden of the recurrence of cancer. Further intervention carries the risks of treatment related complications and effects on quality of life. **No evidence was identified for this outcome.**
Health related quality of life (QoL)	Health related QoL is important to patients because it provides a holistic evaluation and indication of the patient's general health and their perceived well-

Outcome	Evidence statement

Certainty of evidence: Very low	being and their ability to participate in activities of daily living. This outcome is both a key indicator of the effectiveness of treatment and provides an insight into the patient's perception of the effectiveness of treatment.
	
	One prospective case series provided evidence relating to health related QoL measured at different time points up to 6 months after SABR. The study did not include a comparator group. For the EQ-5D-3L scores, higher values indicate improvement. For the EORTC-QLQ-C15-PAL scores, higher values indicate, depending on the measure, higher quality of life, higher functioning or higher symptom burden. For the overall converted FACT FKSI-19 score, higher scores indicate fewer symptoms. For each of the three QoL tools used, the MCID in each direction (improvement or worsening) was reported and was used in making the assessment regarding "stable", "better" or "worse" QoL. For EORTC, the MCID used was 10 points in either direction, for the EQ-5D-3L overall health state score it was 0.08 and for the FACT total score it was 5 points.
	
	At 1 week follow-up
	• One prospective case series (Swaminath et al 2021) (n=32) reported changes in the EQ-5D-3L scores from baseline:
	  • Visual analogue scale (n=16): -0.938
	  • Health utility score (n=20): 0.050 (85.0% stable or better vs 15.0% worse).
	  (VERY LOW)
	• The same prospective case series (Swaminath et al 2021) (n=32) reported changes in the EORTC-QLQ-C15-PAL scores from baseline together with the % that were stable or better vs the % that were worse: (p-value only reported for Global QoL score)
	  • Global QoL score (n=20): -8.345 (45.0% vs 55.0%) (p=0.046)
	  • Physical functioning (n=20): -0.665 (80.0% vs 20.0%)
	  • Emotional functioning (n=20): -2.920 (65.0% vs 35.0%)
	  • Fatigue (n=20): 7.225 (60.0% vs 40.0%)
	  • Nausea and vomiting (n=20): 5.000 (90.0% vs 10.0%)
	  • Dyspnoea (n=19): 0.005 (95.0% vs 5.0%)
	  • Pain (n=20): 1.667 (70.0% vs 30.0%)
	  • Insomnia (n=20): -5.000 (85.0% vs 15.0%)
	  • Appetite (n=20): 5.000 (80.0% vs 20.0%)
	  • Constipation (n=19): 1.754 (90.0% vs 10.0%).
	  (VERY LOW)
	• The same prospective case series (Swaminath et al 2021) (n=32) reported the change in the overall converted FACT FKSI-19 score from baseline (n=20): 0.430 (85.0% stable or better vs 15.0% worse) **(VERY LOW)**
	
	At 1 month follow-up
	• One prospective case series (Swaminath et al 2021) (n=32) reported changes in the EQ-5D-3L scores from baseline:
	  • Visual analogue scale (n=22): 1.500
	  • Health utility score (n=23): 0.022 (79.2% stable or better vs 20.8% worse)
	  (VERY LOW)
	• The same prospective case series (Swaminath et al 2021) (n=32) reported changes in the EORTC-QLQ-C15-PAL scores from baseline together with the % that were stable or better vs the % that were worse:
	  • Global QoL score (n=24): -3.479 (70.8% vs 29.2%)
	  • Physical functioning (n=24): 1.388 (83.3% vs 16.7%)
	  • Emotional functioning (n=24): 2.087 (75.0% vs 25.0%)
	  • Fatigue (n=24): 4.642 (62.5% vs 37.5%)
	  • Nausea and vomiting (n=24): 0.000 (87.5% vs 12.5%)
	  • Dyspnoea (n=24): -0.008 (83.3% vs 16.7%)
	  • Pain (n=24): 0.694 (66.7% vs 37.3%)
	  • Insomnia (n=24): -2.778 (79.2% vs 20.8%)
	  • Appetite (n=24): 1.383 (70.8% vs 29.2%)

Outcome	Evidence statement
	• Constipation (n=23): 4.348 (79.2% vs 20.8%) **(VERY LOW)** • The same prospective case series (Swaminath et al 2021) (n=32) reported the change in the overall converted FACT FKSI-19 score from baseline (n=24): 0.908 (70.8% stable or better vs 29.2% worse) **(VERY LOW)** **At 3 months follow-up** • One prospective case series (Swaminath et al 2021) (n=32) reported changes in the EQ-5D-3L scores from baseline: • Visual analogue scale (n=16): 4.125 • Health utility score (n=17): -0.020 (76.5% stable or better vs 23.5% worse) **(VERY LOW)** • The same prospective case series (Swaminath et al 2021) (n=32) reported changes in the EORTC-QLQ-C15-PAL scores from baseline together with the % that were stable or better vs the % that were worse: • Global QoL score (n=17): -0.982 (70.6% vs 29.4%) • Physical functioning (n=16): -5.000 (68.3% vs 31.3%) • Emotional functioning (n=17): 1.471 (76.5% vs 23.5%) • Fatigue (n=17): 1.318 (70.6% vs 29.4%) • Nausea and vomiting (n=17): -6.859 (100% vs 0%) • Dyspnoea (n=17): 1.969 (88.2% vs 11.8%) • Pain (n=17): -3.922 (76.5% vs 23.5%) • Insomnia (n=17): 3.922 (64.7% vs 25.3%) • Appetite (n=17): -9.812 (94.1% vs 5.9%) • Constipation (n=16): 4.167 (94.1% vs 5.9%) **(VERY LOW)** • The same prospective case series (Swaminath et al 2021) (n=32) reported the change in the overall converted FACT FKSI-19 score from baseline (n=17): -2.188 (64.7% stable or better vs 35.3% worse) **(VERY LOW)** **At 6 months follow-up** • A prospective case series (Swaminath et al 2021) (n=32) reported changes in the EQ-5D-3L scores from baseline: • Visual analogue scale (n=15): 1.667 (p=0.398, appears to be p-value for trend[7]) • Health utility score (n=16): 0.038 (81.3% stable or better vs 18.8% worse) (p=0.493, appears to be p-value for trend) **(VERY LOW)** • The same prospective case series (Swaminath et al 2021) (n=32) reported changes in the EORTC-QLQ-C15-PAL scores from baseline, together with the % that were stable or better vs the % that were worse, and p-values which appear to relate to trend over the 6 month period: • Global QoL score (n=16): -2.083 (68.8% vs 31.3%) (p=0.390) • Physical functioning (n=16): -7.494 (56.3% vs 43.8%) (p=0.225) • Emotional functioning (n=16): -3.119 (75.0% vs 25.0%) (p=0.848) • Fatigue (n=16): 2.781 (68.8% vs 31.3%) (p=0.586) • Nausea and vomiting (n=16): -3.125 (100.0% vs 0.0%) (p=0.401) • Dyspnoea (n=16): 14.581 (68.8% vs 31.3%) (p=0.126) (p=0.048 at 6 months compared to baseline) • Pain (n=16): -6.250 (81.3% vs 18.8%) (p=0.979) • Insomnia (n=16): 4.167 (68.8% vs 31.3%) (p=0.543) • Appetite (n=16): -2.088 (93.8% vs 6.3%) (p=0.279) • Constipation (n=16): 4.167 (81.3% vs 18.8%) (p=0.838) **(VERY LOW)**

[7] P-values were reported below graphs showing baseline, 1 week and 1, 3 and 6 month mean scores and standard errors. It is not clear if they are p-values for trend. The narrative reports that “Means of converted scores (+/-standard deviations) were also compared at each time point to the baseline using paired t-tests.” However only 2 of these p-values were reported (these have been included here).

Outcome	Evidence statement
	• The same prospective case series (Swaminath et al 2021) (n=32) reported the change in the overall converted FACT FKSI-19 score from baseline (n=16): -0.181 (68.8% stable or better vs 31.3% worse) (p=0.330, presumed to be p-value for trend) **(VERY LOW)** **One prospective case series that included patients with medically inoperable localised RCC provided very low certainty evidence relating to health related QoL outcomes over a six month follow-up period using three different tools that include a variety of QoL-related metrics. No statistically significant change in any QoL metric was reported over the 6 month period. Two of the many comparisons of individual time points to baseline for individual metrics resulted in p-values just below 0.05, but given the number of comparisons made, they do not reliably indicate statistical significance. The large amount of missing data at each time point further reduces the certainty of the results. In addition, without a comparator group included in the study, it is not clear how the results reported in this case series compare with health related QoL for people who receive other treatments or supportive care instead of SABR.**
Organ specific disease response **Certainty of evidence:** Very low	Organ specific disease response is important to patients because reduction in renal function may lead to requirement for renal replacement therapies such as dialysis which have a significant impact on mortality, morbidity and quality of life. Two prospective case series and one retrospective case series provided evidence relating to organ specific disease response or kidney function measured at different time points up to four years. None of the studies included a comparator group. **At 6 months follow-up** • One prospective case series (Zarkar et al 2023) (n=19) (median follow-up 17 months, range 5 to 32 months) reported a mean change in eGFR from baseline of -5.4 ml/min (95% CI -10.3 to -0.6). **(VERY LOW)** **At 12 months follow-up** • One prospective case series (Zarkar et al 2023) (n=19) (median follow-up 17 months, range 5 to 32 months) reported a mean change in eGFR from baseline to 12 months of -8.7 ml/min (95% CI -15.3 to -2.1) and from 6 months to 12 months of -5.1 ml/min (95% CI -9.0 to -1.1). **(VERY LOW)** • One retrospective case series (Glicksman et al 2023) (n=74) (median follow-up 27.8 months, IQR 17.6 to 41.7) reported a median change in eGFR from baseline of -7.0ml/min (IQR -14.5 to -1.0). This study also reported that 18.8% of patients had an improved eGFR compared to baseline and that the proportion of renal function from the ipsilateral (SABR-treated) kidney changed from 47% (IQR 44 to 53) at baseline to 39% (IQR 37 to 48) at 12 months. **(VERY LOW)** • One prospective case series (Siva et al 2017) (n=33) (median follow-up 24 months, minimum 12 months) reported a mean change in eGFR from baseline of -11ml/min (95% CI -6 to -17), p<0.001. **(VERY LOW)** **At 20 to 28 months follow-up** • One retrospective case series (Glicksman et al 2023) (n=74) (median follow-up 27.8 months, IQR 17.6 to 41.7) reported a median change in eGFR from baseline to 2 years of -11.5ml/min (IQR -19.5 to -4.0) and reported that over the whole study follow-up period (median 27.8 months) there was a *statistically significant* decrease in eGFR (p<0.0001) and the proportion of patients with stage 3+ chronic kidney disease increased over time (p-value not reported). The number of patients on dialysis also increased from 2 (2.7%) to an additional 4 (5.4%) patients. This study also reported that 15% of patients had an improved eGFR at 2 years compared to baseline and that the proportion of renal function from the ipsilateral (SABR-treated) kidney changed from 47% (IQR 44 to 53) at baseline to 36% (IQR 36 to 42) at 2 years, with the proportion of renal function from the

Outcome	Evidence statement
	ipsilateral kidney decreasing significantly over the period of the study (p<0.0001). **(VERY LOW)** • One retrospective case series (Correa et al 2019) (n=81) (median follow-up 2.57 years, 95% CI 2.12 to 3.33) reported a mean change in eGFR from baseline to the latest time point measured (median 20.4 months) for patients with a solitary kidney of -5.8 ml/min (SD ± 10.8). The median change was -3.3 ml/min (range -35.1 to 18.7). The mean eGFR before SABR was 64.6 ml/min (SD ± 21.7, median 67.6, range 13.0 to 126.3). The mean eGFR after SABR was 59.2 ml/min (SD ± 23.9, median 62.1, range 8.0 to 100.4). After SABR, the percentage of patients with normal renal function was 10.8%, mild CKD 44.6%, mild to moderate CKD 20.0%, moderate to severe CKD 10.8% and severe CKD 13.9%.[8] This study also reported that at last measurement, 14 patients (21.5%) had an eGFR that was reduced compared to baseline by ≥15 ml/min, 17 patients (26.2%) had an increase in eGFR compared to baseline and no patients were on dialysis. **(VERY LOW)** • One prospective case series (Siva et al 2017) (n=33) (median follow-up 24 months, minimum 12 months) reported a mean change in eGFR from baseline to 2 years of -11ml/min (95% CI -3 to -19) for a subset of n=9 patients. **(VERY LOW)** **At 4 years follow-up** • One retrospective case series (Glicksman et al 2023) (n=74) (median follow-up 27.8 months, IQR 17.6 to 41.7) reported a median change in eGFR from baseline of -14.0ml/min (IQR -28.0 to -10.0). This study also reported that 0% of patients had an improved eGFR compared to baseline and that the proportion of renal function from the ipsilateral (SABR-treated) kidney had changed from 47% (IQR 44 to 53) at baseline to 32.5% (IQR 29 to 39.5) at 4 years. **(VERY LOW)** **Four case series that included patients with medically inoperable localised RCC provided very low certainty evidence relating to changes in renal function, with one study reporting results up to four years after SABR treatment. The studies reported a *statistically significant* reduction in eGFR of -5.4ml/min at six months to a larger reduction (-14ml/min) at four years, although confidence intervals were relatively wide. One study also reported improvements in eGFR in 18.8% of patients at one year and 15% at two years reducing to 0% at four years and another study reported an increase in eGFR in 26.2% of patients with a solitary kidney at a median of 20.4 months. One study reported an increase in the number of patients on dialysis (5.4% increase) and the number with stage 3 chronic kidney disease, as well as a reduction in the proportion of renal function from the SABR-treated kidney over the course of the study (median follow-up 28 months). A second study (in patients with a solitary kidney) reported no patients on dialysis at a median of 20.4 months after SABR. Without a comparator group in any of the studies, it is not clear how these changes compare with changes in renal function in people who receive other treatments or supportive care instead of SABR.**
Safety	
Safety outcomes **Certainty of evidence:** Very low	Safety is important to patients as it reflects the risks involved in treatment. This allows a risk benefit assessment to be undertaken. Two prospective case series provided evidence relating to safety, reporting on adverse events up to a median of 24 months follow-up. Neither of the studies included a comparator group.

[8] Correa et al (2019) defined the stages of CKD as follows: normal renal function: eGFR≥90; mild CKD: eGFR 60 to <90; mild to moderate CKD: eGFR 45 to <60; moderate to severe CKD: eGFR 30 to <45; severe CKD: eGFR <30. The percentage of patients in each CKD category at baseline was 5.0%, 62.5%, 15.0%, 8.8% and 8.8% respectively.

Outcome	Evidence statement

	Acute adverse events ≤90 days after SABR (median follow-up 24 months, minimum 12 months)
	• One prospective case series (Siva et al 2017) (n=33) reported acute adverse events by Grade as follows:
	  • Grade 1: 11 patients (33%) had at least one event (chest wall pain 5, dermatitis 2, diarrhoea 3, fatigue 11, gastritis 1, nausea 5, right flank pain 1)
	  • Grade 2: 7 patients (21%) had at least one event (dyspnoea 1, fatigue 6, gastritis 1, nausea 2)
	  • Grade 3: none
	  (VERY LOW)
	
	Late adverse events >90 days after SABR (median follow-up 24 months, minimum 12 months)
	• One prospective case series (Siva et al 2017) (n=33) reported late adverse events by Grade as follows:
	  • Grade 1: 17 patients (52%) had at least one event (chest wall pain 12, diarrhoea 1, dyspnoea 2, fatigue 7, gastritis 1, haematuria 3, nausea 2, skin induration 1)
	  • Grade 2: 2 patients (6%) had at least one event (abdominal pain 1, haematuria 1)
	  • Grade 3: 1 patient (3%) had fatigue
	  (VERY LOW)
	
	Acute plus late adverse events after SABR (median follow-up 24 months, minimum 12 months)
	• One prospective case series (Siva et al 2017) (n=33) reported adverse events by Grade as follows:
	  • Grade 1: 19 patients (58%) had at least one event (chest wall pain 15, dermatitis 2, diarrhoea 3, dyspnoea 2, fatigue 14, gastritis 2, haematuria 3, nausea 5, right flank pain 1, skin induration 1)
	  • Grade 2: 7 patients (21%) had at least one event (abdominal pain 1, dyspnoea 1, fatigue 5, gastritis 1, haematuria 1, nausea 2)
	  • Grade 3: 1 patient (3%) had fatigue
	  (VERY LOW)
	
	Worst grade of each type of adverse event over each patient's follow-up period (median follow-up 17 months, range 5 to 32 months)
	• One prospective case series (Zarkar et al 2023) (n=19) reported patients' worst grade of adverse event by type of adverse event. They reported that the number (and %) of patients having a Grade 0, 1, 2, 3 and 4 adverse event as the worst grade of that type of adverse event for that patient was as follows:
	  Grade 0, 1, 2, 3, 4
	  • Fatigue: 4 (21.1%), 12 (63.3%, 3 (15.8), 0 and 0 patients
	  • Gastritis: 17 (89.5%), 1 (5.3%), 1 (5.3%), 0, 0 patients
	  • Anaemia: 17 (89.5%), 0, 1 (5.3%), 1 (5.3%), 0 patients
	  • Pain: 18 (97.4%), 1 (5.3%, 0, 0, 0 patients
	  • Nausea: 14 (73.7%), 1 (5.3%), 4 (21.1%), 0, 0 patients
	  • Vomiting: 17 (89.5%), 1 (5.3%), 1 (5.3%), 0, 0
	  • Colitis: 18 (94.7%), 0, 0, 1 (5.3%), 0 patients
	  • Diarrhoea: 17 (89.5%), 2 (10.5%), 0, 0, 0 patients
	  • Haematuria: 18 (94.7%), 0, 0, 1 (5.3%), 0 patients
	  • Haemorrhage: 18 (94.7%), 1 (5.3%), 0, 0, 0 patients
	  (VERY LOW)
	
	Two case series that included patients with medically inoperable localised RCC provided very low certainty evidence relating to adverse events following SABR. One study (n=33) reported that 58% of patients had at least one Grade 1 adverse event, 21% had at least one Grade 2 event and 3% had at least one Grade 3 event, with the Grade 3 event being fatigue in one

Outcome	Evidence statement
	patient more than 90 days after SABR. The second study (n=19) reported the worst Grade of each type of adverse event over each patient's follow-up period. Most types of adverse events listed were not reported at all by over 89% of patients, except for fatigue (63.3% of patients had Grade 1 fatigue and 15.8% had Grade 2 fatigue) and nausea (5.3% of patients had Grade 1 nausea and 21.1% had Grade 2 nausea). Grade 3 adverse events (anaemia, colitis and haematuria) were experienced by single patients. Without a comparator group in either of the studies, it is not clear how many of these events are experienced by people who receive other treatments or supportive care instead of SABR.
Abbreviations CI: confidence interval; cm^3: cubic centimetres; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; EORTC QLQ-C15-PAL: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 15 Palliative Care; EQ-5D-3L: European Quality of Life 5 Dimensions 3 Level; FACT FKSI: Functional Assessment of Cancer Therapy – Kidney Specific Index; IQR: Interquartile range; ml/min: MCID: minimal clinically important difference; millilitres per minute; mm: millimetres; QoL: quality of life; RCC: renal cell carcinoma; RECIST: Response Evaluation Criteria in Solid Tumours; SABR: stereotactic ablative body radiotherapy	

In people with medically inoperable localised primary kidney cancer, what is the cost-effectiveness of SABR treatment +/- supportive care compared with current standard care alone?

Outcome	Evidence statement
Cost effectiveness	One study was identified that provided evidence for the cost effectiveness of SABR compared to RFA over a 5-year time horizon for people with inoperable early stage (confined to the kidney, node negative) RCC. It was based on using 5 fractions of SABR, with costs based on the Canadian public health care payer's perspective (1.5%/year discount rate) including costs of supplies, personnel and capital/machinery but not individual patient rehabilitation or medication costs. Outcomes were based on data obtained on review of literature, with varying rates used for sensitivity analyses. **5-year time horizon:** *SABR vs RFA* • One analysis (Donovan et al 2022) reported that SABR was cost effective compared to RFA (ICER CAD -4,490 per QALY gained (95% CI not reported)). This was based on costs of SABR and RFA of CAD 16,097 and CAD 18,324 respectively and QALYs gained of 4.109 and 3.607 for SABR and RFA respectively. Sensitivity analysis suggested significant variability in the ICER with variations in rates of distant metastases having the greatest implications followed by utility values.[9] Varying other parameters resulted in smaller changes to the ICER. **One recent cost effectiveness analysis compared treatment of patients with inoperable early stage RCC with SABR compared to treatment with RFA over a 5-year time horizon based on the Canadian health care payer's perspective (including costs of personnel, supplies and capital but not rehabilitation and medication costs). This study reported that SABR was cost effective compared to RFA (ICER of CAD -4,490 per QALY gained). Sensitivity analyses suggested that the rate of distant metastasis had the greatest impact on calculated ICERs followed by utility values. The Canadian perspective of this study and any recent changes in treatment of metastatic RCC may limit its generalisability to the current NHS in England.**
Abbreviations CAD: Canadian dollar; CI: confidence interval; ICER: Incremental cost effectiveness ratio; QALY: Quality-adjusted life year; RCC: renal cell carcinoma; RFA: radiofrequency ablation; SABR: stereotactic ablative body radiotherapy	

[9] In health economics, a 'utility' is the measure of the preference or value that an individual or society gives a particular health state.

From the evidence selected, are there any subgroups of patients that may benefit from SABR treatment +/- supportive care more than the wider population of interest?

Subgroup	Evidence statement
T1a vs T1b tumours[10]	From the studies selected for inclusion in this review, one retrospective case series reported subgroup results for treatment of T1a vs T1b inoperable RCCs with SABR for the critical outcomes of local control, overall survival and progression free survival. The study did not include a comparator group of patients that did not receive SABR. **Critical Outcomes** **Local control** • One retrospective case series (Glicksman et al 2023) (n=74) (median follow-up 27.8 months, IQR 17.6 to 41.7) reported a univariate analysis of local control rates (based on RECIST criteria[11]) for T1b tumours (n=34) vs T1a tumours (n=32) and reported a HR of 1.1 (95% CI 0.08 to 14.0), p=0.97. **Overall survival** • One retrospective case series (Glicksman et al 2023) (n=74) (median follow-up 27.8 months, IQR 17.6 to 41.7) reported a univariate analysis of overall survival rates for T1b tumours (n=34) vs T1a tumours (n=32) and reported a HR of 0.51 (95% CI 0.007 to 35.5), p=0.76. **Progression free survival** • One retrospective case series (Glicksman et al 2023) (n=74) (median follow-up 27.8 months, IQR 17.6 to 41.7) reported a univariate analysis of progression free survival rates for T1b tumours (n=34) vs T1a tumours (n=32) and reported a HR of 2.5 (95% CI 0.30 to 20.6), p=0.40. A corresponding HR for distant metastasis rates was reported as HR 1.6 (95% CI 0.13 to 18.9), p=0.72. **Important Outcomes** **Organ specific disease response** • One retrospective case series (Correa et al 2019) (n=81) (median follow-up 2.57 years, 95% CI 2.12 to 3.33) reported that tumour diameter ≥4.0cm was *statistically significantly* associated with an eGFR decrease of 15 ml/min or greater (OR 4.21 (95% CI 1.16 to 15.31), p=0.029, univariable logistic regression analysis). **Cost effectiveness** • One cost effectiveness analysis (Donovan et al 2023) reported the cost effectiveness of SABR compared to RFA over a 5-year time horizon for people with inoperable early stage RCC from the perspective of the Canadian public health care payer and included a comparison of ICERs for T1b vs T1a tumours. This suggested that SABR was considerably more cost effective compared to RFA for T1b tumours (ICER per QALY gained CAD -22,904) compared to T1a tumours (ICER per QALY gained CAD 2,207).[12] (T1b tumours: cost of SABR CAD 19,245, cost of RFA CAD 37,427, QALYs gained with SABR 4.067, QALYs gained with RFA 3.459 vs T1a tumours: cost of SABR CAD 14,993, cost of RFA CAD 13,940, QALYs gained with SABR 4.119, QALYs gained with RFA 3.641). **One retrospective case series reported HRs for the critical outcomes of local control, overall survival and progression free survival for people with T1b vs T1a inoperable RCC who received treatment with SABR. No statistically**

[10] The term T1a includes patients with tumours between 0 and 4cm in maximum diameter; the term T1b includes patients with tumours between 4 and 7cm in maximum diameter.
[11] RECIST is a set of published rules that define when tumours in cancer patients improve ("respond"), stay the same ("stabilize"), or worsen ("progress") during treatment.; follow-up every 3 to 6 months till 5 years.
[12] These ICER results were reported in the abstract and narrative; Table 3 of the paper reported slightly different results: ICER per QALY gained of CAD -29,905 for T1b tumours and CAD 2,208 for T1a tumours.

Subgroup	Evidence statement
	significant differences were observed in these outcomes for T1b compared to T1a tumours. Another retrospective case study reported a *statistically significant* association between having a tumour of ≥4cm and having a 15ml/min or greater decrease in eGFR after SABR treatment. Without a comparator group included in these studies, it is not clear whether outcomes are significantly different for T1b vs T1a tumours in people who receive other treatments or supportive care instead of SABR. **One recent cost effectiveness analysis reported a substantially higher cost effectiveness of SABR for people with T1b tumours (ICER per QALY gained CAD -22,904) compared to T1a tumours (ICER per QALY gained CAD 2,207).**
T1a tumours suitable for ablative procedures vs not suitable for ablative procedures	**No evidence was identified pertaining to these subgroups from the studies selected for inclusion in this review.**
Solitary kidney vs 2 kidneys	**No evidence was identified pertaining to these subgroups from the studies selected for inclusion in this review.[13]**
Anticoagulant use vs no anticoagulant use	**No evidence was identified pertaining to these subgroups from the studies selected for inclusion in this review.**
Abbreviations CAD: Canadian dollars; CI: confidence interval; HR: hazard ratio; ICER: incremental cost effectiveness ratio; OR: odds ratio; QALY: quality adjusted life years; RCC: renal cell carcinoma; RECIST: Response Evaluation Criteria in Solid Tumours; SABR: stereotactic ablative body radiotherapy; T stage: tumour stage	

From the evidence selected, what dose, fractionation and duration of SABR were used?

Outcome	Evidence statement
Dose, fractionation and duration of SABR	One retrospective case series (Correa et al 2019) reported outcomes for patients with RCC in a solitary kidney who were treated with SABR (n=81). The mode of SABR treatment was not reported. The mean total dose used was 28.9Gy (SD ± 12.3), with a median dose of 25.0Gy (range 14.0 to 70.0). The mean number of treatment fractions provided was 1.9 (SD ± 2.5) (range 1 to 10). 13 patients (16.1%) received a single fraction. The mean fraction dose was 22.1Gy (SD ± 6.0), and the median dose was 25.0Gy (range 6.0 to 26.0). The mean biological equivalent dose was also reported: 86.8Gy (SD ± 14.4, median 87.5Gy, range 33.6 to 124.8). The timing of fractions and the duration of time required to deliver the SABR treatment were not reported. One retrospective case series (Glicksman et al 2023) (n=74) reported outcomes for patients with localised RCC who were deemed medically inoperable or unresectable or declined surgery who were treated with SABR (intensity modulated radiotherapy (2 patients, 2.7%) or volumetric modulated arc therapy (72 patients, 97.3%)) with either 30 to 45Gy in 5 fractions or 42Gy in 3 fractions, based on physician decision. Treatment was delivered on alternate days: 1 patient (1.4%) received 30Gy in 5 fractions; 22 patients (29.7%) received 35Gy in 5 fractions; 41 patients (55.4%) received 40Gy in 5 fractions; 6 patients (5.4%) received 45Gy in 5 fractions; 4 patients (8.1%) received 42Gy in 3 fractions.[14] The duration of time required to deliver the SABR treatment was not reported. One prospective case series (Siva et al 2017) (n=37) reported outcomes for patients with small RCC who were medically inoperable, high risk for surgery or refused surgery who were treated with SABR using conventional c-arm linear

[13] Although Correa et al 2019 compared outcomes for a group of patients with a solitary kidney and a group with two kidneys, there was no indication that patients in the group with two kidneys were medically inoperable. Hence the group with two kidneys and the comparison between the two groups were not within the scope of the PICO framework for this review.
[14] These figures were reported in Table 2 of the paper. However, 6/74 is in fact 8.1% and 4/74 is 5.4%.

Outcome	Evidence statement
	accelerator. RCCs that were <5cm maximum dimension were treated with 26Gy in a single fraction (n=17). RCCs that were ≥5cm maximum dimension were treated with 42 Gy in 3 fractions on non-consecutive days (n=17). 33 of the 37 patients received all treatments (to 34 RCCs) (1 patient died prior to SABR; 1 patient completed 2 of 3 planned fractions because of social difficulties; 2 patients could not meet planned dose constraints). The duration of time required to deliver the SABR treatment was not reported. One retrospective case series (Sun et al 2016) (n=40, 41 tumours) reported outcomes for patients with renal masses deemed to be poor candidates for surgery or minimally invasive tumour ablation who were treated with SABR using the CyberKnife system with the Synchrony system (Accuracy) to track movement. The mean SABR dose used was 38Gy (range 21 to 48) delivered in daily fractions. Initially 21 Gy was delivered in 3 fractions. Over the course of the study, this was gradually increased to 48 Gy delivered in 3 fractions (3 tumours were treated with 21Gy, 1 with 24Gy, 4 with 27Gy, 5 with 30Gy, 2 with 33Gy, 2 with 36Gy, 8 with 39Gy, 1 with 45Gy and 15 with 48Gy). The duration of time required to deliver the SABR treatment was not reported. One prospective case series (Swaminathan et al 2021) (n=32) reported outcomes for patients with non-metastatic RCC who were medically inoperable, ineligible for other locally ablative treatments or refused surgery who were treated with SABR using a volumetric modulated arc therapy approach. Patients received either 35 to 45Gy in 5 fractions (35Gy: 16 patients, 50%; 40Gy: 11 patients, 34.4%; 45Gy: 1 patient, 3.1%) or 42Gy in 3 fractions (4 patients, 12.5%) delivered every second day. The dose was selected based on tumour size, location within the kidney, and proximity to upper abdominal organs at risk. The duration of time required to deliver the SABR treatment was not reported. One prospective case series (Zarkar et al 2023) (n=19) reported outcomes for patients with T1 stage RCC who were non-surgical candidates and were treated with SABR using volumetric modulated arc therapy (n=11) or CyberKnife (n=8). Patients received either 26Gy in 1 fraction (n=8) or 42Gy in 3 fractions on alternate days (n=11). The duration of time required to deliver the SABR treatment was not reported. One cost effectiveness study (Donovan et al 2022) based the cost effectiveness analysis on treatment with 5 fractions of SABR. The dose and duration of treatment were not reported. **The six included case series delivered SABR treatment (volumetric arc therapy, intensity modulated therapy, CyberKnife) at doses varying from 21Gy to 70Gy in different numbers of fractions ranging from one to ten. Different regimens tended to be used within individual studies. Where reasons for this were reported it was either based on physician decision, tumour size, location within the kidney, proximity to upper abdominal organs at risk or changes in practice over the duration of the study. Where multiple fractions were used, one study reported these being daily and four studies reported that fractions were delivered on alternate or non-consecutive days. None of the studies reported the duration of time required to deliver the SABR treatment.**
Abbreviations Gy Gray; RCC: renal cell carcinoma; SABR: stereotactic ablative body radiotherapy; T stage: tumour stage	

6. Discussion

This evidence review aimed to examine the clinical effectiveness, safety and cost effectiveness of SABR +/- supportive care for the treatment of medically inoperable localised primary kidney cancer compared with current standard care alone. The critical outcomes of interest were local control, overall survival and progression free survival. Important outcomes were cancer specific survival, time to further intervention, health related quality of life, organ specific disease response and safety (complications of SABR treatment).

Evidence was available from three prospective case series (Siva et al 2017 (n=37), Swaminath et al 2021 (n=32), Zarkar et al 2023 (n=19)) and three retrospective case series (Glicksman et al 2023 (n=74), Correa et al 2019 (n=81), Sun et al 2016 (n=40)), none of which included a comparator group. These studies ranged in follow-up duration from 6 months to a median of 2.57 years, with the latest time point reported being four years.

The six case series included patients with early RCC. Although all studies aimed to include only patients with RCC, some patients had not had histological confirmation of RCC, including 7 patients (8.6%) in Correa et al 2019, 39 patients (52.7%) in Glicksman et al 2023, 3 patients (9%) in Siva et al (2017), nine patients (21.9%) including one who had urothelial carcinoma in Sun et al (2016), 9 patients (28.1%) in Swaminath et al (2021). Zarkar et al (2023) only included patients with biopsy confirmed RCC.

The studies were not always restricted to stage T1 tumours. However, the proportion that were not T1 tumours was relatively small (11% in one study (Glicksman et al 2023); 2% to 3% in two studies (Sun et al 2016 and Siva et al 2017) and none in two studies (Swaminath et al 2021 and Zarkar et al 2023). The proportion was not reported in Correa et al (2019) but the reported interquartile range for maximum tumour dimensions suggested that most or all were T1 tumours.

Overall, these differences from the PICO specified population for this review were relatively small and the studies generally represented the population of interest.

The patients included in the six case series were all inoperable, despite having localised early stage RCC. The reasons given for being inoperable were described in a variety of ways by the study authors including being medically inoperable, unfit for a general anaesthetic, at high risk of surgery because of the likelihood of post-surgical dialysis, deemed to be poor candidates for surgery or minimally invasive tumour ablation (for example because of the location of the tumour), unresectable, having a solitary kidney or declined surgery. The example reasons for being medically inoperable provided in the PICO framework for this review suggested that this wide range of reasons was within the scope of the review and this was confirmed with the NHS England team. The median patient age in the included studies ranged from 66.5 to over 80 years.

Between the six case series, the study outcomes reported included the critical outcomes of local control (five studies), overall survival (four studies) and progression free survival (four studies) and the important outcomes of cancer specific survival (two studies), health related quality of life (one study), organ specific disease (four studies) and safety (two studies). No studies were identified that reported the important outcome of time to further intervention.

The studies were mainly carried out in other countries (Canada, Australia, Germany, Japan and the USA) and four were in single institutions. One study Zarker et al (2023) (n=19) was the only UK study. Care is therefore needed in generalising to the NHS in England where other aspects of care may differ. Other limitations that reduce the level of certainty in the outcomes reported in these studies include the fact that three of the studies were retrospective case series and none of the studies clearly reported including all consecutive patients or the number that declined to participate. In addition, the study by Siva et al (2017) did not present an intention to treat analysis,

as it excluded the results of four of the 37 patients who did not receive all of the planned SABR treatments. There was also unclear reporting of the number and reasons for those lost to follow-up. This was particularly true for the study reporting on QoL outcomes (Swaminath et al 2021) where of the 32 patients enrolled in the study, only between 16 and 24 completed the QoL questionnaires at each time point. Reasons for non-completion included patient relocation, hospitalisation for different reasons, follow-up not by the oncology team, patient refusal and missed appointments. The analyses assumed that missing values were random and that domains were highly correlated over the time periods analysed in the study. Although a statistical test was carried out which failed to reject the hypothesis that the data were missing completely at random (p=1.0000), the large loss to follow-up and relatively small sample size at follow-up means that the results should be interpreted with caution because it is possible that there were in fact reasons for patients not completing questionnaires that were linked to outcomes rather than being random. None of the authors reported that outcome measures had been prespecified. In addition, Correa et al (2019) and Glicksman et al (2023) did not report any statistical tests for the outcomes of interest and the statistical testing in Swaminath et al (2021) was not reported clearly with no indication of adjustment for multiple testing. Patients and clinicians were not blinded to the treatment received.

The fact that none of the studies included a comparator group means that it is not clear how any of the outcomes reported from these studies differ from outcomes for people with localised medically inoperable RCC who receive other treatments or supportive care instead of SABR.

Only two case series reported subgroup analyses. This was for T1a vs T1b tumours for the critical outcomes of local control, overall survival and progression free survival (Glicksman et al 2023) and for the important outcome of organ specific disease response (Correa et al 2019). No statistically significant differences in any of the critical outcomes were observed between these two subgroups. For the important outcome of organ specific disease response, Correa et al (2019) reported a *statistically significant* association between a fall in eGFR of ≥15ml/min and having a RCC of ≥4cm. None of the studies reported subgroup results for stage T1a tumours that were vs were not suitable for ablative procedures, for patients with solitary kidneys vs two kidneys or for patients using anticoagulants vs not using anticoagulants.

In addition, one cost effectiveness study (Donovan et al 2022) which compared SABR with radiofrequency ablation (RFA) over a five-year time horizon was identified for inclusion. This study also included a subgroup analysis for T1b vs T1a tumours. This study was based on the Canadian health care payer's perspective and did not include individual patient costs after treatment such as rehabilitation and medication costs (it included costs of personnel, supplies and capital). This limits the generalisability of the results to the NHS in England. The study used outcome data obtained from a review of the literature (which assumed that the studies mainly included patients that were inoperable) and, where different studies reported different probabilities, sensitivity analyses were carried out. The sensitivity analyses suggested that rate of distant metastasis had the greatest impact on the calculated ICERs, followed by utility (QoL) values. Some of the outcome data used came from relatively old studies. The increasing availability of immunotherapies for treatment of metastatic RCC since the search dates used in this cost effectiveness study may have an important impact on the generalisability of the results to the current NHS in England.

7. Conclusion

This evidence review includes six case series reporting outcomes after treatment with SABR for patients with localised medically inoperable early stage RCC followed up for up to a median of 2.57 years, with one study reporting outcomes up to four years after SABR. With respect to critical outcomes, overall, these case series reported a relatively low rate of failure of local control (2% and 7.77% at four years in two studies respectively), overall survival rates of over 90% in most studies (91.6% at four years in one study, 73.6% at four years in a second study), and progression free survival rates of close to 90% at up to four years after SABR in one study and 68.3% in a second study. For the important outcomes, two studies reported cancer specific survival rates of over 90%; one study of health related QoL outcomes reported no statistically significant trends in a number of QoL measures over the 6 months after SABR treatment; and four of the studies reported renal function outcomes after SABR. These studies reported a statistically significant reduction in average eGFR up to four years after SABR, although some patients had in improved eGFR initially (15% of patients at 2 years in one study and 26.2% at a median of 20.4 months in a second study). One study reported that patients had a reduction in the proportion of renal function from the SABR-treated kidney.

Safety outcomes were reported by two case series. Most adverse events were Grade 1 or Grade 2. The most common adverse events reported were fatigue, nausea and chest wall pain. The only Grade 3 adverse events reported were fatigue (one patient) in one study (n=33) and anaemia, colitis and haematuria in another study (1 patient each, n=19). No Grade 4 adverse events were reported.

Subgroup analysis in one study did not show any statistically significant differences in outcomes for T1b tumours compared to T1a tumours, while another study reported a statistically significant association between a fall in eGFR after SABR and having a tumour of 4cm or greater. No subgroup results were reported by the included studies in relation to patients suitable vs unsuitable for ablative procedures, patients with one vs two kidneys or patients using vs not using anticoagulants.

The treatment schedules for SABR in the included studies varied from 21Gy to 70Gy delivered in one to ten fractions usually on alternate days, with decisions about treatment schedules based on a variety of reasons including physician decision, tumour characteristics and changes in clinical practice over time.

The most important limitation relating to the evidence identified is the lack of a comparator group. This means that it is not clear whether the outcomes reported are different from those for patients with localised medically inoperable RCC who receive other treatments or supportive care instead of SABR. Other limitations included the retrospective nature of three of the studies, five of the studies not being UK based and most being single centre studies, the varying reasons for patient inclusion from being unfit for a general anaesthetic to high risk of post-surgical need for dialysis to patient refusal of surgery; unclear reporting relating to complete inclusion of patients; and missing data, particularly for the study of health related QoL.

One recent cost effectiveness analysis from the Canadian public health care payer's perspective over a 5-year time horizon reported an ICER of CAD -4,490 per QALY gained for SABR compared to RFA, with the cost effectiveness being substantially higher for T1b tumours (ICER per QALY CAD -22,904) compared to T1a tumours (ICER per QALY CAD 2,207).[15] The Canadian perspective of this study, together with the variability reported in the sensitivity analyses and the

[15] These results were reported in the abstract and narrative; Table 3 of the paper reported slightly different results: ICER per QALY gained of CAD -29,905 for T1b tumours and CAD 2,208 for T1a tumours.

use of relatively older literature relating to outcomes (particularly if newer treatments are now available for metastatic RCC), may limit the generalisability of these results to the NHS in England.

Overall, these case series reported relatively good outcomes following SABR in relation to local control, overall survival, progression free survival, other important outcomes and safety, but it is not clear how the reported outcomes compare with outcomes in the same patient group who do not receive SABR. In addition, SABR was assessed to be cost effective compared to RFA, although there may be limitations in the generalisability of the study to the NHS in England.

Appendix A PICO Document

The review questions for this evidence review are:

1. In people with medically inoperable localised primary kidney cancer, what is the clinical effectiveness of SABR treatment +/- supportive care compared with current standard care alone?

2. In people with medically inoperable localised primary kidney cancer, what is the safety of SABR treatment +/- supportive care compared with current standard care alone?

3. In people with medically inoperable localised primary kidney cancer, what is the cost-effectiveness of SABR treatment +/- supportive care compared with current standard care alone?

4. From the evidence selected, are there any subgroups of patients that may benefit from SABR treatment +/- supportive care more than the wider population of interest?

5. From the evidence selected, what dose, fractionation and duration of SABR were used?

P-Population and Indication	Medically inoperable patients with T1 primary kidney cancer [The term medically inoperable includes patients with comorbidities precluding surgery, including but not limited to patients unfit for a general anaesthetic, those with a solitary kidney or those using anticoagulants] [The terms primary kidney cancer and renal cell carcinoma are used interchangeably] Subgroups: - T1a suitable for ablative procedures versus those who are not - Solitary kidney - Anticoagulant use - T1a vs T1b [The term T1a includes patients with tumours between 0 and 4cm in maximum diameter] [The term T1b includes patients with tumours between 4 and 7cm in maximum diameter] [The terms ablative procedures, cryotherapy, radiofrequency ablation (RFA) and microwave ablation and are used interchangeably] [The term not suitable for ablative procedures would include tumours close to vessels or the renal pelvis, and less fit patients not suitable for general anaesthesia and/or insertion of large catheters/probe]
I-Intervention	SABR (+/- supportive care) as 1st line treatment [Delivered in a single, 3 or 5 fractions] [Supportive care for these patients would include management of local symptoms such as haematuria with non-invasive treatments, or pain with analgesia. It would exclude palliative radiotherapy and systemic anticancer therapy]
C-Comparator	Standard care if medically inoperable includes • Ablation

	[Such as cryotherapy, radiofrequency ablation (RFA) and microwave ablation, however exclusion criteria apply for example if the tumour is close to vessels or the renal pelvis] • Watchful waiting • Supportive care [Supportive care for these patients would include no intervention, or management of local symptoms such as haematuria with invasive, non-invasive treatments and/or palliative radiotherapy, or pain with analgesia and/or palliative radiotherapy. It would exclude systemic anticancer therapy] [Standard care could vary based on tumour size and patient fitness, for example if tumour size <4cm this would include ablative procedures but not if >4cm]
O-Outcomes	**Clinical Effectiveness** *Unless stated for the outcome, minimum clinically important differences (MCIDs) are unknown. Outcomes ideally measured at 6, 12, 24, 36, 60 months as well as longer-term outcomes.* *Critical to decision making* • **Local control** *This outcome is important to patients because it reflects how effective the treatment is at preventing the cancer from growing or spreading. Local failure carries detrimental symptoms for the patient alongside the psychological burden of the recurrence of cancer.* [Outcomes measured may include local control rate, freedom from local failure, freedom from local progression] • **Overall survival** *This outcome is important to patients because it reflects how long people live after treatment, although it does not take the cause of death into account, or provide information about their health and wellbeing during that time.* [Other terms used to describe or indicate survival may include survival rate, death] • **Progression free survival** *This outcome is important to patients because it represents the time for which their disease is not progressing. Stable disease might represent longer survival and that patients experience less symptoms from the disease itself. It can be determined sooner than overall survival outcome measure and therefore a useful outcome for studies with shorter follow-up periods.* [The time interval from treatment until progression of the cancer, or death from any cause, whichever occurs first. This may be measured in days, weeks, months, or years. Progression is defined as local recurrence or detection of metastases] *Important to decision making* • **Cancer specific survival** *This outcome is important to patients because it reflects how long people live after treatment and excludes death due to causes unrelated to the cancer, although it does not provide information about their health and wellbeing during that time.*

- **Time to further intervention**
  This outcome is important to patients because it is linked to disease progression, which carries detrimental symptoms for the patient alongside the psychological burden of the recurrence of cancer. Further intervention carries the risks of treatment related complications and effects on quality of life.

  [Interventions may include systemic anti-cancer therapy, including immunotherapy and/or tyrosine kinase inhibitors. Patients are eligible for these if the disease progresses from localised to metastatic]

- **Health related quality of life (HRQL)**
  This outcome is important to patients because it provides a holistic evaluation and indication of the patient's general health and their perceived well-being and their ability to participate in activities of daily living. This outcome is both a key indicator of the effectiveness of treatment and provides an insight into the patient's perception of the effectiveness of treatment.

  [Other terms used to describe or indicate quality of life include; patient-reported quality of life, health related quality of life.

  Examples of general metrics to assess quality of life include Short Form (SF-36) and EuroQuality of Life Five Dimensions (EQ-5D).

  Examples of metrics that may be used in primary kidney cancer include European Organization for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ-C30) and The Functional Assessment of Cancer Therapy–Kidney Symptom Index Disease-Related Symptoms (FKSI-DRS).

  Other methods of assessing quality of life include subjective/self-reported/carer reported quality of life experiences]

- **Organ specific disease response**
  This outcome is important to patients because reduction in renal function may lead to requirement for renal replacement therapies such as dialysis which have a significant impact on mortality, morbidity and quality of life.

  [Renal function can be estimated using eGFR, a blood test that measures level of kidney function and determines stage of kidney disease.

  Outcomes relating to need for dialysis are also of interest]

Safety

- **Complications of SABR treatment**
  Safety is important to patients as it reflects the risks involved in treatment. This allows a risk benefit assessment to be undertaken.

  [Examples include fatigue, nausea, vomiting, gastritis, diarrhoea, colitis, chest wall pain, skin-related toxicity, haematuria. Serious adverse events (grade 3 or 4) are of clinical importance and are critical to decision-making]

	Cost effectiveness
Inclusion criteria	
Study design	Systematic reviews, randomised controlled trials, controlled clinical trials, cohort studies. If no higher level quality evidence is found, case series can be considered.
Language	English only
Patients	Human studies only
Age	All ages
Date limits	2013-2023
Exclusion criteria	
Publication type	Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, pre-prints and guidelines.
Study design	Case reports, resource utilisation studies

Appendix B Search strategy

Medline, Embase, the Cochrane Library and the TRIP database were searched limiting the search to papers published in English language in the last 10 years. Conference abstracts, non-systematic reviews, narrative reviews, commentaries, letters, editorials, pre-prints, case reports and resource utilisation studies were excluded.

Search dates: 1 January 2013 to 15 September 2023.

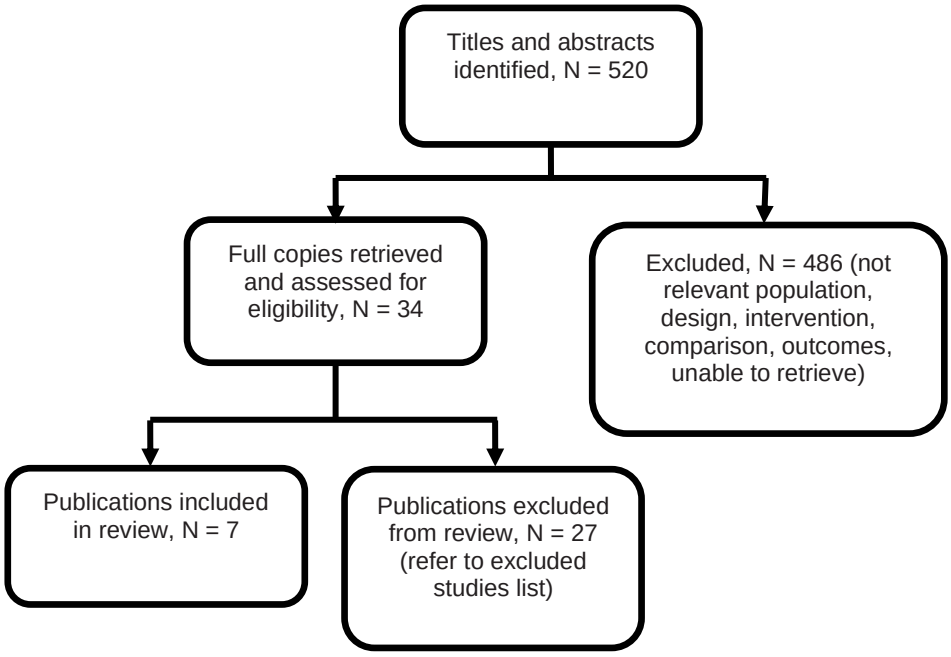
Medline search strategy:

1	*Kidney Neoplasms/
2	Carcinoma, Renal Cell/
3	((renal or renal cell or kidney) adj2 (carcinoma? Or adenocarcinoma?)).ti,ab,kf.
4	(primary adj (renal cancer? Or kidney cancer?)).ti,ab,kf.
5	((nephroid or hyper nephroid or collecting duct) adj2 (carcinoma? Or adenocarcinoma?)).ti,ab,kf.
6	1 or 2 or 3 or 4 or 5
7	Radiosurgery/
8	((stereotactic adj3 (radiotherap* or radiation therap*)) or sabr or sabrt or sbrt or radiosurg*).ti,ab,kf.
9	(linac or cyberknife or cuber knife or gammaknife or gamma knife).ti,ab,kf.
10	7 or 8 or 9
11	6 and 10
12	limit 11 to (english language and yr=”2013 -Current”)
13	exp animals/ not humans/
14	12 not 13
15	limit 14 to (meta analysis or “systematic review” or “reviews (maximizes specificity)”)
16	(comment or editorial or letter or news or review).pt. or case report.ti.
17	14 not 16
18	15 or 17

Appendix C Evidence selection

The literature search identified 520 potential references. These were screened using their titles and abstracts and 34 references potentially relating to the use of SABR for treating medically inoperable patients with T1 primary kidney cancer were obtained and assessed for relevance. Of these, seven references are included in this evidence review. The 27 references excluded are listed in Appendix D.

Figure 1- Study selection flow diagram



References submitted with Preliminary Policy Proposal

Reference	Paper selection decision and rationale if excluded
Siva, S., Pham, D., Kron, T., Bressel, M., Lam, J., Tan, T.H., Chesson, B., Shaw, M., Chander, S., Gill, S. and Brook, N.R., 2017. Stereotactic ablative body radiotherapy for inoperable primary kidney cancer: a prospective clinical trial. BJU international, 120(5), pp.623-630.	Included in the review
Siva, S., Ali, M., Correa, R.J., Muacevic, A., Ponsky, L., Ellis, R.J., Lo, S.S., Onishi, H., Swaminath, A., McLaughlin, M. and Morgan, S.C., 2022. 5-year outcomes after stereotactic ablative body radiotherapy for primary renal cell carcinoma: an individual patient data meta-analysis from IROCK (the International Radiosurgery Consortium of the Kidney). The Lancet Oncology, 23(12), pp.1508-1516.	N=190. Of the 128 of patients assessed for operability, only 91 were inoperable and 37 were assessed as operable. Thus 99/190 patients might be operable. Results were not reported separately for the group of patients that were inoperable. (Study focus was single vs multi-fraction SABR.)
Zarkar, A., Henderson, D., Carver, A., Heyes, G., Harrop, V., Tutill, S., Kilkenny, J., Marshall, A., Elbeltagi, N. and Howard, H., 2022. First UK patient cohort treated with stereotactic ablative radiotherapy for primary kidney cancer. BJUI Compass.	Included in the review

Appendix D Excluded studies table

Reference	Paper selection decision and rationale if excluded
Chang JH, Cheung P, Erler D, Sonier M, Korol R, Chu W. Stereotactic Ablative Body Radiotherapy for Primary Renal Cell Carcinoma in Non-surgical Candidates: Initial Clinical Experience. Clin Oncol (R Coll Radiol). 2016;28(9):e109-14.	N=12. Larger case series reporting the same outcome measures were available for inclusion. In addition, the study included patients with metastases.
Correa RJM, Louie AV, Zaorsky NG, Lehrer EJ, Ellis R, Ponsky L, et al. The Emerging Role of Stereotactic Ablative Radiotherapy for Primary Renal Cell Carcinoma: A Systematic Review and Meta-Analysis. Eur Urol Focus. 2019;5(6):958-69.	12 of the 26 included studies included patients with Stage 3 or Stage 4 tumours. Results for Stage T1 tumours were not reported separately.
Funayama S, Onishi H, Kuriyama K, Komiyama T, Marino K, Araya M, et al. Renal Cancer is Not Radioresistant: Slowly but Continuing Shrinkage of the Tumor After Stereotactic Body Radiation Therapy. Technol Cancer Res Treat. 2019;18:1533033818822329.	N=13. Larger case series reporting the same outcome measures were available for inclusion.
Grelier L, Baboudjian M, Gondran-Tellier B, Couderc AL, McManus R, Deville JL, et al. Stereotactic Body Radiotherapy for Frail Patients with Primary Renal Cell Carcinoma: Preliminary Results after 4 Years of Experience. Cancers (Basel). 2021;13(13):23.	19 patients in scope (4/23 had metastases). Larger case series reporting the same outcome measures were available for inclusion.
Grozman V, Onjukka E, Wersall P, Lax I, Tsakonas G, Nyren S, et al. Extending hypofractionated stereotactic body radiotherapy to tumours larger than 70cc – effects and side effects. Acta Oncol. 2021;60(3):305-11.	The study does not report that patients were medically inoperable or that the treatment was first line.
Grubb WR, Ponsky L, Lo SS, Kharouta M, Traughber B, Sandstrom K, et al. Final results of a dose escalation protocol of stereotactic body radiotherapy for poor surgical candidates with localized renal cell carcinoma. Radiother Oncol. 2021;155:138-43.	N=10. Larger case series reporting the same outcome measures were available for inclusion.
Hannan R, McLaughlin MF, Pop LM, Pedrosa I, Kapur P, Garant A, et al. Phase 2 Trial of Stereotactic Ablative Radiotherapy for Patients with Primary Renal Cancer. Eur Urol. 2023;84(3):275-86.	N=16. Larger case series reporting the same outcome measures were available for inclusion. In addition, the study did not exclude patients with operable RCC and the number that were inoperable was not reported.
Khriguian J, Patrocinio H, Andonian S, Aprikian A, Kassouf W, Tanguay S, et al. Stereotactic Ablative Radiation Therapy for the Treatment of Upper Urinary Tract Urothelial Carcinoma. Pract Radiat Oncol. 2022;12(1):e34-e9.	Indication is out of scope: urothelial carcinoma, not RCC.
Lapierre A, Badet L, Rouviere O, Crehange G, Berthiller J, Paparel P, et al. Safety and Efficacy of Stereotactic Ablative Radiation Therapy for Renal Cell Cancer: 24-Month Results of the RSR1 Phase 1 Dose Escalation Study. Pract Radiat Oncol. 2023;13(1):e73-e9.	N=12. Larger case series reporting the same outcome measures were available for inclusion. In addition, the study included patients with metastases.
Pham D, Thompson A, Kron T, Foroudi F, Kolsky MS, Devereux T, et al. Stereotactic ablative body radiation therapy for primary kidney cancer: a 3-dimensional conformal technique associated with low rates of early toxicity. Int J Radiat Oncol Biol Phys. 2014;90(5):1061-8.	N=20. Size or stage of tumour not reported and some tumours had diameter >5cm so not clear how many were T1. Larger case series reporting the same outcome (toxicity) were available for inclusion.
Ponsky L, Lo SS, Zhang Y, Schluchter M, Liu Y, Patel R, et al. Phase I dose-escalation study of stereotactic body radiotherapy (SBRT) for poor surgical candidates with localized renal cell carcinoma. Radiother Oncol. 2015;117(1):183-7.	Includes T1 to T3 tumours with no report of how many were T1. Results were not reported separately for the in scope patients.
Prins FM, Kerkmeijer LGW, Pronk AA, Vonken EPA, Meijer RP, Bex A, et al. Renal Cell Carcinoma: Alternative Nephron-Sparing Treatment Options for	Inclusion criteria were not clearly specified regarding tumour stage, tumour size, metastases, whether inoperable or not. Three of the 6 included

Reference	Paper selection decision and rationale if excluded
Small Renal Masses, a Systematic Review. J Endourol. 2017;31(10):963-75.	studies of SABR included tumours that were >7cm and hence not stage T1. The total number of patients that were not T1 was not reported. Results for T1 tumours were not reported separately.
Siva S, Ali M, Correa RJM, Muacevic A, Ponsky L, Ellis RJ, et al. 5-year outcomes after stereotactic ablative body radiotherapy for primary renal cell carcinoma: an individual patient data meta-analysis from IROCK (the International Radiosurgery Consortium of the Kidney). Lancet Oncol. 2022;23(12):1508-16.	N=190. Of the 128 of patients assessed for operability, only 91 were inoperable. Thus 99/190 patients might be operable. Results were not reported separately for the group of patients that were inoperable. (Study focus was single vs multi-fraction SABR.)
Siva S, Correa RJM, Warner A, Staehler M, Ellis RJ, Ponsky L, et al. Stereotactic Ablative Radiotherapy for >=T1b Primary Renal Cell Carcinoma: A Report From the International Radiosurgery Oncology Consortium for Kidney (IROCK). Int J Radiat Oncol Biol Phys. 2020;108(4):941-9.	N=95. 45 patients were medically inoperable (of 58 assessed). Hence up to 50/95 might not be medically inoperable. Results were not reported separately for the in scope patients.
Siva S, Louie AV, Warner A, Muacevic A, Gandhidasan S, Ponsky L, et al. Pooled analysis of stereotactic ablative radiotherapy for primary renal cell carcinoma: A report from the International Radiosurgery Oncology Consortium for Kidney (IROCK). Cancer. 2018;124(5):934-42.	No indication that tumours were inoperable. Not restricted to T1 tumours; tumour size and standard deviation suggest some were larger than 7cm but no data were reported on how many were larger. Results were not reported separately for the in scope patients.
Siva S, Muacevic A, Staehler M, Warner A, Gandhidasan S, Ponsky L, et al. Individual patient data meta-analysis of sbrt kidney: A report from the international radiosurgery oncology consortium for kidney (IROCK). International Journal of Radiation Oncology Biology Physics. 2017;99(2 Supplement 1):S153-S4.	Conference abstract – excluded by PICO.
Siva S, Jackson P, Kron T, Bressel M, Lau E, Hofman M, et al. Impact of stereotactic radiotherapy on kidney function in primary renal cell carcinoma: Establishing a dose-response relationship. Radiother Oncol. 2016;118(3):540-6.	N=21. Larger case series reporting the same outcome measures were available for inclusion.
Siva S, Jackson P, Kron T, Shaw M, Chander S, Gill S, et al. Kidney function loss is directly dose dependent after SBRT for primary RCC as assessed by Cr-51 EDTA + DMSA SPECT/CT. Radiotherapy and Oncology. 2015;115(SUPPL. 1):S353-S4.	Conference abstract – excluded by PICO
Staehler M, Schuler T, Spek A, Rodler S, Tamalunas A, Furweger C, et al. Propensity Score-Matched Analysis of Single Fraction Robotic Radiosurgery Versus Open Partial Nephrectomy in Renal Cell Carcinoma: Oncological Outcomes. Cureus. 2022;14(1):e21623.	The study included 35 patients who were treated with SABR and 35 propensity score matched patients who were treated with open partial nephrectomy. The authors reported that *"The indication for RRS [stereotactic robotic radiosurgery] was determined by the oncological tumor board with the patients' oncological status and their treatment preference being the most important factors ... Matching criteria were Eastern Cooperative Oncology Group (ECOG) status, age, clinical tumor, nodes, and metastases (TNM), and tumor diameter."* This suggests that a significant proportion of the patients who received SABR may not have been medically inoperable. The number of patients that were medically inoperable was not reported.
Staehler M, Bader M, Schlenker B, Casuscelli J, Karl A, Roosen A, et al. Single fraction radiosurgery for the treatment of renal tumors. J Urol. 2015;193(3):771-5.	Only 29 of 40 had RCC; other patients had transitional cell carcinoma. It is not clear if patients were medically inoperable. Results were not reported separately for the in scope patients.
Stereotactic ablative radiotherapy (SABR). Health Technology Wales. 2022.	Includes studies that included stage T1 and T2 tumours and T2 tumours are not included in

Reference	Paper selection decision and rationale if excluded
	PICO. Results were not reported separately for in scope patients (T1 tumours).
Uhlig A, Uhlig J, Trojan L, Kim HS. Stereotactic Body Radiotherapy for Stage I Renal Cell Carcinoma: National Treatment Trends and Outcomes Compared to Partial Nephrectomy and Thermal Ablation. J Vasc Interv Radiol. 2020;31(4):564-71.	Not clear what % of patients were in scope (localised T1 disease, inoperable). Results were not reported separately for in scope patients.
Wang YJ, Han TT, Xue JX, Chang DS, Li HQ, Li P, et al. Stereotactic gamma-ray body radiation therapy for asynchronous bilateral renal cell carcinoma. Radiol Med (Torino). 2014;119(11):878-83.	N=9. Larger case series reporting the same outcome measures were available for inclusion.
Wegner RE, Abel S, Vemana G, Mao S, Fuhrer R. Utilization of Stereotactic Ablative Body Radiation Therapy for Intact Renal Cell Carcinoma: Trends in Treatment and Predictors of Outcome. Adv Radiat Oncol. 2020;5(1):85-91.	Not clear what proportion of patients were in scope (localised T1 disease, inoperable). Results were not reported separately for in scope patients.
Yamamoto T, Kawasaki Y, Umezawa R, Kadoya N, Matsushita H, Takeda K, et al. Stereotactic body radiotherapy for kidney cancer: a 10-year experience from a single institute. J Radiat Res (Tokyo). 2021;62(3):533-9.	N=29. Of these only 19 (66%) were reported to be inoperable and hence in scope. Results were not reported separately for the group that were inoperable. In addition, 4 patients (16%) were out of scope because they had recurrent tumours.
Yamamoto T, Kadoya N, Takeda K, Matsushita H, Umezawa R, Sato K, et al. Renal atrophy after stereotactic body radiotherapy for renal cell carcinoma. Radiat. 2016;11:72.	N=14. Larger case series reporting the same outcome measures were available for inclusion.
Yim K, Hsu SH, Nolazco J, Cagney D, Mak RH, D'Andrea V, et al. Stereotactic Magnetic Resonance-guided Adaptive Radiation Therapy for Localized Kidney Cancer: Early Outcomes from a Prospective Phase 1 Trial and Supplemental Cohort. Eur Urol Oncol. 2023;22:22.	N=20, 90% T1. Larger case series reporting the same outcome measures were available for inclusion. In addition, the study does not report whether patients were inoperable (although mentioned in the patient summary).

Appendix E Evidence Table

For abbreviations see list after table. For the JBI checklist for case series see Appendix F.

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
Correa RJM, Louie AV, Staehler M, Warner A, Gandhidasan S, Ponsky L, et al. Stereotactic Radiotherapy as a Treatment Option for Renal Tumors in the Solitary Kidney: A Multicenter Analysis from the IROCK. J Urol. 2019;201(6):1097-104 **Study location** 9 institutions in Germany, Australia, USA, Canada and Japan **Study type** Retrospective case series (most but not all data were retrospective) **Study aim** To evaluate SABR therapy in patients with a solitary kidney, focusing on oncologic and renal function outcomes	Patients with RCC treated with SABR. The study included patients with two kidneys and patients with an anatomically solitary kidney. The group with a solitary kidney are considered medically inoperable and hence are relevant to this review. Only results for this group are reported in this review. **Inclusion criteria** All patients who received SABR between 2007 and 2016 in the participating institutions. Other inclusion criteria not specified but see baseline characteristics below. Only the group with a solitary kidney are reported here. **Exclusion criteria**	SABR (no further detail reported) Mean total dose (Gy): 28.9 (SD ± 12.3), median 25.0 (range 14.0 to 70.0) Mean number of fractions: 1.9 (SD ± 2.5), range 1 to 10 Single fraction only: 13 (16.1%) Mean fraction dose (Gy): 22.1 (SD ± 6.0), median 25.0 (range 6.0 to 26.0) Mean biological equivalent dose (Gy): 86.8 (SD ± 14.4), median 87.5 (range 33.6 to 124.8)	Median follow-up 2.57 years (95% CI 2.12 to 3.33) **Critical outcomes** **Local control**[18] 2 years: 98.0% 4 years: 98.0% *Local disease recurrence* 1 patient (1.2%) **Overall survival** 2 years: 81.5% 4 years: 73.6% **Progression free survival** 2 years: 77.5% 4 years: 68.3% *Local disease recurrence* 1 patient (1.2%) *Distant disease recurrence* 4 patients (4.9%) **Important outcomes**	This study was appraised using the JBI checklist for case series: 1. No 2. Yes 3. Yes 4. Yes 5. Unclear 6. Yes 7. Yes 8. Yes 9. Unclear 10. No **Other comments** This was a prospective multi-centre case series. Inclusion criteria were not reported. However, exclusion criteria and descriptions of patients were included. Loss to follow-up was not reported and few statistical tests were carried out in relation to outcomes of interest for the subgroup of patients with a solitary kidney. In addition, details about the

[18] Based on RECIST criteria. RECIST is a set of published rules that define when tumours in cancer patients improve ("respond"), stay the same ("stabilize"), or worsen ("progress") during treatment.; follow-up every 3 to 6 months till 5 years.

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
Study dates Patients receiving SABR between 2007 and 2016	Active cancer within the last 5 years, prior abdominal radiotherapy, systemic therapy within 2 weeks, urothelial carcinoma **Total sample size** n=81 with solitary kidney (total sample size n=219) **Baseline characteristics** (solitary kidney group) • Median age (years): 66.5 (range 42.2 to 93.3) • Male: 56 (69.1%) • T stage: not reported but see tumour size below • Histology, n (%) Clear cell RCC: 74 (91.4%) Papillary RCC: 0 Chromophobe: 0 Other RCC: 0 No pathological confirmation: 7 • Mean ± SD maximum tumour dimension (mm): 35.0 ± 11.5, median 37.2 (IQR 25.0 to 42.9) • Maximum dimension ≥40mm: 30 (37.0%)		**Cancer specific survival** 2 years: 98.2% 4 years: 98.2% **Organ specific disease response** Post SABR eGFR measured at the latest possible time point following treatment (median 20.4 months) *Mean ± SD eGFR* (ml/min): 59.2 ± 23.9, median 62.1 (range 8.0 to 100.4) *Proportion at each level of CKD as defined by eGFR range:* eGFR≥90 (normal): 7 (10.8%) eGFR 60 to <90 (mild CKD): 29 (44.6%) eGFR 45 to <60 (mild to moderate CKD): 13 (20.0%) eGFR 30 to <45 (moderate to severe CKD): 7 (10.8%) eGFR <30 (severe CKD): 9 (13.9%) *Mean change in eGFR from baseline to latest time point measured ± SD (ml/min):* -5.8 ± 10.8, median -3.3 (range -35.1 to 18.7) *Decrease in eGFR of 15ml/min or greater:* 14 (21.5%) *Increase in eGFR after SABR treatment:* 17 (26.2%) *Number on dialysis after SABR treatment:* 0	treatment centres were not reported, making it more difficult to assess generalisability of the study results. The study reported a comparison of outcomes for patients with a single kidney vs two kidneys. Only the subgroup of patients with a single kidney are of interest to this review because patients with a single kidney are medically inoperable. Hence only information and results for the subgroup with a single kidney are reported here. No comparator group of interest was included (all patients received SABR). It is unclear what the outcomes would have been without SABR or with a different comparator treatment. The authors did not report pre-specification of the outcome measures, and patients and clinicians were not blinded to the study treatment. No information on patient ethnicity or socioeconomic status was reported.

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
	• ECOG[16] group 0 or 1 or Karnofsky Performance Status[17] 70 or greater: 79 (97.5%) • Mean ± SD eGFR (ml/min): 64.6 ± 21.7, median 67.6 (range 13.0 to 126.3) eGFR≥90: 4 (5.0%) eGFR 60 to <90: 50 (62.5%) eGFR 45 to <60: 12 (15.0%) eGFR 30 to <45: 7 (8.8%) eGFR <30: 7 (8.8%) • Surveillance pre-SABR: not reported • Reasons for SABR: not reported		<u>Subgroup analysis</u> Tumour diameter ≥4.0 cm was associated with eGFR decrease of 15 ml/min or greater, OR 4.21 (95% CI 1.16 to 15.31), p=0.029 (univariable logistic regression analysis)	**Source of funding** Not reported but stated that, *"No direct or indirect commercial, personal, academic, political, religious or ethical incentive is associated with publishing this article."*
Donovan EK, Xie F, Louie AV, Chu W, Siva S, Kapoor A, et al. Cost Effectiveness Analysis of Radiofrequency Ablation (RFA) Versus Stereotactic Body Radiotherapy (SBRT) for Early Stage Renal Cell Carcinoma	Patients with early stage kidney confined medically inoperable RCC **Inclusion criteria** Early stage RCC defined as node negative and confined to the kidney, solitary renal masses,	**Intervention** SABR, 5 fractions Included costs of supplies, personnel and capital costs (including costs for MRI, CT simulator and linear accelerators based on	**Important outcomes** **Cost effectiveness** Costs in 2020 Canadian dollars (CAD) 5-year time horizon *ICER per QALY gained:* CAD -4,490 Costs SABR: CAD 16,097	Appraisal with a checklist is not required for cost effectiveness studies. **Other comments** This was a cost effectiveness analysis based on the Canadian healthcare system and literature review

[16] The ECOG performance status score describes a patient's level of functioning in terms of their ability to care for themself, daily activity, and physical ability (walking, working, etc.). Higher score indicates greater disability

[17] The Karnofsky Performance Scale Index is an assessment tool for functional impairment. A status of 70 implies that the patient cares for themselves but is unable to carry on normal activity or do active work. Higher status/score reflects less functional impairment.

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
(RCC). Clin Genitourin Cancer. 2022;20(5):e353-e61. **Study location** Canadian perspective **Study type** Cost effectiveness study using data from literature review **Study aim** To conduct a cost-effectiveness analysis of SABR vs RFA in the non-surgical management of early stage RCC according to CHEERS criteria in the Canadian healthcare system **Study dates** Costs were based on 2020 Canadian dollar costs	unilateral, no evidence of distant metastases. Subgroup analysis included analysis for T1a vs T1b tumours. Inoperable (based on majority of studies including non-surgical candidates). **Exclusion criteria** Not reported. **Total sample size** Outcomes data were based on literature review. Sample size not reported.	service contracts over 10 years). Cost of SABR procedure: CAD 3,804.32 plus weighted cost of complications CAD 21.00. **Comparison** RFA Included costs of machinery, supplies and personnel. Cost of RFA: CAD 5,517.00 plus weighted cost of complications CAD 77.00. For both SABR and RFA: Cost of surveillance CT monthly: CAD 89.00 Cost of metastatic disease monthly: CAD 3,318.00	RFA: CAD 18,324 QALYs gained SABR: 4.109[19] RFA: 3.607 Sensitivity analysis: Significant variability in the ICER: Rate of distant metastases had the greatest implications. Utility values[20] following SABR and RFA also had significant implications. Varying other parameters resulted in smaller changes to the ICER. <u>Subgroup analysis</u> T1a tumours *ICER per QALY gained:* CAD 2,207 Costs SABR: CAD 14,993 RFA: CAD 13,940 QALYs gained SABR: 4.119 RFA: 3.641 T1b tumours *ICER per QALY gained:* CAD -22,904[21] Costs SABR: CAD 19,245	comparing SABR to RFA in terms of ICER for people with inoperable early stage RCC. It included sensitivity analysis. The analysis used a Markov model with a 5 year time horizon. Costs were based on a Canadian public health care payer's perspective and did not include individual patient costs after treatment such as rehabilitation and medication costs. Costs of personnel, supplies and machinery/capital were included. A discount rate of 1.5% per year was applied. Costs for RFA were from costs published by the Canadian Urological Association. Costs for SABR were based on costs at a cancer centre in Canada. Outcome data were obtained from literature review. Where varying rates for transition probabilities and utilities were reported among studies, a

[19] Narrative reports a figure of 4.103; figure of 4.109 reported in Table 3 of paper.
[20] In health economics, a 'utility' is the measure of the preference or value that an individual or society gives a particular health state.
[21] These ICER results were reported in the abstract and narrative; Table 3 of the paper reported slightly different results: ICER per QALY gained of CAD -29,905 for T1b tumours and CAD 2,208 for T1a tumours.

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
			RFA: CAD 37,427 QALYs gained SABR: 4.067 RFA: 3.459	range was created for sensitivity analyses. The authors report that there was significant variation reported among studies in the rates of local progression and distant metastases and in the number of patients receiving salvage treatment and the choice of treatment. QALYs were calculated using utility values from the literature for patients who had SABR treatment for the upper abdomen; and for RCC patients undergoing RFA. QoL studies of SABR treatment for RCC were also used. The authors noted that immunotherapies currently in use for metastatic RCC may result in variations in utility values. The authors assumed that the patient populations in the studies used for outcomes data for this cost effectiveness study were inoperable because “a majority of RFA and SABT [SABR] studies include non-surgical candidates”. Some of the data used came from studies published before 2013 (the

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
				earliest search date for this review). It is not clear what proportion of patients in those studies were in fact medically inoperable. Results should be treated with caution due to uncertain generalisability to the UK NHS context and due to the variation in ICERs calculated in sensitivity analyses, particularly given that sensitivity analyses suggested that the rate of distant metastasis had the greatest implications for the calculated ICERs, and the costs of treatment of metastatic RCC may have changed since the literature review used by the study authors (due to changing costs of immunotherapies and targeted therapies). **Source of funding:** Not reported. Stated that one author received fellowship salary support from Accuray Incorporated and one had research funding from Varian Medical Systems for research related to kidney cancer outside of this work.

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
Glicksman RM, Cheung P, Korol R, Niglas M, Nusrat H, Erler D, et al. Stereotactic Body Radiotherapy for Renal Cell Carcinoma: Oncological and Renal Function Outcomes. Clin Oncol (R Coll Radiol). 2023;35(1):20-8 **Study location** Canada, single centre **Study type** Retrospective case series (some patients were part of a prospective study) **Study aim** To evaluate oncological and renal function outcomes of SABR for medically inoperable patients with localised renal cell carcinoma **Study dates** Patients enrolled 2012 to 2020	Patients localised RCC treated with curative-intent who were deemed medically inoperable or unresectable or declined surgery. **Inclusion criteria** Deemed medically inoperable or unresectable after assessment by urological consultant or made informed decision to decline surgery. T1 to T4 RCC (89% were T1) with no evidence of lymph node or distant metastases. Histological confirmation encouraged. Minimum of 3 months follow-up. **Exclusion criteria** None reported. **Total sample size** n=74 **Baseline characteristics**	SABR using intensity modulated radiotherapy (IMRT) (2 patients, 2.7%) or volumetric modulated arc therapy (VMAT) (72 patients, 97.3%) 30 to 45Gy in 5 fractions or 42Gy in 3 fractions. Based on physician decision. Delivered on alternate days. 30Gy in 5 fractions: 1 (1.4%) 35Gy in 5 fractions: 22 (29.7%) 40Gy in 5 fractions: 41 (55.4%) 45Gy in 5 fractions: 6 (5.4%)[23] 42Gy in 3 fractions: 4 (8.1%)[24]	Median follow-up 27.8 months (IQR 17.6 to 41.7) **Critical outcomes** **Local control[25]** *Cumulative incidence of local failure* 1 year: 5.85% 2 years: 7.77% 4 years: 7.77% 3/5 patients with local failure underwent nephrectomy; all had histological confirmation of recurrence. Subgroup analysis: Local control Univariate analysis for T1b vs T1a tumours: HR 1.1 (95% CI 0.08 to 14.0), p=0.97 **Overall survival** 1 year: 100% 2 years: 100% 4 years: 91.6% Subgroup analysis: overall survival Univariate analysis for T1b vs T1a tumours: HR 0.51 (95% CI 0.007 to 35.5), p=0.76 **Progression free survival** *Progression free survival*	This study was appraised using the JBI checklist for case series: 1. Yes 2. Yes 3. Yes 4. Yes 5. Uncertain 6. Yes 7. Yes 8. Yes 9. Unclear 10. No **Other comments** This was a retrospective single centre case series that included some patients from a prospective study. It reported including consecutive patients but does not report the number that declined to participate or were lost to follow-up. The authors reported their inclusion criteria and baseline clinical data. Details about the treatment centre in Canada were not reported, hence the level of generalisability of the study results is unclear. Few

[23] This figure was reported in Table 2 of the paper. However, 6/74 is in fact 8.1%.
[24] This figure was reported in Table 2 of the paper. However, 4/74 is in fact 5.4%.
[25] Based on RECIST criteria.

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
	• Median age (years): 80 (IQR 73 to 86) • Male: 49 (66.2%) • T stage, n (%) T1a: 32 (43.2%) T1b: 34 (46.0%) T2a: 2 (2.7%) T3: 5 (6.7%) T4: 1 (1.4%) • Histology, n (%) Clear cell RCC: 25 (33.8%) Papillary RCC: 6 (8.1%) Other: 4 (5.4%) Not available: 39 (52.7%) • Median tumour size: 4.6cm (IQR 3.0 to 5.6) • Median Charlson co-morbidity score[22]: 7 (IQR 6 to 9) • Median eGFR (ml/min): 56 (range 38 to 72) eGFR>90: 2 (2.7%) eGFR 60 to 89: 26 (35.1%) eGFR 45 to 59: 18 (24.3%) eGFR 30 to 44: 15 (20.3%)		1 year: 91.4% 2 years: 89.7% 4 years: 89.7% Subgroup analysis: progression free survival Univariate analysis for T1b vs T1a tumours: HR 2.5 (95% CI 0.30 to 20.6), p=0.40 See under local control above for cumulative incidence of local failure. *Cumulative incidence of distant metastasis* 1 year: 4.24% 2 years: 4.24% 4 years: 4.24% Includes 1 patient each with lung, spine and adrenal metastasis. Subgroup analysis: distant metastasis Univariate analysis for T1b vs T1a tumours: HR 1.6 (95% CI 0.13 to 18.9), p=0.72 **Important outcomes** **Organ specific disease response** *Median change in eGFR from baseline* 1 year: -7.0ml/min (IQR -14.5 to -1.0) 2 years: -11.5ml/min (IQR -19.5 to -4.0) 4 years: -14.0ml/min (IQR -28.0 to -10.0)	statistical analyses relating to the outcomes of interest were reported. The study included some of the patients from the prospective study by Swaminath et al (2021) (see below) who were enrolled between 2016 and 2018, together with a cohort of patients who were treated before or after that study or declined to participate in that study. No comparator group was included. It is unclear what the outcomes would have been without SABR or with a different comparator treatment. The authors did not report pre-specification of the outcome measures, and patients and clinicians were not blinded to the study treatment. No information on patient ethnicity or socioeconomic status was reported.

[22] Charlson Comorbidity Index predicts the mortality for a patient who may have a range of concurrent conditions (comorbidities), such as heart disease, AIDS, or cancer (considering a total of 17 categories). A score of zero means that no comorbidities were reported; the higher the score, the higher the predicted mortality rate.

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
	eGFR 15 to 29: 9 (12.2%) eGFR<15: 2 (2.7%) eGFR not available: 2 (2.7%) 2 patients had 1 kidney and 2 had 0 kidneys (on dialysis) • Surveillance pre-SABR: 26 (35.1%) for median 35 months (IQR 24 to 49.9) with median tumour size of 2.4 cm (IQR 1.7 to 2.7) at start of surveillance • Reasons for SABR: Medically inoperable: 56 (75.6%) Patient declined surgery: 16 (21.6%) Other: 1 (1.4%) Not available: 1 (1.4%)		eGFR significantly decreased over time: p<0.0001 *% of patients with improved eGFR compared to baseline* 1 year: 18.8% 2 years: 15% 4 years: 0% "The proportion of patients in stage 3+[26] chronic kidney disease increased over time" (no further detail reported) Two patients (2.7%) were on dialysis before SABR; 4 additional patients (5.4%) were on dialysis after SABR treatment. *Proportion of renal function from the ipsilateral (SABR-treated) kidney* Baseline: 47% (IQR 44 to 53) 1 year: 39% (IQR 37 to 48) 2 years: 36% (IQR 36 to 42) 4 years: 32.5% (IQR 29 to 39.5) Proportion decreased significantly over time (p<0.0001)	**Source of funding** Not reported
Siva S, Pham D, Kron T, Bressel M, Lam J, Tan TH, et al. Stereotactic ablative body radiotherapy for inoperable primary kidney cancer: a prospective	Patients with small RCC who were medically inoperable, high risk for surgery or refused surgery.	SABR using conventional c-arm linear accelerator RCCs <5cm maximum dimension: 26Gy, 1 fraction: n=17	Median follow-up 24 months, minimum 12 months **Critical outcomes** **Local control[29]** At 1 year:	This study was appraised using the JBI checklist for case series: 1. Yes 2. Yes 3. Yes

[26] Stage 3+ chronic kidney disease = eGFR <60ml/min
[29] Based on RECIST criteria; CT scan 3-monthly for minimum of 12 months.

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
clinical trial. BJU Int. 2017;120(5):623-30 **Study location** Australia, single centre **Study type** Prospective case series **Study aim** To assess the feasibility and safety of SABR for RCC in patients unsuitable for surgery **Study dates** Patients enrolled 2012 to 2014	**Inclusion criteria** Aged ≥18 years, ECOG performance score 0 to 2 inclusive, single lesion within the target kidney. Medically inoperable, high risk for surgery because of likelihood of post-surgical dialysis, or refused surgery. **Exclusion criteria** Receiving prior or concurrent systemic therapy; previously received high-dose radiotherapy to upper abdomen. Patients with T1a disease[27] were evaluated closely for the need for treatment factoring the existing comorbidities; these patients had documented growth on serial imaging, and/or were symptomatic with haematuria or pain. **Total sample size** n=37	RCCs ≥5cm maximum dimension: 42 Gy in 3 fractions delivered on non-consecutive days: n=17 33/37 received all treatments (to 34 RCCs); 1 patient died prior to SABR (pulmonary embolus after international flight); 1 patient completed 2 of 3 planned fractions because of social difficulties; 2 patients could not meet planned dose constraints.	Objective tumour size reduction: 61% of RCCs At last follow-up (time period not reported): Partial response: n=4 Stable disease: n=28 **Overall survival** 1 year: 100% 2 years: 92% (95% CI 81% to 100%) **Progression free survival** Freedom from local progression 1 year: 100% 2 years: 100% Freedom from distant progression rates 1 year: 97% (95% CI 91% to 100%) 2 years: 89% (95% CI 78% to 100%) These are equivalent to overall freedom from progression rates as freedom from local progression was 100% to 2 years. **Important outcomes** **Organ specific disease response** Mean change in eGFR Baseline to 1 year: -11ml/min (95% CI -6 to -17) p<0.001 Baseline to 2 years (subset of n=9): -11ml/min (95% CI -3 to -19)	4. Yes 5. No 6. Yes 7. Yes 8. Yes 9. Unclear 10. Yes **Other comments** This was a prospective single-centre case series with clear inclusion and exclusion criteria and descriptions of patients included. However, 4 of the 37 patients who consented to SABR were not included in the analysis of outcomes because they did not receive all of the planned SABR treatments. In addition, details about the (Australian) treatment centre were not reported, hence the level of generalisability of the study results is unclear. No comparator group was included and limited statistical analyses were carried out. It is unclear what the outcomes would have been without SABR or with a different comparator treatment.

[27] T1a disease = tumour 0 to 4cm maximum diameter; T1b disease = tumour 4 to 7cm maximum diameter.

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
	Baseline characteristics • Median age (years): 78 (range 42 to 91) • Male: 28 (76%) • T stage, n (%) T1a: 13 (35%) T1b: 23 (62%) T2: 1 (3%) • Histology, n (%) Clear cell: 30 (88%) Papillary/chromophilic: 3 (9%) Mixed: 1 (3%) Not reported: 3 • Tumour size, mm Mean: 49.2 (SD 12.6) Median: 48 (21 to 75) • Bilateral tumour: 1 • Charlson co-morbidity score: Score 1 to 2: 2 (5%) Score 4 to 6: 7 (19%) Score 6: 7 (19%) Score 7: 9 (24%) Score 8: 6 (16%) Score 9 to 11: 6 (16%) • Mean eGFR: 55mL/min (range 18 to 97) • Reason for SABR: High risk of post-surgical dialysis: 11 (30%) Refused surgery: 1		**Safety** *Adverse events* *Overall* Grade 1: at least 1 event: 19 (58%): chest wall pain 15, dermatitis 2, diarrhoea 3, dyspnoea 2, fatigue 14, gastritis 2, haematuria 3, nausea 5, right flank pain 1, skin induration 1 Grade 2: at least 1 event: 7 (21%): abdominal pain 1, dyspnoea 1, fatigue 5, gastritis 1, haematuria 1, nausea 2 Grade 3: at least 1 even: 1 (3%): fatigue 1 *Acute (≤90 days after SABR)* Grade 1: at least 1 event: 11 (33%): chest wall pain 5, dermatitis 2, diarrhoea 3, fatigue 11, gastritis 1, nausea 5, right flank pain 1 Grade 2: at least 1 event: 7 (21%): dyspnoea 1, fatigue 6, gastritis 1, nausea 2 Grade 3: none *Late (>90 days after SABR)* Grade 1: at least 1 event: 17 (52%): chest wall pain 12, diarrhoea 1, dyspnoea 2,	The authors did not report pre-specification of the outcome measures, and patients and clinicians were not blinded to the study treatment. No information on patient ethnicity or socioeconomic status was reported. No subgroup analyses were reported. **Source of funding** The study was supported by a CASS Science and Medicine grant SM/11/3784, and the Royal Australia and New Zealand College of Radiation Oncology / Ferring Pharmaceutical Fellowship Award

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
	Medically inoperable: 25[28]		fatigue 7, gastritis 1, haematuria 3, nausea 2, skin induration 1 Grade 2: at least 1 event: 2 (6%): abdominal pain 1, haematuria 1 Grade 3: at least 1 event: 1 (3%): fatigue 1	
Sun MR, Brook A, Powell MF, Kaliannan K, Wagner AA, Kaplan ID, et al. Effect of Stereotactic Body Radiotherapy on the Growth Kinetics and Enhancement Pattern of Primary Renal Tumors. AJR Am J Roentgenol. 2016;206(3):544-53 **Study location** USA, single centre **Study type** Retrospective case series **Study aim** **To assess the growth rate and enhancement of** renal masses before and after treatment with SABR **Study dates**	Patients with renal masses deemed to be poor candidates for surgery or minimally invasive tumour ablation. **Inclusion criteria** All patients treated with SABR for renal masses who had at least 2 imaging studies before treatment and one after treatment. The centre provided SABR to patients who were deemed, after MDT review, to be poor candidates for partial or total nephrectomy or minimally invasive tumour ablation.	SABR using CyberKnife system with Synchrony system (Accuracy) to track movement SABR dose (Gy): mean 38, range 21 to 48 Delivered in daily fractions: Initially 21 Gy in 3 fractions. Gradually increased during the study period to 48 Gy in 3 fractions. Number of tumours: 21Gy: 3 24Gy: 1 27Gy: 4 30Gy: 5 33Gy: 2 36Gy: 2 39Gy: 8 45Gy: 1	Mean follow-up duration after SABR: 561 days (range 83 to 1,366), median 489 n=41 (tumours) **Critical outcomes** **Local control** Tumour responses to SABR[30], n (%): Progressive disease: 1 (2.4%) Stable disease: 31 (75.6%) Partial response: 8 (19.5%) Complete response: 1 (2.4%) “Statistically significant decrease of … the size of renal tumours” after SABR. p-value not reported. Subsequent growth during further follow-up: none that met criteria for response to treatment subsequently did not meet criteria (by end of follow-up period)	This study was appraised using the JBI checklist for case series: 1. Unclear 2. Yes 3. Yes 4. Yes 5. Yes 6. Yes 7. Yes 8. Yes 9. Unclear 10. Yes **Other comments** This was a retrospective single centre case series which reported results for all patients with a renal mass treated with SABR at the institution who had data (at least 2 scan results) available from pre-treatment surveillance as well as at least one post-treatment

[28]Number not reported, assumed given other numbers/details reported.
[30] Based on RECIST criteria.

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
Treated with SABR 2006 to 2011	**Exclusion criteria** Repeat cycles of SABR were excluded from analysis. **Total sample size** n=40 patients, 41 renal tumours **Baseline characteristics** • Median age (years): 74.5 (range 45 to 93) • Male: 20 (50%) • T stage, n (%) T1a: 22 (53.7%) T1b: 18 (43.9%) T2a: 1 (2.4%) • Histology, n (%) Clear cell RCC: 16 (39.0%) Papillary RCC: 6 (14.6%) Oncocytic neoplasm: 8 (19.5%) Unclassified RCC: 2 (4.9%) Urothelial carcinoma: 1 (2.4%) No pathologic diagnosis: 8 (19.5%) • Renal mass size, cm: mean 3.9 (range 1.6 to 8.3)	48Gy: 15	Local control (<5mm growth[31]): 38/41 (92.7%) Mean tumour growth rate (average of 3 linear dimensions): Before SABR: 0.68 cm/year After SABR: -0.37 cm/year p<0.0001 for each dimension Mean tumour volume growth rate: Before SABR: 21.21 cm^3/year After SABR: -5.35 cm^3/year p=0.002	scan. However, the authors did not report clearly the criteria for stopping surveillance and proceeding to treatment (although they reported in the discussion section which patients tended to be offered SABR in the institution). Details about the treatment centre in the USA were not reported, hence the level of generalisability of the study results is unclear. No comparator group was included. It is unclear what the outcomes would have been without SABR or with a different comparator treatment. The authors did not report pre-specification of the outcome measures, and patients and clinicians were not blinded to the study treatment. No information on patient ethnicity or socioeconomic status was reported. No subgroup analyses were reported.

[31] This included tumours that decreased in size or did not change in size

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
	• Renal mass volume, cm^3: mean 31.02 (range 1.1 to 185.6) • All unilateral tumours; 1 patient had 2 tumours in a solitary kidney • Mean pre-treatment length of observation: 416 days (range 2 to 1800), median 237			**Source of funding** M. R. M. Sun has received research support from GlaxoSmithKline.
Swaminath A, Cheung P, Glicksman RM, Donovan EK, Niglas M, Vesprini D, et al. Patient-reported Quality of Life following Stereotactic Body Radiation Therapy for Primary Kidney Cancer - Results from a Prospective Cohort Study. Clin Oncol (R Coll Radiol). 2021;33(7):468-75 **Study location** Canada, 2 institutions **Study type** Prospective case series	Patients with non-metastatic RCC who were medically inoperable, ineligible for other locally ablative treatments or refused surgery. **Inclusion criteria** Aged ≥18 years. Able and willing to complete QoL assessments at baseline, 1 week and 1, 3 and 6 months after SABR. Evidence of non-metastatic RCC	SABR using volumetric modulated arc therapy approach 35Gy in 5 fractions: 16 patients, 50% 40Gy in 5 fractions: 11 patients, 34.4% 45Gy in 5 fractions: 1 patient, 3.1% 42Gy in 3 fractions: 4 patients, 12.5% Fractions delivered every second day. Selected dose based on tumour size, location	Outcomes analysed for 28/32 patients (4 did not complete baseline assessments) **Important outcomes** **Health related QoL** Mean change (% stable or better vs % worse) <u>Baseline vs 1 week after SABR</u> *EQ-5D-3L*[32] Visual analogue scale (n=16): -0.938 Health utility score (n=20): 0.050 (85.0% vs 15.0%) *EORTC-QLQ-C15-PAL*[33]	This study was appraised using the JBI checklist for case series: 1. Yes 2. Yes 3. Yes 4. Yes 5. No 6. Yes 7. Yes 8. Yes 9. Unclear 10. Unclear **Other comments** This was a prospective two-centre case series with clear

[32] EuroQol-5D-3L (EQ-5D-3L) is a standardised health questionnaire that provides a simple descriptive profile and a single value for health status. It is made up of five dimensions (mobility, self-care, usual activities, pain or discomfort and anxiety or depression), each of which are rated at one of three levels (no, some or severe problems). Higher health utility and visual analogue scale scores indicate higher quality of life.
[33] QLQ-C15-PAL is the abbreviated version of EORTC-QLQ-C30 (an established core cancer questionnaire). It consists of 15 categories, including functional scales (physical, emotional function), symptom scales (fatigue, pain, nausea, dyspnoea, insomnia, anxiety, depression, appetite loss, constipation) and a final question on global QoL. Depending on the metric, higher scores indicate higher quality of life, higher functioning and higher symptom burden.

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
Study aim To prospectively assess the longitudinal QoL in patients treated with SBRT for primary RCC **Study dates** Patients enrolled June 2016 to December 2018	(pathological confirmation or radiological evidence). Deemed medically inoperable by urological oncologist, ineligible for other locally ablative treatments or not operable due to patient refusal. **Exclusion criteria** ECOG performance status 3 or more. **Total sample size** n=32 **Baseline characteristics** • Age (years): <70: n=5 71 to 80: n=9 81 to 90: n=15 >90: n=3 • Male: 22 (68.8%) • Lesion size (T stage), n (%) ≤4cm (T1a): 13 (40.6%) 4 to 7cm (range 1.9 to 6.6cm) (T1b): 19 (59.4%) • Histology, n (%)	within kidney, and proximity to upper abdominal organs at risk.	Global QoL score (n=20): -8.345 (45.0% vs 55.0%) (p=0.046) Physical functioning (n=20): -0.665 (80.0% vs 20.0%) Emotional functioning (n=20): -2.920 (65.0% vs 35.0%) Fatigue (n=20): 7.225 (60.0% vs 40.0%) Nausea and vomiting (n=20): 5.000 (90.0% vs 10.0%) Dyspnoea (n=19): 0.005 (95.0% vs 5.0%) Pain (n=20): 1.667 (70.0% vs 30.0%) Insomnia (n=20): -5.000 (85.0% vs 15.0%) Appetite (n=20): 5.000 (80.0% vs 20.0%) Constipation (n=19): 1.754 (90.0% vs 10.0%) *FACT FKSI-19*[34] Overall converted score (n=20): 0.430 (85.0% vs 15.0%) <u>Baseline vs 1 month after SABR</u> *EQ-5D-3L*	inclusion and exclusion criteria and descriptions of patients included. Relatively large and varying proportions of patients did not complete QoL questionnaires at each time point and assumptions were made regarding missing data. Statistical analysis was not clearly reported, including no mention of adjusting for multiple tests (scores at each time point were compared to baseline but not all p-values were reported). Details about the two treatment centres in Canada were not reported, hence the level of generalisability of the study results is unclear. No comparator group was included. It is unclear what the outcomes would have been without SABR or with a different comparator treatment. The analysis of the results included stated assumptions around missing values and a before vs after analysis of QoL. For each of the 3

[34] FACT FKSI-19 is a 19-item questionnaire for the functional assessment of cancer therapy that includes disease-related symptoms specific to kidney cancer. It was developed with input from patients with kidney cancer and clinical experts. Higher scores indicate fewer symptoms.

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
	Clear cell RCC: 16 (50%) Papillary RCC: 5 (15.6%) Other: 2 (6.3%) No biopsy: 9 (28.1%) • Reason for SABR Medically inoperable: 24 (75%) Patient refused surgery/RFA: 8 (25%)		Visual analogue scale (n=22): 1.500 Health utility score (n=23): 0.022 (79.2% vs 20.8%) *EORTC-QLQ-C15-PAL* Global QoL score (n=24): -3.479 (70.8% vs 29.2%) Physical functioning (n=24): 1.388 (83.3% vs 16.7%) Emotional functioning (n=24): 2.087 (75.0% vs 25.0%) Fatigue (n=24): 4.642 (62.5% vs 37.5%) Nausea and vomiting (n=24): 0.000 (87.5% vs 12.5%) Dyspnoea (n=24): -0.008 (83.3% vs 16.7%) Pain (n=24): 0.694 (66.7% vs 37.3%) Insomnia (n=24): -2.778 (79.2% vs 20.8%) Appetite (n=24): 1.383 (70.8% vs 29.2%) Constipation (n=23): 4.348 (79.2% vs 20.8%) *FACT FKSI-19* Overall converted score (n=24): 0.908 (70.8% vs 29.2%)	validated QoL tools used, the MCID in each direction (improvement or worsening) was reported and was used in making the assessment regarding “stable”, “better” or “worse” QoL. For EORTC, the MCID used was 10 points in either direction, for the EQ-5D-3L overall health state score it was 0.08 and for the FACT total score it was 5 points. The authors did not report whether this analysis plan was pre-specified. Of the 32 patients enrolled, the highest number completing the follow-up QoL assessments was at 1 month after SABR (24 patients). 6 months after SABR treatment, 16 patients completed the QoL assessments. Reasons for lower compliance at longer-term follow-up were reported to include patient relocation, hospitalisation for different reasons, follow-up not by the oncology team, patient refusal and missed appointments. The analyses assumed that missing values were random and that domains were highly correlated over the time

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
			<u>Baseline vs 3 months after SABR</u> *EQ-5D-3L* Visual analogue scale (n=16): 4.125 Health utility score (n=17): -0.020 (76.5% vs 23.5%) *EORTC-QLQ-C15-PAL* Global QoL score (n=17): -0.982 (70.6% vs 29.4%) Physical functioning (n=16): -5.000 (68.8% vs 31.3%) Emotional functioning (n=17): 1.471 (76.5% vs 23.5%) Fatigue (n=17): 1.318 (70.6% vs 29.4%) Nausea and vomiting (n=17): -6.859 (100% vs 0%) Dyspnoea (n=17): 1.969 (88.2% vs 11.8%) Pain (n=17): -3.922 (76.5% vs 23.5%) Insomnia (n=17): 3.922 (64.7% vs 25.3%) Appetite (n=17): -9.812 (94.1% vs 5.9%) Constipation (n=16): 4.167 (94.1% vs 5.9%)	periods analysed in the study. If, in fact, the patients who did not complete the follow-up assessments had a lower QoL than the patients who did complete them, the results reported may overestimate the QoL at follow-up; or vice versa. A statistical test (Little's test) was carried out which failed to reject the hypothesis that the data were missing completely at random (p=1.0000). However, the large loss to follow-up and relatively small sample size at follow-up means that the results should be interpreted with caution. Mean scores and standard errors (SEs) were presented on graphs. However, numerical results for the SEs were not provided. The p-values reported were not clearly described in relation to the time points compared. Patients and clinicians were not blinded to the study treatment. No information on patient ethnicity or socioeconomic status was reported.

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
			FACT FKSI-19 Overall converted score (n=17): -2.188 (64.7% vs 35.3%) <u>Baseline vs 6 months after SABR</u> p-values reported below graphs showing baseline, 1 week and 1, 3 and 6 month mean scores and SEs. Not clear if they are p-values for trend.[35] *EQ-5D-3L* Visual analogue scale (n=15): 1.667 (p=0.398) Health utility score (n=16): 0.038 (81.3% vs 18.8%) (p=0.493) *EORTC-QLQ-C15-PAL* Global QoL score (n=16): -2.083 (68.8% vs 31.3%) (p=0.390) Physical functioning (n=16): -7.494 (56.3% vs 43.8%) (p=0.225) Emotional functioning (n=16): -3.119 (75.0% vs 25.0%) (p=0.848) Fatigue (n=16): 2.781 (68.8% vs 31.3%) (p=0.586) Nausea and vomiting (n=16): -3.125 (100.0% vs 0.0%) (p=0.401)	No subgroup analyses were reported. **Source of funding** Not reported

[35] Narrative reports that “Means of converted scores (+/-standard deviations) were also compared at each time point to the baseline using paired t-tests.”

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
			Dyspnoea (n=16): 14.581 (68.8% vs 31.3%) (p=0.126) (p=0.048[36]) Pain (n=16): -6.250 (81.3% vs 18.8%) (p=0.979) Insomnia (n=16): 4.167 (68.8% vs 31.3%) (p=0.543) Appetite (n=16): -2.088 (93.8% vs 6.3%) (p=0.279) Constipation (n=16): 4.167 (81.3% vs 18.8%) (p=0.838) *FACT FKSI-19* Overall converted score (n=16): -0.181 (68.8% vs 31.3%) (p=0.330)	
Zarkar A, Henderson D, Carver A, Heyes G, Harrop V, Tutill S, et al. First UK patient cohort treated with stereotactic ablative radiotherapy for primary kidney cancer. BJUI Compass. 2023;4(4):464-72 **Study location** UK, single institution	Patients with T1 RCC who were non-surgical candidates. **Inclusion criteria** Biopsy-proven RCC <6cm maximum diameter, non-surgical candidates with consensus at urological MDT that radical treatment was appropriate.	SABR using standard Linear Accelerator, using volumetric modulated arc therapy (VMAT): n=11 or CyberKnife: n=8 1 fraction, 26Gy: n=8 3 fractions, alternate days, total 42Gy: n=11	Median follow-up 17 months (range 5 to 32 months) **Critical outcomes** **Local control[37]** At 6 months Partial response: 3/15 Stable disease: 12/15 Median reduction in tumour size from baseline: 16.67% (IQR 2.7 to 28.0) Rate of local control: 94.4% (95% CI 66.6% to 99.2%)	This study was appraised using the JBI checklist for case series: 1. Yes 2. Yes 3. Yes 4. Unclear 5. Unclear 6. Yes 7. Yes 8. Yes 9. Unclear

[36] P-value 0.048 reported in narrative: “Dyspnoea scores were relatively unchanged compared with baseline, except for at 6 months post-SBRT where a statistically significant worsening was seen (p = 0.048)”. It was not clear from the graph what timepoints this analysis referred to but likely to be 6 months compared to baseline. The p-value reported in the graph was p=0.126, which may represent a p-value for trend over the 6 months but this is not clear.
[37] Based on RECIST criteria; CT scans; not assessed for some patients at 6 or 12 months due to earlier death or due to COVID-19 pandemic affecting CT bookings.

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
Study type Prospective case series **Study aim** To assess the feasibility of the delivery of SABR using CyberKnife and Linear Accelerator platforms **Study dates** Not reported but "Some imaging was delayed during the coronavirus disease 2019 (COVID-19) pandemic". 36 month period.	Decision to treat with SABR was because patient was not fit for general anaesthetic needed for surgery or cryoablation (CA) or radiofrequency ablation (RFA) or unsuitable for CA/RFA due to location of tumour. **Exclusion criteria** Metastatic disease, factors precluding abdominal radiotherapy. **Total sample size** n=19 **Baseline characteristics** • Median age (years): 76 (IQR 64 to 82) • Male: 47.4% • Median tumour size (cm): 4.5 (IQR 3.8 to 5.2) • Tumour <4cm: n=5; ≥4cm: n=14 • Median baseline eGFR: 62 (IQR 43 to 74) • Charlson co-morbidity score: scores of 11, 9, 8, 7, 6, 5: 1, 5, 4, 1, 4 ,4 patients respectively		At 12 months: Partial response: 5/14 Stable disease: 9/14 Median reduction in tumour size from baseline: 26.5% (IQR 7.9 to 34.5) Rate of local control: 94.4% (95% CI 66.6% to 99.2%) **Overall survival** At 6 months: 94.7% (95% CI 68.1% to 99.2%) At 12 months: 78.3% (95% CI 51.9% to 91.3%) 7 deaths of which 6 not related to SABR or RCC (cardiac arrest, sepsis, heart failure, left ventricular failure, pneumonia (2)) **Progression free survival** Over whole follow-up period: Local progression: 1/19 Metastatic disease: 2/19 **Important outcomes** **Cancer specific survival** 1/19 deaths related to the cancer **Organ specific disease response** Mean change in eGFR Baseline to 6 months: -5.4 ml/min (95% CI -10.3 to -0.6) 6 months to 12 months: -5.1 ml/min (95% CI -9.0 to -1.1)	10. Yes **Other comments** This was a prospective single-centre case series from the UK with clear inclusion and exclusion criteria and descriptions of patients included. However, the dates of the study and details of the treatment centre were not reported and it is unclear whether all consecutive patients were included. No comparator group was included and limited statistical analyses were carried out. It is unclear what the outcomes would have been without SABR or with a different comparator treatment. The case series was relatively small with relatively short follow-up. The authors did not report pre-specification of the outcome measures, and patients and clinicians were not blinded to the study treatment. No information on patient ethnicity or socioeconomic status was reported.

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
	• Biopsy confirmed RCC: 19 patients Majority who had >4cm tumour had period of surveillance confirming progressive disease. 1 patient had 2 RCCs in same kidney; “one patient had solitary kidney with a large RCC”.		Baseline to 12 months: -8.7 ml/min (95% CI -15.3 to -2.1) **Safety** Worst grade of each type of AE over each patient’s f/u period (number (%)) • Fatigue: 4 (21.1%), 12 (63.3%, 3 (15.8), 0 and 0 patients had Grade 0, 1, 2, 3, 4 fatigue respectively • Gastritis: 17 (89.5%), 1 (5.3%), 1 (5.3%), 0, 0 patients had Grade 0, 1, 2, 3, 4 gastritis respectively • Anaemia: 17 (89.5%), 0, 1 (5.3%), 1 (5.3%), 0 patients had Grade 0, 1, 2, 3, 4 anaemia respectively • Pain: 18 (97.4%), 1 (5.3%, 0, 0, 0 patients had Grade 0, 1, 2, 3, 4 pain respectively • Nausea: 14 (73.7%), 1 (5.3%), 4 (21.1%), 0, 0 patients had Grade 0, 1, 2, 3, 4 nausea respectively • Vomiting: 17 (89.5%), 1 (5.3%), 1 (5.3%), 0, 0 Grade 0, 1, 2, 3, 4 vomiting respectively • Colitis: 18 (94.7%), 0, 0, 1 (5.3%), 0 patients had Grade 0, 1, 2, 3, 4 colitis respectively • Diarrhoea: 17 (89.5%), 2 (10.5%), 0, 0, 0 patients had Grade 0, 1, 2, 3, 4 diarrhoea respectively • Haematuria: 18 (94.7%), 0, 0, 1 (5.3%), 0 patients had Grade 0, 1, 2, 3, 4 haematuria respectively	No subgroup analyses were reported. **Source of funding** “Funding information Queen Elizabeth Hospital Birmingham” No further statement on funding was reported.

Study details	Population	Intervention	Study outcomes	Appraisal and Funding
			Haemorrhage: 18 (94.7%), 1 (5.3%), 0, 0, 0 patients had Grade 0, 1, 2, 3, 4 haemorrhage respectively	

Abbreviations
CA: cryoablation; CAD Canadian dollar; CHEERS criteria: Consolidated Health Economic Evaluation Reporting Standards criteria; CI: confidence interval; CKD: chronic kidney disease; cm^3: cubic centimetres; ECOG: Eastern Cooperative Oncology Group; eGFR: estimated glomerular filtration rate; EORTC QLQ-C15-PAL: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 15 Palliative Care; EQ-5D-3L: European Quality of Life 5 Dimensions 3 Level; FACT FKSI: Functional Assessment of Cancer Therapy – Kidney Specific Index; Gy Gray; HR: Hazard ratio; ICER: Incremental cost effectiveness ratio; IMRT: intensity modulated radiotherapy; IQR: Interquartile range; MCID: minimal clinically important difference; MDT: multi-disciplinary team; ml/min: millilitres per minute; mm: millimetres; QoL: quality of life; QALY: Quality-adjusted life year; RCC: renal cell carcinoma; RECIST: Response Evaluation Criteria in Solid Tumours; RFA: radiofrequency ablation; SABR: stereotactic ablative body radiotherapy; SD: standard deviation; SE: standard error; T stage: tumour stage; UK: United Kingdom; USA: United States of America; VMAT: volumetric modulated arc therapy

Appendix F Quality appraisal checklists

JBI Critical Appraisal Checklist for case series

1. Were there clear criteria for inclusion in the case series?
2. Was the condition measured in a standard, reliable way for all participants included in the case series?
3. Were valid methods used for identification of the condition for all participants included in the case series?
4. Did the case series have consecutive inclusion of participants?
5. Did the case series have complete inclusion of participants?
6. Was there clear reporting of the demographics of the participants in the study?
7. Was there clear reporting of clinical information of the participants?
8. Were the outcomes or follow-up results of cases clearly reported?
9. Was there clear reporting of the presenting site(s)/ clinic(s) demographic information?
10. Was the statistical analysis appropriate?

Appendix G GRADE profiles

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	SABR	Standard care	Result		
Local control (2 prospective case series and 3 retrospective case series)									
Local control at 6 months (based on RECIST criteria) (n), median follow-up 17 months (range 5 to 32 months)									
Prospective case series Zarkar et al 2023	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	15	0	Partial response: 3 Stable disease: 12	Critical	Very low
Median reduction in tumour size from baseline at 6 months (%, IQR), median follow-up 17 months (range 5 to 32 months)									
Prospective case series Zarkar et al 2023	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	15	0	16.67% (IQR 2.7 to 28.0)	Critical	Very low
Rate of local control at 6 months, (median follow-up 17 months (range 5 to 32 months)									
Prospective case series Zarkar et al 2023	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	15	0	94.4% (95% CI 66.6% to 99.2%)	Critical	Very low
Local control at 12 months (based on RECIST criteria) (n), median follow-up 17 months (range 5 to 32 months)									
Prospective case series Zarkar et al 2023	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	14	0	Partial response: 5 Stable disease: 9	Critical	Very low
Median reduction in tumour size from baseline at 12 months (%, IQR), median follow-up 17 months (range 5 to 32 months)									
Prospective case series	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	15	0	26.5% (IQR 7.9 to 34.5)	Critical	Very low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**SABR**	**Standard care**	**Result**		
Zarkar et al 2023									
Rate of local control at 12 months, (median follow-up 17 months (range 5 to 32 months)									
Prospective case series Zarkar et al 2023	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	15	0	94.4% (95% CI 66.6% to 99.2%)	Critical	Very low
Cumulative incidence of local failure at 1 year (%), median follow-up 27.8 months (IQR 17.6 to 41.7)									
Retrospective case series Glicksman et al 2023	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	74	0	5.85%	Critical	Very low
Objective tumour size reduction at 1 year (%), median follow-up 24 months, minimum 12 months									
Prospective case series Siva et al 2017	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	33	0	61% of RCCs	Critical	Very low
Local control (based on RECIST criteria) (n, %), mean follow-up 561 days (range 83 to 1,366), median 489 days									
Retrospective case series Sun et al 2016	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	41 tumours	0	Progressive disease: 1 (2.4%) Stable disease: 31 (75.6%) Partial response: 8 (19.5%) Complete response: 1 (2.4%)	Critical	Very low
<5mm growth (n, %), mean follow-up 561 days (range 83 to 1,366), median 489 days									
Retrospective case series Sun et al 2016	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	41 tumours	0	38 (92.7%)	Critical	Very low
Mean tumour growth rate (average of 3 linear dimensions) (cm/year, p-value), mean follow-up 561 days (range 83 to 1,366), median 489 days									
Retrospective case series Sun et al 2016	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	41 tumours	0	Before SABR: 0.68 After SABR: -0.37 p<0.0001 for each dimension	Critical	Very low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**SABR**	**Standard care**	**Result**		
Mean tumour volume growth rate (cm3/year, p-value), mean follow-up 561 days (range 83 to 1,366), median 489 days									
Retrospective case series Sun et al 2016	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	41 tumours	0	Before SABR: 21.21 cm^3/year After SABR: -5.35 cm^3/year p=0.002	Critical	Very low
Change in size of tumours (narrative), mean follow-up 561 days (range 83 to 1,366), median 489 days									
Retrospective case series Sun et al 2016	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	41 tumours	0	*"Statistically significant decrease of … the size of renal tumours"* after SABR (p-value not reported) No subsequent growth that met criteria for response to treatment subsequently did not meet criteria	Critical	Very low
Cumulative incidence of local failure at 2 years (%), median follow-up 27.8 months (IQR 17.6 to 41.7)									
Retrospective case series Glicksman et al 2023	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	74	0	7.77%	Critical	Very low
Local control at 2 years (based on RECIST criteria) (%), median follow-up 2.57 years (95% CI 2.12 to 3.33)									
Retrospective case series Correa et al 2019	Very serious limitations[4]	Serious indirectness[2]	Not applicable	Not calculable	81	0	98.0% 1 patient had local disease recurrence	Critical	Very low
Local control at last follow-up (based on RECIST criteria) (n), median follow-up 24 months, minimum 12 months									
Prospective case series Siva et al 2017	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	33	0	Partial response: n=4 Stable disease: n=28	Critical	Very low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**SABR**	**Standard care**	**Result**		
Cumulative incidence of local failure at 4 years (%), median follow-up 27.8 months (IQR 17.6 to 41.7)									
Retrospective case series Glicksman et al 2023	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	74	0	7.77%	Critical	Very low
Local control at 4 years (based on RECIST criteria) (%), median follow-up 2.57 years (95% CI 2.12 to 3.33)									
Retrospective case series Correa et al 2019	Very serious limitations[4]	Serious indirectness[2]	Not applicable	Not calculable	81	0	98.0% 1 patient had local disease recurrence	Critical	Very low
Overall survival (2 prospective case series and 2 retrospective case series)									
Overall survival at 6 months (%, 95% CI), median follow-up 17 months (range 5 to 32 months)									
Prospective case series Zarkar et al 2023	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	19	0	94.7% (95% CI 68.1% to 99.2%)	Critical	Very low
Overall survival at 12 months (%, 95% CI), median follow-up 17 months (range 5-32 months)									
Prospective case series Zarkar et al 2023	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	19	0	78.3% (95% CI 51.9% to 91.3%) 7 deaths of which 6 not related to SABR or RCC (cardiac arrest, sepsis, heart failure, left ventricular failure, pneumonia (2))	Critical	Very low
Overall survival at 1 year (%), median follow-up 27.8 months (IQR 17.6 to 41.7)									
Retrospective case series Glicksman et al 2023	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	74	0	100%	Critical	Very low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	SABR	Standard care	Result		
Overall survival at 1 year (%), median follow-up 24 months, minimum 12 months									
Prospective case series Siva et al 2017	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	33	0	100%	Critical	Very low
Overall survival at 2 years (%), median follow-up 27.8 months (IQR 17.6 to 41.7)									
Retrospective case series Glicksman et al 2023	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	74	0	100%	Critical	Very low
Overall survival at 2 years (%), median follow-up 2.57 years (95% CI 2.12 to 3.33)									
Retrospective case series Correa et al 2019	Very serious limitations[4]	Serious indirectness[2]	Not applicable	Not calculable	81	0	81.5%	Critical	Very low
Overall survival at 2 years (%, 95% CI), median follow-up 24 months, minimum 12 months									
Prospective case series Siva et al 2017	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	33	0	92% (95% CI 81% to 100%)	Critical	Very low
Overall survival at 4 years (%), median follow-up 27.8 months (IQR 17.6 to 41.7)									
Retrospective case series Glicksman et al 2023	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	74	0	91.6%	Critical	Very low
Overall survival at 4 years (%), median follow-up 2.57 years (95% CI 2.12 to 3.33)									
Retrospective case series Correa et al 2019	Very serious limitations[4]	Serious indirectness[2]	Not applicable	Not calculable	81	0	73.6%	Critical	Very low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**SABR**	**Standard care**	**Result**		
Progression free survival (2 prospective case series and 2 retrospective case series)									
Progression free survival at 1 year (%), median follow-up 27.8 months (IQR 17.6 to 41.7)									
Retrospective case series Glicksman et al 2023	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	74	0	91.4% (cumulative incidence of local progression 5.85%; cumulative incidence of distant metastasis 4.24%, 1 lung, 1 spine, 1 adrenal)	Critical	Very low
Progression free survival at 1 year (%, 95% CI), median follow-up 24 months, minimum 12 months									
Prospective case series Siva et al 2017	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	33	0	97% (95% CI 91% to 100%) (freedom from distant progression; freedom from local progression 100%)	Critical	Very low
Progression over whole follow-up period (n), median follow-up 17 months (range 5 to 32 months)									
Prospective case series Zarkar et al 2023	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	19	0	Local progression: 1 Metastatic disease: 2	Critical	Very low
Progression free survival at 2 years (%), median follow-up 27.8 months (IQR 17.6 to 41.7)									
Retrospective case series Glicksman et al 2023	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	74	0	89.7% (cumulative incidence of local progression 7.77%; cumulative incidence of distant metastasis 4.24%, 1 lung, 1 spine, 1 adrenal)	Critical	Very low
Progression free survival at 2 years (%), median follow-up 2.57 years (95% CI 2.12 to 3.33)									
Retrospective case series Correa et al 2019	Very serious limitations[4]	Serious indirectness[2]	Not applicable	Not calculable	81	0	77.5%	Critical	Very low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**SABR**	**Standard care**	**Result**		
Progression free survival at 2 years (%, 95% CI), median follow-up 24 months, minimum 12 months									
Prospective case series Siva et al 2017	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	33	0	89% (95% CI 78% to 100%) (freedom from distant progression; freedom from local progression 100%)	Critical	Very low
Local and distant disease recurrence over whole follow-up period (%), median follow-up 2.57 years (95% CI 2.12 to 3.33)									
Retrospective case series Correa et al 2019	Very serious limitations[4]	Serious indirectness[2]	Not applicable	Not calculable	81	0	Local disease recurrence 1 patient (1.2%) Distant disease recurrence 4 patients (4.9%)	Critical	Very low
Progression free survival at 4 years (%), median follow-up 27.8 months (IQR 17.6 to 41.7)									
Retrospective case series Glicksman et al 2023	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	74	0	89.7% (cumulative incidence of local progression 7.77%; cumulative incidence of distant metastasis 4.24%, 1 lung, 1 spine, 1 adrenal)	Critical	Very low
Progression free survival at 4 years (%), median follow-up 2.57 years (95% CI 2.12 to 3.33)									
Retrospective case series Correa et al 2019	Very serious limitations[4]	Serious indirectness[2]	Not applicable	Not calculable	81	0	68.3%	Critical	Very low
Cancer specific survival (1 prospective case series and 1 retrospective case series)									
Deaths related to cancer (n), median follow-up 17 months (range 5 to 32 months)									
Prospective case series Zarkar et al 2023	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	19	0	1	Important	Very low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	SABR	Standard care	Result		
Cancer specific survival at 2 years (%), median follow-up 2.57 years (95% CI 2.12 to 3.33)									
Retrospective case series Correa et al 2019	Very serious limitations[4]	Serious indirectness[2]	Not applicable	Not calculable	81	0	98.2%	Important	Very low
Cancer specific survival at 4 years (%), median follow-up 2.57 years (95% CI 2.12 to 3.33)									
Retrospective case series Correa et al 2019	Very serious limitations[4]	Serious indirectness[2]	Not applicable	Not calculable	81	0	98.2%	Important	Very low
Health related quality of life (QoL) (1 prospective case series)									
Change in EQ-5D-3L scores from baseline to 1 week (mean change, % stable or better vs % worse), higher scores indicate higher quality of life									
Prospective case series Swaminath et al 2021	Very serious limitations[5]	Serious indirectness[2]	Not applicable	Not calculable	32[a]	0	Visual analogue scale (n=16): -0.938 Health utility score (n=20): 0.050 (85.0% vs 15.0%)	Important	Very low
Change in EORTC-QLQ-C15-PAL scores from baseline to 1 week (mean change, % stable or better vs % worse), higher scores indicate higher quality of life, higher functioning and higher symptom burden									
Prospective case series Swaminath et al 2021	Very serious limitations[5]	Serious indirectness[2]	Not applicable	Not calculable	32[a]	0	Global QoL score (n=20): -8.345 (45.0% vs 55.0%) (p=0.046) Physical functioning (n=20): -0.665 (80.0% vs 20.0%) Emotional functioning (n=20): -2.920 (65.0% vs 35.0%) Fatigue (n=20): 7.225 (60.0% vs 40.0%) Nausea and vomiting (n=20): 5.000 (90.0% vs 10.0%)	Important	Very low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	SABR	Standard care	Result		
							Dyspnoea (n=19): 0.005 (95.0% vs 5.0%) Pain (n=20): 1.667 (70.0% vs 30.0%) Insomnia (n=20): -5.000 (85.0% vs 15.0%) Appetite (n=20): 5.000 (80.0% vs 20.0%) Constipation (n=19): 1.754 (90.0% vs 10.0%)		
Change in FACT FKSI-19 score from baseline to 1 week (mean change, % stable or better vs % worse), higher scores indicate fewer symptoms									
Prospective case series Swaminath et al 2021	Very serious limitations[5]	Serious indirectness[2]	Not applicable	Not calculable	32[a]	0	Overall converted score (n=20): 0.430 (85.0% vs 15.0%)	Important	Very low
Change in EQ-5D-3L scores from baseline to 1 month (mean change, % stable or better vs % worse), higher scores indicate higher quality of life									
Prospective case series Swaminath et al 2021	Very serious limitations[5]	Serious indirectness[2]	Not applicable	Not calculable	32[a]	0	Visual analogue scale (n=22): 1.500 Health utility score (n=23): 0.022 (79.2% vs 20.8%)	Important	Very low
Change in EORTC-QLQ-C15-PAL scores from baseline to 1 month (mean change, % stable or better vs % worse), higher scores indicate higher quality of life, higher functioning and higher symptom burden									
Prospective case series Swaminath et al 2021	Very serious limitations[5]	Serious indirectness[2]	Not applicable	Not calculable	32[a]	0	Global QoL score (n=24): -3.479 (70.8% vs 29.2%) Physical functioning (n=24): 1.388 (83.3% vs 16.7%)	Important	Very low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	SABR	Standard care	Result		
							Emotional functioning (n=24): 2.087 (75.0% vs 25.0%) Fatigue (n=24): 4.642 (62.5% vs 37.5%) Nausea and vomiting (n=24): 0.000 (87.5% vs 12.5%) Dyspnoea (n=24): -0.008 (83.3% vs 16.7%) Pain (n=24): 0.694 (66.7% vs 37.3%) Insomnia (n=24): -2.778 (79.2% vs 20.8%) Appetite (n=24): 1.383 (70.8% vs 29.2%) Constipation (n=23): 4.348 (79.2% vs 20.8%)		
Change in FACT FKSI-19 score from baseline to 1 month (mean change, % stable or better vs % worse), higher scores indicate fewer symptoms									
Prospective case series Swaminath et al 2021	Very serious limitations[5]	Serious indirectness[2]	Not applicable	Not calculable	32[a]	0	Overall converted score (n=24): 0.908 (70.8% vs 29.2%)	Important	Very low
Change in EQ-5D-3L scores from baseline to 3 months (mean change, % stable or better vs % worse), higher scores indicate higher quality of life									
Prospective case series Swaminath et al 2021	Very serious limitations[5]	Serious indirectness[2]	Not applicable	Not calculable	32[a]	0	Visual analogue scale (n=16): 4.125 Health utility score (n=17): -0.020 (76.5% vs 23.5%)	Important	Very low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	SABR	Standard care	Result		
Change in EORTC-QLQ-C15-PAL scores from baseline to 3 months (mean change, % stable or better vs % worse), higher scores indicate higher quality of life, higher functioning and higher symptom burden									
Prospective case series Swaminath et al 2021	Very serious limitations[5]	Serious indirectness[2]	Not applicable	Not calculable	32[a]	0	Global QoL score (n=17): -0.982 (70.6% vs 29.4%) Physical functioning (n=16): -5.000 (68.8% vs 31.3%) Emotional functioning (n=17): 1.471 (76.5% vs 23.5%) Fatigue (n=17): 1.318 (70.6% vs 29.4%) Nausea and vomiting (n=17): -6.859 (100% vs 0%) Dyspnoea (n=17): 1.969 (88.2% vs 11.8%) Pain (n=17): -3.922 (76.5% vs 23.5%) Insomnia (n=17): 3.922 (64.7% vs 25.3%) Appetite (n=17): -9.812 (94.1% vs 5.9%) Constipation (n=16): 4.167 (94.1% vs 5.9%)	Important	Very low
Change in FACT FKSI-19 score from baseline to 3 months (mean change, % stable or better vs % worse), higher scores indicate fewer symptoms									
Prospective case series Swaminath et al 2021	Very serious limitations[5]	Serious indirectness[2]	Not applicable	Not calculable	32[a]	0	Overall converted score (n=17): -2.188 (64.7% vs 35.3%)	Important	Very low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	SABR	Standard care	Result		
Change in EQ-5D-3L scores from baseline to 6 months (mean change, % stable or better vs % worse, p-value presumably for trend[b]), higher scores indicate higher quality of life									
Prospective case series Swaminath et al 2021	Very serious limitations[5]	Serious indirectness[2]	Not applicable	Not calculable	32[a]	0	Visual analogue scale (n=15): 1.667 (p=0.398) Health utility score (n=16): 0.038 (81.3% vs 18.8%) (p=0.493)	Important	Very low
Change in EORTC-QLQ-C15-PAL scores from baseline to 6 months (mean change, % stable or better vs % worse, p-value presumably for trend[b] unless stated otherwise), higher scores indicate higher quality of life, higher functioning and higher symptom burden									
Prospective case series Swaminath et al 2021	Very serious limitations[5]	Serious indirectness[2]	Not applicable	Not calculable	32[a]	0	Global QoL score (n=16): -2.083 (68.8% vs 31.3%) (p=0.390) Physical functioning (n=16): -7.494 (56.3% vs 43.8%) (p=0.225) Emotional functioning (n=16): -3.119 (75.0% vs 25.0%) (p=0.848) Fatigue (n=16): 2.781 (68.8% vs 31.3%) (p=0.586) Nausea and vomiting (n=16): -3.125 (100.0% vs 0.0%) (p=0.401) Dyspnoea (n=16): 14.581 (68.8% vs 31.3%) (p=0.126) (p=0.048 at 6 months compared to baseline) Pain (n=16): -6.250 (81.3% vs 18.8%) (p=0.979) Insomnia (n=16): 4.167 (68.8% vs 31.3%) (p=0.543)	Important	Very low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	SABR	Standard care	Result		
							Appetite (n=16): -2.088 (93.8% vs 6.3%) (p=0.279) Constipation (n=16): 4.167 (81.3% vs 18.8%) (p=0.838)		
Change in FACT FKSI-19 score from baseline to 6 months (mean change, % stable or better vs % worse, p-value presumably for trend[b]), higher scores indicate fewer symptoms									
Prospective case series Swaminath et al 2021	Very serious limitations[5]	Serious indirectness[2]	Not applicable	Not calculable	32[a]	0	Overall converted score (n=16): -0.181 (68.8% vs 31.3%) (p=0.330)	Important	Very low
Organ specific disease response (2 prospective case series and 2 retrospective case series)									
Mean change in eGFR from baseline to 6 months (ml/min, 95% CI), median follow-up 17 months (range 5 to 32 months), benefit indicated by higher eGFR									
Prospective case series Zarkar et al 2023	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	19	0	-5.4 ml/min (95% CI -10.3 to -0.6)	Critical	Very low
Mean change in eGFR from 6 months to 12 months (ml/min, 95% CI), median follow-up 17 months (range 5 to 32 months), benefit indicated by higher eGFR									
Prospective case series Zarkar et al 2023	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	19	0	-5.1 ml/min (95% CI -9.0 to -1.1)	Critical	Very low
Mean change in eGFR from baseline to 12 months (ml/min, 95% CI), median follow-up 17 months (range 5 to 32 months), benefit indicated by higher eGFR									
Prospective case series Zarkar et al 2023	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	19	0	-8.7 ml/min (95% CI -15.3 to -2.1)	Critical	Very low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**SABR**	**Standard care**	**Result**		
Median change in eGFR from baseline to 1 year (ml/min, IQR), median follow-up 27.8 months (IQR 17.6 to 41.7), benefit indicated by higher eGFR									
Retrospective case series Glicksman et al 2023	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	74	0	-7.0ml/min (IQR -14.5 to -1.0)	Important	Very low
Mean change in eGFR from baseline to 1 year (ml/min, 95% CI, p-value), median follow-up 24 months, minimum 12 months, benefit indicated by higher eGFR									
Prospective case series Siva et al 2017	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	33	0	-11ml/min (95% CI -6 to -17), p<0.001	Important	Very low
% of patients with improved eGFR compared to baseline at 1 year (%), median follow-up 27.8 months (IQR 17.6 to 41.7), benefit indicated by higher eGFR									
Retrospective case series Glicksman et al 2023	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	74	0	18.8%	Important	Very low
Proportion of renal function from the ipsilateral (SABR-treated) kidney at 1 year compared to baseline (%, IQR), median follow-up 27.8 months (IQR 17.6 to 41.7)									
Retrospective case series Glicksman et al 2023	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	74	0	Baseline: 47% (IQR 44 to 53) 1 year: 39% (IQR 37 to 48)	Important	Very low
Change in eGFR from baseline to latest time point measured (ml/min) (mean ± SD, median, range), median 20.4 months, benefit indicated by higher eGFR									
Retrospective case series Correa et al 2019	Very serious limitations[4]	Serious indirectness[2]	Not applicable	Not calculable	81	0	Mean change -5.8 ± 10.8, median -3.3 (range -35.1 to 18.7) Before SABR: mean 64.6 ± 21.7, median 67.6 (range 13.0 to 126.3)	Important	Very low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	SABR	Standard care	Result		
							After SABR: mean 59.2 ± 23.9, median 62.1 (range 8.0 to 100.4)		
Proportion at each level of CKD (defined by eGFR range, ml/min) (n, %), median 20.4 months, benefit indicated by higher eGFR									
Retrospective case series Correa et al 2019	Very serious limitations[4]	Serious indirectness[2]	Not applicable	Not calculable	81	0	Before SABR eGFR≥90 (normal renal function): 4 (5.0%) eGFR 60 to <90 (mild CKD): 50 (62.5%) eGFR 45 to <60 (mild to moderate CKD): 12 (15.0%) eGFR 30 to <45 (moderate to severe CKD): 7 (8.8%) eGFR <30 (severe CKD): 7 (8.8%) After SABR eGFR≥90: 7 (10.8%) eGFR 60 to <90: 29 (44.6%) eGFR 45 to <60: 13 (20.0%) eGFR 30 to <45: 7 (10.8%) eGFR <30: 9 (13.9%)	Important	Very low
Decrease in eGFR of 15 ml/min or greater after SABR treatment (n, %), median 20.4 months, benefit indicated by higher eGFR									
Retrospective case series Correa et al 2019	Very serious limitations[4]	Serious indirectness[2]	Not applicable	Not calculable	81	0	14 (21.5%)	Important	Very low
Increase in eGFR after SABR treatment (n, %), median 20.4 months, benefit indicated by higher eGFR									
Retrospective case series Correa et al 2019	Very serious limitations[4]	Serious indirectness[2]	Not applicable	Not calculable	81	0	17 (26.2%)	Important	Very low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**SABR**	**Standard care**	**Result**		
Number on dialysis after SABR treatment (n, %), median 20.4 months									
Retrospective case series Correa et al 2019	Very serious limitations[4]	Serious indirectness[2]	Not applicable	Not calculable	81	0	0	Important	Very low
Median change in eGFR from baseline to 2 years (ml/min, IQR), median follow-up 27.8 months (IQR 17.6 to 41.7), benefit indicated by higher eGFR									
Retrospective case series Glicksman et al 2023	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	74	0	-11.5ml/min (IQR -19.5 to -4.0)	Important	Very low
Mean change in eGFR from baseline to 2 years (ml/min, 95% CI, p-value), median follow-up 24 months, minimum 12 months, benefit indicated by higher eGFR									
Prospective case series Siva et al 2017	Very serious limitations[6]	Serious indirectness[2]	Not applicable	Not calculable	9	0	-11ml/min (95% CI -3 to -19)	Important	Very low
Proportion of renal function from the ipsilateral (SABR-treated) kidney at 2 years compared to baseline (%, IQR), median follow-up 27.8 months (IQR 17.6 to 41.7)									
Retrospective case series Glicksman et al 2023	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	74	0	Baseline: 47% (IQR 44 to 53) 2 years: 36% (IQR 36 to 42)	Important	Very low
% of patients with improved eGFR compared to baseline at 2 years (%), median follow-up 27.8 months (IQR 17.6 to 41.7), benefit indicated by higher eGFR									
Retrospective case series Glicksman et al 2023	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	74	0	15%	Important	Very low
Median change in eGFR over time (p-value), median follow-up 27.8 months (IQR 17.6 to 41.7), benefit indicated by higher eGFR									
Retrospective case series	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	74	0	eGFR significantly decreased over time, p<0.0001	Important	Very low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**SABR**	**Standard care**	**Result**		
Glicksman et al 2023									
% of patients with stage 3+ chronic kidney disease, median follow-up 27.8 months (IQR 17.6 to 41.7)									
Retrospective case series Glicksman et al 2023	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	74	0	"The proportion of patients in stage 3+ chronic kidney disease increased over time" (no further detail reported)	Important	Very low
Additional patients on dialysis (n, %), median follow-up 27.8 months (IQR 17.6 to 41.7)									
Retrospective case series Glicksman et al 2023	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	74	0	Before SABR: 2 (2.7%) After SABR: 4 additional patients (5.4% additional)	Important	Very low
Change in proportion of renal function from the ipsilateral (SABR-treated) kidney over time (p-value), median follow-up 27.8 months (IQR 17.6 to 41.7)									
Retrospective case series Glicksman et al 2023	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	74	0	Proportion decreased significantly over time, p<0.0001	Important	Very low
Median change in eGFR from baseline to 4 years (ml/min, IQR), median follow-up 27.8 months (IQR 17.6 to 41.7), benefit indicated by higher eGFR									
Retrospective case series Glicksman et al 2023	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	74	0	-14.0ml/min (IQR -28.0 to -10.0)	Important	Very low
% of patients with improved eGFR compared to baseline at 4 years (%), median follow-up 27.8 months (IQR 17.6 to 41.7), benefit indicated by higher eGFR									
Retrospective case series	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	74	0	0%	Important	Very low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	SABR	Standard care	Result		
Glicksman et al 2023									
Proportion of renal function from the ipsilateral (SABR-treated) kidney at 4 years compared to baseline (%, IQR), median follow-up 27.8 months (IQR 17.6 to 41.7)									
Retrospective case series Glicksman et al 2023	Very serious limitations[3]	Serious indirectness[2]	Not applicable	Not calculable	74	0	Baseline: 47% (IQR 44 to 53) 4 years: 32.5% (IQR 29 to 39.5)	Important	Very low
Safety (2 prospective case series)									
Acute adverse events ≤90 days after SABR (n, %), median follow-up 24 months, minimum 12 months									
Prospective case series Siva et al 2017	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	33	0	Number of patients with at least 1 Grade 1 event: 11 patients (33%). Grade 1 events were: chest wall pain 5, dermatitis 2, diarrhoea 3, fatigue 11, gastritis 1, nausea 5, right flank pain 1. Number of patients with at least 1 Grade 2 event: 7 patients (21%): Grade 2 events were: dyspnoea 1, fatigue 6, gastritis 1, nausea 2. Grade 3: none	Important	Very low
Late adverse events >90 days after SABR (n, %), median follow-up 24 months, minimum 12 months									
Prospective case series Siva et al 2017	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	33	0	Number of patients with at least 1 Grade 1 event: 17 patients (52%). Grade 1 events were: chest wall pain 12, diarrhoea 1, dyspnoea 2, fatigue 7, gastritis 1,	Important	Very low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	SABR	Standard care	Result		
							haematuria 3, nausea 2, skin induration 1. Number of patients with at least 1 Grade 2 event: 2 patients (6%). Grade 2 events were: abdominal pain 1, haematuria 1 Number of patients with at least 1 Grade 3 event: 1 patient (3%). This was fatigue.		
All (acute plus late) adverse events after SABR (n, %), median follow-up 24 months, minimum 12 months									
Prospective case series Siva et al 2017	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	33	0	Number of patients with at least 1 Grade 1 event: 19 patients (58%). Grade 1 events were: chest wall pain 15, dermatitis 2, diarrhoea 3, dyspnoea 2, fatigue 14, gastritis 2, haematuria 3, nausea 5, right flank pain 1, skin induration 1. Number of patients with at least 1 Grade 2 event: 7 patients (21%). Grade 2 events were: abdominal pain 1, dyspnoea 1, fatigue 5, gastritis 1, haematuria 1, nausea 2. Number of patients with at least 1 Grade 3 event: 1 patient (3%). This was fatigue.	Important	Very low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	SABR	Standard care	Result		
Worst grade of adverse events over each patient's follow-up period (n, %), median follow-up 17 months (range 5 to 32 months)									
Prospective case series Zarkar et al 2023	Serious limitations[1]	Serious indirectness[2]	Not applicable	Not calculable	19	0	Fatigue: 4 (21.1%), 12 (63.3%), 3 (15.8), 0 and 0 patients had Grade 0, 1, 2, 3, 4 fatigue respectively Gastritis: 17 (89.5%), 1 (5.3%), 1 (5.3%), 0, 0 patients had Grade 0, 1, 2, 3, 4 gastritis respectively Anaemia: 17 (89.5%), 0, 1 (5.3%), 1 (5.3%), 0 patients had Grade 0, 1, 2, 3, 4 anaemia respectively Pain: 18 (97.4%), 1 (5.3%, 0, 0, 0 patients had Grade 0, 1, 2, 3, 4 pain respectively Nausea: 14 (73.7%), 1 (5.3%), 4 (21.1%), 0, 0 patients had Grade 0, 1, 2, 3, 4 nausea respectively Vomiting: 17 (89.5%), 1 (5.3%), 1 (5.3%), 0, 0 Grade 0, 1, 2, 3, 4 vomiting respectively Colitis: 18 (94.7%), 0, 0, 1 (5.3%), 0 patients had Grade 0, 1, 2, 3, 4 colitis respectively Diarrhoea: 17 (89.5%), 2 (10.5%), 0, 0, 0 patients had Grade 0, 1, 2, 3, 4 diarrhoea respectively	Critical	Very low

QUALITY					Summary of findings			IMPORTANCE	CERTAINTY
					No of patients		Effect		
Study	Risk of bias	Indirectness	Inconsistency	Imprecision	SABR	Standard care	Result		
							Haematuria: 18 (94.7%), 0, 0, 1 (5.3%), 0 patients had Grade 0, 1, 2, 3, 4 haematuria respectively Haemorrhage: 18 (94.7%), 1 (5.3%), 0, 0, 0 patients had Grade 0, 1, 2, 3, 4 haemorrhage respectively		

Abbreviations
CI: confidence interval; cm^3: cubic centimetres; eGFR: estimated glomerular filtration rate; EORTC QLQ-C15-PAL: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 15 Palliative Care; EQ-5D-3L: European Quality of Life 5 Dimensions 3 Level; FACT FKSI: Functional Assessment of Cancer Therapy – Kidney Specific Index; IQR: Interquartile range; ml/min: millilitres per minute; mm: millimetres; QoL: quality of life; RCC: renal cell carcinoma; RECIST: Response Evaluation Criteria in Solid Tumours; SABR: stereotactic ablative body radiotherapy; SD: standard deviation

1. Risk of bias: Serious limitations due to unclear reporting of study participants (in relation to non-consecutive and/or incomplete inclusion)
2. Indirectness: Serious indirectness due to lack of a comparator treatment group
3. Risk of bias: Very serious limitations due to unclear reporting of study participants (in relation to non-consecutive and/or incomplete inclusion) and few statistical analyses
4. Risk of bias: Very serious limitations due to lack of reporting of inclusion criteria and loss to follow up and few statistical analyses
5. Risk of bias: Very serious limitations due to relatively large and variable proportion not followed up at each time point and assumptions made about missing values; unclear reporting of statistical tests including whether adjustment was made for multiple testing
6. Risk of bias: Very serious limitations due to unclear reporting of study participants (in relation to non-consecutive and/or incomplete inclusion) and large proportion (28/37) not followed up

a. Total number that completed each question varied; missing numbers were imputed
b. p-values were reported below graphs showing baseline, 1 week and 1, 3 and 6 month mean scores and SEs. Not clear if they are p-values for trend. Narrative reports that "Means of converted scores (+/-standard deviations) were also compared at each time point to the baseline using paired t-tests." However very few of these p-values were reported (included where reported).

Glossary

Adverse event	Any undesirable event experienced by a person while they are having a drug or any other treatment or intervention, regardless of whether or not the event is suspected to be related to or caused by the drug, treatment or intervention.
Bias	Systematic (as opposed to random) deviation of the results of a study from the 'true' results, which is caused by the way the study is designed or conducted.
Blinding	A way to prevent researchers, doctors and patients in a clinical trial from knowing which study group each patient is in so they cannot influence the results. The best way to do this is by sorting patients into study groups randomly. The purpose of 'blinding' or 'masking' is to protect against bias.
Clinical importance	A benefit from treatment that relates to an important outcome such as length of life and is large enough to be important to patients and health professionals.
Confidence interval (CI)	A way of expressing how certain we are about the findings from a study, using statistics. It gives a range of results that is likely to include the 'true' value for the population. A wide confidence interval indicates a lack of certainty about the true effect of the test or treatment - often because a small group of patients has been studied. A narrow confidence interval indicates a more precise estimate (for example, if a large number of patients have been studied).
Cost effectiveness study	An analysis that assesses the cost of achieving a benefit by different means. The benefits are expressed in non-monetary terms related to health, such as life years gained (that is, the number of years by which life is extended as a result of the intervention). Options are often compared on the cost incurred to achieve 1 outcome (for example, cost per life year gained).
Discounting	Costs and perhaps benefits incurred today have a higher value than costs and benefits occurring in the future. Discounting health benefits reflects individual preference for benefits to be experienced in the present rather than the future. Discounting costs reflects individual preference for costs to be experienced in the future rather than the present.
GRADE (Grading of recommendations assessment, development and evaluation)	A systematic and explicit approach to grading the quality of evidence and the strength of recommendations developed by the GRADE working group.
Hazard ratio	The hazard or chance of an event occurring in the treatment arm of a study as a ratio of the chance of an event occurring in the control arm over time.
Incremental cost-effectiveness ratio (ICER)	The difference in the change in mean costs in the population of interest divided by the difference in the change in mean outcomes in the population of interest.
PICO (population, intervention, comparison and outcome) framework	A structured approach for developing review questions that divides each question into 4 components: the population (the population being studied); the interventions (what is being done); the comparators (other main treatment options); and the outcomes (measures of how effective the interventions have been).
p-value (p)	The p-value is a statistical measure that indicates whether or not an effect is statistically significant. For example, if a study comparing 2 treatments found that 1 seems to be more effective than the other, the p-value is the probability of obtaining these results by chance. By convention, if the p-value is below 0.05 (that is, there is less than a 5% probability that the results occurred by chance), it is considered that there probably is a real difference between treatments. If the p-value is 0.001 or less (less than a 0.1% probability that the results occurred by chance), the result is seen as highly significant. If the p-value shows that there is likely to be a difference between treatments, the confidence interval describes how big the difference in effect might be.
Quality-adjusted life year (QALY)	A measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life.

	One QALY is equal to 1 year of life in perfect health. QALYs are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality-of-life score (on a 0 to 1 scale). It is often measured in terms of the person's ability to carry out the activities of daily life, and freedom from pain and mental disturbance.
Statistical significance	A statistically significant result is one that is assessed as being due to a true effect rather than random chance.
Time horizon	The time period over which the main differences between interventions in effects and the use of resources in health and social care are expected to be experienced, taking into account the limitations of the supporting evidence.

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NHS England
Wellington House
133-155 Waterloo Road
London
SE1 8UG