Technoleg Iechyd Cymru
Health Technology Wales

Evidence Appraisal Report

Stereotactic ablative radiotherapy to treat people with primary kidney cancer

Executive summary

- The aim of this review was to address the following question: what is the clinical and cost effectiveness of stereotactic ablative radiotherapy (SABR) for primary renal cancer compared to standard care?

- Surgery is currently the standard of care for the treatment of T1 tumours (seven centimetres [cm] or less). However, many older patients have comorbidities which may preclude them from major surgery. SABR is a non-invasive therapy (if given without fiducial markers) that can be given in the outpatient setting, thus eliminating the need for general anaesthesia and theatre time.

- We identified two systematic reviews and one meta-analysis investigating the use of SABR in renal cell carcinoma, but we were unable to use the pooled results from the meta-analysis as some of the included patients had metastatic disease. The vast majority of the evidence we identified comes from single-arm studies. The only studies we found involving a comparator came from two retrospective analyses of the same cancer database. However, the analyses were based on American data and so generalisability to the Welsh NHS is uncertain. We also included three additional single-arm primary studies because they were not included in the systematic reviews or reported outcomes not reported elsewhere.

- Most of the studies consisted of retrospective data, increasing susceptibility to selection bias and recall bias. The number of participants in the studies identified ranged from 21 to 223. Although the SABR techniques used in the different studies were comparable, the prescribed doses and fractionation schemes varied, sometimes even within studies. Tumours were not always biopsied, and so the subtype of the tumour wasn't reported in all studies. Post-SABR follow-up times were usually less than five years.

- Local control in clinical trials was mainly assessed using Response Evaluation Criteria in Solid Tumours (RECIST) to assess tumour size. Local control rates ranged from 75% to 100% in 236 patients in the secondary evidence (follow-up times ranging from nine to 57.5 months) and between 97.8% and 100% in the primary evidence (follow-up times between 24 and 60 months). However, challenges exist regarding the optimal response assessment tool post-SABR. Using RECIST may result in misinterpreting any initial increase in tumour size as disease progression, as the increase may actually be due to treatment-induced inflammation. Experts

contacted by HTW stated that SABR-induced inflammation usually persists up to six months post-treatment.

- Survival was inconsistently reported, and when it was reported, was difficult to interpret as most patients were medically inoperable with multiple comorbidities and most death occurred with the renal disease controlled. Overall survival was the only outcome with comparative data. In the comparative primary studies, SABR was associated with an increased overall survival compared with observation, but a worse overall survival compared to partial nephrectomy or thermal ablation. However, experts noted that those patients treated by radiofrequency ablation could have been fitter patients and/or with smaller tumours than those in the SABR-treated group.

- The majority of reported adverse events with SABR were mild. Serious adverse events were reported as occurring in between 0 to 19% of patients for primary and secondary evidence, with no treatment-related mortality reported in any of the studies.

- Only one primary study assessed tumour relapse rate with SABR and reported recurrence rates of between 0% and 8.1% (median follow-up: 2.6 years).

- The meta-analysis reported that post-SABR estimated glomerular filtration rate (eGFR) changes ranged from -18 millilitres per minute (ml/min) to +6 ml/min. In one of the primary studies, eGFR significantly decreased by -5.5 ml/min (standard deviation: ± 13.3 ml/min) at last follow-up (median follow-up: 2.6 years). However, another primary study reported that the change in glomerular filtration rate post-SABR was not significant. Although some studies reported that a few patients developed chronic kidney disease post-SABR, with some needing dialysis, many of these patients had some degree of renal failure before SABR.

- Whilst quality of life appears to be well-preserved at six-months following kidney SABR, there was poor compliance with completing the questionnaires.

- We did not identify any evidence for healthcare utilisation, but one small randomised controlled trial comparing SABR with radiofrequency ablation in small renal masses is due to report on duration of hospital stay, and has an anticipated publication date of December 2022.

- No relevant health economic studies were identified in the literature review. An economic analysis developed by HTW considering the cost-effectiveness of SABR in people who cannot be managed using surgery or invasive ablation techniques found SABR to be more effective but more costly than standard care. The resulting ICER of £1,675 per QALY indicates that SABR is cost effective. This conclusion was found to be robust to changes modelled in sensitivity analysis.

1. Purpose of the evidence appraisal report

This report aims to identify and summarise evidence that addresses the following question: what is the clinical and cost effectiveness of stereotactic ablative radiotherapy (SABR) for primary kidney cancer compared to standard care?

Evidence Appraisal Reports are based on rapid systematic literature searches, with the aim of published evidence identifying the best clinical and economic evidence on health technologies. Researchers critically evaluate this evidence. The draft Evidence Appraisal Report is reviewed by experts and by Health Technology Wales multidisciplinary advisory groups before publication.

2. Health problem

Kidney cancer develops when abnormal cells in either of the kidneys start to divide and grow in an uncontrolled way (Cancer Research UK 2020c). The cells can grow into surrounding tissues or organs and may spread to other areas of the body (this is known as metastatic cancer) (Cancer Research UK 2020c). The main factor for deciding on the best treatment for the kidney cancer is whether the cancer is metastatic or localised to the kidney (Cancer Research UK 2020b).

Renal cell carcinoma (RCC) is the most common type of kidney cancer in adults; more than 80% of kidney cancers are RCC. In RCC, the cancerous cells start in the lining of the tubules inside the nephrons (Cancer Research UK 2020b). Clear cell RCC accounts for 75% of RCC cases, papillary RCC accounts for around 15% of cases, and chromophobe RCC accounts for approximately 5% of cases (Kidney Cancer UK 2020). Other types of kidney cancer include rare carcinoma of the collecting ducts and renal medullary carcinoma, sarcomatoid, transitional cell carcinoma of the kidney or ureter, or Wilm's tumour (Cancer Research UK 2020b). RCC is sometimes used synonymously with kidney cancer.

In 2015 to 2017, kidney cancer was the seventh most common cancer in adults in the UK (Kidney Cancer UK 2020). There were around 12,973 new cases of kidney cancer in the UK in 2017, with 631 of them being in Wales. Some reports have indicated an increasing incidence of kidney cancer globally, including in the UK. This increase is due in part to the wider application of diagnostic imaging techniques. In 2014 to 2016, there were 4,619 kidney cancer deaths, accounting for about 3% of all cancer deaths in the UK (Kidney Cancer UK 2020).

Kidney cancer is rare in young adults and children, but rates begin to rise after the age of 40 years old (Kidney Cancer UK 2020). About three-quarters of people diagnosed with kidney cancer are over 60 years old and the highest rates are in the 70 to 74 years old age range for men and 75 to 79 years old age range for women. More than a third of kidney cancer cases (36%) were diagnosed in people aged over 75 years old between 2015 and 2017 (Kidney Cancer UK 2020).

3. Health technology

Chemotherapy isn't generally used to treat RCC (Cancer Research UK 2020a). Surgical therapy (ideally partial nephrectomy) is currently the standard of care for the treatment of T1 tumours (seven centimetres [cm] or less) in relatively fit patients with adequate renal function (Escudier B et al. 2019). However, as the highest cancer-specific RCC mortality rates are seen in older patients, many older patients have comorbidities which may preclude them from major surgery (Correa et al. 2019). Active surveillance is commonly utilised in elderly, frail patients with decreased performance status, higher burden of comorbidities and small tumours (less than four cm). However, after a period of monitoring, up to 42% of patients on active surveillance may require delayed intervention, often triggered by tumour growth (Correa et al. 2019). Definitive

management, either upfront or after a period of active surveillance, is likely to involve cryotherapy, radiofrequency ablation or microwave ablation. These have emerged as potentially curative treatment approaches for patients who refuse or are unsuitable for surgery. However, these minimally invasive therapies are limited to small renal masses distant from vascular structures and the upper urinary tract (Correa et al. 2019).

SABR, also known as stereotactic body radiotherapy (SBRT), is a type of external radiotherapy (Macmillan Cancer Support 2018), which, in general, has no limitations to the location it can be used on (Prins et al. 2017). SABR uses many smaller, thinner beams of radiation than standard radiotherapy, and delivers precise beams of radiation at various intensities guided by sophisticated imaging systems that track the exact three-dimensional location of a tumour (Macmillan Cancer Support 2018). Such precision allows high doses of radiation to be delivered to the tumour while minimising damage to healthy tissue. It can be given with fewer treatments than standard radiotherapy: treatment is normally divided into one to eight sessions, and the sessions are spread over a few days, and may take up to two weeks (Macmillan Cancer Support 2018). SABR is a non-invasive treatment (if used without fiducial markers) and is delivered in the outpatient setting (Siva et al. 2018). Experts contacted by HTW suggest that SABR could be used as an option for non-surgical and non-invasive ablative candidates with primary RCC.

Some evidence suggests that SABR of kidney cancer is confounded by motion: as the tumour moves during treatment with respiratory motion, the interplay between the moving radiotherapy machine and tumour motion may result in discrepancies between planned and delivered doses (Gaudreault et al. 2021). However, experts contacted by HTW state that interplay effects are minimal as SABR systems have taken different approaches to this issue. In addition, tumour biopsy confirmation is not achieved at the same time as SABR delivery (Siva et al. 2012).

Different machines can be used to give SABR (Macmillan Cancer Support 2018). The linear accelerator (LINAC) that delivers standard radiotherapy can be used to give SABR. There are also specially designed LINACs for SABR such as CyberKnife, Varian and Elekta (Macmillan Cancer Support 2018). Experts contacted by HTW note that fiducial markers are not required for conventional LINACs with image-guided radiation therapy capability, but that they are required for the CyberKnife platform. Some experts stated that LINAC machines are currently being used in Wales to deliver SABR.

According to the topic proposer, SABR is currently used in Wales for conditions including lung and prostate primary cancers and oligometastatic disease (for example, cancer in the lungs, nodes and liver).

3.1 Guidance

An NHS England Specialised Commissioning Policy (2016) states that, at the time of the report, there was not enough evidence to support use of SABR for primary kidney cancer outside of clinical trials. The Royal College of Radiologists (2019) also does not recommend SABR outside of clinical trials, but states that doses of 40 to 45 Grays (Gy) in five fractions have been used for highly selected patients with localised primary tumours (> T1a) who are not able to have surgery. The American Urological Association (2021) produced a guideline on the management of renal cancer which states that SABR in the management of localised renal masses, at the time of the report, remains investigational and should be primarily considered for patients who are medically inoperable and are not candidates for established thermal ablation approaches. None of the guidance we identified was specific to Wales.

4. Clinical effectiveness

We identified two systematic reviews (Prins et al. 2017, Siva et al. 2012) and a more recent systematic review and meta-analysis by Correa et al. (2019) investigating the use of SABR in RCC. The references included in the systematic reviews by Prins et al. (2017) and Siva et al. (2012) were different and so both reviews were included; Prins et al. (2017) only included tumours that were less than 7 cm, whereas Siva et al. (2012) did not have a limit on the tumour size. We were unable to use the pooled results from the meta-analysis by Correa et al. (2019) as some of the included patients had metastatic disease; we only reported outcomes from studies in Correa et al. (2019) if participants had stage one to two localised kidney cancer only and were not used in any of the other secondary evidence we included. None of the secondary evidence we identified included a comparator.

We identified two published studies comparing SABR to observation (Grant et al. 2020) or to either partial nephrectomy or thermal ablation (Uhlig et al. 2020). Although both studies appear to analyse a similar dataset (both analysed data from the National Cancer Database in USA over a similar timeframe), they provide different comparison data and so were both included in this EAR. To attempt to minimise confounding from differences between people receiving each intervention, both studies used propensity score matching . This generated a matched cohort of patients from each treatment arm with similar demographic and tumour characteristics (these characteristics can be found in Appendix 4 [Table 2]).

We also identified one multi-centre pooled analysis by the International Radiosurgery Oncology Consortium of Kidney (IROCK) (Siva et al. 2018). In addition to assessing the safety, efficacy and survival following SABR for RCC, the pooled analysis by Siva et al. (2018) also compared outcomes between single-fraction and multi-fraction SABR (see Appendix 6). We identified two additional single-arm primary studies not included in the secondary evidence, one of which reported on the same outcomes as those in the secondary evidence (Peddada et al. 2020), and one which investigated quality of life (an outcome not reported in the secondary evidence) (Swaminath et al. 2021).

Table 1 summarises the evidence found for each clinical outcome; Tables 2 to 7, in the main body of the EAR, report clinical outcomes of all studies. Appendix 4 (Table 1) reports all study designs and characteristics for secondary evidence, and Appendix 4 (Table 2) reports all study designs and characteristics for primary evidence.

Table 1. Summary of outcomes measured and sources of evidence used

Outcome (report section)	Comparison	Study design(s)	Follow-up period
Local tumour control (4.1)	No comparator	2 systematic reviews of prospective and retrospective studies (Siva et al. 2012, Correa et al. 2019), 1 multi-centre pooled analysis (Siva et al. 2018), 1 retrospective non-randomised study (Peddada et al. 2020)	• Follow-up in systematic reviews ranged from 9 to 57.5 months • Median follow-up in primary studies ranged from 31.2 months to 78 months
Overall survival (4.2.1.1 [secondary evidence] and 4.2.2.1 [primary evidence])	Observation	Retrospective analysis of USA National Cancer Database over 10-year period (Grant et al. 2020)	• Median follow-up SABR: 37 months • Median follow-up observation: 19 months
	Partial nephrectomy, or cryoablation, or radiofrequency ablation/microwave ablation	Retrospective analysis of USA National Cancer Database over 11-year period (Uhlig et al. 2020)	• Median follow-up time: 58.1 months (inter-quartile range: 34.7 to 86.6 months)
	No comparator	2 systematic reviews (Siva et al. 2012, Prins et al. 2017), 1 multi-centre pooled analysis (Siva et al. 2018)	• Follow-up in systematic reviews ranged from 6 to 57.5 months • Median follow-up in primary study: 31.2 months
Recurrence-free survival (4.2.1.2)	No comparator	Systematic review of 6 cohort single-arm studies (Prins et al. 2017)	• Median follow-up times post-SABR (months): 6 to 31.2
Cancer-specific survival (4.2.2.2)	No comparator	1 multi-centre pooled analysis (Siva et al. 2018)	• Median follow-up: 31.2 months
Progression-free survival (4.2.2.3)	No comparator	1 multi-centre pooled analysis (Siva et al. 2018)	• Median follow-up: 31.2 months
Adverse events (4.3)	No comparator	3 systematic review (Siva et al. 2012, Correa et al. 2019, Prins et al. 2017), 1 multi-centre pooled analysis (Siva et al. 2018), 1 retrospective non-randomised study (Peddada et al. 2020)	• Follow-up in systematic reviews ranged from 6 to 57.5 months • Median follow-up in primary studies ranged from 31.2 months to 78 months
Tumour relapse/recurrence (4.4)	No comparator	1 multi-centre pooled analysis (Siva et al. 2018)	• Median follow-up: 31.2 months
Renal function (4.5)	No comparator	1 systematic review of prospective and retrospective studies (Correa et al. 2019), 1 multi-centre pooled analysis (Siva et al. 2018), 1 retrospective non-randomised study (Peddada et al. 2020)	• Range of follow-up in times in systematic review from 6 to 57.5 months • Median follow-up in primary studies: 31.2 months to 78 months
Quality of life and patient satisfaction (4.6)	No comparator	1 prospective cohort study (Swaminath et al. 2021)	• 1 week to 6 months post-SABR
Healthcare utilisation (4.7)	No evidence found		

4.1 Local tumour control

Local control is commonly defined as the proportion of stable disease or decreased tumour size (partial or complete response) following treatment (Correa et al. 2019). Local control for kidney cancer can be determined using computed tomography imaging and size-based Response Evaluation Criteria in Solid Tumours (RECIST). RECIST is only used for clinical trials and not used as standard assessment of cases in routine clinical care. Most of the studies we identified assessing local control used RECIST. However, challenges exist regarding the optimal response assessment tool after SABR. Using RECIST may result in misinterpreting any initial increase in tumour size as disease progression, as the increase may actually be due to treatment-induced inflammation. Experts contacted by HTW state that SABR-induced inflammation usually persists up to six months post-treatment.

4.1.1 Secondary evidence

Local control in 236 patients ranged from 75% to 100% after treatment with SABR, for a follow-up time ranging from nine to 57.5 months (Correa et al. 2019, Siva et al. 2012). However, Siva et al. (2012) crudely weighted the control rates according to the studies' sizes, without testing for heterogeneity, and we were unable to use the pooled results from the systematic review by Correa et al. (2019) due to some of them involving people with metastatic disease. The two-year estimated mean local control rate in Siva et al. (2012) was 92.9%; two-year local control data, when not reported, were extrapolated from reported time points assuming a constant hazard (see Appendix 4 [Table 1] for study description and Table 2 in the main text of the EAR for study outcomes).

4.1.2 Primary evidence

In the pooled data analysis by IROCK, SABR was associated with a two-year and four-year local control rate of 97.8% (see Appendix 4 [Table 2] for study description and Table 2 in the main text of the EAR for study outcomes) (Siva et al. 2018).

Peddada et al. (2020) reported that the local tumour control rate was 100% at five-years post-SABR treatment for 21 patients with stage I kidney cancer. According to RECIST criteria, complete response, partial response, and stable disease were obtained in 5, 13 and 3 patients, respectively, at last follow-up (median follow-up was 78 months [range 5 to 107 months]) (see Appendix 4 [Table 2] for study description and Table 2 in the main text of the EAR for study outcomes).

4.2 Survival

A number of different survival outcomes were measured: overall survival, cancer-specific survival (CSS), recurrence-free survival (RFS) and progression-free survival (PFS).

4.2.1 Secondary evidence

4.2.1.1 Overall survival

Four studies (34 participants) in the systematic review by Siva et al. (2012) reported overall survival. Two studies reported a median overall survival ranging between 32 months and 58 or more months, one study reported a five-year survival rate of 74% and one study reported a survival rate of 44% after a median follow-up of 26.7 months. Overall survival, when reported, was difficult to interpret as most patients were medically inoperable with multiple comorbidities and most death occurred with the renal disease controlled (see Appendix 4 [Table 1] for study description and Table 3 in the main text of the EAR for study outcomes).

4.2.1.2 Recurrence-free survival

In a systematic review by Prins et al. (2017), the RFS was reported between 63% and 98% (median follow-up time of 6 to 31.2 months) (see Appendix 4 [Table 1] for study description and Table 3 in the main text of the EAR for study outcomes).

4.2.2 Primary evidence

4.2.2.1 Overall survival

Grant et al. (2020) and Uhlig et al. (2020) conducted retrospective analyses of a 10-year sample and 11-year sample, respectively, of cancer patients in the USA, comparing the overall survival of different interventions in people with stage I RCC.

On multivariable analysis with propensity score adjustment, SABR was associated with a decreased risk of death compared with observation, with a hazard ratio (HR) of 0.56 (95% confidence interval [CI]: 0.39 to 0.79, p < .001) (Grant et al. 2020) (see Appendix 4 [Table 2] for study description and Table 3 in the main text of the EAR for study outcomes).

Surgery and tumour ablation were also associated with a decreased risk of death compared with observation, with HRs of 0.25 (95% CI: 0.24 to 0.26, p < .001) and 0.36 (95% CI: 0.35 to 0.38, p < .001), respectively (Grant et al. 2020).

Uhlig et al. (2020) reported that overall survival rates at three- and five-years for SABR were 76% and 58%, respectively. Compared to partial nephrectomy or thermal ablation, overall survival after SABR was statistically significantly lower (partial nephrectomy versus SABR, HR = 0.29, 95% CI: 0.19 to 0.46, p < .001; cryoablation versus SABR, HR = 0.40, 95% CI: 0.26 to 0.60, p < .001; radiofrequency ablation/microwave ablation versus SABR, HR =0.46, 95% CI: 0.31 to 0.67, p <.001). Thermal ablation and partial nephrectomy demonstrated comparable outcomes compared to each other. However, 4.6% of patients who had SABR also had systemic therapy administered (unclear whether this was at the same time as SABR), which might not be reflective of practice in Wales (Uhlig et al. 2020) (see Appendix 4 [Table 2] for study description and Table 3 in the main text of the EAR for study outcomes). In addition, experts noted that those patients treated by radiofrequency ablation could have been fitter patients and/or with smaller tumours than those in the SABR-treated group.

In the pooled analysis by IROCK, overall survival was 82.1% at two-years post SABR and 70.7% at four-years (Siva et al. 2018) (see Appendix 4 [Table 2] for study description and Table 3 in the main text of the EAR for study outcomes).

4.2.2.2 Cancer-specific survival

CSS was 95.7% at two years post-SABR, and 91.9% at four years (Siva et al. 2018) (see Appendix 4 [Table 2] for study description and Table 3 in the main text of the EAR for study outcomes). This study also included a multivariable analysis comparing CSS in patients treated with multi-fraction SABR compared to single-fraction SABR (see Appendix 6).

4.2.2.3 Progression-free survival

PFS was 77.4% at two years post-SABR, and 65.4% at four years (Siva et al. 2018) (see Appendix 4 [Table 2] for study description and Table 3 in the main text of the EAR for study outcomes). This study also included a multivariable analysis comparing PFS in patients treated with multi-fraction SABR compared to single-fraction SABR (see Appendix 6).

4.3 Safety

In all of the studies, adverse events were scored using the Common Terminology Criteria for Adverse Events. No treatment-related mortality was reported in any of the studies.

4.3.1 Secondary evidence

4.3.1.1 Grade I to II toxicity

In the systematic reviews by Siva et al. (2012) and Prins et al. (2017), the reported grade I to II toxicities varied between 0% and 93% (a breakdown of results by study can be found in Appendix 5). Siva et al. (2012) reported the weighted rate of minor toxicity as 21.4%. Most reported grade I and II toxicities were nausea, fatigue, dermatitis, and local pain (see Appendix 4 [Table 1] for study description and Table 4 in the main text of the EAR for study outcomes).

4.3.1.2 Grade III to IV toxicity

Secondary evidence reported a range of 0% to 19% for severe toxicity (Correa et al. 2019, Siva et al. 2012). Siva et al. (2012) reported the weighted rate of severe grade III or higher adverse events as 3.8%: grade III events included possibly treatment-related pyelonephritis and fatigue, and grade IV included skin toxicity (Siva et al. 2012). The grade IV event reported in Correa et al. (2019) was chronic kidney disease (CKD). In the systematic review by Prins et al. (2017), two out of six studies reported grade III or IV adverse events: including renal toxicity in patients with pre-existing renal dysfunction and a duodenal ulcer. However, many of the patients in these studies had pre-existing renal dysfunction (see Appendix 4 [Table 1] for study description and Table 4 in the main text of the EAR for study outcomes).

4.3.2 Primary evidence

4.3.2.1 Grade I to II toxicity

In the IROCK study by Siva et al. (2018), 38.6% patients had at least grade I toxicity and 35.6% patients experienced grade I or II toxicity only. Peddada et al. (2020) reported that of 21 patients, two patients experienced grade I back pain, one experienced grade I constipation and one experienced grade I nausea (see Appendix 4 [Table 2] for study description and Table 4 in the main text of the EAR for study outcomes). This study also included a multivariable analysis comparing toxicity in patients treated with multi-fraction SABR compared to single-fraction SABR (see Appendix 6).

4.3.2.2 Grade III to IV toxicity

In the IROCK study by Siva et al. (2018), 1.3% had grade III or IV toxicities: one patient had simultaneous grade III nausea and grade II bowel toxicity (0.5 months after starting SABR), 1 had grade IV bowel toxicity alone (4.3 years after starting SABR), and 1 had both grade IV gastritis and grade IV bowel toxicity (at 1.4 months and 15.8 months after starting SABR, respectively) (see Appendix 4 [Table 2] for study description and Table 4 in the main text of the EAR for study outcomes).

4.4 Tumour relapse/recurrence

We did not identify any secondary evidence for this outcome.

4.4.1 Primary evidence

In the IROCK pooled analysis (Siva et al. 2018), 8.1% of patients had disease recurrence, 1.4% had local recurrence, 7.2% had distant recurrence, and one patient had both local and distant recurrence as the first sites of failure. All local failures occurred within two years of SABR (see Appendix 4 [Table 2] for study description and Table 5 in the main text of the EAR for study outcomes). This study also included a multivariable analysis comparing tumour relapse/recurrence in patients treated with multi-fraction SABR compared to single-fraction SABR (see Appendix 6).

4.5 Post-SABR renal function

Experts noted that glomerular filtration rate results can vary significantly day to day for the same patient, so caution may be needed when comparing results across patients with and without SABR.

4.5.1 Secondary evidence

In the meta-analysis by Correa et al. (2019), post-SABR estimated glomerular filtration rate (eGFR) changes ranged from -18 millilitres per minute (ml/min) to +6 ml/min. Most patients had some degree of renal-function impairment before SABR (mild-moderate CKD) and so it is unclear whether it is the SABR or CKD affecting renal function in these studies (see Appendix 4 [Table 1] for study description and Table 6 in the main text of the EAR for study outcomes).

4.5.2 Primary evidence

In the pooled analysis by IROCK (Siva et al. 2018), the mean (± standard deviation) estimated eGFR at baseline was 59.9 ± 21.9 ml/min, and it decreased by -5.5 ± 13.3 ml/min ($p < 0.001$) by the last follow-up (median follow-up was 2.6 years). The corresponding rise in serum creatinine was 28.1 ± 74.4 micromoles per litre (micromol/L). There was no difference in mean renal function change in patients who had T1a disease (-4.0 ml/min) versus those who had > T1a disease (-6.8 ml/min, $p = 0.129$). In the study by Peddada et al. (2020), glomerular filtration rate decreased by a median value of 1.5% at one-year post SABR treatment, 7.0% at two-years and 14.2% at five-years post-treatment. The change in glomerular filtration rate post-treatment was not significant ($p = 0.12$) (see Appendix 4 [Table 2] for study description and Table 6 in the main text of the EAR for study outcomes).

In the Siva et al. (2018) study, 2.7% of patients underwent dialysis during the study period. However, many of the patients in the IROOCK study had pre-existing renal dysfunction. In the Peddada et al. (2020) study, no patients required dialysis post-SABR. After treatment, three patients who did not previously have CKD developed moderate CKD, and three who had moderate CKD developed severe CKD.

4.6 Quality-of -life and patient satisfaction

We did not identify any secondary evidence reporting this outcome.

4.6.1 Primary evidence

One prospective cohort study reported patient quality-of-life post-SABR (Swaminath et al. 2021). Of the 28 patients treated with SABR, only 16 of them (56%) completed the questionnaires at six-months post-SABR. The authors reported that quality of life appears to be well-preserved following kidney SABR as no significant difference was observed across three different questionnaires at baseline, one-week, one-month, three-months and six-months post-SABR,

using univariate repeated-measures mixed modelling methods. However, with pairwise analysis, there were statistically significant reductions in global quality of life at one-week (with subsequent recovery) and dyspnoea at six-months post-SBRT (see Appendix 4 [Table 2] for study description and Table 7 in the main text of the EAR for study outcomes).

4.7 Healthcare utilisation

HTW researchers did not identify any studies reporting on healthcare utilisation outcomes for SABR for kidney cancer.

4.8 Subgroup analysis

In the protocol for this appraisal, we stated that where the evidence allows, we would report outcomes separately for people not fit for nephrectomy and people who refuse surgery, and RCC and other renal cancer subtypes. Only one primary study by Peddada et al. (2020) mentioned numbers of patients who refused surgery. This study also included people with RCC or transitional cell carcinoma. Another study by Grant et al. (2020) reported data for people with RCC and those with unspecified carcinoma, and the study by Uhlig et al. (2020) reported different types of RCC and 'other histology'. However, neither study reported SABR outcomes separately for these groups, so we were unable to perform subgroup analyses.

Table 2. Stereotactic ablative therapy: local tumour control

Evidence source(s)	Number of studies and participants	Absolute effect (95% CI [%])	Comments on reliability
Secondary evidence			
Siva et al. (2012)	• Systematic review of 10 studies (3 prospective and 7 retrospective) with 126 patients • Mean follow-up: ranged from 9 to 57.5 months	• Weighted crude overall local control: 93.1% (range 84% to 100%) • Estimated mean local control at 2 years: 92.9% *See Appendix 5 (Table 1) for breakdown of results*	• Author crudely weighted the control rates without testing for heterogeneity. • Mainly retrospective studies, which are more susceptible to selection bias and recall bias than prospective studies. • No comparative data. • Technique and dose fractionation varied. • Little information on the median ages of the participants or the use of other treatments. No information on whether the tumours were biopsied before treatment. • 1 study used a heavy carbon-ion particle accelerator, which is not currently readily available for medical use outside of Japan.
Correa et al. (2019)	• 9 studies, 110 participants, 111 treated tumours: - 2 prospective single-arm published studies, - 2 prospective single-arm studies in conference abstracts, - 5 Retrospective single-arm published studies. - 1 retrospective single-arm study in conference abstract • Range of follow-up times (months): 13 to 48.3	LC range: 75% to 100% *See Appendix 5 (Table 2) for breakdown of results*	• Could not use pooled analysis as some of the patients had metastatic RCC (HTW only included those patients with no metastases). • Author states very little heterogeneity existed among studies with respect to the definition of LC. • Use of RECIST criteria may result in misinterpreting any initial increase in tumour size as disease progression (up to 6 months post-SABR). • Some of the included studies are from conference abstracts. • Mainly retrospective studies, which are more susceptible to selection bias and recall bias than prospective studies. • No comparative data.
Primary evidence			
Siva et al. (2018)	• 223 participants from 9 global institutions • Median follow-up: 2.6 years	• LC at 2 years: 97.8% • LC at 4 years: 97.8%	• LC determined using RECIST criteria, which may result in misinterpreting any initial increase in tumour size (up to 6 months post-SABR). • Mainly retrospective studies, which are more susceptible to selection bias and recall bias than prospective studies. • No comparative data. • None of data were from UK.

Evidence source(s)	Number of studies and participants	Absolute effect (95% CI [%])	Comments on reliability
			• No pre- and post-treatment comorbidity assessment, and not all data requested could be collected for all patients.
Peddada et al. (2020)	• 1 single-arm study, 21 participants • Median follow-up: 78 months (range 5 to 107 months)	• LC at 5 years post-SABR: 100% • Median tumour size decrease at 1 year post-SABR: 5.3% (range -17.6 to 100%) • Median tumour size decrease at 2 years post-SABR: 15.6% (range -17.6 to 100%) • Median tumour size decrease at 5 years post-SABR: 15.4%	• LC determined using RECIST criteria, which may result in misinterpreting any initial increase in tumour size (up to 6 months post-SABR). • Retrospective data, which are more susceptible to selection bias and recall bias than prospective studies. • No comparative data.

LC: local control; RCC: renal cell carcinoma; RECIST: Response evaluation criteria in solid tumours; SABR: stereotactic ablative radiotherapy

Table 3. Stereotactic ablative therapy: Survival

Type of survival	Evidence source(s)	Number of studies and participants	Absolute effect (95% CI [%])	Relative effect [95% CI] (interpretation)	Comments on reliability
RFS	Prins et al. (2017) (systematic review)	• 6 cohort single-arm studies, 149 participants. • Median follow-up times post-SABR (months): 6 to 31.2	RFS range: 63% to 98% *See Appendix 5 (Table 3) for breakdown of results*		• Only looked at tumours < 7 cm diameter. • No comparative data. • Although the SABR techniques used in the different studies were comparable, the prescribed doses and fractionation schemes varied. • Some of the patients did not have the subtype of their tumour histopathologically confirmed.
Overall survival	Siva et al. (2012) (systematic review)	• 10 studies (3 prospective and 7 retrospective) with 126 patients • Mean follow-up: ranged from 9 to 57.5 months	4/10 included studies reported overall survival: • Beitler et al. (2004): 4/9 alive at median follow-up of 26.7 months • Wersäll et al. (2005): median survival is 58+ months • Svedman et al. (2006): Median survival 32 months • Nomiya et al. (2008): 5-year overall survival 74% *See Appendix 5 (Table 4) for breakdown of results*		• Two-year overall survival, when not reported, were extrapolated from reported time points assuming a constant hazard. • Overall survival was inconsistently reported. Survival, when reported, was difficult to interpret as most patients were medically inoperable with multiple comorbidities, and most death occurred with the renal disease controlled. • The author notes the inconsistent reporting of survival after treatment. • Mainly retrospective studies, which are more susceptible to selection bias and recall bias than prospective studies. • No comparative data. • Technique and dose fractionation varied. • Little information on the median ages of the participants or the use of other treatments. No information on whether the tumours were biopsied before treatment. • 1 study used a heavy carbon-ion particle accelerator, which is not currently readily available for medical use outside of Japan.

Type of survival	Evidence source(s)	Number of studies and participants	Absolute effect (95% CI [%])	Relative effect [95% CI] (interpretation)	Comments on reliability
	Siva et al. (2018) (primary study: multi-centre pooled analysis)	• 223 participants from 9 global institutions • Median follow-up: 2.6 years	• 2-years post SABR: 82.1% • 4-years post SABR: 70.7%	<u>*Multivariable model:*</u> Maximum dimension per 10-mm increase in overall survival: HR (1.18 [1.12 to 1.25]), p < 0.001	• Mainly retrospective studies, which are more susceptible to selection bias and recall bias than prospective studies. • No comparative data. • None of data were from UK. • The authors notes there was no pre- and post-treatment comorbidity assessment, and not all data requested could be collected for all patients.
	Grant et al. (2020) (primary study: retrospective comparative analysis)	• Retrospective analysis of National Cancer Database over 10-year period (2004 to 2014) • Median follow-up observation: 19 months		<u>*5-year overall survival with propensity score adjustments:*</u> • **SABR vs observation:** HR: 0.56 (0.39-0.79), *P* < .001 ***Favours SABR***	• No information available in cancer-specific mortality or cause of death • People treated with SABR were staged clinically, whereas those with surgery were staged pathologically • Retrospective data, which are more susceptible to selection bias and recall bias than prospective studies. • American data • As this study covered a period of 10 years, changes in treatment techniques might have biased observations
	Uhlig et al. (2020) (primary study: retrospective comparative analysis)	• Retrospective analysis of National Cancer Database over 11-year period (2004 to 2015) • Median follow-up time: 58.1 months (IQR: 34.7 to 86.6 months)	• 3-years post-SABR: 76% • 5-years post-SABR: 58%	• Partial nephrectomy versus SABR, HR = 0.29, 95% CI: 0.19 to 0.46, p < 0.001 ***Favours partial nephrectomy*** • Cryoablation versus SABR HR = 0.40, 95% CI 0.26 to 0.60, p < .001; ***Favours cryoablation*** • Radiofrequency/microwave ablation versus SABR, HR = 0.46, 95% CI: 0.31 to 0.67, p < .001) ***Favours radiofrequency/microwave ablation***	• Retrospective data, which are more susceptible to selection bias and recall bias than prospective studies. • 4.6% of patients treated with SABR also had systemic therapy administered (unsure whether at same time as SABR) and this may not be reflective of Welsh practice. • It is unclear whether some of the patients had an RCC as secondary to other neoplasms. • The data set do not allow for categorisation of patients with RCC according to their prognosis, which might influence the effectiveness of SABR • Information on individual comorbidities was not included in the study • As this study covered a period of 11 years, changes in treatment techniques might have biased observations

Type of survival	Evidence source(s)	Number of studies and participants	Absolute effect (95% CI [%])	Relative effect [95% CI] (interpretation)	Comments on reliability
CSS	Siva et al. (2018) (primary study: multi-centre pooled analysis)	• 223 participants from 9 global institutions • Median follow-up: 2.6 years	• 2-years post SABR: 95.7% • 4-years post SABR: 91.9%	• Maximum dimension per 10-mm increase in CSS: HR (1.28 [1.19 to 1.39]), p < 0.001 • No. of fractions per 1-unit increase in CSS: HR (1.33 [1.07 to 1.66]), p = 0.011	• Mainly retrospective studies, which are more susceptible to selection bias and recall bias than prospective studies. • No comparative data. • None of data were from UK. • The authors notes there was no pre- and post-treatment comorbidity assessment, and not all data requested could be collected for all patients.
PFS	Siva et al. (2018) (primary study: multi-centre pooled analysis)	• 223 participants from 9 global institutions • Median follow-up: 2.6 years	• 2-years post SABR: 77.4% • 4-years post SABR: 65.4%	• Maximum dimension per 10-mm increase in PFS: HR (1.16 [1.10 to 1.23]), p < 0.001 • No. of fractions per 1-unit increase in PFS: HR (1.13 [1.02 to 1.24]), p = 0.017	• Mainly retrospective data, which are more susceptible to selection bias and recall bias than prospective studies. • No comparative data. • None of data were from UK. • The authors notes there was no pre- and post-treatment comorbidity assessment, and not all data requested could be collected for all patients.

CI: confidence interval; CSS: cancer-specific survival; HR: hazard ratio; IQR: inter-quartile range; mm: millimetres; PFS: progression-free survival; RCC: renal cell carcinoma; RFS: recurrence-free survival; SABR: stereotactic ablative radiotherapy

Table 4. Stereotactic ablative therapy: Adverse events

Grade of toxicity	Evidence source(s)	Number of studies and participants	Absolute effect	Comments on reliability
CTCAE Grade I to II	Prins et al. (2017) (systematic review)	• Six cohort single-arm studies, 149 participants • Median follow-up times post-SABR (months): 6 to 31.2 *See Appendix 5 (Table 5) for breakdown of results*	4/6 studies in systematic review reported toxicity in 18.7% to 60% of patients	• Only looked at T1 tumours (less than 7 cm diameter) • Whilst the SR reported outcomes from the different treatments, only single-arm cohort studies for SABR were included and so there were no comparative data • Although the SABR techniques used in the different studies were comparable, the prescribed doses and fractionation schemes varied sometimes even within studies. • Some of the patients included did not have their tumours histopathologically identified.
	Siva et al. (2012) (systematic review)	• Systematic review: 10 studies (3 prospective and 7 retrospective) with 126 patients • Mean follow-up: ranged from 9 to 57.5 months	7/10 studies included studies with grade I to II toxicity, ranging from 0% to 89% of patients *See Appendix 5 (Table 6) for breakdown of results*	• Mainly retrospective studies, which are more susceptible to selection bias and recall bias than prospective studies • Technique and dose fractionation varied • Little information is available on the median ages of the participants or the use of other treatments. There is no information on whether the tumours were biopsied before treatment • 1 study used a heavy carbon-ion particle accelerator, which is not currently readily available for medical use outside of Japan.
	Siva et al. (2018) (primary study: multi-centre pooled analysis)	• Primary study: pooled analysis of 223 participants from 9 global institutions • Median follow-up: 2.6 years	• At least grade 1 toxicity: 86 patients (38.6%) • Grade 1 or 2 toxicity only: 83 patients (35.6%)	• Mainly retrospective data, which are more susceptible to selection bias and recall bias than prospective studies. Authors noted that it may also have resulted in possible under-reporting of toxicity. • No comparative data. • None of data were from UK. • The authors note there was no pre- and post-treatment comorbidity assessment, and not all data requested could be collected for all patients.
	Peddada et al. (2020) (primary study: single-arm study)	• 1 single-arm study, 21 participants • Median follow-up: 78 months (range 5 to 107 months)	• Grade I toxicity (CTCAE): 3/21 (14%)	• Retrospective data, which are more susceptible to selection bias and recall bias than prospective studies. • No comparative data.

Grade of toxicity	Evidence source(s)	Number of studies and participants	Absolute effect	Comments on reliability
CTCAE Grade III to IV	Siva et al. (2012) (systematic review)	• 10 studies (3 prospective and 7 retrospective) with 126 patients • Mean follow-up: ranged from 9 to 57.5 months	7/10 studies included grade III to IV toxicity, ranging from 0% to 19% of patients *See Appendix 5 (Table 6) for breakdown of results*	• Mainly retrospective studies, which are more susceptible to selection bias and recall bias than prospective studies. • Technique and dose fractionation varied • Little information is available on the median ages of the participants or the use of other treatments. There is no information on whether the tumours were biopsied before treatment • 1 study used a heavy carbon-ion particle accelerator, which is not currently readily available for medical use outside of Japan.
	Prins et al. (2017) (systematic review)	• Systematic review: Six cohort single-arm studies, 149 participants • Median follow-up times post-SABR (months): 6 to 31.2	2/6 studies included grade III to IV toxicity	• Only looked at T1 tumours (less than 7 cm diameter) • Whilst the SR reported outcomes from the different treatments, only single-arm cohort studies for SABR were included and so there were no comparative data • Although the SABR techniques used in the different studies were comparable, the prescribed doses and fractionation schemes varied, sometimes even within studies. • Some of the patients did not have the subtype of their tumour histopathologically confirmed.
	Correa et al. (2019) (systematic review and meta-analysis)	• Systematic review: 9 studies, 110 participants, 111 treated tumours: - 2 prospective single-arm published studies, - 2 prospective single-arm studies in conference abstracts, - 5 Retrospective single-arm published studies. - 1 retrospective single-arm study	Ranged from 0% (95% CI: 0.0 to 69.7) to 15.4% (95% CI: 0.4 to 41.0) of patients in studies *See Appendix 5 (Table 7) for breakdown of results*	• Could not use pooled analysis as some of the patients had metastatic RCC (HTW only included those patients with no metastases). • Some of the included studies are from conference abstracts. • Mainly retrospective studies, which are more susceptible to selection bias and recall bias than prospective studies. • No comparative data.

Grade of toxicity	Evidence source(s)	Number of studies and participants	Absolute effect	Comments on reliability
		in conference abstract • Range of follow-up times (months): 13 to 48.3		
	Siva et al. (2018) (primary study: multi-centre pooled analysis)	• Primary study: pooled analysis of 223 participants from 9 global institutions • Median follow-up: 2.6 years	• Grade 3 and 4 toxicities: 3 patients (1.3%). • Simultaneous grade 3 nausea and grade 2 bowel toxicity: 1 patient (0.4%) Grade 4 bowel toxicity alone: 1 patient (0.4%) Simultaneous grade 4 gastritis and grade 4 bowel toxicity: 1 patient (0.4%)	• Mainly retrospective data, which are more susceptible to selection bias and recall bias than prospective studies. Authors noted that it may also have resulted in possible under-reporting of toxicity. • No comparative data. • None of data were from UK. • The authors note there was no pre- and post-treatment comorbidity assessment, and not all data requested could be collected for all patients.
	Peddada et al. (2020) (primary study: single-arm study)	• 1 single-arm study, 21 participants • Median follow-up: 78 months (range 5 to 107 months)	0%	• Retrospective data, which are more susceptible to selection bias and recall bias than prospective studies. • No comparative data.

CI: confidence interval; CTCAE: common terminology criteria for adverse events reporting criteria; RCC: renal cell carcinoma; SABR: stereotactic ablative radiotherapy; SR: systematic review

Table 5. Stereotactic ablative therapy: Tumour relapse/recurrence

Evidence source(s)	Number of studies and participants	Absolute effect	Comments on reliability
Primary evidence			
Siva et al. (2018)	• 223 participants from 9 global institutions • Median follow-up: 2.6 years	• Disease recurrence: Eighteen patients (8.1%): • Local recurrence: 3 patients (1.4%) • Distant recurrence: 16 patients (7.2%). • Both local and distant recurrence as the first sites of failure: 1 patient (0.4%)	• Mainly retrospective data, which are more susceptible to selection bias and recall bias than prospective studies. • No comparative data. • None of data were from UK. • The authors note there was no pre- and post-treatment comorbidity assessment, and not all data requested could be collected for all patients.

Table 6. Stereotactic ablative therapy: Post-SABR change in renal function

Evidence source(s)	Number of studies and participants	Absolute effect	Comments on reliability
Secondary evidence			
Correa et al. (2019)	• 9 studies, 110 participants, 111 treated tumours: - 2 prospective single-arm published studies, - 2 prospective single-arm studies in conference abstracts, - 5 Retrospective single-arm published studies. - 1 retrospective single-arm study in conference abstract • Range of follow-up times (months): 13 to 48.3	Range of post-SABR changes in eGFR (ml/min): -18 to +6 *See Appendix 5 (Table 8) for breakdown of results*	• Most patients had some degree of renal-function impairment before SABR • Some of the included studies are from conference abstracts • Mainly retrospective studies, which are more susceptible to selection bias and recall bias than prospective studies. • No comparative data. • Experts noted that glomerular filtration rate results can vary significantly day to day for the same patient, so caution may be needed when comparing results across patients with and without SABR.
Primary evidence			
Siva et al. (2018)	• 223 participants from 9 global institutions • Median follow-up: 2.6 years	• Mean ± SD change in eGFR at the last follow-up: -5.5 ± 13.3 mL per minute ($p < 0.001$). ***Significant difference*** • Corresponding rise in serum creatinine: 28.1 ± 74.4 micromol/L. • Mean renal function change in patients with T1a disease: (-4.0 ml/min) • Mean renal function change in patients with > T1a disease: (-6.8 ml/min, $p = 0.129$). ***No significant difference between cancer staging***	• Many patients had pre-existing renal dysfunction • Mainly retrospective data, which are more susceptible to selection bias and recall bias than prospective studies. • No comparative data. • None of data were from UK. • The authors note there was no pre- and post-treatment comorbidity assessment, and not all data requested could be collected for all patients.
Peddada et al. (2020)	• 1 single-arm study, 21 participants • Median follow-up: 78 months (range 5 to 107 months)	• Median glomerular filtration rate decrease 1-year post-SABR: 1.5% (range: -21.3% to 21.4%) • Median glomerular filtration rate decrease 2-years post-SABR: 7.0% (range: -13.6% to 28.9%) • Median glomerular filtration rate decrease 5-years post-SABR: 14.2%	• Retrospective data, which are more susceptible to selection bias and recall bias than prospective studies. • No comparative data.

eGFR: estimated glomerular filtration rate; micromole/L: micromoles per litre; ml/min: millilitres per minute; SABR: stereotactic ablative radiotherapy; SD: standard deviation; SR: systematic review

Table 7. Stereotactic ablative therapy: Quality of life

<table>
<tr><th>Evidence source(s)</th><th>Number of studies and participants</th><th>Absolute effect</th><th>Relative effect</th><th>Comments on reliability</th></tr>
<tr><td colspan="5">Primary evidence</td></tr>
<tr>
<td>Swaminath et al. (2021)</td>
<td>

1 prospective cohort study:

28 patients
20 (71%) patients completed questionnaires at 1-week post-SABR
24 patients (86%) completed questionnaires at 1-month post-SABR
17 patients (61%) completed questionnaires at 3-months post-SABR
16 patients (57%) completed questionnaires at 6-months post-SABR

Times: baseline, 1-week, 1-month, 3-months, 6-months post-SABR

</td>
<td>Global QOL was stable or better at 6-months post-SABR in about 70% of evaluable patients using EORTC QLQ C-15 PAL. EQ-5D-3L health utility and FACT QoL scores were stable or better in about 70–80% of all patients assessed across all time points.</td>
<td>
<table>
<tr><th rowspan="2">QOL score</th><th colspan="4">Mean change</th></tr>
<tr><th>Baseline vs 1 week</th><th>Baseline vs 1 month</th><th>Baseline vs 3 months</th><th>Baseline vs 3 months</th></tr>
<tr><td colspan="5">EQ-5D-3L</td></tr>
<tr><td>Visual analogue scale</td><td>−0.938</td><td>1.500</td><td>4.125</td><td>1.667</td></tr>
<tr><td>Health utility score</td><td>0.050</td><td>0.022</td><td>−0.020</td><td>0.038</td></tr>
<tr><td colspan="5">EORTC-QLQ-C15-PAL</td></tr>
<tr><td>Global QOL score</td><td>−8.345</td><td>−3.479</td><td>−0.982</td><td>−2.083</td></tr>
<tr><td>Physical functioning</td><td>−0.665</td><td>1.388</td><td>−5.000</td><td>−7.494</td></tr>
<tr><td>Emotional functioning</td><td>−2.920</td><td>2.087</td><td>1.471</td><td>−3.119</td></tr>
<tr><td>Fatigue</td><td>7.225</td><td>4.642</td><td>1.318</td><td>2.781</td></tr>
<tr><td>Nausea/vomiting</td><td>5.000</td><td>0.000</td><td>−6.859</td><td>−3.125</td></tr>
<tr><td>Dyspnoea</td><td>0.005</td><td>−0.008</td><td>1.969</td><td>14.581</td></tr>
<tr><td>Pain</td><td>1.667</td><td>0.694</td><td>−3.922</td><td>−6.250</td></tr>
<tr><td>Insomnia</td><td>−5.000</td><td>−2.778</td><td>3.922</td><td>4.167</td></tr>
<tr><td>Appetite</td><td>5.000</td><td>1.383</td><td>−9.812</td><td>−2.088</td></tr>
<tr><td>Constipation</td><td>1.754</td><td>4.348</td><td>4.167</td><td>4.167</td></tr>
<tr><td colspan="5">FACT FKSI-19</td></tr>
<tr><td>Overall converted score</td><td>0.430</td><td>0.908</td><td>−2.188</td><td>−0.181</td></tr>
</table>
</td>
<td>

Not all patients completed questionnaires. At the following time points, at least some questionnaires were collected from the following proportion of patients:

1 week: 20/28 (71%)
1 month 24/28 (86%)
3 months 17/28 (61%)
6 months 16/28 (57%)

</td>
</tr>
<tr><td colspan="5">EORTC QLQ C-15 PAL: European Organization for Research and Cancer Treatment Quality of Life Core Questionnaire-15 Palliative; EQ-5D; EuroQol-5D; FACT-FKSI-19: Functional Assessment of Cancer Therapy-Kidney Symptoms Index; Qol: quality of life; SABR: stereotactic ablative radiotherapy</td></tr>
</table>

4.9 Ongoing trials

We identified one ongoing Canadian randomised controlled trial comparing SABR to radiofrequency ablation in 24 adults with small renal masses (≤ 4.0 cm) with no metastatic disease (NCT03811665). The primary outcome will be treatment failure, overall survival, disease free survival and disease recurrence, all after 12 months. Quality of life, duration of hospital stay and cost will be included as secondary outcomes. The study is due to be completed in December 2022.

Another Canadian study of 30 people treated with SABR for primary RCC was due to publish in December 2021, but we have not been able to find it at the time of writing this EAR (NCT03108703). It is a single-arm study and will report on quality of life and cost effectiveness at five-years post-SABR. An interventional study of 46 patients treated with Cyberknife in the USA is due to complete in December 2023 (NCT01890590). This study will measure quality of life at a two-year timeframe.

5. Economic evaluation

5.1 Economic evidence review

A review of the economic evidence on the use of SABR for primary kidney cancer was conducted. The titles and abstracts of records identified in the search for this research question were screened but no relevant health economic studies were identified.

5.2 Intervention costs

The costs associated with each intervention were estimated using sources relevant to the UK NHS. We considered the cost of SABR alongside other interventions that may be used in this patient group. Costs were identified for SABR, nephrectomy and radiofrequency ablation. No suitable cost estimates were identified for microwave ablation or cryoablation.

5.2.1 SABR Cost

No UK studies were identified which reported treatment costs for SABR when used to treat primary kidney cancer.

The cost associated with the planning and delivery of SABR was estimated using costs provided through personal communication with the finance department at Velindre Cancer Centre, Wales (for the 2019/2020 cost year). A total cost of £5,081 was estimated based upon a radiotherapy regimen of five 30-minute fractions with fiducial markers and planning with a CT simulator.

Alternative estimates were sourced based on the use of SABR in other disease areas. Jin et al. (2021) estimated SABR treatment costs of £4,433 and £4,807 when used to treat oligometastatic liver cancer and hepatocellular carcinoma, respectively.

5.2.2 Nephrectomy cost

The cost of nephrectomy was estimated using values reported in the National Schedule of NHS Costs (NHS England 2021). The cost of nephrectomy when performed as an open procedure was estimated to be £8,136. This was calculated as the weighted average of comorbidity and complication scores for 'major, open or percutaneous, kidney or ureter procedures, 19 years and over'. The cost of nephrectomy when performed as a laparoscopic procedure was estimated to be £7,371. This was calculated as the weighted average of comorbidity and complication scores for 'major laparoscopic, kidney or ureter procedures, 19 years and over' (NHS England 2021).

5.2.3 Radiofrequency ablation cost

No UK studies were identified which reported treatment costs for radiofrequency ablation when used to treat primary kidney cancer. Therefore, alternative estimates were sourced based on the use of radiofrequency ablation in other disease areas. Jin et al. (2021) estimated that radiofrequency ablation costs £4,961 and £5,089 when used to treat oligometastatic liver cancer and hepatocellular carcinoma, respectively.

5.3 De novo economic analysis for SABR in comparison to observation

A de novo economic model was developed to estimate the cost-effectiveness of SABR in comparison to observation in people who cannot be managed using surgery or invasive ablation techniques from the perspective of UK NHS and personal social services (PSS). The analysis considered a lifetime horizon with future costs and benefits discounted at 3.5% per year.

A partitioned survival analysis was developed using evidence identified from Grant et al. (2020) which showed that SABR was associated with a decreased risk of death compared with observation, (HR of 0.56 95%CI: 0.39 to 0.79). Directly comparative evidence was not available for progression free survival and so evidence has been sourced from disparate sources. Siva et al. (2018) showed that progression free survival was 65% at four years in people treated with SABR. Prospective data from the DISSRM Registry showed that progression free survival was 71% for people on active surveillance.

A cost of £5,081 was used for SABR based on costs provided through personal communication with the finance department at Velindre Cancer Centre, Wales (see section 5.2.1 above). The costs of subsequent treatment options for managing metastatic disease were based on costs reported in a previous cost-utility analysis of kidney cancer screening by (Rossi et al. 2021). The quality of life implications associated with recurrence and progressive disease were also sourced from (Rossi et al. 2021).

The results of the analysis are presented in Table 8. The results show SABR to be more effective and more costly than observation. The resulting ICER of £1,675 per QALY is below the commonly applied threshold of £20,000 per QALY, indicating that SABR is cost effective. However, the results should be interpreted with some caution as the analysis is partly based on effectiveness evidence from different sources for the SABR and observation arms.

The conclusion of the analysis did not change in any of the alternative scenarios modelled in sensitivity analysis, with SABR found to be cost effective in all scenarios. In probabilistic sensitivity analysis, it was found that SABR had a 100% probability of being cost-effective at a threshold of £20,000 per QALY.

Table 8. Base case results

Treatment strategy	Cost		QALYs		ICER (cost per QALY)
	Total	Incremental	Total	Incremental	
Observation	£8,898	-	9.85	-	-
SABR	£12,634	£3,736	12.08	2.23	£1,675

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year

6. Organisational Issues

Whilst experts contacted by HTW noted that LINAC machines are currently used to deliver SABR in Wales for conditions including lung and prostate primary cancers and oligometastatic disease, and that SABR can be routinely delivered in almost all radiotherapy centres in Wales, a number of organisational issues were identified by experts should SABR be used for primary kidney cancer in Wales:

- Funding for a SABR service would be needed.
- SABR multidisciplinary teams (MDTs) would need to be established to discuss all potential cases (combined with other SABR cases). Whilst histological proof of RCC is not essential, expert uro-radiology input at MDTs is required to confirm a radiological diagnosis.
- Capacity within radiotherapy departments/cancer centres would need to be established.
- Use of SABR for primary kidney cancer would require suitably trained staff.
- There would need to be referral pathways to specialist radiotherapy centres with the appropriate equipment for SABR.
- The technology assessment needs to be in place along with an assessment of access to SABR for patients in Wales to ensure that there are no experience/resource barriers, or inequities.

7. Patient issues

Experts contacted by HTW were asked their opinions on the benefits and issues of SABR to patients. Potential benefits to patients being treated with SABR include:

- A potential cure for medically unfit patients with no other treatment options who have to wait until they develop metastatic disease (affecting their wellbeing). This group of patients are likely to be unfit for drug treatment when they develop metastatic disease.
- An option for organ preservation for patients with solitary kidney (where partial nephrectomy is not possible due to size or location of the tumour). This can reduce the need for dialysis.
- Improved quality of life.
- Good long-term local tumour control.
- Limited toxicity.
- Rapid recovery in a painless, non-invasive, outpatient procedure (can be a single procedure [up to 3 fractions] and so less trips for treatment needed). There is no need to insert the needles or catheters needed for invasive ablation.
- No need for general anaesthesia.
- No need to take systemic anticancer treatment.

Potential issues for patients being treated with SABR include:

- Pre-existing biases against radiation treatment. Urologists may dissuade patients from SABR, sometimes unconsciously.
- Concerns over travelling to a radiotherapy centre and potentially multiple visits.
- Concerns over radiation toxicities (short and long term, e.g. secondary cancers)
- Patients may still prefer limited resection (“I want the tumour out”)
- Patients may prefer the active surveillance option, especially for tumours < 3 cm, as prognosis is very good.
- Some patients may have the inability to lie flat (comfortably) for > 15 minutes.
- Concerns of bowel toxicity, especially in patients with inflammatory bowel disease.

8. Conclusions

We identified two systematic reviews and one meta-analysis investigating the use of SABR in RCC, but we were unable to use the pooled results from the meta-analysis as some of the included patients had metastatic disease. HTW researchers identified two additional single-arm primary studies, a retrospective data analysis with comparative data, and a prospective cohort study, not included in the secondary evidence.

Whilst some of the clinical evidence suggests that SABR might improve the outcomes reported in this EAR, and is mainly associated with minor adverse events, the data should be interpreted with caution as most of it comes from single-arm, retrospective studies, involving between 21 and 223 participants, with variation in prescribed SABR doses and fractionation schemes and also in whether the histopathology of the tumour was obtained. The only studies we found involving comparators comes from two retrospective analyses of the same cancer database, which reported that SABR improved overall survival compared to observation, but did not improve overall survival as well as partial nephrectomy or thermal ablation. However, they were based on American data and so generalisability to the Welsh NHS is uncertain, and experts noted that those patients treated by radiofrequency ablation could have been fitter patients and/or with smaller tumours than those in the SABR-treated group.

We did not identify any evidence for healthcare utilisation, but one small randomised controlled trial comparing SABR with radiofrequency ablation in small renal masses is due to report on duration of hospital stay, and has an anticipated publication date of December 2022.

No relevant health economic studies were identified in the literature review. An economic analysis developed by HTW considering the cost-effectiveness of SABR in people who cannot be managed using surgery or invasive ablation techniques found SABR to be more effective but more costly than standard care. The resulting ICER of £1,675 per QALY indicates that SABR is cost effective and this conclusion was robust to changes in sensitivity analysis.

9. Contributors

This topic was proposed by Dr Jacob Tanguay, Consultant Oncologist, Uro-oncology Team Lead, Velindre NHS Trust

The HTW staff and contract researchers involved in writing this report were:

- A Evans – patient and public involvement author
- D Jarrom – quality assurance of clinical section
- E Hasler – literature searches and information management
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The HTW Assessment Group advised on methodology throughout the scoping and development of the report.

A range of clinical experts from the UK provided material and commented on a draft of this report. Their views were documented and have been actioned accordingly. All contributions from reviewers were considered by HTW's Assessment Group. However, reviewers had no role in authorship or editorial control, and the views expressed are those of Health Technology Wales.

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11. Evidence review methods

We searched for evidence that could be used to answer the review question: What is the clinical and cost effectiveness of stereotactic ablative radiotherapy for primary renal cancer compared to standard care?

The criteria used to select evidence for the appraisal are outlined in Appendix 1. These criteria were developed following comments from the Health Technology Wales (HTW) Assessment Group and UK experts.

The systematic search followed HTW's standard rapid review methodology. A search was undertaken of Medline, Embase, CINAHL, Cochrane Library, the International Network of Agencies for Health Technology Assessment (INAHTA) HTA database, the Centre for Reviews and Dissemination (CRD) database & Epistemonikos. Additionally, searches were conducted of key websites and clinical trials registries.

The searches were conducted in October 2021, with an update search of Medline, Embase, CINAHL, Cochrane Library, and INAHTA HTA database run on the 1 March 2022.

Appendix 3 gives details of the search strategy used for MEDLINE. Search strategies for other databases are available on request.

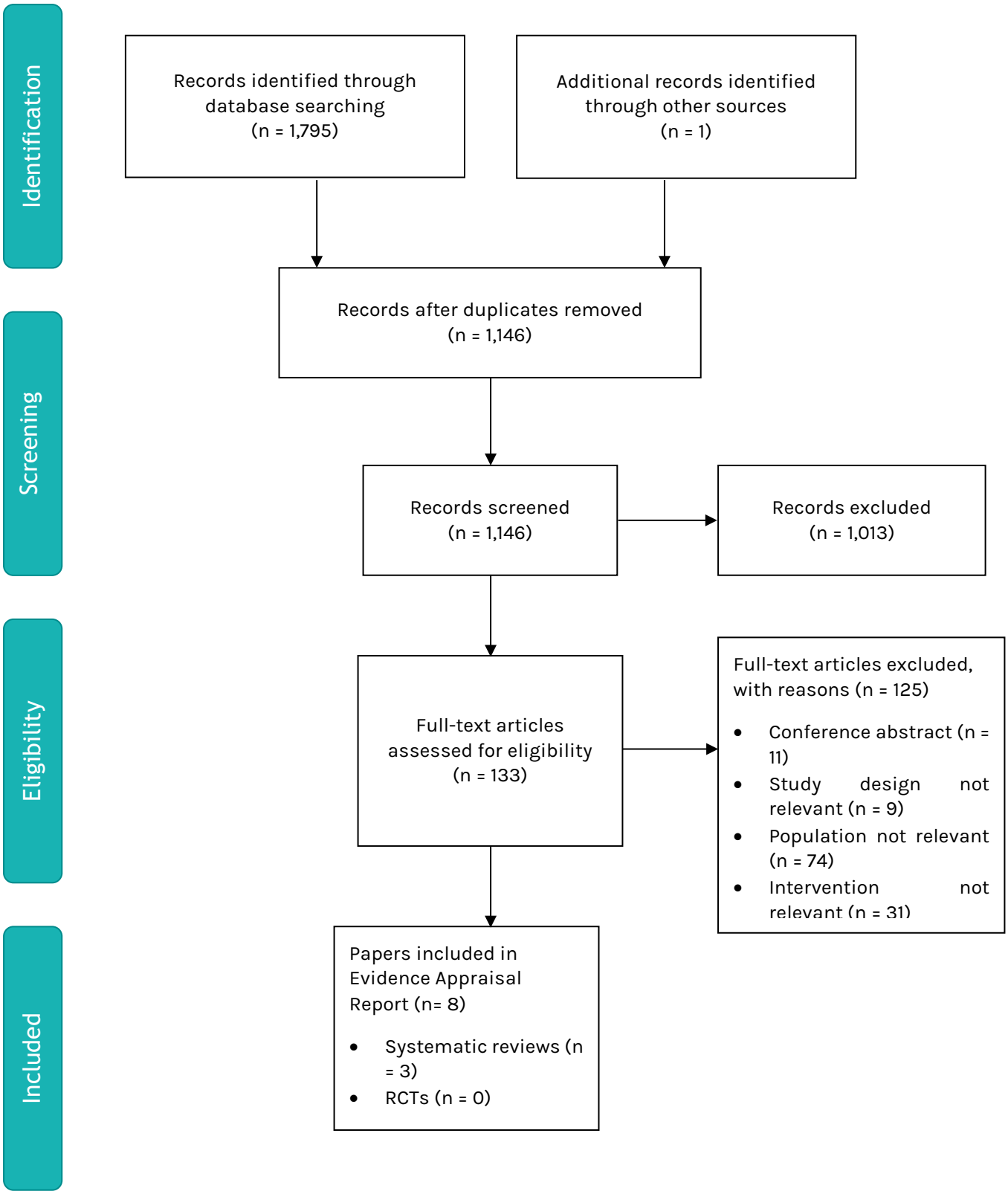
Appendix 2 summarises the selection of articles for inclusion in the review.

Appendix 1. Inclusion and exclusion criteria for evidence included in the review

	Inclusion criteria	Exclusion criteria
Population	People with primary renal cancer	People with metastatic renal cancer
Intervention	Stereotactic ablative radiotherapy (SABR), also known as stereotactic body radiation therapy (SBRT)	In combination with other treatments, such as immunological checkpoint inhibitors
Comparison/ Comparators	We will compare SABR to any other care option, including but not limited to: • Definitive management (using techniques such as partial or radical nephrectomy [including laparoscopic surgery], cryoablation or radiofrequency ablation, chemotherapy) • Active surveillance/best supportive care In the absence of any evidence directly comparing SABR to control treatments for particular outcomes, we will also include studies comparing outcomes before/after treatment with the intervention.	
Outcome measures	• Local tumour control (defined as proportion of stable disease or decreased tumour size [partial or complete response] as per the Response Evaluation Criteria in Solid Tumours [RECIST] criteria) • Tumour relapse/recurrence rate • Healthcare utilisation • Safety (including treatment toxicity) • Renal function post-treatment • Survival rates/mortality • Quality of life and patient satisfaction • Cost effectiveness	

Study design	We will prioritise the following study types, in the order listed: • Systematic reviews of randomised controlled trials • Randomised controlled trials • Non-randomised comparative trials • Single-arm (no control group) trials that report any relevant outcome We will only include evidence from "lower priority" sources where this is not reported by a "higher priority" source. This could be because higher priority evidence: • Does not cover all relevant populations • Does not compare the technology of interest to all relevant comparators • Does not cover all outcomes of interest • Reports over short-term follow up periods, and longer follow up data is required to facilitate decision making. Where relevant and well-conducted systematic reviews exist we will use these by: • Reporting or adapting their reported outcome measures where these are fully relevant to the scope of our review, and appropriate synthesis methods have been used • Using these reviews as a source of potentially relevant studies where the review cannot be used as a source of outcome data We will prioritise systematic reviews in terms of the sources of evidence they include, using the order described above. Due to the high number of very small, non-comparative studies identified, we only included studies with more than 10 participants.
Search limits	No date limits apply
Other factors	Where the evidence allows, we will report outcomes separately for: • People not fit for partial or complete nephrectomy and people who refuse surgery • Renal cell carcinoma and other renal cancer subtypes (including transitional cell carcinoma)

Appendix 2. Flow diagram outlining selection of relevant evidence sources



Appendix 3. MEDLINE Search strategy

Ovid MEDLINE(R) ALL 1946 to February 25, 2022		
Kidney Cancer		
1	Carcinoma, Renal Cell/	36948
2	Kidney Neoplasms/	74792
3	Carcinoma, Transitional Cell/	19935
4	Urologic Neoplasms/	5584
5	((renal or kidney) adj3 (cancer* or neoplas* or malignan* or tumo?r* or carcinoma* or lesion* or mass or masses)).tw,kf.	92914
6	RCC.tw,kf.	17513
7	or/1-6	138452
SABR		
8	Radiosurgery/	18107
9	*Stereotaxic Techniques/	6455
10	((stereotac* or stereotax*) adj5 (radiotherap* or radiat* or irradiat* or RT or surg* or radiosurg* or ablat* or radioablat*)).tw,kf.	21170
11	((stereotac* or stereotax*) adj (procedure* or method* or technique* or approach* or treatment*)).tw,kf.	1955
12	(SABR or SBRT).tw,kf.	6164
13	(cyberknife* or cyber-knife*).tw,kf.	1741
14	(gammaknife* or gamma-knife*).tw,kf.	5495
15	or/8-14	35322
Set Combinations		
16	7 and 15	706
17	(renal or kidney).tw.	905376
18	15 and 17	755
19	16 or 18	856
Exclusions		
20	limit 19 to english language	790
21	Letter/	1170353
22	Editorial/	596348
23	News/	211153
24	exp Historical Article/	407668
25	Anecdotes as Topic/	4746
26	Comment/	952410
27	Case Reports/	2250117
28	(letter or comment*).ti.	174113
29	or/23-30	4705242
30	Randomized Controlled Trial/ or random*.ti,ab.	1422636
31	31 not 32	4675354
32	exp Animals/ not Humans/	4963784
33	exp Animals, Laboratory/	933844
34	exp Animal Experimentation/	10080
35	exp Models, Animal/	621905
36	exp Rodentia/	3422003
37	(rat or rats or mouse or mice).ti.	1391227
38	or/21-37	10477266
39	20 not 38	608

Appendix 4. Full sources of evidence (study designs and characteristics)

Table 1. Included systematic reviews: designs and characteristics

Study reference	Search period	Eligibility criteria	Trial/patient characteristics	Outcomes measured
Siva et al. (2012)	January 1995 to February 2012	• Primary RCC	• 7 retrospective trials, 3 prospective trials • 126 patients worldwide (exact locations NR) • 1 to 6 fractions of SABR used. Most commonly used was 40 Gy delivered over 5 fractions • Median/mean follow-up: 9 to 57.5 months • Devices used: 1 study used a robotic arm-held linear accelerator system • 1 study used a heavy carbon-ion particle accelerator • 8 studies used conventional gantry –operated linear accelerators • No tumour-size restrictions • No exclusions/restrictions based on tumour proximity to collecting vessels/renal vasculature • No pathological (biopsy) confirmation of tumour response • The BED calculated using the α/β estimates of the 2 common RCC cell lines, Caki-1 and A498. The estimated BED for the Caki-1 cell line ranged from 86.4 Gy and 159.3 Gy. The estimated BED ranged from 163.1 Gy and 343.4 Gy for the A498 cell line	• Local control (crude local control and estimated 2-year local control). Two-year local control, when not reported, was extrapolated from reported time points assuming a constant hazard) • Toxicity • Overall survival. Two-year overall survival, when not reported, was extrapolated from reported time points assuming a constant hazard)
Prins et al. (2017)	2010 to December 2016	• Primary treatment with AS, RFA, MWA, CA or SABR • Primary RCC (only looked at T1 tumours < 7 cm) or SRM (SRMs are renal masses ≤ 4 cm).	• 6 cohort single-arm studies, 149 participants. • Mean tumour diameter: 3 to 4 cm (range: 1.0 to 14.6 cm) • Fractionation schemes: Varied between 25 Gy and 48 Gy, in 1 to 5 fractions • Cyberknife used, although number of studies NR • Biopsy proven RCC: 4/6 included studies (ranged from 56% of participants to 100%) • Median follow-up time (months): 6 to 31.2	• CSS • RFS • Toxicity

Correa et al. (2019)	1995 to 2019	• Studies in the metastatic RCC setting, wherein SABR targeted the primary tumour (HTW only included studies which didn't include metastatic cancer and which weren't included in any of the other secondary evidence we used) • SABR ≥ 5 Gy per fraction	• 110 participants, 111 treated tumours: • 2 prospective single-arm published studies • 2 prospective single-arm studies in conference abstracts • 5 retrospective single-arm published studies • 1 retrospective single-arm study in conference abstract • Stage: I to II localised RCC • Criteria to assess LC: RECIST • Range of follow-up times (months): 13 to 48.3 • Average age: 74 years • Range of tumour size (cm): 2.28 to 5.1 • Dose (Gy)/fractions: 2 studies using 40/5, 2 studies using 39/3, 1 study using 21-48/3, 1 study using 15/1, 1 study using 26/1 or 42/3, 1 study using 48-60/3, 1 study using 60 or 70/10 (CIRT) • Range of pre-SABR eGFR (ml/min): 28.7 to 55	• Local control • Toxicity • Renal function
AS: active surveillance; BED: biological equivalent doses; CA: cryoablation; CIRT: carbon ion radiotherapy; cm: centimetres; CSS: cancer-specific survival; Gy: Gray; LC: local control; ml/min: millilitres per minute; MWA: microwave ablation; NR: not reported; RCC: renal cell carcinoma; RECIST: Response evaluation criteria in solid tumours; RFA: radiofrequency ablation; RFS: recurrence-free survival; SABR: stereotactic ablative radiotherapy; SRM: small renal masses				

Table 2. Included non-randomised trials: designs and characteristics

Study reference	Setting and design	Participants	Intervention	Outcomes	Follow-up period	Comments
Siva et al. (2018)	IROCK multi-centre pooled analysis (some retrospective data, amount NR)	• 223 participants from 9 global institutions in Germany, USA, Canada Japan • Mean patient age: 72 years • Men: 69.5%, Women: 31.5% • Pre-SABR biopsy confirmation: 84.8%: Clear cell RCC: 86.2%, papillary: 4.8%, Chromophobe: 1.1% , Other RCC: 5.8%, urothelial: 2.1% • ECOG performance of 0 or 1: 87.4% • Mean ± SD maximal tumour dimension (mm): 43.6 ± 27.7 • Mean time between initial diagnosis and treatment with SABR: 28.1 months	• Single-fraction SABR: 118 patients • Median SABR dose: 25 Gy (range 14 to 26 Gy) • Multi-fraction SABR: 105 patients • Median SABR dose: 40 Gy (range 24 to 70 Gy) delivered in 2 to 10 fractions	• Local control • Distant control • Overall survival • PFS • CSS	• Median follow-up: 2.6 years	• All participants received SABR between 2007 and 2016 • Local control determined using size-based RECIST criteria • Toxicities recorded using Common Terminology Criteria for Adverse Events, version 4.0 • For patients with unknown eGFR and known creatinine values, the eGFR was estimated from the CKD Epidemiology Collaboration equation
Peddada et al. (2020)	1 single-arm, retrospective study	• 21 participants • Stage of cancer: stage I • Histologic confirmation before SABR: 100% of patients: • 2/21 had transitional cell carcinoma, 19/21 had RCC • Number of patients who refused surgery: 14/21 (66%) • Median age: 71 years (range 58 to 88 years) • Median time from diagnosis to SABR: 3 months (range 0 to 37 months) • Median axial dimension of tumour: 2.85 cm (range, 1.2 to 7.7 cm) • 19 renal lesions < 4 cm • Men: 12/21, Women: 9/21	• SABR dose regimen: 20/21 patients received 48 Gy in 3 fractions; • 1/21 received 42 Gy in 3 fractions • SABR device: CyberKnife robotic radiosurgery system	• Local control • Glomerular filtration rate • Toxicity	• Median follow-up: 78 months (range 5 to 107 months)	• Patients treated between November 2009 and August 2018 • RECIST used to assess local control • Adverse events were scored using Common Terminology Criteria for Adverse Events, version 4.03 • Fiducial placement used (number of patients NR)

		• ECOG score of 0: 8/21; ECOG score of 1: 8/21; ECOG score of 2: 5/21 • RENAL complexity score: low (4 to 6) in 10 patients, moderate (7 to 9) in 6, high (10 to 12) in 2				
Grant et al. (2020)	Retrospective analysis of American database over 10-year period (2004 to 2014)	• A total of 200,839 patients identified • Diagnosis: T1N0M0 kidney cancer (7 cm or less) • Type of cancer: • RCC: 93%. Clear cell carcinoma: 55.8%, papillary carcinoma: 16%, RCC NOS: 28.1% • carcinoma NOS: 6.7%	• SABR (5 fractions or less to a total BED10 of 72 or more), n = 104; partial/total nephrectomy, n = 165,298; tumour ablation, n = 17,196; observation, n = 18,241 • SABR stratified by Bed10: patients with a Bed10 $\geq$ 100 (n = 62) and Bed10 < 100 (n = 42) • In the study, SABR was compared to observation only	• Overall survival	• Median follow-up surgery: 57 months • Median follow-up tumour ablation: 50 months • Median follow-up SABR: 37 months • Median follow-up observation: 19 months	• National Cancer Database, USA • Propensity score matching procedure undertaken by multinomial logistic regression. • Patients were propensity score–matched to account for potential confounders, including: patient age, sex, race Charlson-Deyo comorbidities score, tumour size, laterality, histology, grade, insurance plan, rurality, median income, education, academic hospital, and distance travelled for treatment • No information available in CSS or cause of death • People treated with SABR were staged clinically, whereas those with surgery were staged pathologically
Uhlig et al. (2020)	Retrospective analysis of American database over 11-year period (2004 to 2015)	• A total of 91,965 patients were identified (SABR, n = 174; partial nephrectomy, n = 82,913; cryoablation, n = 5,446; radiofrequency/microwave ablation, n = 3,432)	• Median SABR radiation dose: 40 Gy (IQR: 32 to 48 Gy) over a median course of 3 fractions (IQR: 2 to 4 fractions)	• Overall survival	• Median follow-up time: 58.1 months (IQR: 34.7 to 86.6 months)	• 4.6% of patients were treated with systemic therapy (unsure whether this was at same time as SABR), which might not be reflective of practice in Wales.

		• Propensity score matching procedure: 636 patients • Histopathologically proven stage I RCC	• Compared with partial nephrectomy or thermal ablation (cryoablation/ radiofrequency ablation/ microwave ablation)			• It is unclear whether some of the patients had an RCC as secondary to other neoplasms. • Patients were propensity score–matched to account for potential confounders, including: patient age, sex, race comorbidities, tumour size, histology, grade, tumour sequence, administration of systemic therapy, treatment in academic versus non-academic centres, year of diagnosis
Swaminath et al. (2021)	Prospective cohort study	• 28 patients included: • 71% completed questionnaires at 1-week post-SABR • 86% completed questionnaires at 1-month post-SABR • 61% completed questionnaires at 3-months post-SABR • 57% completed questionnaires at 6-months post-SABR	• Dosing regimen: five-fraction SABR, ranging from 35 to 45 Gy in total dose	• Quality of life	• Baseline, 1-week, 1-month, 3-months, 6-months post-SABR	• Qol assessment tools: EORTC QLQ C-15 PAL, FACT-FKSI-19 and the EQ-5D

BED: biological equivalent doses; CKD: chronic kidney disease; CSS: cancer-specific survival; ECOG: Eastern Cooperative Oncology Group; eGFR: estimated glomerular filtration rate; EORTC QLQ C-15 PAL: European Organization for Research and Cancer Treatment Quality of Life Core Questionnaire-15 Palliative; EQ-5D; EuroQol-5D; FACT-FKSI-19: Functional Assessment of Cancer Therapy-Kidney Symptoms Index; Gy: grays; IQR: inter-quartile range; IROCK: International Radiosurgery Oncology Consortium for Kidney; mm: millimetres; ablation; n: number of participants; NOS: not otherwise specified; NR: not reported; PFS: progression-free survival; Qol: quality of life; RCC: renal cell carcinoma; RECIST: Response Evaluation Criteria in Solid Tumours; RENAL: radius, exophytic and endophytic, nearness of tumour to collecting system or sinus, anterior or posterior, and hilar tumour touching main renal artery or vein and location relative to polar lines); SABR: stereotactic ablative radiotherapy; SD: standard deviation

Appendix 5. Studies included in systematic reviews

Table 1. Breakdown of studies in Siva et al. (2012) for weighted crude overall local control and estimated 2-year local control

Study	Crude overall local control	Estimated 2-year local control
Qian et al. (2003)	93%	86%
Beitler et al. (2004)	100%	100%
Wersäll et al. (2005)	100%	100%
Gilson et al. (2006)	92%	92%
Svedman et al. (2006)	91%	91%
Teh et al. (2007)	100%	100%
Svedman et al. (2008)	91%	91%
Nomiya et al. (2008)	100%	100%
Kaplan et al. (2010)	NR	NR
Ponsky & Vricella (2012)	NR	NR

Table 2. Breakdown of studies measuring local control in Correa et al. (2019)

Study	Local control (95% CI)
Wurzer et al. (2012)	87.0% (69.6 to 98.2)
Nair et al. (2013)	100.0% (30.3 to 100.0)
McBride et al. (2013)	80.0% (55.4 to 97.0)
Lo et al. (2014)	100.0% (50.0 to 100.0)
Hanzly et al. (2014)	75.0% (20.7 to 100.0)
Kaidar-Person et al. (2017)	100.0% (73.2 to 100.0)
Siva et al. (2017)	100.0% (94.9 to 100.0)
Grubb et al. (2018)	90.9% (65.0 to 100.0)
Funayama et al. (2019)	92.3% (69.9 to 100.0)

Table 3. Breakdown of studies for RFS in Prins et al. (2017)

Study	RFS (%)
Pham et al. (2014)	NR
Staehler et al. (2015)	98%
Ponsky et al. (2015)	63 to 84%
Yamamoto et al. (2016)	NR
Sun et al. (2016)	93%
Chang et al. (2016)	100%

Table 4. Breakdown of studies for median overall survival in Siva et al. (2012)

Study	RFS (%)
Qian et al. (2003)	NR
Beitler et al. (2004)	4/9 alive at median follow-up of 26.7 months
Wersäll et al. (2005)	median survival 58+ months
Gilson et al. (2006)	NR
Svedman et al. (2006)	Median survival 32 months
Teh et al. (2007)	NR
Svedman et al. (2008)	NR
Nomiya et al. (2008)	5-year overall survival 74%
Kaplan et al. (2010)	NR
Ponsky & Vricella (2012)	NR

Table 5. Breakdown of studies for Grade I to II toxicity in Prins et al. (2017)

StudyR	Toxicity (%)
Pham et al. (2014)	60%
Staehler et al. (2015)	30%
Ponsky et al. (2015)	37%
Yamamoto et al. (2016)	NR
Sun et al. (2016)	NR
Chang et al. (2016)	18.7%

Table 6. Breakdown of studies for grade I to IV+ toxicity in Siva et al. (2012)

Study	Toxicity
Qian et al. (2003)	NR
Beitler et al. (2004)	33% grade I to II, 0% grade III+
Wersäll et al. (2005)	20% grade I to II, 19% grade III, 0% grade IV+
Gilson et al. (2006)	NR
Svedman et al. (2006)	89% grade I to II, 4% grade III
Teh et al. (2007)	NR
Svedman et al. (2008)	58% grade I to II, nil else
Nomiya et al. (2008)	10% grade IV, no other toxicities > grade I
Kaplan et al. (2010)	0%
Ponsky & Vricella (2012)	0%

Table 7. Breakdown of studies for grade III to IV toxicity in Correa et al. (2019)

Study	Toxicity (95% CI)
Wurzer et al. (2012)	0.0% (0.0 to 7.3)
Nair et al. (2013)	0.0% (0.0 to 69.7)
McBride et al. (2013)	0.0% (0.0 to 11.2)
Lo et al. (2014)	0.0% (0.0 to 50.0)
Hanzly et al. (2014)	0.0% (0.0 to 38.9)
Kaidar-Person et al. (2017)	0.0% (0.0 to 26.8)
Siva et al. (2017)	3.0% (0.0 to 12.5)
Grubb et al. (2018)	9.0% (0.0 to 34.9)
Funayama et al. (2019)	15.4% (0.4 to 41.0)

Table 8. Breakdown of studies for post-SABR change in eGFR in Correa et al. (2019)

Study	Change in eGFR (ml/min) (95% CI)
Wurzer et al. (2012)	NR
Nair et al. (2013)	+6.0 (-10.8 to +22.8)
McBride et al. (2013)	-18 (NR)
Lo et al. (2014)	-6.7 (-20.9 to +7.5)
Hanzly et al. (2014)	Unchanged
Kaidar-Person et al. (2017)	Unchanged
Siva et al. (2017)	-11.5 (-21.4 to -1.6)
Grubb et al. (2018)	NR
Funayama et al. (2019)	-16.7 (-32.7 to -0.7)

Appendix 6: Multivariable analysis of multi-fraction SABR compared to single-fraction SABR (Siva, 2018)

A multivariable analysis by Siva et al. (2018) demonstrated poorer progression-free survival (PFS) (hazard ratio [HR], 1.13; p = .017) and cancer-specific survival (CSS) (HR per one fraction increase, 1.33; p = .011) among patients who received multi-fraction SABR compared to single-fraction SABR. It also demonstrated that larger tumour dimension was associated with poorer PFS (HR per 10 millimetre [mm] increase, 1.16; p > 0.001) and CCS (HR per 10 mm increase, 1.28; p < 0.001). However, the single-fraction SBRT cohort was younger and had smaller tumours. Interaction testing between tumour size and fractionation indicated that they were non-significant for both PFS survival (p = 0.714) and CSS (p = 0.255). With respect to overall survival, the maximum tumour dimension was a significant predictor of death (HR per 10-mm increase, 1.18, p < 0.001).

There was no observed difference in reduction of mean renal function in patients who received single-fraction SABR (-6.1 mL/min) and those who received multi-fraction SABR (-4.9 mL/min; P = .660)

Patients experienced more nausea when treated with single-fraction SABR as opposed to multi-fraction SABR (17.0% vs 6.8%; p = 0.005), although otherwise there was no difference in toxicity (see Table 3 for study details).

No difference was observed between single-fraction (n = 1) and multi-fraction (n = 2) cohorts (p = 0.603) for tumour relapse/recurrence rate.

Appendix 7: Cost effectiveness analysis of SABR in comparison to observation

1. Background and objective

HTW initially planned to develop an economic analysis to estimate the cost effectiveness of stereotactic ablative radiotherapy (SABR) for primary renal cancer in comparison to standard care, such as surgery and invasive ablative techniques. However, the only evidence identified which compared these techniques was a retrospective analysis which showed overall survival after SABR to be statistically significantly lower than after partial nephrectomy or thermal ablation (Uhlig et al. 2020). As such, an economic analysis based on this evidence base was deemed to be of limited value as the likely conclusion of the analysis at the outset i.e. SABR is unlikely to be cost-effective if it is less effective than the comparators. Furthermore, clinical experts suggested the result of Uhlig et al. 2020 should be interpreted with caution as it is possible that those patients treated by radiofrequency ablation could have been fitter patients and/or with smaller tumours than those in the SABR-treated group.

Evidence from Grant et al. (2020) showed the potential for SABR to lead to improvements in overall survival in comparison to observation. Therefore, a de novo economic model was developed to estimate the cost-effectiveness of SABR in comparison to observation in people with primary renal cancer who cannot be managed using surgery or invasive ablation techniques from the perspective of UK NHS and personal social services (PSS).

2. Methods

2.1 Model structure

A de novo economic model was developed to estimate disease progression in people with primary renal cancer who cannot be managed using surgery or invasive ablation techniques. The analysis considered a lifetime horizon with future costs and benefits discounted at 3.5% per year.

The approach adopted in the analysis was a form of partitioned survival analysis. In this analysis, overall survival and progression free survival estimates are used to categorise a cohort of hypothetical patients can be categorised into three distinct groups; alive and progression free, alive with progressed disease and dead (see figure 1). A slight modification was made in this analysis to distinguish between patients that die of disease specific causes and general mortality. The clinical, cost and quality of life (QoL) data used to inform the analysis are described in detail in subsequent sections.

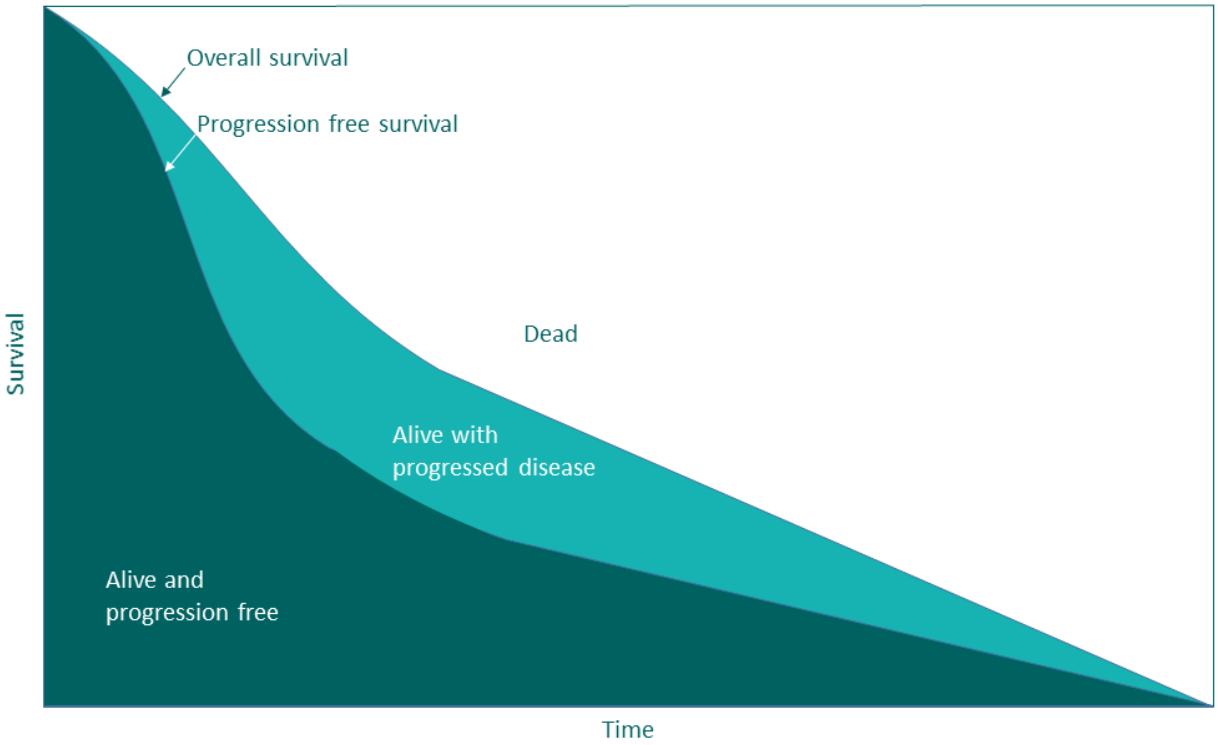


Figure 1. Partitioned survival analysis

2.2 Clinical data

2.2.1 Overall survival

Overall survival estimates for people managed with SABR and observation were based on evidence from Grant et al. (2020). The study showed that 48% of people managed with observation were alive at five years. Overall survival estimates for people treated with SABR were then estimated by applying the treatment effect reported in Grant et al. (2020). The study showed that SABR was associated with a decreased risk of death compared with observation, (HR of 0.56 95%CI: 0.39 to 0.79). Applying this HR results in an overall survival estimate of 67% at five years in people managed with SABR. The overall survival estimates applied in the model for people managed with SABR and observation are shown in figure 2.

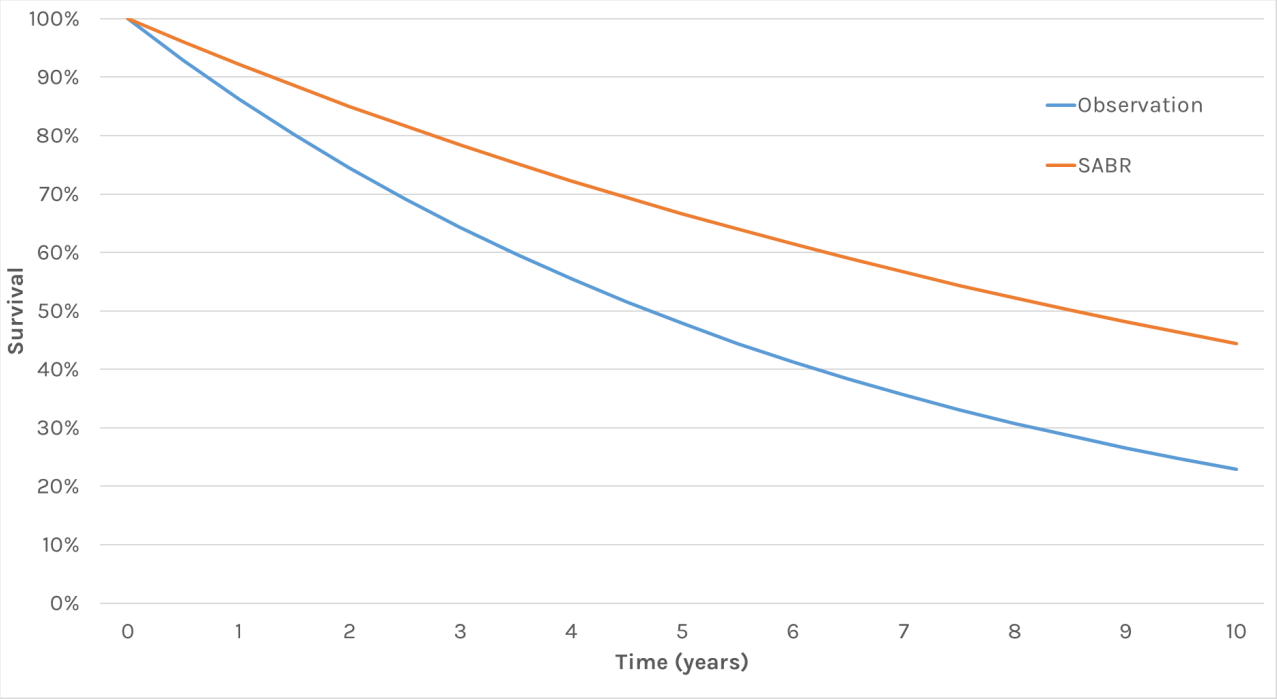


Figure 2. Overall survival estimates applied in the analysis

The overall survival estimates capture general mortality as well as disease specific mortality. General mortality was estimated separately such that it could be subtracted from the overall estimate and the two mortality types could be distinguished.

Life tables for the UK population 2018-20 from the Office for National Statistics (ONS) were used to estimate the general mortality that would be anticipated for the modelled population (Office for National Statistics 2021). The life tables give the general mortality rate for the UK population, based on age and sex. The baseline age and sex of the modelled population was based upon Grant et al. (2020), which reported that 58% of the population were male with an average age of 74 years old.

2.2.2 Progression free survival

Directly comparative evidence was not available for progression free survival and so evidence has been sourced from disparate sources. Progression free survival in people treated with SABR was sourced from Siva et al. (2018), which was a multi-centre pooled analysis of mainly retrospective data in people treated with SABR. The study showed that progression free survival was 65% at four years in people treated with SABR. Progression free survival in people managed with observation was sourced from Metcalf et al. (2021), which analysed data from the Delayed Intervention and Surveillance for Small Renal Masses (DISSRM) registry. The analysis showed that there were 20 progression events in the 68 people undergoing active surveillance over a median follow-up of 4.9 years. This equates to a progression free survival estimate of 71%.

Note that this estimate implies that progression free survival is better in people managed with observation rather SABR. This is most likely a result of using non-comparative data and probably reflects differences in the populations of the two studies. However, in the absence of comparative data, it was determined that the evidence was the most suitable available for the base case analysis. The impact of using alternative estimates was considered in sensitivity analysis.

It should also be noted that in order for the analysis to be coherent, rules were enforced when combining estimates of overall survival and progression free survival from different sources. This reflects that it is not possible for progression free survival to exceed overall survival in people treated with the same intervention. This because 'progression events' include deaths as well as progression to worse disease stages and therefore the mortality captured within overall survival should also be captured within progression. Therefore, in instances where the data from different sources does cause a diversion from this logic, a correction was applied whereby it was assumed that progression free survival was equal to overall survival.

The progression free survival estimates applied in the model for people managed with SABR and observation are shown in figure 3. Note that progression free survival is better in people managed with SABR rather than observation due to the application of a 'correction' as described above.

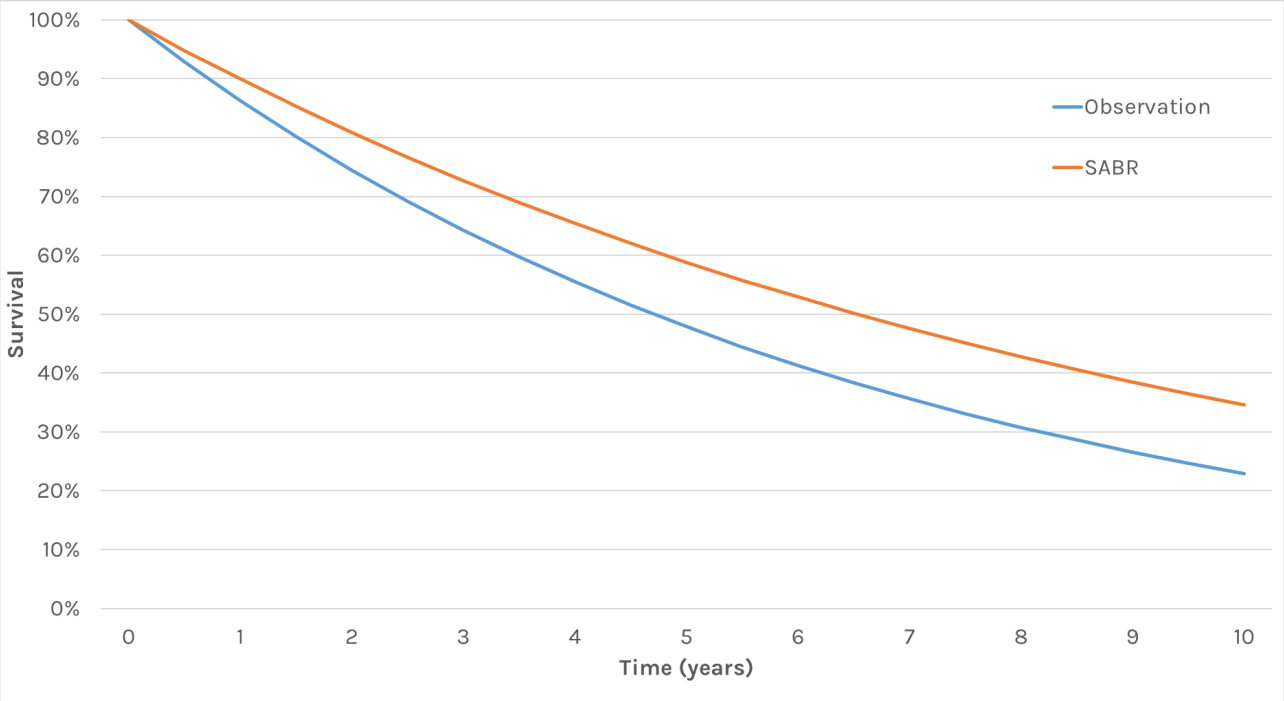


Figure 3. Progression free survival estimates applied in the analysis

2.3 Costs

The costs considered in the model reflect the perspective of the analysis, thus only costs that are relevant to the UK NHS & PSS were included. Where possible, all costs were estimated in 2021 prices.

2.3.1 SABR cost

No UK studies were identified which reported treatment costs for SABR when used to treat primary kidney cancer.

The cost associated with the planning and delivery of SABR was estimated using costs provided through personal communication with the finance department at Velindre Cancer Centre, Wales (for the 2019/2020 cost year). The cost estimates were based upon the use of EHFRT for the treatment of lung cancer, under the advice from experts who advised that the cost was likely to be similar for SABR treatment for kidney cancer. Costs were estimated for a radiotherapy regiment consisting of five 30-minute fractions. This was based upon advice from clinical experts as well as the regimens, which appeared to be most commonly used in the studies included in the clinical evidence review. The cost associated with planning using a CT simulator

was estimated to be £2,754. The cost of delivering a 30-minute fraction of complex radiotherapy was estimated to be £321 (£1,605 for five fractions).

There was some uncertainty around whether fiducial markers would be required when delivering SABR. Clinical experts in Wales advised that fiducial markers are unlikely to be required if a conventional linear accelerator (LINAC) is used but that they would be required when using the CyberKnife system. However, fiducial markers are used more commonly outside of Wales and may become part of standard care in Wales in the near future. Thus, in order to follow a conservative approach and ensure that the full potential costs of SABR are captured, the cost of fiducial markers was included in the cost estimate for SABR. A cost of £722 for fiducial markers was applied in the base case, based on an estimate obtained from the finance department at Velindre Cancer Centre, Wales.

The impact of using alternative estimates for the cost of SABR was explored in sensitivity analysis. This includes scenarios where costs from Jin et al. (2021) were applied. Jin et al. (2021) estimated SABR treatment costs as part of an economic analysis, which aimed to assess the cost effectiveness of SABR in comparison to surgery and radiofrequency ablation in people with oligometastatic live cancer and people with hepatocellular carcinoma. SABR treatments costs were estimated to be £4,433 and £4,807 when used to treat oligometastatic liver cancer and hepatocellular carcinoma, respectively.

2.3.2 Subsequent management costs

The costs of subsequent treatment options for managing metastatic disease were based on costs reported in a previous UK cost-utility analysis of kidney cancer screening by (Rossi et al. 2021). The study estimated annual costs in patients with metastatic disease managed with sunitinib (£16,120), pazopanib (£16,304), everolimus (£25,765), axitinib (£29,543), cabozantinib (£54,002), nivolumab (£57,625), lenvatinib and everolimus (£51,668).

Following the approach adopted in (Rossi et al. 2021), it was assumed that 72% of people with metastatic disease would receive systemic therapy while 28% were assumed to receive no systemic therapy. Of those receiving systemic therapy, 43% were assumed to receive sunitinib. (Rossi et al. 2021) applied this estimate based on data from the Systemic Anti-Cancer Therapy (SACT) Dataset. An average cost based on the other regimens was estimated and applied to the remaining 57% of patients receiving systemic therapy.

2.3.3 Palliative care costs

The cost of palliative care at the end of life was estimated using values reported in 'Unit costs of health and social care 2021' by the Personal Social Services Research Unit (PSSRU) (Jones & Burns 2021). The PSSRU reported the results of research carried out by the Nuffield Trust on behalf of the National End of Life Care Intelligence Network.

The total cost of care services received in the last twelve months of life were estimated for people with various medical conditions using data on health and social care service use patterns in seven local authorities. End of life costs for people diagnosed with cancer (n=19,934) were estimated from to be £11,242 and £1,655 for hospital care and social care, respectively. Thus, a total cost of £12,897 was applied for people dying of disease specific causes in the model.

A limitation of this approach is that it relies upon a cost that is generic to all cancers rather than a specific cost for palliative care in renal cancer. However, in the absence of more robust data, it

has been assumed that palliative care costs in renal cancer would not differ substantially to such costs in other cancer. The influence of changing the cost of palliative care was explored in sensitivity analysis.

2.3.4 Follow-up costs

The costs associated with the routine follow-up of patients with primary renal cancer were not considered in the analysis. Such follow-up would be undertaken in patients managed with both SABR and observation and it was therefore deemed unnecessary to consider in the analysis.

2.4 Health-related quality of life

As recommended in the NICE reference case, the model estimates effectiveness in terms of quality adjusted life years (QALYs). These are estimated by combining life year estimates with quality of life (QoL) values associated with being in a particular health state.

Quality of life values were sourced from a previous UK cost-utility analysis of kidney cancer screening by (Rossi et al. 2021). The quality of life associated with being progression free was based on values reported for newly diagnosed stage I T1a or T1b disease (0.934). The quality of life implications associated with recurrence and progressive disease were also sourced from (Rossi et al. 2021), which presented quality of life values in people with stage IV disease in first and subsequent treatment lines.

Table 1 presents the QoL values applied in the economic analysis.

Table 1. Quality of life values

Health state	QoL value	Source
Progression free	0.934	Rossi et al. (2021) (values for T1a and T1b disease)
Progression		
Stage IV - first line	0.780	Rossi et al. (2021)
Stage IV - second line	0.700	Rossi et al. (2021)
Stage IV - third line	0.700	Rossi et al. (2021)
Stage IV, fourth line	0.690	Rossi et al. (2021)
Progressive disease	0.610	Rossi et al. (2021)

QoL: quality of life

3. Results

3.1 Base case results

The base case results of the analysis are shown in Table 2. The results show SABR to be more effective (2.23 QALYs) and more costly than observation (£3,736). The resulting ICER of £1,675 per QALY is below the commonly applied threshold of £20,000 per QALY, indicating that SABR is cost effective.

The key driver of the results of the analysis is the improved effectiveness of SABR in comparison to observation, which is driven by the improvements in overall survival reported in Grant et al. (2020).

Table 2. Base case results

Treatment strategy	Cost		QALYs		ICER (cost per QALY)
	Total	Incremental	Total	Incremental	
Observation	£8,898	-	9.85	-	-
SABR	£12,634	£3,736	12.08	2.23	£1,675

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year; SABR: stereotactic ablative radiotherapy

3.2 Deterministic sensitivity analysis results

A series of deterministic sensitivity analyses were conducted, whereby an input parameter is changed, the model is re-run and the new cost-effectiveness result is recorded. This is a useful way of estimating uncertainty and determining the key drivers of the model result. The results of the deterministic sensitivity analyses are presented in Table 3.

It can be seen that the analysis was insensitive to the variations considered within the sensitivity analysis. The conclusion of the analysis did not change in any of the alternative scenarios with SABR found to be cost effective in all modelled scenarios.

Table 3. Deterministic sensitivity analysis results

Modelled scenario	ICER result (cost per QALY)
Base case	£1,675
Upper HR for overall mortality (0.39)	£1,516
Lower HR for overall mortality (0.79)	£3,246
Assume equivalent PFS in observation and SABR treatment arms	£595
SABR cost of £4,433 (oligometastatic liver cancer in Jin et al. (2021))	£1,384
SABR cost of £4,807 (hepatocellular carcinoma in Jin et al. (2021))	£1,552
No fiducial markers included in SABR costs	£1,351
Assumed 3 fractions of SABR	£1,387
Assumed 7 fractions of SABR	£1,962
SABR cost 50% higher	£2,813
SABR cost 50% lower	£536
Assume 100% of patients with metastatic disease receive systemic therapy	£1,987
Average of all systemic therapy costs used for all patients treated	£1,939
Palliative care costs with health costs only (£11,242)	£1,853
No palliative care costs	£3,062
QoL for progression free disease = 0.869 (value for stage II-III disease in Rossi et al. (2021)	£1,664
QoL for stage IV – first line applied for all progressive disease	£1,680

ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life-year; SABR: stereotactic ablative radiotherapy; HR: hazard ratio; QoL: quality of life

3.3 Probabilistic sensitivity analysis results

Probabilistic sensitivity analysis (PSA) was conducted to assess the combined parameter uncertainty in the model. In this analysis, the mean values that were utilised in the base case were replaced with values drawn from distributions around the mean values. The results of 10,000 runs of the PSA are shown using ICER scatterplots and cost-effectiveness acceptability curves (CEAC). The ICER scatter plots show the incremental costs and QALYs associated with each of the 10,000 runs of the PSA along with the mean result. The CEAC graphs show the probability of each strategy being considered cost effective at the various cost-effectiveness thresholds on the x axis.

Figure 4 shows the ICER scatterplot for SABR in comparison to observation. It can be seen that the vast majority of the results reside in the northeast quadrant of the graph, indicating that CXL is more costly and more effective than standard treatment in most modelled scenarios.

Figure 5 shows the CEAC for SABR in comparison to observation. It can be seen that the probability of SABR being cost effective increases as the cost-effectiveness threshold increases. At a threshold of £20,000 per QALY, SABR was found to have a 100% probability of being cost effective while observation was found to have a 0% probability of being cost-effective.

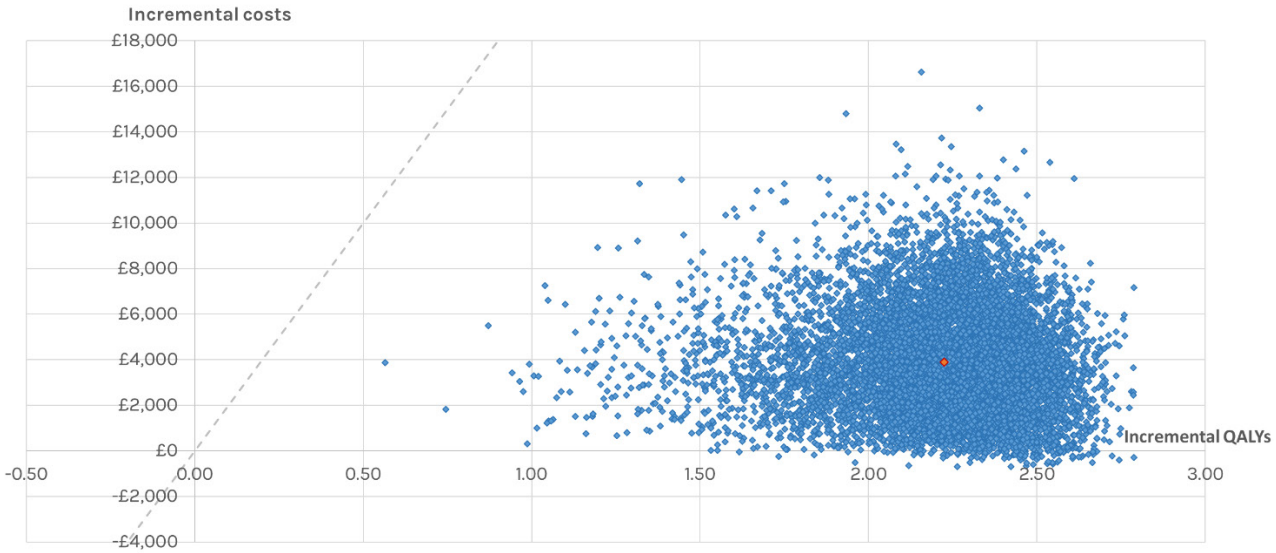


Figure 4. ICER scatterplot for SABR compared to observation

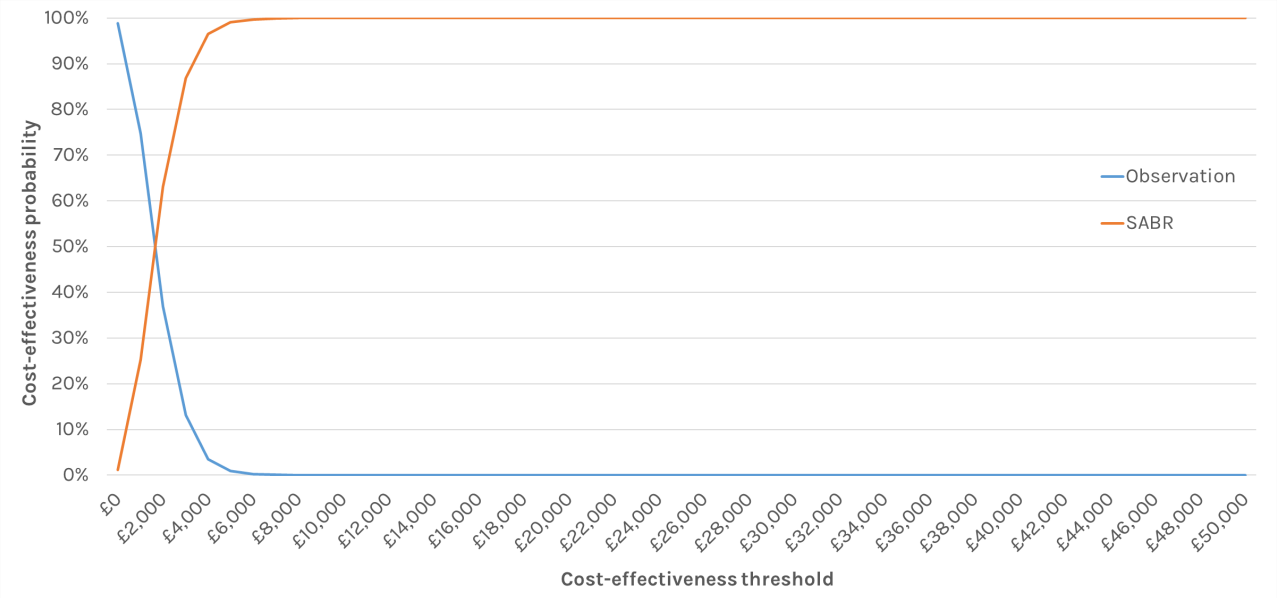


Figure 5. Cost-effectiveness acceptability curves for SABR in comparison to observation