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Cost-effectiveness analysis of stereotactic body radiation therapy compared with surgery and radiofrequency ablation in two patient cohorts: metastatic liver cancer and hepatocellular carcinoma *(Accepted by Clinical Oncology on 26 August 2020)*

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Abstract

Purpose: To compare the cost-effectiveness of stereotactic body radiation therapy (SABR) with radiofrequency ablation (RFA) and surgery in adult patients with metastatic liver cancer and hepatocellular carcinoma (HCC).

Materials and methods: Two patient cohorts were assessed: liver oligometastases and HCC. For each patient cohort, a decision analytic model was constructed to assess the cost-effectiveness of interventions over a 5-year horizon. A Markov process was embedded in the decision model to simulate the possible prognosis of cancer. Data on transition probabilities, survival, side-effects, quality of life, and costs were obtained from published sources and the Commissioning through Evaluation (CtE) scheme. The primary outcome was the incremental cost-effectiveness ratio (ICER) with respect to quality adjusted life-years. The robustness of the results was examined in sensitivity analysis. Analyses were conducted from an NHS and Personal Social Services perspective.

Results: In the base case analysis, which assumes that all three interventions are associated with the same cancer progression rates and mortality rates, SABR is the most cost-effective intervention for both patient cohorts. This conclusion is sensitive to the cancer progression rate, mortality rate and cost of interventions. Assuming a willingness-to-pay threshold of £20,000 per QALY, the probability that SABR is cost-effective is 57% and 50% in liver oligometastases and HCC, respectively.

Conclusions: Our results indicate a potential for SABR to be cost-effective for patients with liver oligometastases and HCC. This finding supports further investigation in clinical trials directly comparing SABR with surgery and RFA.

Key words: cost-effectiveness analysis; stereotactic body radiation therapy; radiofrequency ablation; surgery; liver oligometastases; hepatocellular carcinoma

Introduction

For patients with liver oligometastases and hepatocellular carcinoma (HCC), the accepted treatment options include surgical resection, systemic treatments and local ablative treatments such as radiofrequency ablation (RFA) in case of liver malignancies. Surgery is the preferred treatment option for patients with liver disease. Tumour burden and location, liver function and overall functional status are key factors when surgery is considered and ablative methods (such as RFA) are accepted alternatives in patients that cannot undergo surgery. In cases when standard treatment options are not feasible due to functional status or tumour location, or may result in high toxicity rates, Stereotactic Ablative Body Radiotherapy (SABR) – an emerging radiation technology – can be considered as an alternative treatment option. SABR delivers a high, biologically effective dose (BED) to the tumour while minimising the dose received by normal tissues, and thus could potentially minimise radiotherapy treatment toxicity and side effects. In addition, as the technique uses a smaller number of fractions (and, consequently, requires a smaller number of hospital visits) than standard fractionated radiotherapy, it may provide the opportunity for financial savings and improved patient experience. In the light of this, SABR is increasingly being considered as an alternative to surgery or RFA [1, 2].

Despite the potential of SABR, there is limited high level evidence of its effectiveness. In the UK extracranial SABR is currently only commissioned by National Health Service (NHS) England for early stage non-small cell lung cancer. In 2015, NHS England launched the Commissioning through Evaluation (CtE) scheme for SABR in order to address this evidence gap. The CtE programme provides funding to enable patients to access promising new treatments, whilst data is collected within a formal evaluation programme [3]. The resulting evaluation informs a review of clinical commissioning policy. The SABR CtE scheme included patients with a number of different diagnoses. A detailed description of the SABR CtE scheme is provided here [4].

This study examines the cost-effectiveness of SABR as an alternative to surgery or RFA in patients with HCC or liver oligometastases. Treatment outcomes following SABR were informed by data collected by the SABR CtE scheme. Data from the literature informed outcomes of surgery and RFA. This study was reported according to the CHEERS recommendations for reporting health economic evaluations [5].

Material and methods

Population & Intervention

This analysis compared the cost-effectiveness of SABR with surgery and RFA in two subgroups of the patients included in the SABR CtE scheme: those with HCC; and liver oligometastases. Costs and outcomes over a period of five year were estimated using a Markov model to simulate outcomes following each of the treatment strategies. The primary outcome was quality adjusted life-years (QALYs); QALYS are a composite measure of quality of life and survival [6]. This is the recommended outcome for decision making by the National Institute for Health and Care Excellence (NICE) in the United Kingdom (UK) [7]. Acceptable thresholds with regard to the additional cost per unit gain in health are £20,000-£30,000 per QALY [7]. This study applied the perspective of the NHS and Personal Social Services, as recommended by NICE [8].

Parameters to populate the model were taken from the literature, and for SABR, from the CtE scheme. The inclusion criteria of the XXXX are summarised below and reported in detail in Appendix B:

- Cancer diagnosis established with histology or cytology
- No chemotherapy within 28 days.
- At least 6 months disease free interval from primary diagnosis or previous radiotherapy treatment.
- Expected life expectancy > 6 months.
- WHO performance status $\leqslant$ 2.

Model structure

The Markov model applied to both patient subgroups is illustrated in Fig. 1. Patients enter the model following initial treatment with either SABR, surgery, or RFA. Each circle represents a health state and arrows represent possible transitions at the end of each monthly time cycle. The model allows for the occurrence of severe adverse events (SAEs) after treatment and the possibility of retreatment after local progression. Patients who experience distant/regional progression will receive palliative care. SAEs were defined as Grade 3 (severe or medically significant) or Grade 4 toxicities (life-threatening consequences), as measured by Common Terminology Criteria for Adverse Events (CTCAE) [9]. Mortality is also captured in the model structure. Decision analytic models were developed using TreeAge 2014 (TreeAge Software, Williamstown, MA).

Input data

The model required input parameters for transitions between health states, treatments costs, and health related quality of life in each health state. Data were taken from the SABR CtE scheme and from the literature. We

undertook an extensive search to source appropriate parameters for the model, the details of which are reported in Appendix A.

The key clinical inputs to the model inform cancer progression, mortality, probability of retreatment, and probability of SAEs. Due to a lack of head to head comparisons between SABR and other treatment modalities, the base case analysis assumed that cancer progression rates and mortality rates did not differ by treatment modality; studies reporting surgery were used to estimate progression and mortality rates for all three intervention strategies. In order to differentiate progression and mortality according to cancer stage we estimated parameters by calibration to match reported outcomes (details see Appendix C). Hence our base case analysis assumed that SABR and RFA achieve similar mortality and progression rates to those observed after surgery. We relaxed this assumption in sensitivity analyses in which cancer progression and mortality rates were allowed to vary by treatment modality. For surgery and RFA, the probability of retreatment and the probability of SAEs were obtained from published literature. Given the limited literature on SABR, the probability of retreatment and probability of SAEs for patients who received SABR were obtained from the SABR CtE scheme.

Unit costs were predominantly obtained from the NHS reference costs 2015-16 [10] or the Unit Costs of Health and Social Care 2016 [11]. Where appropriate, costs were uplifted to 2015/16 values using healthcare inflation indices [11]. The cost components considered in the model include initial treatment (SABR, RFA or surgery), treatment for SAEs, outpatient follow-up, retreatment, and palliative chemotherapy for patients with regional/distant progression. The cost of SABR, according to the number of units delivered, was taken as the agreed NHS England tariff [12]. The mean number of units delivered in each patient subgroup was calculated from data from the SABR CtE scheme. The costs for RFA or surgery were obtained from published literature.

The model required utility weights for four health states: progression free without SAEs, progression free with SAEs, local progression, and regional/distant progression. The utility weights for health state ‘progression free without SAEs’ were obtained from data collected from the relevant patient subgroup in the SABR CtE scheme. The utility weights for the other three health states were derived from published literature.

A summary of the key parameters used in the models for each cancer subgroup is reported in Table 1. A summary of all parameters used in the models, including their fixed values, ranges, distributions and sources, is reported in Appendix C.

Cost-effectiveness analysis

The models estimated costs and QALYs over the relevant time horizon for each patient subgroup after discounting costs and outcomes at 3.5% p.a., the recommended discount rate for the UK [7]. Patients accrued costs for initial and retreatment of tumours (surgery, RFA or SABR), hospital-bed days, outpatient follow-ups, treatment of SAEs, and palliative cancer care. Patients accrued QALYs in each health state as the product of the quality of life tariff attached to the health state and the time spent in that health state. Each model was fully probabilistic; a distribution reflecting underlying uncertainty was specified for each parameter and a value for each parameter sampled from the respective distribution prior to evaluating each model. Mean costs and mean QALYs for each treatment strategy are reported after 5,000 simulations for each model. Details on the probabilistic analysis and the specification of distributions for each interval are provided in Appendix C.

Cost-effectiveness is reported as the incremental cost-effectiveness ratio (ICER) and the cost-effectiveness acceptability curve (CEAC) [7]. The ICER is the ratio of the additional cost divided by the additional effectiveness of a treatment strategy compared to the next most effective strategy. Where one strategy is more effective and less costly than a comparator, the comparator is dominated. Where three strategies are compared, the strategy ranked in the middle for effectiveness may be less effective and more costly than some combination of the most and the least effective strategy. Such a strategy is extendedly dominated. We excluded dominated and extendedly dominated strategies prior to calculating ICERs, as recommended [7]. The CEAC is the plot of the likelihood an intervention is cost-effective as the value placed on the outcome is varied. We calculated the proportion of the 5,000 simulations for which each intervention had the highest net monetary benefit (NMB) across a range of values for a QALY from zero to £50,000. The NMB is calculated by multiplying QALYs by the monetary value of a QALY and the subtracting the cost. The strategy with the highest NMB is the most cost-effective at that value of a QALY. The CEAC captures the overall impact of sampling uncertainty; the impact changes as the value of a QALY varies.

Additional sensitivity analysis

In additional to the probabilistic analysis which captures the impact of joint uncertainty in model parameters, we undertook structural sensitivity analysis to test the impact of modelling assumptions. In the base case we assumed no difference in mortality or cancer progression rates according to treatment modality. In structural sensitivity analysis we assumed that different treatment modality is associated with different mortality and/or different cancer progression rates. We also report one-way sensitivity analysis to quantify the robustness of results to variation in individual parameters. Further details are provided in Appendix C.

Model verification and validation

Model verification and validation steps included: checking appropriateness of the model structure and input data, comparing the model outputs with source data for calibration (Appendix D), testing extreme values, checking the plausibility of results with clinical experts in oncology, and comparing results of the model with published literature (reported in the "Discussion" section).

Results

Between 2015 and 2018, the SABR CtE scheme collected outcomes from 101 patients with liver oligometastases and 88 patients with HCC from 17 centres in England. The baseline demographics and clinical information of patients for both patient cohorts are reported in Table 2.

Base case, structural sensitivity analysis and PSA

The results of base-case analysis and structural sensitivity results for patients with liver oligometastases and HCC are reported in Table 3 and 4, respectively. The base case results showed that:

- For patients with liver oligometastases, SABR dominates all other interventions;
- For patients with HCC, SABR dominates surgery, and is less effective and less expensive compared to RFA. However, the ICER of RFA compared to SABR (£516,974 per QALY) exceeds the NICE £20,000 willingness-to-pay threshold. Therefore, SABR is considered the most cost-effective intervention.

The base case analysis assumes similar survival and cancer progression across all three treatment modalities. The results for liver oligometastases are driven by a lower probability of SAEs, and the higher probability of receiving re-treatment after SABR compared with surgery or RFA. For HCC patients the probability of SAEs

was slightly higher after SABR than after RFA; the difference was sufficient to generate slightly more QALYs after RFA compared to SABR, but the QALY gain was insufficient to justify the additional cost of RFA.

The results were sensitive to structural assumptions on mortality and cancer progression rates. For patients with liver oligometastases, SABR remained cost-effective when mortality rates were estimated independently for each treatment strategy; when cancer progression rates were estimated independently for each treatment strategy surgery became cost-effective. For patients with HCC, surgery was the most cost-effective treatment strategy when either mortality or cancer progression were estimated independently for each treatment strategy.

In summary, analysis indicates that SABR is potentially cost-effective in patients with liver oligometastases if it can achieve cancer progression rates similar to rates expected from surgery. In patients with HCC, SABR would need to achieve similar cancer progression and mortality rates to surgery or RFA to become a cost-effective alternative treatment.

The CEACs for the base case analysis are shown in Fig. 2. Both show considerable uncertainty. At a value of £20,000 per QALY the probability that SABR is most cost-effective is 57% and 50% for patients with liver oligometastases and HCC, respectively.

One-way sensitivity analysis

The results of one-way sensitivity analysis are reported in detail in Appendix E. results were most sensitive to the cost of SABR and RFA. For patients with liver oligometastases, RFA became cost-effective when the cost difference between RFA and SABR reduced by around £550. For patients with HCC, RFA became cost-effective when the cost difference between RFA and SABR reduced by around £212.

Discussion

The main findings and interpretation

Our findings indicate a potential for SABR to be cost-effective in the treatment of liver oligometastases if treatment can achieve similar cancer progression rates to those obtained through surgery in that patient group. In patients for whom surgery is not feasible, SABR offers a superior alternative to RFA. The results for patients with HCC show greater uncertainty; SABR would need to achieve similar cancer progression and mortality rates

to surgery or RFA to be a cost-effective alternative to these treatments. These findings need to be considered with regard to the patient population which provided data on SABR. Patients eligible for the SABR CtE scheme were those considered unsuitable for surgery. It is possible that cancer progression is elevated in this population. It is also possible that mortality rates are raised when compared to patients who are suitable for surgery. Hence we might expect SABR to generate better outcomes in patients suitable for surgery. These findings strengthen the case for a clinical trial comparing treatment modalities in patients with liver oligometastases, and for a trial comparing SABR with RFA in patients with HCC who are unsuitable for surgery.

There is some limited evidence in the literature, albeit in patients with pulmonary metastases, that treatment with SABR can result in equivalent survival to surgery [13-15]. Two of the studies [13, 15], used propensity scoring to account for the differences between SABR and the comparator. In addition, overall survival achieved with SABR reported in these studies is comparable to survival in the largest international retrospective pulmonary metastasectomy analysis, which reports 1- and 2-year survival rates for complete resection of approximately 85% and 70%, respectively [16]. More recent studies have reported similar findings [17]. Similar survival outcomes were reported for patients with HCC treated with RFA or SABR after matching on propensity scores. Wahl *et al.* (2016) reported overall survival (OS) at 1 and 2 years of 70% and 53% after RFA and 74% and 46% after SABR in patients with inoperable and not metastatic HCC [18]. Parikh *et al.* (2018) reported similar survival outcomes in patients with non-metastatic stage I or II HCC treated with SABR or RFA [19]. Rajyaguru *et al.* (2018) analysed patients' data with inoperable not metastatic HCC using the National Cancer Database, which includes about 70% of all newly diagnosed patients with cancer in the United States who had undergone SABR or RFA as their primary treatment [20]. In the propensity score matched analysis, RFA was associated with a significant OS benefit (HR 0.67; 95% CI 0.55-0.81; $p<0.001$). However, there was no difference in OS between the two cohorts after excluding 36% of the patients in the SABR cohort (n = 296) who were treated with lower than standard radiotherapy dose [21].

Comparing with existing evidence on cost-effectiveness

The literature on cost-effectiveness of alternative treatments for liver oligometastases is limited. A health technology assessment comparing surgery and RFA for patients with surgically resectable aligometastases found that surgery was cost-effective due to a higher survival rate [22]. A recent US study compared SABR with RFA in unresectable liver oligometastases and found SABR is associated with an ICER of $164,660 per QALY

gained [23]. In a US setting, SABR was found to be more expensive than RFA but to provide 0.05 more QALYs. Both studies report findings broadly in line with our results, albeit our costs for SABR were based on UK evidence which suggests lower costs than those for RFA. The literature on HCC is more extensive. In HCC patients meeting the Milan criteria, surgery was found to be cost-effective compared with RFA in patients for whom it conveyed a survival advantage; in very early stage HCC where survival was similar, RFA was cost-effective [24]. Comparison of SABR with RFA in which permutations of both treatments as first and second line therapies were compared found that SABR as first and second line treatment generated the highest cost but the highest QALYs [25]. Again, the difference between these findings and ours is driven predominantly by an assumption of much higher costs for SABR compared to RFA. Two studies compared treatment modalities for HCC using observational data rather than a Markov model. Analysis of a matched sample of patients from the SEER-Medicare database found no significant difference in costs between patients treated with RFA and SABR [26]. Analysis of patients in the Ontario cancer registry generated an ICER of $470,000 CAD for surgery compared to SABR. The analysis found an incremental gain of 0.145 QALYs for surgery, larger than any we found, but the use of regression may have been insufficient to fully control for differences in case mix.

Strengths and limitations

There are three strengths of our study. Firstly, to our knowledge, this study presents the first economic analysis which compares surgery, RFA and SABR for people with liver oligometastases and HCC. Secondly, the clinical data for comparators (surgery and RFA) were carefully selected from the best evidence sources identified from the literature review, while the clinical data for SABR were mainly obtained from a large national UK study. The SABR CtE scheme prospectively recruited and analysed a contemporary cohort of patients with predefined intervention and timepoints for assessments. Thirdly, extensive structural sensitivity analyses have been conducted to test the robustness of the base case conclusion under different assumptions and different sets of input data, in addition to capturing parameter uncertainty in a fully probabilistic model.

There are a number of limitations of the economic analyses presented here, the majority of which derive from limitations in the evidence base. The principal limitation is the lack of randomised clinical evidence comparing SABR with surgery or RFA. We utilised evidence on SABR from a cohort that would not have been eligible for surgery or RFA. It seems likely that mortality will be higher in this group compared to patients eligible for surgery and RFA, and progression of disease may be faster. We tested alternative assumptions on mortality and cancer progression in sensitivity analysis, and cost-effectiveness is sensitive to these assumptions. The existing

evidence base on surgery and RFA is also subject to limitations. A lack of granularity in the evidence on mortality and cancer progression rates for patients receiving surgery or RFA necessitated estimation of these parameters by calibration of the models to published data to reflect the impact of progression status on rates. We considered a limited range of treatments to keep the analysis tractable. In practice, these treatments may be supplemented with others, notably systemic therapies. We had no direct comparative data on quality of life after different treatment modalities and assumed that any difference in quality of life arose purely from a difference in the incidence of adverse events. In addition, we lacked data on the relative impact of different adverse events on quality of life and so we did not differentiate the impact of different Grade 3 or 4 toxicities. Our estimates of the cost of SABR are based on the agreed remuneration tariffs for SABR CtE scheme, which may or may not reflect the true cost of the procedure in the UK NHS. The cost of RFA procedure was uplifted from a previous HTA due to lack of more recent data [22].

Conclusions

Our analyses indicated a potential for SABR to be cost-effective for adult patients with liver oligometastases and HCC. This finding hinges on an assumption of similar local control and overall survival rates for SABR when compared to surgery or RFA, and therefore should be interpreted with caution. Evidence from randomised trials directly comparing SABR with surgery and RFA is required to robustly demonstrate the cost-effectiveness of SABR.

Data Statement

All data generated or analysed during this study are included in this published article and supplementary material.

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Table 1-4

Table 1 Summary of key input data*

Parameters	Liver oligometastases		HCC	
	Value	Reference	Value	Reference
Cancer progression rates (monthly)				
No progression to local progression	2.10%	Calibrated from de Haas et al [27]	1.12%	Calibrated from Tabrizian *et al.* [28]
No progression to regional/distant progression	0.93%	As above	0.16%	As above
Local progression to regional/distant progression	3.58%	As above	0.90%	As above
Mortality rates (monthly)				
Operative mortality	0.00%	[29]	0.00%	[30, 31]
Patients with no progression	0.13%	Calibrated from de Haas et al [27]	0.26%	Calibrated from Lee *et al.* [32]
Patients with local progression	1.55%	Calibrated from de Haas et al [27] and mortality rate for patients with other progression status	3.21%	Calibrated from Grieco *et al.* [33]
Patients with regional/distant progression	3.06%	Rees et al [34]	12.65%	As above
Probability of retreatment (monthly)				
For patients receiving surgery	30.74%	[35-37]	25.09%	[38]
For patients receiving RFA	34.78%	[39-44]	69.46%	[45]
For patients receiving SABR	As above	As above	As above	As above
SAEs (monthly)				

Parameters	Liver oligometastases		HCC	
	Value	Reference	Value	Reference
Probability of SAEs after surgery	16.55%	Calculated from Kim et al [46]	5.56%	Calculated based on probability of developing SAEs for RFA and Wang *et al.* [47]
Probability of SAEs after RFA	5.08%	As above	1.00%	[25]
Probability of SAEs after SABR	2.97%	SABR Commissioning through Evaluation (CtE) scheme	4.55%	CtE scheme
Cost of interventions				
Cost of surgery (initial treatment)	£6,938.15	NHS reference cost 2015-16 [10]	£6,272.87	NHS reference cost 2015-16 [10]
Cost of surgery (retreatment)	As above	As above	As above	As above
Cost of RFA (initial treatment and retreatment)	£4,961.46	Uplifted from Loveman et al [22] and adjusted for days of additional hospital stay [46]	£5,089.17	Uplifted from Loveman *et al.* [22] and adjusted for days of additional hospital stay [47]
Cost for SABR (initial treatment and retreatment)	£4,433.00	[12]	£4,807.00	As above [48]
Cost of treating SAEs				
Cost of treating SAEs	£557.49	Uplifted from Loveman et al [22]	£2,849	[49]
Utility				
Progression free without SAEs	0.86	CtE scheme and other published data [50-52]	0.74	CtE scheme, Lim *et al.* [53]
Progression free with SAEs	0.40	[52, 54, 55]	0.50	[56, 57]
Local progression	0.65	[52, 54, 55]	0.63	[24]

Parameters	Liver oligometastases		HCC	
	Value	Reference	Value	Reference
Regional/ distant progression	0.19	[52, 54, 55]	0.40	[58]

Footnotes:

* A complete list of all parameters used in the model, their fixed values, ranges, distributions and references are reported in Appendix B.

Table 2 Baseline demographics and clinical information of patients with liver oligometastases and hepatocellular carcinoma (HCC)

	Liver oligometastases (n=101)	HCC (n=88)
Age (years)		
Median (interquartile range)	69 (62-76)	72 (67-80)
Sex - N (%)		
Male	947 (66.6%)	66 (72.5%)
Female	475 (33.4%)	25 (27.5%)
Ethnicity - N (%)		
White - British	1,094 (76.9%)	61 (72.5%)
Others	328 (23.1%)	25 (27.5%)
WHO performance status - N (%)		
0 - Fully active, able to carry on all pre-disease performance without restriction	1,000 (76.9%)	28 (72.5%)
1 - Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work	342 (24.1%)	50 (54.9%)
2 - Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours	64 (4.5%)	13 (14.3%)
Not reported	16 (1.1%)	0 (0.0%)
Prior systemic therapy - N (%)		
Yes	850 (59.8%)	29 (31.9%)
No	572 (40.2%)	62 (68.1%)
Primary tumour diagnosis		
Prostate cancer	406 (28.6%)	N/A
Colon cancer	233 (16.4%)	N/A
Rectal cancer	164 (11.5%)	N/A
Renal cancer	143 (10.1%)	N/A
Breast cancer	78 (5.5%)	N/A
Lung cancer	64 (4.5%)	N/A
Other	334 (23.5%)	N/A

Table 3 Base case and structural sensitivity analyses for patients with liver oligometastases*

Intervention	Cost (£)	QALY	Incremental cost	Incremental QALY	ICER	Ranking of NMB (WTP=£20,000 per QALY)	Ranking of NMB (WTP=£30,000 per QALY)
Base case results							
SABR	16,863	2.5601	–	–	Dominating	1	1
RFA	17,496	2.5596	–	–	Dominated	2	2
Surgery	19,775	2.5387	–	–	Dominated	3	3
SA 1: Different cancer progression rate for patients receiving different interventions † (base case assumes same cancer progression rate for all three interventions)							
SABR	28,378	1.5626	–	–	Dominated	2	2
RFA	29,024	1.5620	–	–	Dominated	3	3
Surgery	21,898	2.2848	–	–	Dominating	1	1
SA 2: Different morality rate for patients receiving different interventions ‡ (base case assumes the same mortality rate for all three interventions)							
SABR	18,332	2.2430	189	0.1039	1,821	1	1
RFA	18,142	2.1391	–	–	–	2	2
Surgery	21,898	2.2848	3,566	0.0418	85,354	3	3
SA 3: Different mortality rate for patients who received different interventions. § Mortality for SABR was assumed to be the same as RFA.							
SABR	17,528	2.1396	–	–	–	1	1
RFA	18,142	2.1391	–	–	Dominated	2	3
Surgery	21,898	2.2848	4,370	0.1451	30,111	3	2
*SA 4: Different cancer progression rate and different mortality rate for patients receiving different interventions ** (base case assumes same cancer progression rate and same mortality rate for all three interventions)*							
SABR	27,418	1.5307	–	–	Dominated	2	2
RFA	26,755	1.4667	–	–	Dominated	3	3

Surgery	21,898	2.2848	–	–	Dominating	1	1

Abbreviations: ICER: Incremental cost-effectiveness ratio; NMB: net monetary benefit; QALY: quality-adjusted life of years; SA: sensitivity analysis; WTP: willingness to pay threshold.

Footnotes:

* Within each analysis, the intervention in bold is the intervention which is considered to be most cost-effective under the NICE £20,000 per QALY decision rule.

† Assuming different cancer progression rate for patients receiving different interventions. The cancer progression rates for patients who received surgery were calibrated from published literature (Table 1). The cancer progression rate for patients who receiving SABR was obtained from CtE scheme: no progression to local recurrence (Weibull distribution, η=1.000, β=1.4928), no progression to regional/distant recurrence (exponential distribution monthly transition rate=3.99%). The cancer progression rate for patients receiving RFA was assumed to be the same as SABR due to lack of data.

‡ Assuming different mortality rates for patients receiving different interventions. The monthly mortality rate for patients receiving surgery was obtained from published literature (0.87% per month) [27]. The monthly mortality rate for patients receiving RFA was calculated based on a recent published meta-analysis: mortality relative risk (RFA vs surgery): 1.361 [59]. The mortality rates up to 2 years for patients receiving SABR was obtained from the CtE scheme (exponential distribution, monthly mortality rate=0.90%). The mortality rate post two years for patients receiving SABR was assumed to be the same as patients who receiving RFA.

§ Assuming different mortality rates for patients receiving different interventions. The monthly mortality rate for patients receiving surgery was obtained from published literature (0.87% per month) [27]. The monthly mortality rate for patients receiving RFA was calculated based on a recent published meta-analysis: mortality relative risk (RFA vs surgery): 1.361. The mortality rate for patients receiving SABR was assumed to be the same as patients receiving RFA.

** Assuming different cancer progression rate and different mortality rate for patients receiving different interventions. The cancer progression rates for patients who received surgery were calibrated from published literature. The cancer progression rate for patients who receiving SABR was obtained from the CtE scheme: no progression to local recurrence (Weibull distribution, η=1.000, β=1.4928), no progression to regional/distant recurrence (exponential distribution monthly transition rate=3.99%). The cancer progression rate for patients receiving RFA was assumed to be the same as SABR due to lack of data. The monthly mortality rate for patients receiving surgery was obtained from published literature (0.87% per month) [27]. The monthly mortality rate for patients receiving RFA was calculated based on a recent published meta-analysis: mortality relative risk (RFA vs surgery): 1.361 [59]. The mortality rates up to 2 years for patients receiving SABR was obtained from the CtE scheme (exponential distribution, monthly mortality rate=0.90%). The mortality rate post two years for patients receiving SABR was assumed to be the same as patients who receiving RFA.

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3

4 **Table 4 Base case and structural sensitivity analyses for patients with hepatocellular carcinoma (HCC)***

Intervention	Cost (£)	QALY	Incremental cost	Incremental QALY	ICER	Ranking of NMB (WTP=20,000 per QALY)	Ranking of NMB (WTP=30,000 per QALY)
Base case results							
SABR	10,979	2.8334	–	–	–	1	1
RFA	11,261	2.8340	281	0.0005	516,974	2	2
Surgery	11,571	2.7008	–	–	Dominated	3	3
SA 1: Assuming different cancer progression rate for patients receiving different interventions † (base case analysis assumes same cancer progression rate for all three interventions)							
SABR	13,533	2.6624	–	–	Dominated	3	3
RFA	12,553	2.8682	–	–	Dominated	2	2
Surgery	12,489	2.8795	–	–	Dominating	1	1
SA 2: Assuming different mortality rates for patients receiving different interventions ‡ (base case analysis assumes same mortality rate for all three interventions)							
SABR	10,552	2.4522	–	–	–	3	3
RFA	11,132	2.5811	580	0.1289	4,498	2	2
Surgery	12,489	2.8795	1,357	0.2984	4,548	1	1
SA 3: Assuming the same mortality rate for RFA and SABR, and a different mortality rate for patients receiving surgery § (base case analysis assumes same mortality rate for all three interventions)							
SABR	10,856	2.5806	–	–	–	2	2
RFA	11,132	2.5811	–	–	Extendedly dominated	3	3
Surgery	12,489	2.8795	1,357	0.2984	4,548	1	1
*SA 4: Different cancer progression rate and different mortality rate for patients receiving different interventions ** (base case assumes same cancer progression rate and same mortality rate for all three interventions)*							

Intervention	Cost (£)	QALY	Incremental cost	Incremental QALY	ICER	Ranking of NMB (WTP=20,000 per QALY)	Ranking of NMB (WTP=30,000 per QALY)
SABR	12,159	2.2607	–	–	Dominated	3	3
RFA	11,661	2.5403	–	–	–	2	2
Surgery	12,489	2.8795	828	0.3392	£2,440	1	1

Abbreviations: ICER: Incremental cost-effectiveness ratio; NMB: net monetary benefit; QALY: quality-adjusted life of years; SA: sensitivity analysis.

Footnotes:

* Within each analysis, the intervention in bold is the intervention which is considered to be most cost-effective under the NICE £20,000 per QALY decision rule.

† Assuming different cancer progression rate for patients receiving different interventions. The cancer progression rates for patients who received surgery were calibrated from published literature (Table 1). The cancer progression rates for patients who received RFA were calculated based on the RR (RFA vs surgery) reported by a recently published meta-analysis of five trials including 742 patients: 1.42 for local progression and 1.36 for regional/distant progression [60]. The short-term cancer progression rate for patients who receiving SABR was obtained from the CtE scheme. The exponential distribution provided the closest fit to the data for both local and regional/distant progression: from no progression to local recurrence (monthly transition rate=3.00%), and from no progression to regional/distant recurrence (monthly transition rate=1.01%)). The long-term cancer progression rate for patients receiving SABR was assumed to be the same as RFA due to lack of long-term data.

‡ Assuming different mortality rates for patients receiving different interventions. The monthly mortality rate for patients who received surgery and RFA were calculated based on a recent published meta-analysis (0.37% for surgery and 0.85% for RFA) [60]. The mortality rates up to 2 years for patients receiving SABR was obtained from the CtE scheme (exponential distribution, monthly mortality rate=1.15%). The mortality rate post two years for patients receiving SABR was assumed to be the same as patients who received RFA.

§ Assuming the same mortality rate for RFA and SABR, and a different mortality rate for patients receiving surgery. The monthly mortality rate for patients who received surgery and RFA were calculated based on a recent published meta-analysis (0.37% for surgery and 0.85% for RFA) [60]. The mortality rate for patients receiving SABR was assumed to be the same as patients receiving RFA.

** Assuming different cancer progression rate and different mortality rate for patients receiving different interventions. The cancer progression rates for patients who received surgery were calibrated from published literature (Table 1). The cancer progression rates for patients who received RFA were calculated based on the RR (RFA vs surgery) reported by a recently published meta-analysis of five trials including 742 patients: 1.42 for local progression and 1.36 for regional/distant progression [60]. The short-term cancer progression rate for patients who receiving SABR was obtained from the CtE scheme. The exponential distribution provided the closest fit to the data for both local and regional/distant progression: from no progression to local recurrence (monthly transition rate=3.00%), and from no progression to regional/distant recurrence (monthly transition rate=1.01%)). The long-term cancer progression rate for patients receiving SABR was assumed to be the same as RFA due to lack of long-term data. The monthly mortality rate for patients who received surgery and RFA were calculated based on a recent published meta-

analysis (0.37% for surgery and 0.85% for RFA) [60]. The mortality rates up to 2 years for patients receiving SABR was obtained from the CtE scheme (exponential distribution, monthly mortality rate=1.15%). The mortality rate post two years for patients receiving SABR was assumed to be the same as patients who received RFA.

28 **Fig 1-2**

Fig. 1 Markov model structure

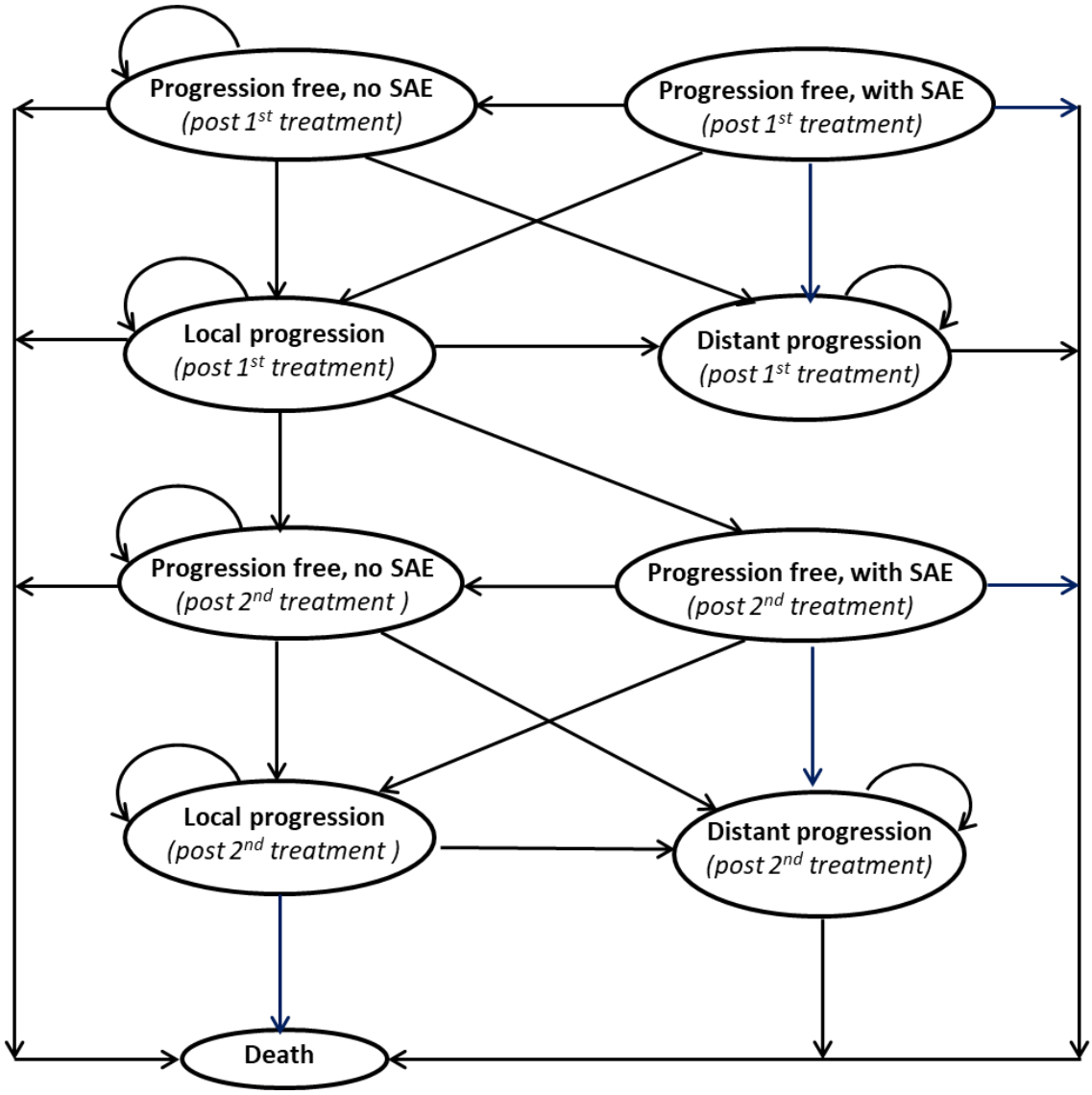

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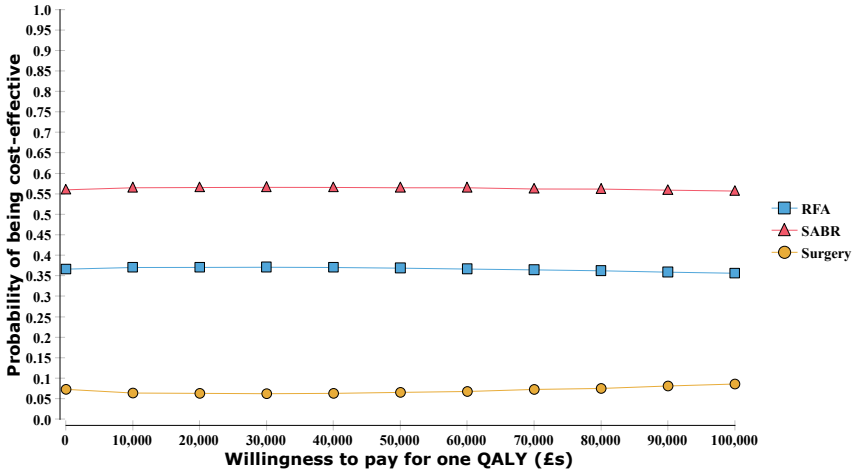
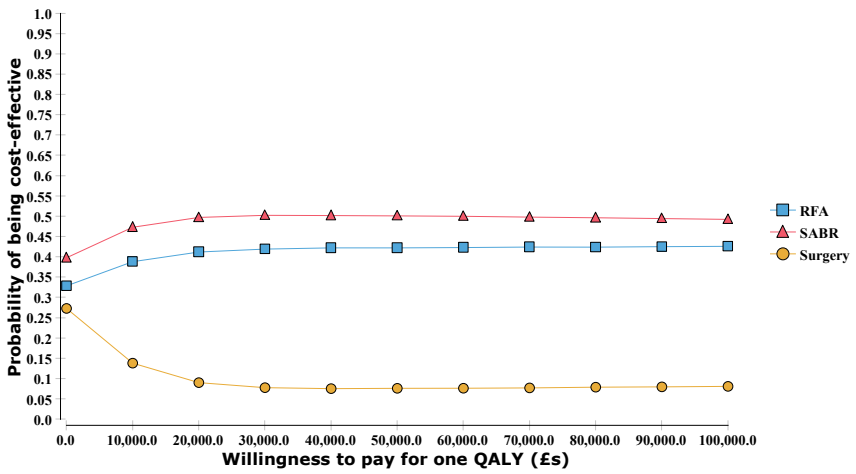
Fig. 2 Cost-effectiveness acceptability curve for patients with liver oligometastases and hepatocellular carcinoma (HCC)

2A Liver oligometastases



2B Hepatocellular carcinoma (HCC)



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