Cost–utility analysis of selective internal radiation therapy with Y-90 resin microspheres in hepatocellular carcinoma

Noemi Muszbek^{*,1} , Edit Remak², Rachel Evans¹, Victoria K Brennan³, Fabien Colaone³ , Suki Shergill³, Damian Mullan⁴ & Paul J Ross⁵

¹Visible Analytics, Oxford, OX2 0DP, UK

²Visible Analytics, Budapest, 1025, Hungary

³SIRTEX Medical United Kingdom Ltd, London, EC4A 3TR, UK

⁴The Christie NHS Foundation Trust, Manchester, M20 4BX, UK

⁵Department of Medical Oncology, Guy's & St Thomas' NHS Foundation Trust, London, SE1 9RT, UK

*Author for correspondence: noemi.muszbek@visibleanalytics.co.uk

Background: The study assessed the cost-utility of selective internal radiation therapy (SIRT) with Y-90 resin microspheres versus sorafenib in UK patients with unresectable hepatocellular carcinoma ineligible for transarterial chemoembolization. **Materials & methods:** A lifetime partitioned survival model was developed for patients with low tumor burden ($\leq 25\%$) and good liver function (albumin–bilirubin grade 1). Efficacy, safety and quality of life data were from a European Phase III randomized controlled trial and published studies. Resource use was from registries and clinical surveys. **Results:** Discounted quality-adjusted life-years were 1.982 and 1.381, and discounted total costs were £29,143 and 30,927, for SIRT and sorafenib, respectively. **Conclusion:** SIRT has the potential to be a dominant (more efficacious/less costly) or cost-effective alternative to sorafenib in patients with unresectable hepatocellular carcinoma.

Lay abstract: Hepatocellular carcinoma is a complex disease, where in advanced stages there are limited treatment options. Among patients who are not eligible for liver transplant, removal of the tumor (resection or ablation) or localized chemotherapy (transarterial chemoembolization), the current gold standard in the UK is sorafenib and lenvatinib, which while efficacious has important adverse effects. Selective internal radiation therapy (SIRT) provides an alternative treatment option, that potentially avoids the serious adverse effects of systemic treatments and, for a small proportion of patients, may allow the patient to become eligible for either liver transplant or removal of the tumor. This study aimed to assess if SIRT is cost-effective, in other words, provides 'value for money' compared with sorafenib in selected patients with low tumor burden and good liver function. A cost-effectiveness model was built based on a Phase III randomized controlled trial, published studies and clinical surveys. The analyses showed that SIRT resulted in higher quality-adjusted life-years and lower or slightly higher healthcare cost depending on the selectiveness of the patient population, and thereby has the potential to be a cost-effective alternative to sorafenib.

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Hepatocellular carcinoma (HCC) can be complex both in presentation and management, due to the interaction between the two aspects of the disease: impaired liver function and cancer. In Western Europe, the majority of HCC occurs in patients with underlying liver disease (cirrhosis), with 32% of HCC cases in patients with underlying alcohol abuse, 13% with chronic hepatitis B virus infection, 44% with chronic hepatitis C virus infection and 10% due to other causes [1]. HCC poses a significant burden in the UK, with primary liver cancer accounting for 6836 deaths in 2018, 3.8% of all cancer deaths that year [2]. HCC also results in a health-related quality of life (HRQL)

burden which increases with advanced stage disease [3,4], and has a high economic burden driven by hospitalization costs [5].

For patients with early-stage HCC, treatments with curative intent (TCIs), such as liver transplantation, surgical resection (removal of tumors) or local ablation, offer the potential for long-term survival. As a result, all clinical guidelines recommend liver transplantation or tumor removal for first-line treatment for patient meeting indications [1,6,7]. However, approximately 80% of UK patients with HCC are not eligible for potentially curative therapy at diagnosis. Among these patients in 2014, 22% had intermediate (Barcelona Clinic Liver Cancer [BCLC] stage B), 25% had advanced (BCLC stage C) and 33% had end-stage disease (BCLC stage D) [8]. For patients with unresectable HCC who are not amenable to potentially curative therapy, recommended treatment options are generally restricted to transarterial chemoembolization (TACE), or for those not eligible for TACE, systemic therapy, of which sorafenib is the most established in current practice [1,6,7]. Sorafenib, however, has important side effects, such as the commonly reported fatigue, diarrhea and skin disorders (including hand-foot skin reaction) [9–12], which, in a survey of 256 patients with HCC (including 32 patients in the UK), have the biggest impact on the HRQL of patients receiving sorafenib out of all side effects resulting from cancer treatments [13]. Alternatively, selective internal radiation therapy (SIRT) delivers radiation to liver tumors by intra-arterial infusion and minimizes the exposure of nontumoral liver tissue, therefore allowing patients who are not eligible for TACE to benefit from a locoregional therapy and potentially avoid the serious adverse events (AEs) of systemic treatments.

Patients considered for SIRT undergo a workup. This is used both to confirm eligibility of the patient for the SIRT procedure and to plan the administration of this procedure. Depending on the patient selection, most patients who undergo workup will subsequently receive SIRT.

The efficacy of SIRT with (SIR-Spheres Y-90 resin microspheres, Sirtex Medical United Kingdom Ltd., London, UK) has been assessed in the SARAH trial, a multicenter, open-label, randomized, controlled, investigator-initiated, Phase III trial comparing SIRT with sorafenib in locally advanced and inoperable HCC [9]. The aim of the SARAH trial was to assess the efficacy and safety profile of SIRT compared with sorafenib in this population. While in the intention-to-treat (ITT) population, the trial did not detect significant differences in overall survival (OS), only 73% of patients in the SIRT group were treated with SIRT with no major protocol deviation. Among the patients treated with SIRT a significantly higher proportion of patients achieved complete or partial response ($p = 0.0421$), and improved global health status based on the European Organisation for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ-C30) (group effect; $p = 0.0048$). Additionally, a recent *post-hoc* subgroup analysis of the SARAH trial found that, in line with the recommendations of clinical guidelines [1,6], it may be possible to select patients with HCC with low tumor burden ($\leq 25\%$) and good liver function (albumin–bilirubin [ALBI] grade 1), who would derive a meaningful benefit from treatment with SIRT compared with sorafenib (median OS 21.8 months [95% CI: 15.1 to not reached] for SIRT vs 17.0 months [95% CI: 11.6–20.9] for sorafenib; hazard ratio [HR]: 0.73 [95% CI: 0.44–1.21]) [14].

Besides establishing clinical effectiveness, many countries also require assessment of ‘value for money’ with the help of cost–effectiveness, including the UK, where for England and Wales, the National Institute for Health and Care Excellence (NICE) provides health technology appraisals (TAs) for selected new technologies.

This study assessed the economic value of SIRT with SIR-Spheres Y-90 resin microspheres versus sorafenib in UK patients with unresectable HCC ineligible for TACE according to the NICE reference case [15].

Materials & methods

The base case population has been defined based on the marketing authorization of SIRT with SIR-Spheres Y-90 resin microspheres [15], clinical guidelines [1,6] and the identification of patients most likely to benefit from SIRT [14]:

- Patients with unresectable intermediate (BCLC stage B) or advanced (BCLC stage C) HCC;
- For whom any transarterial embolization therapies (e.g., TACE or transcatheter arterial embolization) are inappropriate;
- Without extrahepatic disease;
- With low tumor burden ($\leq 25\%$);
- And with a preserved liver function (ALBI grade 1).

This targeted population also allows a higher probability of receiving subsequent TCIs even in the advanced population and minimizes unnecessary workup by selecting patients most likely to be eligible for SIRT [14]. Since

Figure 1. Partitioned survival analyses.

OS: Overall survival; PFS: Progression-free survival.

This figure has also been presented by the same authors in a report submitted to the National Institute for Health and Care Excellence [23].

this population represents a *post-hoc* analyses of the SARAH trial, the ITT population was also assessed as a scenario analysis.

The main comparator was sorafenib, which until the end of 2018 was the only option for untreated advanced HCC in the UK and was the comparator in the SARAH trial. Lenvatinib, which is also recommended by NICE [16] for this population was not included in the base case, as an indirect comparison was not feasible without major assumptions [17]. However, it has been included in a scenario analysis. While other SIRT interventions are available in the UK, no randomized studies have compared these interventions to SIRT with SIR-Spheres Y-90 resin microspheres or sorafenib, therefore these have not been included.

Model structure

A lifetime partitioned survival analysis model was developed. This is commonly used in modeling oncology [18,19] and is in line with prior NICE TAs in HCC [16,20–22]. The model, as most partitioned survival analyses, is based on OS and progression-free survival (PFS) curves that determine the three commonly used health states: progression free, postprogression and dead (Figure 1). These models estimate the proportion of patients in each health state in each time period (cycle) based on the survival curves.

In addition to the treatment pathway used in partitioned survival analyses, there is evidence that SIRT allows for downstaging to subsequent TCIs [9] (13.5% of patients in the SIRT vs 2.1% in the sorafenib arm of the SARAH trial in the model base case population, and 5.1 vs 1.4% for SIRT and sorafenib in the ITT population, respectively). Downstaging with SIRT, while rare with systemic therapies, was also seen with SIRT in the retrospective Post-SIR-Spheres Surgery Study (P4S) study [24] and two prospective studies [25,26]. As TCIs offer significantly extended survival [27] and can affect quality of life (QoL) and costs, they are an important aspect of the patient pathway. Therefore, an additional health state (received curative therapy) was incorporated into the model compared with the previous HCC partitioned survival analyses [16,20–22] which only tracked progression and death.

This resulted in four health states. Patients start in ‘progression free’ health state and can move to ‘received curative therapy’ on average at 15.84 months as per the SARAH trial [14], or ‘postprogression’ and ‘dead’ in monthly cycles (Figure 2).

While the partitioned survival analyses rely on OS/PFS from the SARAH trial, the highly informative censoring (with only one down-staged patient dying within follow-up period in the SARAH trial and the rest of the patients being alive and censored at the end of the follow-up period) results in the SARAH trial OS excluding the survival

Figure 2. Cost-effectiveness model structure. Bubbles represent the health states; solid arrows represent movement of patients between these health states estimated by survival curves or probabilities; and dashed arrow represent movement of patients between these health states implicitly included in the survival curves.

BSC: Best supportive care; OS: Overall survival; PFS: Progression-free survival.

This figure has also been presented by the same authors in a report submitted to the National Institute for Health and Care Excellence [23].

benefit of TCIs, underestimating long-term efficacy. The inclusion of the benefit from TCIs for these patients therefore required separate modeling of OS for the patients who receive TCIs in the model.

Furthermore, some patients may be deemed ineligible for SIRT after receiving a workup, for example, because of unsuitable tumor vascularization, and may receive other treatments. The consequences on efficacy and safety outcomes of these patients are included in the SARAH trial, thus the costs of the workups together with the additional treatments were also included.

Inputs

The efficacy inputs of OS and PFS matched the primary and secondary outcomes of the SARAH trial. However, because the model evaluates the impact of treatment on costs and health benefits over a lifetime horizon, and OS and PFS curves were not complete, the survival curves needed to be extrapolated beyond the end of the SARAH trial follow-up using parametric models [15,23,28]. Parametric models assume that survival times for patients follow a given theoretical distribution [29].

Extrapolations were performed by digitizing the survival curves for the target population reported by Palmer *et al.* [14] and fitting parametric models to the observed time-to-event data from the SARAH trial, using R. Commonly used parametric survival models (Weibull, log-normal, log-logistic, exponential, generalized gamma and Gompertz distributions) were fitted to the observed data. The fit of the distributions was tested using parametric plots, observed and predicted plots, long-term projections, and goodness-of-fit statistics (i.e., Akaike Information Criterion [AIC] and Bayesian Information Criterion [BIC]) for each treatment arm (SIRT and sorafenib and a combined model for both groups with treatment as a predictor). The proportional hazard assumption was tested using log-cumulative hazards plots. Diagnostic plots and goodness-of-fit statistics were used to identify plausible fits; graphs of fit against the observed data provided an assessment of internal accuracy, and long-term projections served to assess the clinical plausibility of the fits [23,30].

For OS, based on the results, it was inconclusive if the proportional hazards assumption holds. However, in the previous sorafenib TAs [20,21] the proportional hazard assumption did not hold. Thus, the curves were fitted separately. According to AIC/BIC statistics, all models with the exception of the exponential distribution fitted well. In the visual inspection, log-normal and log-logistic distribution were the most appropriate. In the ITT population, with the most data, log-normal distribution fitted the best both in terms of goodness-of-fit statistical criteria and visual inspection. Additionally, in the literature based on a systematic literature review of HCC survival, log-normal

Table 1. Model inputs.

Input	Value (standard error)	Study (year)	Ref.
Efficacy			
– Overall survival for SIRT and sorafenib	Log-normal curves	SARAH trial, Palmer <i>et al.</i> (2020)	[9,14]
– Progression-free survival for SIRT and sorafenib	Log-normal curves	SARAH trial, Palmer <i>et al.</i> (2020)	[9,14]
– Time to sorafenib discontinuation	Log-normal curves	SARAH trial	[9]
– Proportion of patients not eligible for SIRT after workup	2.9% (2.8%)	SARAH trial, Palmer <i>et al.</i> (2020)	[9,14]
– HR for TCIs	0.29 (0.074)	Kanwal <i>et al.</i> (2012)	[27]
Costs and resource use			
– Sorafenib 112 × 200 mg	£3576.56	BNF (2019)	[32]
– Workups for SIRT (n)	1.05 (0.05)	Resource use survey	
– Procedures for SIRT (n)	1.20 (1.16)	Resource use survey	
– Length of stay for SIRT workup (days)	0.69	Resource use survey	
– Length of stay for SIRT treatment (days)	1.19	Resource use survey	
– Outpatient costs for SIRT	£1123.15	National Schedule of Reference Costs 2017–18	[33]
– Inpatient cost/day for workup/procedure	£1757.45		
– SIRT	£8000.00		
Subsequent treatments after SIRT			
– Sorafenib	42.1%	Resource use survey	
– Regorafenib	1.5%	Resource use survey	
– BSC	32.2%	Resource use survey	
– Treatments with curative intent	13.5% (5.6%) [†]	SARAH trial, Palmer <i>et al.</i> (2020)	[9,14]
Subsequent treatments after sorafenib			
– Lenvatinib	1.0%	Resource use survey	
– Regorafenib	18.9%	Resource use survey	
– BSC	55.6%	Resource use survey	
– Treatments with curative intent	2.1% (2.1%) [‡]	SARAH trial, Palmer <i>et al.</i> (2020)	[9,14]
– Sorafenib daily dose	648.5 mg	SARAH trial	[9]
– Total adverse event cost for SIRT	£434.05 (44.29)	AEs incidence: SARAH trial, costs:	[9,16,21,22,33,34]
– Total adverse event cost for sorafenib	£947.44 (96.68)	National Schedule of Reference Costs 2017–18 and NICE TAs	

[†]A total of 33% liver resection, 17% liver transplantation and 58% ablation.

[‡]A total of 33% transplantation and 67% ablation.

AE: Adverse event; BNF: British National Formulary; BSC: Best supportive care; HR: Hazard ratio; NICE TA: National Institute for Health and Care Excellence technology appraisal; SIRT: Selective internal radiation therapy; TCI: Treatment with curative intent.

distribution was found to be the most appropriate [23,31]. As a result, in the base case log-normal distribution was used (Table 1).

For PFS, jointly fitted log-normal, independently fitted log-normal and the jointly fitted log-logistic distributions had the lowest AIC/BIC. Similarly, to OS, none of the diagnostic plots indicated that any one model fitted better than another, and there was uncertainty about whether the proportional hazards assumption holds. As a result, in the base case independently fitted log-normal distributions were used. Alternative distributions for both OS and PFS were tested in scenario analyses.

For the scenario analysis including lenvatinib, a network meta-analysis was conducted based on a systematic literature review, which included an additional randomized controlled trial (RCT) that compared sorafenib with lenvatinib (the REFLECT trial) [17,35]. Eligibility criteria differed between trials: the REFLECT trial excluded patients with main portal vein invasion and included patients with extrahepatic spread (EHS), while the SARAH trial included patients with main portal vein invasion and excluded patients with EHS. As a result, only patients without EHS or main portal vein invasion were analyzed, resulting in an OS HR for lenvatinib versus sorafenib of 1.05 (95% CI: 0.79–1.39), and for PFS 0.73 (95% CI: 0.55–0.97) using the fixed effects model.

To assess OS after TCIs, a targeted literature review for survival after hepatic resection and tumor ablation (the most common TCIs after downstaging) was conducted. In the base case the HR comparing patients with intermediate or advanced HCC receiving and not receiving TCIs was used from a prospective study in the USA [27] (HR for OS with TCIs vs noncurative treatment was 0.29; 95% CI: 0.18–0.47).

Table 2. Health state cost and utility values in the model.

Comparator	Mean health state costs	Source of data	Mean utility value (standard error)	Source of data	Ref.
Preprogression – SIRT arm	£245.74	Resource use survey	0.762 (0.078)	Mapped EORTC QLQ-C30 values from the SARAH trial	[37,38]
Preprogression – sorafenib arm	£287.19		0.746 (0.076)		
At progression (one-off cost)	£207.79		–		
Postprogression – SIRT arm	£499.37	Assumed same as preprogression for the SIRT	0.738 (0.075)	Assumed same as the preprogression utilities with SIRT	
Postprogression – sorafenib arm	£499.37		0.722 (0.074)		
After subsequent treatment with curative intent	£245.74		0.762 (0.078)		

EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer quality of life questionnaire; SIRT: Selective internal radiation therapy.

Utilities were EQ-5D scores mapped from EORTC QLQ-C30 results from the SARAH trial using the algorithm by Longworth *et al.* [36] and with UK weights [37]. (Table 2). Utility consequences of AEs were assumed to be captured in the trial values. Mean health state utility values were estimated using multivariable analysis. While utilities for patients in the SIRT arm were only slightly higher than for patients on sorafenib, EORTC QLQ-C30 showed a statistically significant improvement in global health status subscore in the SIRT group compared with the sorafenib group (group effect: $p = 0.0048$; time effect: $p < 0.0001$) with the between-group difference tending to increase with time (group–time interaction: $p = 0.0447$) [9]. This suggested that, although the utility values might not have been able to fully capture it, SIRT and sorafenib can have different impact on QoL, and therefore, treatment-specific utilities are the most appropriate in the model.

Due to the lack of recent data in the literature for the resource use implications of SIRT and disease management in HCC for the target population resource use was elicited with the help of survey of eleven medical professionals (two oncologists, one hepatologist, three specialist nurses and five interventional radiologists) experienced in the care of patients with HCC and with SIRT [38]. A similar approach was used for the sorafenib and lenvatinib appraisals [16,20,21]. The surveys (including background information, administration, medical staff contacts, monitoring, hospitalizations and social care) were developed based on the previous surveys [16,20,21] and clinical guidelines [1,6] and were validated by a medical oncologist. Health state costs ranged from £207.79 for preprogression health state after SIRT to £499.37 for postprogression costs (Table 2).

The number of SIRT workups, number of treatments, the length of hospital stays and the subsequent treatments after SIRT/sorafenib (excluding TCIs) were also elicited from the survey to reflect current UK clinical practice. The proportion of patients receiving TCIs in the target population was estimated from the SARAH trial [14]. After SIRT, 42% of the patients were assumed to receive sorafenib, and 2% regorafenib; and after sorafenib, 19% of patients were assumed to receive regorafenib, and 1% lenvatinib. The rest of the patients received best supportive care or TCIs.

Time to treatment discontinuation (TTD) for sorafenib was obtained from the SARAH trial [9]. Based on visual inspection of the TTD curves and AIC and BIC statistics, the best fitting model was the log-normal distribution [23]. The daily dose of sorafenib was also from the SARAH trial (648.5 mg) [9]; to make sure no partial pills are included, this was estimated to be equivalent to 24% of patients receiving four pills (800 mg) and 76% of patients three pills (600 mg). As sorafenib has a confidential discount in the UK, scenario analysis was conducted assuming a 20 and a 40% discount. In scenario analyses including lenvatinib, the average daily dose of 9.4 mg for lenvatinib retrieved from the NICE TA [16] was estimated to be equivalent to 65% receiving 8 mg and the remaining patients 12 mg. TTD was estimated using a HR compared with sorafenib (0.75; 95% CI: 0.65–0.85) [16].

AE rates were calculated based on the reported incidence of relevant grade 3–4 treatment-related AEs that affected $\geq 5\%$ of the population in the SARAH trial [9]. AE costs were taken from previous NICE appraisals [16,21,22,34] or estimated from National Health Service (NHS) reference costs [33].

Unit costs of resources were obtained from National Schedule of Reference Costs 2017–18 [33] and the Personal Social Services Research Unit report [39] and unit costs of drugs were obtained from British National Formulary [32] and where available, the NHS Drugs and Pharmaceutical Electronic Market Information Tool [40]. Costs, where required, were inflated to 2018/2019 using the Health Services Index presented in the Personal Social Services Research Unit report [23,39].

Table 3. Base case – incremental results (discounted).

Technologies	Total costs (£)	Total LYs	Total QALYs	Incr. costs (£)	Incr. LYs	Incr. QALYs	ICER (£/QALY)	INB (£) with £20,000 threshold
Sorafenib	£30,957	1.890	1.381	–	–	–	–	–
SIRT	£29,530	2.637	1.982	-£1427	0.748	0.601	Dominant [†]	£13,443

[†] SIRT results in more QALYs and less costs than sorafenib.
ICER: Incremental cost–effectiveness ratio; INB: Incremental net benefit; Incr.: Incremental; LY: Life year; QALY: Quality-adjusted life-year; SIRT: Selective internal radiation therapy.

Analyses

As SIRT affects the differences in health outcomes (estimated as quality-adjusted life-years [QALYs]) and costs between the technologies being compared over the patients' lifetime, a lifetime horizon was used, which is in line with previous TAs in HCC [16,20–22]. Incremental cost–effectiveness ratios (ICERs) were estimated by dividing the additional (incremental) costs of SIRT by the additional (incremental) QALYs gained. As recommended in the NICE methods guidance, costs and health benefits were discounted with 3.5% discount rate, and half cycle correction was applied to all outcomes with the exception of drug and procedure costs, because these are accrued at the beginning of each cycle [15].

Parameter uncertainty was assessed in the univariate (one-way) sensitivity analysis and probabilistic sensitivity analysis. Univariate deterministic sensitivity analysis was performed with each parameter varied according to its 95% CI or standard error, while holding all other parameters constant. Where the published study or source for parameter values did not report standard errors or CIs, a 20% variation of the mean was assumed. Results were depicted with the help of tornado diagrams showing the variation from the base-case result using the high and low value for each parameter.

Probabilistic sensitivity analysis were run for 1000 replications where parameter estimates were repeatedly sampled from probability distributions simultaneously to determine an empirical distribution for costs and QALYs. A gamma distribution was applied to the costs, a beta distribution for utilities and the Cholesky decomposition method was used to preserve correlation between variables of parametric distributions, which were varied using normal distribution [18]. Results were depicted with cost–effectiveness acceptability curves showing the probability of each treatment being cost-effective over a range of willingness-to-pay thresholds.

Structural uncertainty was explored using the partitioned survival analysis without TCIs and in a series of scenario analyses, including assumptions around the structural form of OS and PFS, the inclusion of lenvatinib, the sources used to inform parameters (including the use of health state costs from prior NICE TAs) and assumptions regarding the underlying calculations.

Results

Over a lifetime horizon SIRT resulted in 2.64 discounted life years and 1.982 discounted QALYs, while sorafenib led to 1.89 life years and 1.381 QALYs. The 0.60 QALY benefit with SIRT was mostly due to the longer time spent progression free with SIRT, and the higher proportion of patients receiving TCIs and benefiting from its survival advantage.

The discounted total costs were £29,530 and £30,957 for SIRT and sorafenib, respectively. While the costs due to TCIs were higher with SIRT and the longer time preprogression led to higher disease management costs, SIRT resulted in savings in the treatment, AEs and postprogression disease management costs. With higher efficacy and lower costs, SIRT dominated sorafenib (Table 3).

Results were robust in the sensitivity analyses. The probability of SIRT being cost-effective at a willingness-to-pay threshold of £20,000/QALY was 95% (Figure 3). The most influential inputs driving the results were the survival estimates for SIRT and sorafenib, the proportion of patients downstaged to TCIs with SIRT and the average number of SIRT procedures required per patient (Figure 4). SIRT remained cost-effective in all scenario analyses, including 40% reductions in the price of sorafenib (Table 4).

In the overall trial population SIRT was cost saving, and resulted in slightly less QALYs, leading to sorafenib not being cost-effective compared with SIRT (ICER of £58,298/QALY).

The comparison with lenvatinib should be treated with caution due to the differences in patient populations. Including a comparable population of patients from the ITT population with neither main portal vein invasion (inclusion criteria of the lenvatinib trial) nor EHS (inclusion criteria of the SARAH trial) led to lenvatinib not being

Table 4. Scenario analyses.

Scenario	Technologies	Total costs (£)	Total QALYs	ICER SIRT vs sorafenib (£/QALY)	INB (£) with £20,000 threshold	Ref.
Base case	SIRT	£29,530	1.981	Dominant (-£2374)	£13,443	
	Sorafenib	£30,957	1.381			
Time horizon (5 years)	SIRT	£27,262	1.577	Dominant (-£7934)	£9343	
	Sorafenib	£29,915	1.243			
Discount cost and benefits (0%)	SIRT	£30,780	2.185	Dominant (-£1368)	£15,350	
	Sorafenib	£31,763	1.467			
Discount cost and benefits (5%)	SIRT	£29,080	1.910	Dominant (-£2807)	£12,782	
	Sorafenib	£30,654	1.349			
Population, ITT	SIRT	£22,204	0.881	Sorafenib vs SIRT: £58,298	£4003	
	Sorafenib	£28,298	0.986			
Not allowing downstaging	SIRT	£31,648	1.907	£2848	£10,660	
	Sorafenib	£29,878	1.285			
PFS, separately fitted log-logistic	SIRT	£29,359	1.983	Dominant (-£3105)	£13,889	
	Sorafenib	£31,226	1.382			
PFS, separately fitted Weibull	SIRT	£29,649	1.980	Dominant (-£273)	£12,165	
	Sorafenib	£29,813	1.380			
OS, separately fitted log-logistic	SIRT	£29,011	1.906	Dominant (-£4548)	£12,038	
	Sorafenib	£31,241	1.416			
OS, separately fitted Weibull	SIRT	£26,388	1.484	Dominant (-£10,891)	£8897	
	Sorafenib	£29,525	1.196			
Utilities, NICE TA189 sorafenib, NICE TA474 sorafenib	SIRT	£29,530	1.840	Dominant (-£2793)	£11,643	
	Sorafenib	£30,957	1.329			
Utilities for treatments with curative intent, literature: 0.82	SIRT	£29,530	2.023	Dominant (-£2243)	£14,146	[41]
	Sorafenib	£30,957	1.387			
Utilities for treatments with curative intent, literature: 0.88	SIRT	£29,530	2.065	Dominant (-£2122)	£14,873	[42]
	Sorafenib	£30,957	1.393			
Utilities for treatments with curative intent, literature: 0.71	SIRT	£29,530	1.944	Dominant (-£2506)	£12,813	[43]
	Sorafenib	£30,957	1.375			
Costs, health state costs from NICE lenvatinib TA	SIRT	£55,346	1.981	Dominant (-£5993)	£15,618	
	Sorafenib	£58,947	1.381			
Costs, SARAH trial for # procedures	SIRT	£31,811	1.981	£1422	£11,162	
	Sorafenib	£30,957	1.381			
Costs, using NHS reference costs for workup/procedure (assuming no outpatient workup/procedure)	SIRT	£31,959	1.981	£1668	£11,015	
	Sorafenib	£30,957	1.381			
Assuming 20% discount for sorafenib	SIRT	£28,653	1.981	£1816	£10,926	
	Sorafenib	£27,562	1.381			
Assuming 40% discount for sorafenib	SIRT	£27,777	1.981	£6006	£8408	
	Sorafenib	£24,168	1.381			
Comparison to lenvatinib using network meta-analyses of the SARAH and REFLECT trials with the only comparable population of patients with neither extrahepatic spread nor main portal vein invasion from ITT population	SIRT	£22,204	0.881	Lenvatinib vs SIRT: £58,298	£4003	
	Lenvatinib	£40,505	0.944			

Dominant: SIRT results in more QALYs and less costs than sorafenib.
 ICER: Incremental cost-effectiveness ratio; INB: Incremental net benefit; ITT: Intention-to-treat; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; OS: Overall survival; PFS: Progression-free survival; QALY: Quality-adjusted life-year; SIRT: Selective internal radiation therapy; TA: Technology appraisal.

Figure 3. Probabilistic sensitivity analysis: cost-effectiveness acceptability curve.

This figure has also been presented by the same authors in a report submitted to the National Institute for Health and Care Excellence [23].

Figure 4. Deterministic sensitivity analysis – tornado diagram. As the results with the extreme values used in the one-way sensitivity analyses span more than one quadrant of the cost-effectiveness plane, INB with the threshold of £20,000/QALY was used instead of ICERs. INB represents both health outcomes and costs in monetary terms, by estimating the monetary value of the health benefit using the willingness to pay for one unit of that benefit. INB is calculated as (incremental benefit $\times$ threshold) – incremental cost.

HR: Hazard ratio; ICER: Incremental cost-effectiveness ratio; INB: Incremental net benefit; OS: Overall survival; TTD: Time to treatment discontinuation.

This figure has also been presented by the same authors in a report submitted to the National Institute for Health and Care Excellence [23].

cost-effective versus SIRT (ICER of £58,298/QALY for lenvatinib vs SIRT). If it is assumed that no downstaging will take place, despite the RCT evidence from the SARAH trial, the ICER was £2848/QALY versus sorafenib.

Discussion

In a selected subgroup of patients with unresectable HCC for whom TACE therapies are inappropriate, with low tumor burden ($\leq 25\%$) and a preserved liver function (ALBI grade 1), a cost-utility model was built from the UK NHS perspective. The lifetime model compared SIRT and sorafenib using a partitioned survival analysis approach based on the OS and PFS survival curves. To reflect treatment pathways observed in the randomized, controlled SARAH trial, clinical practice and in observational studies, an additional health state for patients receiving TCIs was included. Efficacy, safety and utility inputs were from the SARAH trial for SIRT and sorafenib, and from a targeted review for TCIs, while resource use was based on expert surveys. In the selected population, SIRT with SIR-Spheres Y-90 resin microspheres was a dominant alternative to sorafenib with lower costs and higher QALYs.

Despite the uncertainties, results were robust in the sensitivity analyses with SIRT having a 95% probability of being cost-effective at a threshold of £20,000/QALY. Removing downstaging to TCIs from the model, still resulted in SIRT being cost-effective with a very low ICER. Results were most sensitive to extreme changes in OS, the proportion of patients receiving TCIs after SIRT, and the number of procedures with SIRT.

In an unselected population, SIRT offered lower costs and slightly lower effectiveness for SIRT versus sorafenib, leading to sorafenib not being cost-effective. At the same time, SIRT avoids the debilitating AEs with sorafenib resulting in better QoL and offers a chance for potentially curative treatments (including liver transplantation, liver resection and percutaneous tumor ablation) which are rare following sorafenib [9,14,24].

This analysis is one of the first cost-effectiveness analyses of SIRT among patients who are not eligible for TACE. The present evaluation was based on a range of evidence including a Phase III European RCT, other published data and a resource use survey conducted in the UK. While the cost-effectiveness of SIRT using Y-90 glass microspheres has recently been explored in another, similar population, among patients with unresectable HCC who are eligible for TACE [44], this evaluation was based on a single-center retrospective study and is therefore at risk of bias. However, despite the use of Phase III RCT data, uncertainties remain in the present evaluation as with all economic evaluations. Extrapolation of the survival curves (OS and PFS) was required, which often leads to increased uncertainty. Despite this, univariate sensitivity analysis demonstrated that the choice of parametric survival curves only resulted in minor changes.

For devices like SIRT, increased use and experience allows for better targeting of the appropriate patients who would benefit more from their use. This, as seen in the subgroup analysis of the SARAH trial [14], can result in better effectiveness than in the unselected ITT population [9].

It should be noted that the analysis for the target population used for this model was based on *post-hoc* analyses [14]. A subgroup using a $\leq 25\%$ tumor burden threshold was prespecified in the SARAH trial and reported in the main publication of this trial [9], but not in combination with the ALBI grade. However, there are circumstances when clinically plausible, well-supported subgroups cannot be prespecified. In this instance, although the ALBI grade is estimated based on blood tests for ALBI, for which data was prospectively collected during the SARAH trial, the formula used to determine the ALBI grade was only published [45] in 2015, after the enrolment period of the SARAH trial (from 05 December 2011 to 19 February 2015). The ALBI grade 1 and low tumor burden subgroup could therefore not have been prespecified in the SARAH trial.

Although a *post-hoc* analysis, the clinical plausibility of this subgroup has since become well established. Tumor burden is routinely assessed and the $\leq 25\%$ criterion is already used by NHS England to determine the eligibility for SIRT of patients with colorectal liver metastases [46]. The components of the ALBI grade are also routinely collected, and the score itself was developed in England and validated against UK cohorts of patients [45]. It was reported to outperform the Child-Pugh score as a predictor of OS following SIRT [47,48]. Use of the ALBI grade is also recommended in European clinical guidelines to stratify patients in terms of prognosis within the Child-Pugh A class itself [1,6]. Its calculation is straightforward and can be performed using a published nomogram [45] or with a web-based application.

The use of the ALBI score and tumor burden also adds to the current body of research exploring the use of various clinical (e.g., viral status, diabetes and the use of oral antidiabetics, and AEs due to sorafenib) and biological predictive markers (e.g., alpha-fetoprotein, angiogenetic markers, inflammatory cells, proteins and index, growth factors and other targets, and *miRNAs*) [49]. While sorafenib is currently the gold standard treatment in this patient population, with the increasing number of treatment options, the role of prognostic and predictive factors will potentially become more important to support better patient selection not just for current, but also for upcoming therapies.

Downstaging is new in the advanced HCC patient population, as systemic treatments such as sorafenib only allowed the use of subsequent TCIs in rare cases. There are multiple sources and types of evidence, including both prospective and retrospective, both randomized and observational, that support the role of SIRT in downstaging [9,14,24–26]. As the OS of patients receiving TCIs have been modeled separately, there is a potential double counting of the OS benefit for those whose survival benefit has already been included in the OS curve from the SARAH trial. However, as most patients receiving TCIs have not died during the trial follow-up, this affects a very small proportion of patients, and therefore would have negligible effect on the outcomes.

Due to the limited and current data on SIRT administration and HCC disease management, expert opinion was elicited via resource use surveys. While this increases uncertainty, the use of older health state costs from the most recent NICE TA for this population (lenvatinib TA) [16] or older data for the number of SIRT procedures from the SARAH trial [9] have had only minor effects on the results.

Additionally, SIRT has shown significant QoL benefit compared with sorafenib in the SARAH trial, which could be due to the differences in their safety profile. A survey of 256 patients with HCC, showed that out of all side effects resulting from cancer treatments, fatigue, diarrhea and skin disorders (including hand-foot skin reaction), the three most common AEs associated with sorafenib [9–12], had the biggest impact on the HRQL of patients receiving sorafenib [13]. However, this did not translate fully to utilities, and thus the results could underestimate the benefit from SIRT. Further research into the role of ALBI score in the treatment with SIRT and its effect on the effectiveness outcomes and the eligibility to downstage to TCIs would significantly reduce the uncertainties in this analysis. Additionally, the analysis of patient level information from large databases or registries to estimate the cost of SIRT administration and HCC disease management would provide important information for additional economic evaluations for this population.

Conclusion

In a selected population, SIRT with SIR-Spheres Y-90 resin microspheres has the potential to be a dominant and in an unselected population a cost-effective alternative to sorafenib in patients with unresectable HCC ineligible for TACE. The estimated population average costs and outcomes are likely similar for SIRT and sorafenib in all populations. Additionally, sorafenib is associated with significant adverse effects including diarrhea, fatigue and hand and foot skin reaction compared with SIRT, and there is evidence that treatment with SIRT is associated with a higher likelihood of subsequent TCIs. Thus, the individual patients should have the option to receive SIRT treatment based on their eligibility and their preferences regarding adverse effects, QoL and potential outcomes. Further research is required to confirm the role of the ALBI score in patient selection and resource use and to confirm the prognostic impact of low tumor burden ($\leq 25\%$)/good liver function (ALBI score 1) for SIRT compared with sorafenib and lenvatinib.

Future perspective

In unresectable HCC, the number of treatment options is continuously increasing, offering not just better outcomes for the patients, but also a choice between treatment modalities each with their advantages and disadvantages. Additionally, the increasing knowledge of the disease and the treatments offers more insight into the selection of the right treatment for the right patient. This will allow more personalized treatment that not only delivers the best life expectancy and QoL but also can take into account the patients' preferences.

Author contributions

E Remak has led the programming of the model. N Muszbek has led the conception of the model; E Remak, VK Brennan, F Colaone and S Shergill were also involved in the conception of the model. N Muszbek has led the design of the model; E Remak, R Evans, VK Brennan, F Colaone, S Shergill, D Mullan and PJ Ross were also involved in the design of the model. R Evans led the collection of data, and D Mullan and PJ Ross were also involved in the collection of data. N Muszbek, E Remak and R Evans were involved in analysis of data. N Muszbek has led the interpretation of results; E Remak, R Evans, VK Brennan, F Colaone, S Shergill, D Mullan and PJ Ross were also involved in the interpretation of results. R Evans performed the survival analyses. N Muszbek has led the drafting of the paper; E Remak, R Evans, VK Brennan, F Colaone and S Shergill were also involved in the drafting of the paper. D Mullan and PJ Ross were involved in revising of the paper critically for intellectual content. N Muszbek is responsible for the final approval of the version to be published. All the authors agree to be accountable for all aspects of the work.

Summary points

- Hepatocellular carcinoma (HCC) is a complex disease with multiple treatment modalities including systemic therapies, locoregional therapies and treatments with curative intent (transplant, resection and ablation) that offer the potential for long-term survival.
- There is an important unmet need for patients able to benefit from locoregional therapies but not eligible for transarterial chemoembolization.
- Selective internal radiation therapy (SIRT) delivers radiation to liver tumors by intra-arterial infusion, minimizes the exposure of nontumoral liver tissue and allows downstaging of initially unresectable HCC to treatments with curative intent.
- Recent analysis suggests that it may be possible to select patients with HCC and a low tumor burden ($\leq 25\%$)/good liver function (albumin–bilirubin score 1), who would derive a meaningful benefit from treatment with SIRT compared with sorafenib.
- In this selected patient population in the UK, SIRT with Y-90 resin microspheres results in higher efficacy and lower costs, dominating sorafenib.
- In an unselected population (intention-to-treat population in the SARAH trial), SIRT resulted in lower costs and slightly lower quality-adjusted life-years, leading to sorafenib not being cost-effective versus SIRT (£58,763/quality-adjusted life-year).
- SIRT with Y-90 resin microspheres can be a dominant and cost-effective alternative to sorafenib in patients with unresectable HCC ineligible for transarterial chemoembolization. Further statistically powered controlled studies are required to confirm the prognostic impact of low tumor burden ($\leq 25\%$)/good liver function (albumin–bilirubin score 1) for SIRT compared with sorafenib and lenvatinib.

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No writing assistance was utilized in the production of this manuscript.

Data sharing statement

The data that support the findings of this study are available from the corresponding author, N Muszbek, upon reasonable request.

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