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A cost-utility analysis of SIR-Spheres Y-90 resin microspheres versus best supportive care in the treatment of unresectable metastatic colorectal cancer refractory to chemotherapy in the UK

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ABSTRACT

Background: Limited treatment options are available in chemotherapy-refractory or -intolerant metastatic colorectal cancer (mCRC). The objective of the present analysis was to evaluate the cost-utility of SIR-Spheres Y-90 resin microspheres relative to best supportive care (BSC) in the treatment of chemotherapy refractory mCRC from the perspective of the UK national healthcare payer.

Methods: A cost-utility model was developed in Microsoft Excel to simulate transitions from progression-free survival to post-progression survival and death in patients with mCRC. Unit costs were captured in 2019 pounds sterling (GBP) based on the literature, formulary listings, and National Health Service (NHS) England reference costs. Future costs and effects were discounted at 3.5% *per annum*. A series of one-way sensitivity analyses, and probabilistic sensitivity analysis (PSA) were conducted.

Results: The base case analysis showed that SIR-Spheres Y-90 resin microspheres would result in an increase in discounted quality-adjusted life years gained from 0.69 quality-adjusted life years (QALYs) to 1.50 QALYs, with an associated increase in cost from GBP 15,268 to GBP 34,168 yielding an incremental cost-utility ratio of GBP 23,435 per QALY. PSA showed that there would be a 56% likelihood that SIR-Spheres Y-90 resin microspheres would be cost-effective relative to BSC at a willingness-to-pay threshold of GBP 30,000 per QALY gained.

Conclusions: This cost-utility analysis showed that, relative to BSC, SIR-Spheres Y-90 resin microspheres would be a cost-effective treatment option for patients with mCRC in the UK setting from the national healthcare payer perspective.

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Background

In 2020, colorectal cancer (CRC) is expected to be the third most diagnosed cancer in the world, with an estimated 1.9 million incident cases.[1] CRC ranks second only to lung cancer in terms of the absolute number of deaths, with an estimated 907,000 deaths from colon and rectal cancers in 2020. The annual global incidence of CRC is estimated to rise to over 3 million cases by 2040.[2] Despite the increasing global incidence, in the UK, the age-standardized mortality rate from CRC has dropped from 20.1 per 100,000 in 1990 to 12.0 per 100,000 in 2016 in males, and from 13.55 per 100,000 to 8.10 per 100,000 in females over the same period.[3]

Approximately 25% of patients diagnosed with CRC present with synchronous metastases (metastases detected within 6 months of initial diagnosis), and metastases are ultimately reported in at least half of all CRC cases.[4–12] In metastatic CRC (mCRC), the liver is the most common metastatic site, due in part to the majority (70–75%) of the hepatic blood supply originating from the hepatic portal vein, which carries blood from the gastrointestinal tract. Liver metastases develop in approximately 60–70% of all cases of mCRC, with metastases appearing exclusively in the liver in between 35% and 55% of patients. Despite progress in reducing mortality rates in the overall CRC population, population studies in patients with mCRC report median survival times of less than 12 months in patients with synchronous metastases treated with chemotherapy only.[8] Subsequent lines of treatment with targeted agents and/or checkpoint inhibitors can extend this, with trials in mCRC approaching median OS of 3 years in 2019.[13]

As with all chemotherapy regimens, most patients with mCRC ultimately become unresponsive to treatment (chemotherapy refractory) or cannot tolerate multiple cycles of chemotherapy (chemotherapy intolerant). In mCRC patients receiving first-line chemotherapy, approximately 50% go on to receive second-line chemotherapy and, of these patients, approximately 25% subsequently receive third-line treatment.[14,15] Depending on the stage of the tumor at diagnosis, the mutational status, and the sidedness of the primary tumor, first- and second-line therapies can include

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Table 1. Clinical data sources employed in the model.

Study	Model parameters informed by study	Study design	Intervention	Comparator	Location
Bester et al.[25]	Overall survival	Retrospective, non-randomized interventional study	SIRT ($n = 224$)	BSC (in patients ineligible for SIRT) ($n = 29$)	Australia
Seidensticker et al.[26]	Chemotherapy regimens and dosing	Retrospective, non-randomized observational study (matched-pair analysis based on prior treatment history, tumor burden, liver involvement, synchronous versus metachronous metastases, alkaline phosphatase increase, and carcinoembryonic antigen)	SIRT ($n = 29$)	BSC ($n = 29$)	Germany
Hendlisz et al.[27] (NCT00199173)	Adverse event incidence	Prospective, randomized, open-label trial	SIRT + 5-fluorouracil ($n = 22$)	5-fluorouracil ($n = 21$) Cross-over to SIRT on progression allowed at investigators discretion	Belgium

Abbreviations. BSC, best supportive care; CRC, colorectal cancer; SIRT, selective internal radiation therapy.

leucovorin-, fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy regimens such as FOLFOX, FOLFIRI, and FOLFOXIRI; anti-vascular endothelial growth factor (VEGF) agents; anti-epidermal growth factor receptor (EGFR) agents; BRAF inhibitors; human epidermal growth factor receipt 2 (HER2) inhibitors, and inhibitors of immune checkpoint receptors programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). Patients also commonly have the opportunity to participate in clinical trials of new treatments for mCRC.

For patients with mCRC refractory to multiple previous lines of therapy, the treatment options are limited; in Europe, regorafenib (STIVARGA[i]) and trifluridine-tipiracil (TAS-102, LONSURF[ii]) are approved for patients with mCRC "who have been previously treated with, or are not considered candidates for, available therapies".[16,17] Since standard chemotherapy regimens for these patients typically consist of two lines of therapy with the aforementioned agents, regorafenib and TAS-102 are considered to be third-line therapy. Anti-EGFR re-challenge strategies are also emerging as a treatment option for patients with RAS wild-type mCRC, but options for patients with RAS mutant mCRC remain limited. Third-line treatment of mCRC is therefore an area with substantial unmet clinical need.[18,19]

For patients refractory to third-line therapy or ineligible for current third-line treatments, no other systemic therapy options are currently available and disease management may therefore be restricted to best supportive care (BSC), which is associated with median survival of 4–6 months.[20] However, in patients with liver-only or liver-dominant metastases, selective internal radiation therapy (SIRT) with SIR-Spheres Y-90 resin microspheres represents another potential treatment option. SIRT is recommended in the European Society for Medical Oncology (ESMO) 2016 Guidelines for patients who are refractory or intolerant to chemotherapy (category B recommendation for SIR-Spheres Y-90 resin microspheres) and in the National Comprehensive Cancer Network (NCCN) Guidelines v2.2018 (category 2A recommendation for "arterially directed catheter therapy, and in particular yttrium-90 microsphere selective internal radiation") in this indication.[21,22] In the UK, the National Institute for Health and Care Excellence (NICE) 2020 interventional procedures guidance on the use of SIRT in patients with mCRC recommended that SIRT could be used in patients who cannot tolerate chemotherapy or have liver metastases refractory to chemotherapy, with special arrangements for clinical governance, consent, and audit or research.[23]

Given the ESMO, NCCN, and NICE recommendations to use SIRT in this patient group, the objective of the present study was to conduct a cost-utility analysis comparing SIRT with SIR-Spheres Y-90 resin microspheres versus BSC in the treatment of unresectable liver metastases from CRC in patients who are refractory or intolerant to chemotherapy from the perspective of a UK healthcare payer.

Methods

Evidence synthesis

A cost-utility model and analysis of SIRT with SIR-Spheres Y-90 resin microspheres versus BSC in patients with unresectable liver metastases from chemotherapy refractory or intolerant CRC was published in 2015.[24] Three key clinical studies informed different aspects of the development of the previous model: a retrospective analysis by Bester et al. informed estimates of overall survival (OS), a randomized controlled trial (RCT) by Hendlisz et al. informed the adverse event incidence, and an observational matched-pair analysis by Seidensticker et al. informed the chemotherapy regimens and dosing (Table 1).[25–27] While the Hendlisz et al. RCT would appear to be subject to less bias than the Bester et al. publication and therefore potentially better suited to inform the OS modeling, the study was relatively small ($N = 46$), there was a high level of crossover to SIRT from the chemotherapy arm, and the publication only reported estimates of median overall survival without presenting Kaplan-Meier data, thereby precluding its use in the modeling analysis.[27] Despite the challenges in utilizing the survival and PFS data from Hendlisz et al., the study reported the incidence of adverse events using the Common Terminology Criteria for Adverse Events (CTCAE) and stratified by individual grade

(1–4); these data were therefore used as the basis of the adverse event incidence modeling in the 2015 analysis.

For the present analysis, two systematic literature reviews (SLRs) were conducted to establish if any further applicable clinical data had become available that could be incorporated into the model. The two SLRs were designed to identify evidence on the efficacy and safety of SIR-Spheres Y-90 resin microspheres in patients with unresectable liver metastases from CRC refractory or intolerant to treatment with chemotherapy: one review to identify RCTs, and one "non-randomized" review to identify retrospective and/or non-interventional studies. Searches were conducted from the publication date of the previous cost-utility analysis (in 2015) to September 2019.[24]

Search terms for both SLRs were constructed using a combination of Medical Subject Heading (MeSH) terms and free text queries, combining a search term for CRC with a search term for liver metastases. The search terms for the two SLRs only differed in the term used to specify study type, which was specific to RCTs in the first search (Supplementary Table 1), and to non-randomized studies in the second (Supplementary Table 2). The CRC portion of the search terms was adapted from a 2017 SLR of second-line systemic therapies for colorectal cancer conducted by the Cochrane Collaboration.[28] Study type terms for both searches were obtained from the InterTASC Information Specialists' Sub-Group (ISSG) Search Filter Resource, specifically the Cochrane Collaboration sensitivity- and precision-maximizing search term for RCTs and the University of Texas School of Public Health search term for the "observational" literature search.[29–31]

Inclusion and exclusion criteria were developed in line with the Population, Intervention, Comparator(s), Outcomes, Study design (PICOS) approach to identify studies in the patient population of interest comparing BSC with SIRT with SIR-Spheres Y-90 resin microspheres (Table 2). References were retrieved from PubMed, EMBASE, and the Cochrane Library and, after removal of duplicate studies, the titles and abstracts of each study were screened against the inclusion/exclusion criteria by two independent reviewers using Sourcerer (Covalence Research Ltd, London, UK).[32] Full-text versions of the studies included after title and abstract screening were then obtained and screened against the same inclusion/exclusion criteria.

The RCT literature search retrieved 1,567 studies across PubMed, EMBASE and the Cochrane Library, of which 494 were duplicates, leaving 1,073 unique studies for title and abstract screening. The non-randomized literature search retrieved 2,812 studies, of which 838 were duplicates, leaving 1,974 unique studies for title and abstract screening. The searches ultimately identified no randomized trials and three non-randomized studies that could have potentially informed model updates: the MORE Study (published across two manuscripts by Kennedy et al. in 2017), Jakobs et al., and a prospective, single-arm, observational service evaluation study run as part of an NHS England Commissioning through Evaluation (CtE) program.[33–36] The MORE Study was a retrospective analysis of 606 patients with unresectable colorectal liver metastases treated with SIR-Spheres Y-90 resin microspheres.[33,34] While the MORE Study included a large number of patients overall, the number of patients having received 3 or more lines of therapy was 158, fewer than the 224 patients with primary colorectal tumors in the Bester et al. study used in the 2015 analysis. Jakobs et al. followed 104 consecutively treated patients with unresectable, chemotherapy refractory liver metastases from CRC, but only reported Kaplan-Meier data stratified by carcinoembryonic antigen (CEA) response. Finally, the NHS England CtE program included 399 patients with chemotherapy refractory or intolerant liver metastases from CRC; however, the study included 53 patients who were treated with TheraSphere Y-90 glass microspheres with no stratification of results by SIRT technology. Most importantly, none of the three studies included a control arm or control subjects for comparison.[36] As such, the model structure and clinical data sources from the 2015 publication were retained, and the cost inputs were updated to reflect 2019 values from the UK national healthcare payer perspective.

Model structure

The cost-utility model was developed in Microsoft Excel (Microsoft Corporation, Redmond, WA, USA) and the model structure has been described previously.[24] Microsoft Excel was selected as the modeling software on the basis of its relative ubiquity and its inclusion in the list of acceptable software for submission of economic models to NICE.[37] In brief, the model is structured as a Markov model with three states: pre-progression, post-progression, and death (Figure 1). Transitions into the death health state were governed by a parametric curve fit to Kaplan-Meier data from the 2012 Bester et al. study, a retrospective cohort study including 339 patients in total treated with SIRT with SIR-Spheres Y-90 resin microspheres, of whom 224 had liver

Table 2. Population, intervention, comparators, outcomes, and study design (PICOS) criteria employed in the systematic literature reviews.

Population	Patients with colorectal cancer metastatic to the liver and refractory or intolerant to chemotherapy	
Intervention	SIR-Spheres Y-90 resin microspheres	
Comparators	Best supportive care	
Outcomes	Overall survival	
	Progression-free survival	
	Safety, consisting of any adverse events	
Study design	RCT review	Randomized controlled trials only
	Non-randomized study review	Retrospective, observational or non-interventional studies only
Language	Articles not written in English were excluded unless they were thought to add substantively to the English-language evidence base (e.g. more than 50 patients per trial arm)	

metastases from a primary colorectal tumor.[25] The Bester et al. study also included a standard of care arm, in which 29 of the total 51 patients had metastases from a primary colorectal tumor. At the end of the Bester et al. follow-up period, an estimated 30 of 224 patients in the SIRT arm and 7 of 29 patients in the BSC arm were still alive and extrapolation of the curves by way of parametric curve fitting was therefore required. Nine different model fits to the Kaplan-Meier data were evaluated using the Akaike Information Criterion (AIC) and the model with the lowest score selected for the base case analysis.[38] The best fitting model was used to derive transition probabilities for the daily cycle length employed in the model. The second lowest scoring model was then explored in sensitivity analyses.

As the Bester et al. study did not report Kaplan-Meier data for disease progression, the base case analysis assumed that 50% of living patients would be in the pre-progression state and 50% in the post-progression state, an assumption that was explored comprehensively in one-way sensitivity analyses.

Data from Hendlisz et al. were used to inform the incidence of the seven types of Grade 3 and 4 events that occurred in at least one patient in either arm over the duration of the study: stomatitis, anorexia, fatigue, hand-foot syndrome, dyspnea, pulmonary, and allergy. Grade 1 and 2 events were not captured.

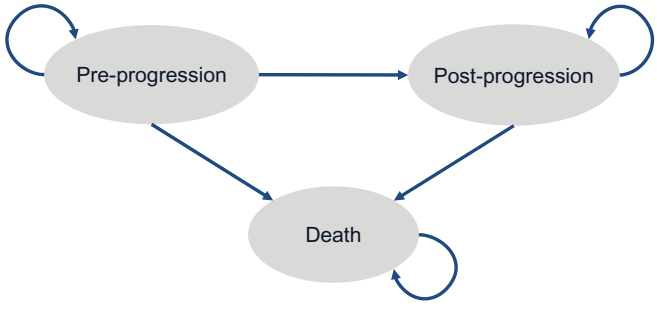

Figure 1. Markov model structure.

Perspective, time horizon, and discounting

The analysis was conducted from the national payer perspective in the UK, which is ultimately that of the Department of Health. The analysis was conducted over a lifetime time horizon. In line with economic modeling guidance from NICE, future costs and effects were discounted at 3.5% *per annum*. All costs were reported in 2019 pounds sterling (GBP).

Cost data

Cost data were obtained from a number of UK-specific sources. In the base case analysis, the cost of SIRT with SIR-Spheres Y-90 resin microspheres in the inpatient setting was modelled based on NHS reference costs in line with the NICE health economic modeling guidance (Table 3). Costs of adverse events were calculated using a combination of costs derived from Healthcare Resource Groups (HRGs) and costs of nurse and clinical examination time from the Personal Social Services Research Unit (PSSRU).[39] Costs associated with chemotherapy regimens were obtained from the British National Formulary in December 2019.[40] Weighting the chemotherapy costs by the doses and regimens reported in Seidensticker et al. resulted in daily chemotherapy cost estimates of GBP 17.66 in the SIRT with SIR-Spheres Y-90 resin microspheres arm, and GBP 20.32 in the BSC arm.

Quality of life

Health-related quality of life (HRQoL) was incorporated into the model using three distinct approaches, of which a state-based approach was adopted in the base case analysis. In the state-based approach, utility values were obtained from

Table 3. Inpatient and outpatient costing of SIR-Spheres based on the 2017–18 National Schedule of Reference Costs.

	SIR-Spheres	
	Value	Source
Outpatient costs for code YR57Z (GBP)	1,123.15	National Schedule of Reference Costs 2017/18
Inpatient cost / day for YR57Z (GBP)	1,757.45	YR57Z Percutaneous, Chemoembolisation or Radioembolisation, of Lesion of Liver
SIR-Spheres Y-90 resin microspheres (GBP)	8,000.00	Sirtex
Costs of inpatient procedure		
Number of work-ups	1.067	Survey and NHS Christie Hospital
Length of stay for work-up (days)	0.69	
Number of procedures	1.022	
Length of stay for procedure (days)	1.19	
Cost of multiple work-ups (GBP)	1,198.40	–
Cost of multiple procedures (GBP)	2,137.38	–
Total inpatient cost with single work-up and procedure (GBP)	11,214.52	–
Total inpatient cost with multiple work-ups and procedures (GBP)	11,511.78	–
Costs of outpatient procedure		
Number of work-ups	1.067	Survey and NHS Christie Hospital
Length of stay for work-up (days)	Outpatient	
Number of procedures	1.022	
Length of stay for procedure (days)	Outpatient	
Cost of multiple work-ups (GBP)	1,198.40	–
Cost of multiple procedures (GBP)	1,147.85	–
Total outpatient cost with single work-up and procedure (GBP)	10,246.30	–
Total outpatient cost with multiple work-ups and procedures (GBP)	10,522.26	–

a 2013 economic evaluation of mCRC treatments after first-line chemotherapy conducted by Hoyle et al.[41] Patients in the pre-progression state were assigned a utility value of 0.75, while patients in the post-progression state were assigned a utility value of 0.69, with the relatively small reduction in HRQoL explained by the expectation that radiological markers would not meaningfully affect patient well-being. In the process of model development, clinicians advised that patients very commonly experience a meaningful reduction in HRQoL shortly before death, which was captured in the model by way of an assumed utility decrement of 0.1 in the 28 days before end-of-life.

The two other approaches to capturing quality of life were a treatment-based approach, in which a single utility value was assigned to patients receiving either BSC or SIRT with SIR-Spheres Y-90 resin microspheres, regardless of progression status, and an approach based on the time since diagnosis. Both of these approaches were explored in sensitivity analyses.

One-way sensitivity analyses

A series of one-way sensitivity analyses were conducted to establish the sensitivity of the model to individual input parameters. One alternative fit to the Kaplan-Meier data (with the second lowest AIC) was explored in the form of a stratified log-normal curve for OS. The split between the pre- and post-progression stages was explored in two analyses by modelling 25% and 75% of the surviving population in the pre-progression state, versus the assumption of 50% in the base case analysis. One sensitivity analysis was run in which 6.7% of patients were modelled as requiring a second work-up and 2.2% of patients were modelled as requiring a second SIRT procedure based on real-world evidence from a cohort of patients treated with SIR-Spheres Y-90 resin microspheres at the Christie Hospital in Manchester. A series of further analyses were then conducted in which the cost and HRQoL assumptions were changed, covering the abolition of adverse event and death costs, and the use of the treatment-based and time since diagnosis-based utilities. One additional utility-based analysis was conducted in which state-based utility values were employed from Sherman et al. 2019 (0.772 in the pre-progression state and 0.672 in the post-progression state).[42] Two analyses were conducted in which the annual discounting rates were set to 0% and 5% for both cost and effectiveness outcomes. Finally, three analyses were conducted in which the cost of SIRT with SIR-Spheres Y-90 resin microspheres was calculated using different methodologies from the base case analysis: one in which the SIRT work-up and procedure were assumed to be conducted in the outpatient setting, and a second analysis in which the NHS reference costs were replaced with 2019/20 HRG tariff values. The third analysis assumed that both the SIRT work-up and procedure would be performed as outpatient procedures on the same day, facilitated by the administration of SIRT through the radial artery (transradial access [TRA]), which significantly reduces recovery time relative to transfemoral access (TFA).[43,44]

Probabilistic sensitivity analyses

Probabilistic sensitivity analysis (PSA) was conducted, sampling from distributions around key model parameters 1,000 times and recording the incremental cost and quality-adjusted life expectancy outcomes from each iteration. The results of each iteration were then plotted on a cost-effectiveness scatterplot and used to generate a cost-effectiveness acceptability curve.

Results

Base case results

The base case analysis showed that SIRT with SIR-Spheres Y-90 resin microspheres would result in undiscounted life expectancy of 2.38 years versus 1.03 years with BSC (Table 4). When also capturing HRQoL, patients treated with SIRT with SIR-Spheres Y-90 resin microspheres experienced a gain of 0.81 quality-adjusted life years (QALYs) relative to patients receiving BSC (1.50 QALYs versus 0.69 QALYs). The increases in quality-adjusted life expectancy were associated with an increase in costs; patients treated with SIR-Spheres Y-90 resin microspheres incurred an average discounted cost of GBP 34,168 versus GBP 15,268 with BSC (Figure 2), corresponding to an increase of GBP 18,900, and yielding an ICER of GBP 23,435 per QALY gained. The higher cost in the SIRT with SIR-Spheres Y-90 resin microspheres arm were driven by the cost of the SIRT procedure (GBP 11,215), and higher costs of monitoring (GBP 3,158 with SIRT versus GBP 1,465 with BSC) and chemotherapy (GBP 13,472 with SIRT versus GBP 7,192 with BSC). These higher monitoring and chemotherapy costs were in turn attributable to the increased survival in the SIRT with SIR-Spheres Y-90 resin microspheres arm.

One-way sensitivity analyses

One-way sensitivity analyses showed that the model was broadly robust and insensitive to changes in individual input parameters, including changes in structural assumptions

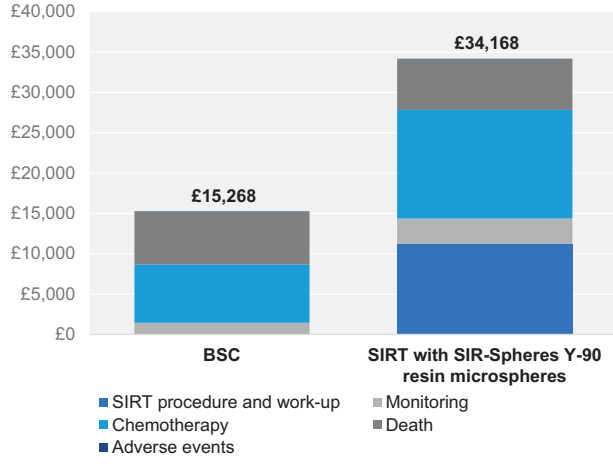

Figure 2. Cost breakdown in the base case analysis. Abbreviations. BSC, best supportive care; SIRT, selective internal radiation therapy.

Table 4. Base case results.

	Undiscounted			Discounted		ICER (GBP per QALY gained)
	Costs (GBP)	QALYs	Life expectancy (years)	Costs (GBP)	QALYs	
Best supportive care	15,954	0.73	1.03	15,268	0.69	
SIR-Spheres Y-90 resin microspheres	36,852	1.71	2.38	34,168	1.50	
Incremental				+18,900	+0.81	23,435

Abbreviations. GBP, 2019 pounds sterling; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SIRT, selective internal radiation therapy.

Table 5. One-way sensitivity analysis results.

Analysis	Cost (GBP)			QALYs			ICER (GBP/QALY)
	SIR-Spheres Y-90 resin microspheres	BSC	Incremental	SIR-Spheres Y-90 resin microspheres	BSC	Incremental	
Base case	34,168	15,268	18,900	1.497	0.690	0.8065	23,435
Bester et al. stratified log-normal curve for OS	34,232	15,085	19,147	1.502	0.675	0.8276	23,135
25% spent in pre-progression state	34,168	15,268	18,900	1.465	0.676	0.7897	23,933
75% spent in pre-progression state	34,168	15,268	18,900	1.528	0.705	0.8233	22,956
Include patients with multiple work-ups and procedures	34,466	15,268	19,197	1.497	0.690	0.8065	23,803
Outpatient reference costs	33,200	15,268	17,932	1.497	0.690	0.8065	22,234
HRG-based costs	43,836	15,268	28,568	1.497	0.690	0.8065	35,421
Transradial SIRT (single day work-up and procedure)	32,077	15,268	16,809	1.497	0.690	0.8065	20,841
Adverse event costs excluded	34,167	15,220	18,947	1.497	0.690	0.8065	23,493
Cost of death excluded	27,846	8,706	19,141	1.497	0.690	0.8065	23,733
Treatment-based utilities	34,168	15,268	18,900	1.725	0.799	0.9253	20,425
Time since diagnosis utilities	34,168	15,268	18,900	1.699	0.789	0.9097	20,776
Progression utilities based as in Sherman et al. 2019	34,168	15,268	18,900	1.501	0.692	0.8087	23,370
0% discount rate for costs and effects	36,852	15,954	20,898	1.705	0.734	0.9713	21,516
5% discount rate for costs and effects	33,339	15,035	18,304	1.433	0.675	0.7578	24,153

Abbreviations. BSC, best supportive care; GBP, 2019 pounds sterling; HRG, healthcare resource group; ICER, incremental cost-effectiveness ratio; OS, overall survival; QALY, quality-adjusted life year; SIRT, selective internal radiation therapy.

around, e.g. the proportions of patients in the pre-progression and post-progression states (Table 5). The largest change from the base case ICER arose in the analysis in which the cost of SIRT with SIR-Spheres Y-90 resin microspheres was based on HRGs rather than NHS reference costs; in this analysis, the cost per SIRT procedure was modelled as GBP 20,882 versus GBP 11,215 in the base case analysis and the resulting ICER was GBP 35,421 per QALY gained, falling above a WTP threshold of GBP 30,000 per QALY gained. All other ICERs fell in the range GBP 20,425 per QALY gained and GBP 24,153 per QALY gained (Table 5).

Two notable sensitivity analyses were those in which the cost of SIRT with SIR-Spheres Y-90 resin microspheres was modelled based on SIRT being performed in the outpatient setting. The first analysis, assuming work-up and procedure were performed on different days showed that the incremental cost of SIRT with SIR-Spheres Y-90 resin microspheres would be reduced to GBP 17,932 with no change in clinical outcomes, resulting in an ICER of GBP 22,234 per QALY gained, GBP 1,201 per QALY less than the base case. The second analysis, assuming that the shorter recovery time associated with TRA versus TFA would allow for both the work-up and SIRT procedures to be performed in one day, demonstrated a further reduction in the incremental cost of SIRT versus BSC to GBP 16,809, resulting in an ICER of GBP 20,841 per QALY gained.

Probabilistic sensitivity analysis

Of the 1,000 model iterations performed during PSA, 99.9% of results fell in the upper right-hand quadrant of the cost-effectiveness scatterplot (Figure 3), corresponding to increased costs and improved quality of life. Plotting these results on a cost-effectiveness acceptability curve over willingness-to-pay (WTP) thresholds of between GBP 0 per QALY gained and GBP 50,000 per QALY gained showed a monotonically increasing likelihood of SIRT with SIR-Spheres Y-90 resin microspheres being cost-effective relative to BSC (Figure 4). At a WTP threshold of GBP 30,000 per QALY gained, there was a 56% likelihood of SIRT with SIR-Spheres Y-90 resin microspheres being cost-effective. Given that patients with mCRC refractory or intolerant are likely to meet NICE end-of-life criteria, with life expectancy of less than 24 months, and SIRT with SIR-Spheres Y-90 resin microspheres improves life expectancy by more than 3 months, a

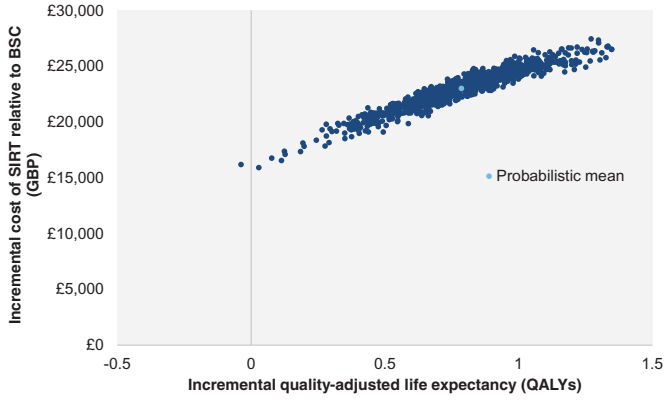

Figure 3. Cost-effectiveness scatterplot showing the results of 1,000 model iterations. Abbreviations. BSC, best supportive care; GBP, 2019 pounds sterling; QALYs, quality-adjusted life years; SIRT, selective internal radiation therapy.

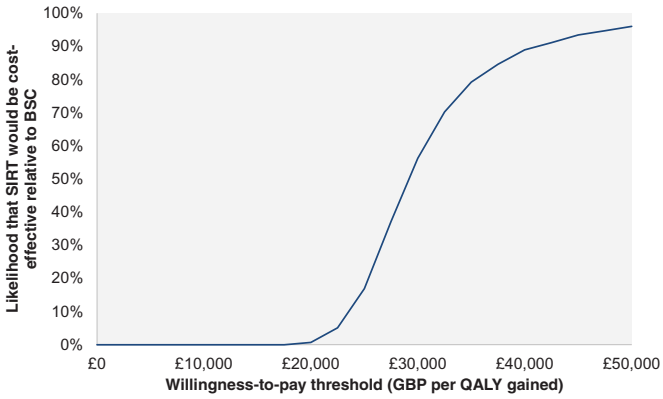

Figure 4. Cost-effectiveness acceptability curve. Abbreviations. BSC, best supportive care; GBP, 2019 pounds sterling; QALYs, quality-adjusted life years; SIRT, selective internal radiation therapy.

WTP threshold of GBP 50,000 per QALY gained may be more applicable based on the 2.5x weight applied to the baseline WTP of GBP 20,000 per QALY.[45,46] At this WTP threshold, the likelihood of SIR-Spheres Y-90 resin microspheres being cost-effective relative to BSC was 96%. When comparing SIRT with TRA versus BSC, the likelihood of cost-effectiveness at a WTP threshold of GBP 50,000 per QALY increased to 100%.

Discussion

The present analysis showed that SIRT with SIR-Spheres Y-90 resin microspheres would be cost-effective relative to BSC in the treatment of patients with unresectable, chemotherapy-refractory liver metastases from CRC from the perspective of the UK national healthcare payer. Using underlying survival data from a retrospective analysis by Bester et al., the model projected a substantial increase in mean life expectancy from 1.03 years to 2.38 years; based on HRQoL utilities from Hoyle et al., this translated to an increase in discounted quality-adjusted life expectancy from 0.69 QALYs to 1.50 QALYs, accompanied by an increase in costs from GBP 15,954 to GBP 36,852 over a lifetime time horizon.

The analysis represents an update to a previously-published UK analysis of SIRT with SIR-Spheres Y-90 resin microspheres versus BSC.[24] Two SLRs conducted ahead of the analysis update only identified three potential candidate studies for updating the previous underlying model of OS based on Bester et al. While none of the studies improved on the previously employed study with regard to methodological rigor or sample size, comparisons of the clinical outcomes with those from the Bester et al. analysis are instructive. The Bester et al. publication reported median OS of 11.9 months with SIRT (95% confidence interval: 10.1–14.9 months) versus 6.6 months in the BSC cohort ($p = .001$). In contrast, in the NHS England CtE analysis, median OS with SIRT was just 7.6 months, but the lack of comparator group limits the interpretability of the findings; the OS of 7.6 months was 0.7 months shorter than that reported in patients treated with SIR-Spheres Y-90 resin microspheres in the Seidensticker et al. matched-pair analysis, in which the median OS in the comparator (BSC) arm was just 3.5 months, strongly suggesting that the prognosis may have been poor in both the NHS England CtE and Seidensticker et al. studies.[26] Notably, in Seidensticker et al. the mortality hazard ratio with SIR-Spheres Y-90 resin microspheres was 0.3 ($p < .001$) in spite of the poor prognosis. The MORE study reported median OS of 9.1 months in 184 patients having failed two lines of chemotherapy, and 8.1 months in 158 patients having received three or more lines of therapy.[34] Overall, the Jakobs et al. study reported median survival of 10.2 months (95% CI: 7.8–13.0 months), but 55% of patients had extrahepatic disease, compared with 37% in the overall Bester et al. population. Jakobs et al. showed that there was a trend toward longer OS in patients without extrahepatic disease, with a median of 13.5 months (95% CI: 8.2–16.4 months) versus 8.7 months (95% CI: 7.4–10.7 months) in patients with extrahepatic disease.

Given the use of the same underlying clinical data, the present analysis yielded the same effectiveness outcomes as the original 2015 analysis, showing incremental quality-adjusted life expectancy of 0.81 QALYs and an improvement in life expectancy of 1.12 years. Since the 2015 analysis, the incremental cost of SIRT with SIR-Spheres Y-90 resin microspheres versus BSC has decreased, partly as a result of a reduced cost of performing the SIRT work-up and procedure from the NHS perspective. In the 2016 analysis, the total modeled cost was GBP 14,248, which has fallen to GBP 11,216 in the inpatient setting, and GBP 10,246 in the outpatient setting; the cost of the SIR-Spheres Y-90 resin microspheres device is unchanged. The overall cost in the BSC also increased from GBP 12,730 in the 2015 analysis to GBP 15,954 in the present analysis, driven primarily by the increased costs associated with death and chemotherapy. Both the reduced costs of SIRT with SIR-Spheres Y-90 resin microspheres and the higher cost of BSC contribute to the reduction in the ICER from GBP 28,216 per QALY gained in 2015 to the present estimate of GBP 23,435 per QALY gained.

While cost-effectiveness analyses in chemotherapy refractory patients with mCRC are relatively scarce, two manuscripts were published in 2018, both detailing evaluations of the cost-utility of TAS-102 relative to BSC in the UK based on a cost-utility model submitted to NICE as part of the Servier company submission to the single technology appraisal (STA) of TAS-102.[47,48] In the STA, the base case ICER submitted by Sevier was GBP 44,032 per QALY gained based on an incremental quality-adjusted life expectancy benefit of TAS-102 of 0.17 QALYs and an incremental cost of GBP 7,574, capturing a discount to the TAS-102 list price negotiated as part of a patient access scheme (PAS). The evidence review group ran different analyses with the same model, yielding ICERs of GBP 52,695 per QALY and GBP 49,392 per QALY based on smaller incremental quality-adjusted life expectancy benefits of 0.14 QALYs and 0.15 QALYs, depending on whether the clinical data were obtained exclusively from the RECOURSE trial or from a pooled analysis of the RECOURSE and J003-10040030 phase II trials, respectively.[49,50] Outside of the STA context, Bullement et al. published a base case cost-effectiveness analysis excluding the PAS discount, and also

comparing regorafenib with TAS-102 and BSC, based on the same trials of TAS-102, and the CORRECT trial of regorafenib.[47,51] The analysis showed an improvement of 0.17 QALYs with TAS-102 versus BSC at an additional cost of GBP 8,479, resulting in an ICER of GBP 51,194. The same study found TAS-102 to be dominant relative to regorafenib.

Three analyses have also recently been published in the US setting and, while they are not therefore entirely comparable with the present analysis in the UK, the modeling approaches may be generalizable even while the findings across all three studies of negligible QALY gains at high costs may be specific to the US setting. A cost-effectiveness analysis published by Goldstein et al., evaluated the cost-effectiveness of regorafenib versus placebo in third-line treatment of mCRC, finding that regorafenib resulted in an additional 0.04 QALYs versus placebo at a cost of USD 39,391, resulting in an incremental cost-effectiveness ratio of USD 897,411 per QALY.[52] Secondly, a 2018 publication by Cho et al. presented the findings of a US cost-effectiveness analysis of regorafenib and TAS-102 relative to BSC.[53] Relative to BSC, regorafenib and TAS-102 resulted in ICERs of USD 395,223 per QALY and USD 399,740 per QALY gained versus BSC, respectively. Finally, the Sherman et al. analysis of maintenance capecitabine and bevacizumab in mCRC informed the HRQoL one-way sensitivity analyses conducted in the present analysis.[42] The analysis evaluated the cost-effectiveness of maintenance capecitabine and bevacizumab versus "observation" over 60 months from the US Medicare perspective, finding that the intervention was not cost-effective with incremental costs of USD 105,217 per patient and minimal gains in incremental QALYs (1.7 quality–adjusted life months) resulting in an ICER of USD 725,601 per QALY gained.[42]

As with all modeling studies, the present analysis had a number of limitations that should be acknowledged. The most notable limitation of the analysis resulted from the lack of PFS data from the Bester et al. study and the resulting need to make assumptions around the rate of disease progression in those patients remaining alive. The assumption that, at any given point, 50% of living patients would be in the pre- and post-progression states was explored in sensitivity analyses with only a limited effect on the ICER; changing the assumption to model 25% and 75% in the pre- and post-progression states resulted in changes of less than GBP 500 per QALY gained from the base case analysis. The stability of the results was driven by the application of the same assumption in both arms, combined with the relatively small reduction in HRQoL associated with progression of 0.06 QALYs per year of life as reported in the Hoyle et al. study.[41]

Other potential limitations arose from the heterogeneity of the data sources; survival estimates were driven by the Bester et al. study, adverse event incidence was driven by data from the Hendlisz et al. RCT, while chemotherapy regimens and dosing data were taken from the Seidensticker et al. matched-pair comparison.[25–27] The assimilation of these data sources was necessary as no single study reported data on all aspects of treatment that would be anticipated to incur substantial costs or result in significant changes in patient survival or HRQoL. Again, each of these individual aspects of the analysis were explored in sensitivity analyses, including the omission of adverse event costs, and the use of alternative models for OS and assumptions for PFS, with no material changes in the findings.

Since the publication of the 2015 cost-effectiveness analysis, the only addition to the treatment armamentarium for patients with chemotherapy refractory mCRC has been TAS-102, which has been approved for use in third-line therapy, joining regorafenib, which was approved in 2013. The adverse event profiles of these agents along with patient performance status typically determine the choice of treatment.[54] The adverse event profile of SIRT is well-studied and is superior to both regorafenib and TAS-102, with a low incidence of all-grade or grade 3–4 AEs known to severely affect patient quality of life, such as diarrhea, hand-foot skin reaction, vomiting or fatigue. Furthermore, the up-front risk of complications from the SIRT procedure can be reduced with adequate treatment planning and patient selection.[55] The use of TRA rather than TFA may further reduce the incidence of complications after SIRT. In 2019, Liu et al. conducted a randomized cross-over study of TFA versus TRA, demonstrating that, relative to TFA, TRA significantly reduced pain scores overall during the procedure, at the access site during the procedure, and in the recovery room in patients with HCC.[44] TRA was also associated with significantly shorter recovery times (108 min versus 153 min, $p = .0193$).[44] As illustrated in the sensitivity analyses, TRA has the potential to reduce the cost, and thereby increase the cost-effectiveness, of SIRT by enabling both work-up and treatment to be performed on the same day. Furthermore, the potential to perform SIRT in an outpatient care setting has the potential to reduce the number of hospital visits, which has become increasingly important during the COVID-19 pandemic, both in terms of reducing patient exposure to infection and freeing up healthcare professionals to assist in the treatment of patients with COVID-19.

One final potential limitation of the analysis was the omission of liver-related laboratory test abnormalities; given the mode of action of SIRT, this could be perceived as a source of bias in the analysis. The MORE Study showed that a high proportion of patients had mild-to-moderate (mostly grade 1 or 2) baseline laboratory abnormalities prior to SIRT with Y-90 resin microspheres, including alkaline phosphatase, AST, albumin and hemoglobin. While MORE showed significant increases in severe (grade 3 and 4) laboratory test values for total bilirubin, albumin, alkaline phosphatase, and aspartate aminotransferase after SIRT with Y-90 microspheres, all incidence rates were below 10% 90 days after treatment.

In indications such as mCRC in which patients are facing an adverse prognosis with limited therapeutic options, the availability of locoregional options such as SIRT in addition to regorafenib and TAS-102 addresses a great unmet clinical need, especially in RAS mutant patients for whom anti-EGFR agents such as cetuximab or panitumumab are ineffective.[18] From the patient perspective, SIRT using Y-90 resin microspheres represents an appealing alternative with lower administration burden and no reduction in quality of life.

Conclusions

The present cost-utility analysis demonstrated that, relative to BSC, SIRT with Y-90 resin microspheres would be a cost-effective treatment option in patients with unresectable chemotherapy refractory liver-only or liver-dominant metastases arising from CRC in the UK. Given the substantial unmet clinical need in this patient population, the finding of cost-effectiveness relative to BSC provides assurances that, in addition to the established safety and efficacy of SIR-Spheres Y-90 resin microspheres, SIRT also has a favorable economic profile.

Notes

i. STIVARGA is a registered trademark of Bayer, Leverkusen, Germany.
ii. TAS-102, LONSURF is a registered trademark of Servier, Suresnes, France and Taiho, Princeton, NJ, USA.

Transparency

Declaration of funding

The study was funded by Sirtex Medical United Kingdom Ltd.

Declaration of financial/other relationships

RFP is a director and shareholder of Covalence Research Ltd, which received consultancy fees from Sirtex Medical United Kingdom Ltd (a wholly-owned subsidiary of the manufacturer of SIR-Spheres Y-90 resin microspheres) to conduct the analysis and prepare the manuscript. VKB and FC are full-time employees of Sirtex Medical United Kingdom Ltd. SS is a director and full-time employee of Sirtex Medical United Kingdom Ltd.

A peer reviewer on this manuscript has disclosed that they have conducted research with Y-90, though received no funding for it. The peer reviewers on this manuscript have no other relevant financial relationships or otherwise to disclose.

Author contributions

VKB, FC, SS, and RFP conceived of the study; RFP conducted the systematic literature reviews; VKB and RFP selected the model base case parameters; VKB, FC, SS, and RFP designed the sensitivity analysis plan; RFP ran the analyses, prepared the tables and figures, and drafted the manuscript; VKB, FC, and SS reviewed the draft manuscript for intellectual content and made substantive revisions. All authors approve of the final version of the manuscript.

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Research involving human participants and/or animals

This article does not contain any studies with human participants or animals performed by any of the authors.

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