Cedar

Healthcare Technology Research Centre

Commissioning through Evaluation: Selective internal radiation therapy (SIRT)

Evaluation report

CONFIDENTIAL

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Key messages

- Published evidence on the clinical efficacy of SIRT compared to best supportive care in patients with unresectable, chemotherapy-refractory colorectal cancer is of limited quality and at risk of bias. Two retrospective studies report a survival benefit from SIRT of approximately 5 months. One small randomised controlled trial showed that disease progression was delayed; overall survival was not improved but the study was not designed to detect a statistically significant difference in this outcome. Adverse event rates were similar between the groups. Studies with no comparator group indicate that patients treated with SIRT live an average of 9.6 months. Patients' quality of life during this time has not been adequately studied.
- Patients with chemotherapy-refractory intrahepatic cholangiocarcinoma live for 15 months on average following SIRT. This is based on small published studies with no comparator group to show whether SIRT confers a survival advantage.
- A new study based on data collected from patients treated recently with SIRT in the NHS was carried out (SIRT CtE registry study), and showed the following:
    - Patients with colorectal cancer who received SIRT lived for a median of 7.6 months, and progressed after 3.0 months; 30% of patients were alive at 12 months following treatment with SIRT.
    - Patients with intrahepatic cholangiocarcinoma lived for a median of 8.7 months after having SIRT, and progressed after 2.8 months; 37% of patients were alive at 12 months following treatment with SIRT.
    - The impact of SIRT on patients' quality of life could not be reliably determined
    - Severe complications were uncommon. Most adverse events were mild, and the most common types were fatigue and abdominal pain.

  The reliability of the results from this study is limited by the absence of a comparator group and a study design which is at risk of bias.
- A new cost-effectiveness model was created by the external assessment centre as part of the commissioning through evaluation project to compare SIRT to best supportive care in patients with colorectal cancer which has progressed following standard treatment. The model showed:
    - SIRT was likely to be clinically effective (increased quality adjusted life years) for an additional cost, but very unlikely to be cost-effective at a willingness to pay threshold of £30K.
    - The incremental cost-effectiveness ratio was £85K, which was mostly due to the cost of the SIRT procedure itself.

  The model is limited by the absence of high quality comparative data, and its results depend on the assumption that SIRT is clinically effective.
- A published cost-effectiveness model created by a different research group (Pennington et al. 2015) was more optimistic with an incremental cost-effectiveness ratio of £28K. The difference is due to the model authors using a lower procedure cost for SIRT and a longer survival time.

Contents

Abbreviations

5-FU	5-fluorouracil
AE	Adverse event
AIC	Akaike Information Criterion
ALT	Alanine aminotransferase
AST	Aspartarte aminotransferase
BSA	Body surface area
BSC	Best supportive care
CDF	Cancer drugs fund
CI	Confidence interval
CisGem	Cisplatin and gemcitabine
CR	Complete response
CRC	Colorectal cancer
CRCLM	Colorectal cancer liver metastases
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CtE	Commissioning through evaluation
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EHM	Extrahepatic metastases
EORTC	European Organisation for Research and Treatment of Cancer
ESMO	European Society for Medical Oncology
FOLFIRI	Folinic acid plus fluorouracil plus irinotecan
FOLFOX	Folinic acid plus fluorouracil plus oxaliplatin
GI	Gastrointestinal
HAI	Hepatic artery infusion
HCC	Hepatic cholangiocarcinoma
HR	Hazard ratio
HRQoL	Health related quality of life
ICC	Intrahepatic cholangiocarcinoma
ICER	Incremental cost-effectiveness ratio
IPO	Interventional procedure overview
IQR	Interquartile range
LPFS	Liver-specific progression-free survival
LTFU	Lost to follow up
MAA	Macro-aggregated albumin
mCRC	Metastatic colorectal cancer
MID	Minimally important difference
MRI	Magnetic resonance imaging
NA	Not applicable
NHS	National Health Service
NHSE	NHS England

NICE	National Institute for Health and Care Excellence
NR	Not reported
OS	Overall survival
PD	Progressive/progressed disease
PFS	Progression-free survival
PR	Partial response
PROM	Patient reported outcome measure
PS	Performance status
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
QOL	Quality of life
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumours
RILD	Radiation-induced liver disease
SC	Standard care
SD	Stable disease
SE	Standard error
SIRT	Selective internal radiation therpay
TACE	Transarterial chemoembolisation
TACI	Transarterial chemoinfusion
TARE	Transarterial radioembolisation
TNM	Tumour node metastases
TTLP	Time to liver progression
TTP	Time to progression
ULN	Upper limit of normal
VAS	Visual analogue scale
VEGF	Vascular endothelial growth factor
XELOX	Capecitabine plus oxaliplatin
Y-90	Yttrium-90

Authorship & acknowledgements

About Cedar

Cedar is an NHS-academic evaluation centre which is part of Cardiff and Vale University Local Health Board and Cardiff University. The majority of Cedar's work is funded by NICE. Cedar has worked as an external assessment centre (EAC) for NICE's medical technologies evaluation programme since 2010. We provide independent assessment of new or innovative medical technologies (including devices and diagnostics). As a healthcare technology research centre, Cedar focuses on research and evaluation involving medical devices and diagnostics. We work with the NHS, academic institutions, commercial sector, publicly funded organisations, and charities. Our areas of expertise include systematic reviewing, health economics, clinical trial facilitation, qualitative research, analysis of routinely-collected and linked health data, and medical device regulations.

Authorship

Dr Judith White was project lead for the SIRT CtE study. JW performed the data analysis of clinical data. JW wrote sections 1, 2, 3, 4, 5, 6, and 7 of this report. JW reviewed Section 8 and carried out the searches in Section 6. JW collated Section 9.

Megan Dale produced the cost-effectiveness model and wrote Section 8. MD also quality checked Section 4.

Dr Helen Morgan carried out the literature searches in Sections 4 and 5 and wrote Sections 4.3 and 4.5. HM also carried out quality assurance on Section 5 and 6.

Dr Grace Carolan-Rees reviewed all sections, provided comments, and approved the final version prior to submission to NICE.

Dr Bernadette Sewell provided guidance on the cost-effectiveness model, provided quality assurance on Section 8 and added comments.

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1 Executive summary

1.1 Background

1.1.1 Colorectal cancer

Colorectal cancer (CRC) includes cancers of the colon, rectum, and appendix. CRC is the third most common cancer in the UK. Approximately 28% of patients diagnosed with CRC are at TNM stage IV where the cancer has metastasised outside of the primary location, which has a 5 year survival of 3%. Systemic chemotherapy is the first choice treatment for unresectable metastatic disease, and NICE recommends a range of chemotherapy combinations for first and second line treatment of metastatic CRC (mCRC). For patients who have progressed following standard therapies, the aim of further treatments is to prolong life, improve symptoms and maintain quality of life. NICE recommends trifluridine-tipiracil for adults who have had previous treatment with available therapies.

1.1.2 Intrahepatic cholangiocarcinoma

Intrahepatic cholangiocarcinoma (ICC) is a rare type of primary liver cancer originating in the bile ducts. Fewer than 1,600 people in Great Britain are diagnosed with ICC each year. The 5 year survival rate for metastasised unresectable ICC is approximately 2%. Most patients are diagnosed with non-resectable disease. For patients with advanced and inoperable ICC, cisplatin and gemcitabine is an effective first line systemic treatment. Second-line chemotherapy is not standard care in patients with ICC.

1.1.3 Selective internal radiation therapy

Selective internal radiation therapy (SIRT) is used to treat cancerous tumours in the liver. It involves delivering microspheres containing a beta−emitting radionuclide, such as yttrium-90, directly into the tumour by infusing them into the hepatic artery.

1.2 Objective

The objective of this Commissioning through Evaluation (CtE) project was to evaluate the clinical and cost-effectiveness of SIRT in the following patient groups:

1. Patients with unresectable mCRC in the liver which has progressed following at least two lines of standard chemotherapy;
2. Patients with unresectable primary ICC which has progressed following at least one previous chemotherapy line.

Clinical outcomes of interest were overall survival (OS), progression free survival (PFS), liver-specific PFS (LPS), health related quality of life (HRQoL), and safety.

The CtE project included a review of published literature on the clinical and cost-effectiveness of SIRT compared to best supportive care (BSC), analysis of new data collected as part of the SIRT CtE registry study, and a *de novo* cost-effectiveness model produced by Cedar.

1.3 Published clinical evidence

A systematic review of evidence on the clinical efficacy of SIRT in the aforementioned patient groups was carried out in January 2017. Medline, EMBASE, Cochrane library, Scopus and EconLit were searched and a total of 1,170 articles were retrieved. In the CRC population, three systematic reviews and 24 primary studies, of which 3 were comparative, were selected for inclusion. In the ICC population, two systematic reviews and 10 non-comparative primary studies comprising a total of 247 patients were included.

1.3.1 Patients with colorectal cancer (CRC) treated with SIRT

In the CRC population, two retrospective comparative studies found statistically significant improvements in OS when SIRT was compared to BSC. In one of these studies, patients receiving BSC survived for a median of 6.6 months compared with 11.9 months in patients who received SIRT (HR 0.5; p=0.001). In the second study, patients receiving BSC had an OS of 3.5 months compared to 8.3 months for patients who received SIRT (HR 0.26; p<0.001). Retrospective matched-pair studies such as these are at risk of bias from imbalanced prognostic factors, poor standardisation of control arm treatments, and variability in outcome measures.

In a small randomised controlled trial comparing fluorouracil chemotherapy alone to SIRT plus chemotherapy, PFS and LPFS were improved in the SIRT arm (PFS 2.1 vs 4.5 months; HR 0.51; p=0.03; LPFS 2.1 vs 5.5 months; HR 0.38; p=0.003) demonstrating prolonged control of liver tumour growth. In this trial, patients were permitted to cross-over following progression. No statistically significant improvement in OS was observed (7.3 vs 10.0 months; HR: 0.92; p=0.80) but this trial was not powered to detect a change in this outcome, and the cross-over design may obscure any survival benefit. Severe adverse event rates were low in the RCT and not significantly different between groups. Mild abdominal pain, nausea, and fatigue were the most common events in patients treated with SIRT in comparative studies.

A large body of evidence from single-arm observational studies on CRC patients was identified. OS was reported in all 23 comparative and non-comparative studies selected (2,517 patients) and ranged from 6.0 to 12.7 months (weighted mean 9.6 months [95% CIs 8.9-10.4]). PFS was reported in 9 studies (437 patients) and ranged from 2.8 to 9.2 months (weighted mean 4.0 months). LPFS was reported in 8 studies (376 patients) and ranged from 2.0 to 9.0 months (weighted mean 4.4 months). HRQoL was an outcome in only one study of patients with CRC and was poorly reported. The non-comparative, observational design of the majority of studies in this area can provide limited evidence on the clinical effectiveness of SIRT.

1.3.2 Patients with intrahepatic cholangiocarcinoma (ICC) treated with SIRT

In the ICC population, two systematic reviews and 10 non-comparative primary studies comprising a total of 247 patients were included. No comparative studies were identified. Median OS ranged from 9.0 to 22.0 months (weighted mean 15.3 months [95% CIs 12.0-18.7]). Median progression free survival was not reported in any of the studies. No studies reported HRQoL as an outcome.

1.3.3 Patients with CRC or ICC treated with best supportive care

A literature review was conducted to identify studies which reported survival estimates from patients with CRC or ICC (matching the population of interest) treated with BSC where the comparator was not SIRT. The purpose was to provide additional context to non-comparative data on SIRT. Direct comparisons to data from patients treated with SIRT in other studies should be avoided due to the high risk of bias. In the CRC population, seven RCTs were identified where BSC was the control treatment (1,156 BSC patients). BSC tended to be poorly defined and varied by institution; usually BSC aimed to provide palliative treatment without using investigational cancer therapies. Median OS in 7 studies ranged from 2.4 months to 6.6 months (weighted mean 5.3 months [95% CIs 4.7-5.8]). Median PFS ranged from 1 month to 7.3 months in 5 studies (weighted mean 3.2 months [95% CIs 2.9-3.5]). No studies were identified which reported OS in patients with chemotherapy-refractory ICC who received BSC.

1.4 Ongoing or recently completed trials

Nine ongoing or recently completed and unpublished studies were identified which were related to the SIRT CtE evaluation. Of these, 7 were RCTs and 2 were registries. No studies were identified which matched the chemotherapy-refractory CRC or ICC populations, and therefore none were directly relevant to the decision problem. A conference abstract recently reported results from a large combined analysis of RCT data from chemotherapy-naive patients, indicating that SIRT does not provide an additional survival benefit to first-line chemotherapy in this population. Generalisability of these results in generally chemotherapy-sensitive patients to the CtE decision problem is limited since the CtE population is chemotherapy-refractory or chemotherapy-intolerant.

1.5 Analysis of data from the SIRT CtE registry study

1.5.1 Methods

A single-arm, observational, service evaluation study aimed to evaluate SIRT in ten NHS centres in England was carried out between December 2013 and March 2017. The two eligible populations were adults with i) unresectable, chemotherapy-refractory CRC liver metastases; and ii) unresectable, chemotherapy-refractory primary ICC. Data on baseline characteristics, the SIRT procedure, safety, survival, and HRQoL were collected on an on-line registry. OS was the primary outcome.

1.5.2 Results

A total of 399 patients with CRC and 61 with ICC were included in the analysis of the SIRT CtE registry. Most patients had an ECOG performance status of 0 or 1 (93% CRC cohort; 91% ICC cohort). In the CRC group, 60% of patients did not show evidence of extrahepatic metastatic disease and 78% had received two or three previous lines of chemotherapy. The majority of ICC patients had received one or two lines of chemotherapy prior to SIRT (81%). In the CRC group 72% of patients had a single SIRT procedure which was of palliative intent; this value was 56% for the ICC group. Patients required hospitalisation for 1 or 2 nights for the SIRT procedure. A minority of patients (35% of CRC cases; 12% of ICC cases) received concomitant chemotherapy and some patients also received chemotherapy following SIRT (22% of CRC cases; 15% of ICC cases).

Patients were followed-up for a median of 14.3 months (95% CIs 9.2-19.4). At the end of the study, 240 (60%) CRC deaths were recorded and 33 (54%) deaths in the ICC cohort. Median OS was 7.6 months (95% CIs 6.9 – 8.3) in the CRC cohort, and 8.7 months (95% CIs 5.3-12.1) in the ICC cohort. Survival at 12 months following SIRT was 30% in the CRC group and 37% in the ICC group. PFS was 3.0 months (95% CIs 2.8-3.1) in the CRC cohort, and 2.8 months (95% CIs 2.6-3.1) in the ICC cohort. LPFS in the CRC cohort was 3.7 months (95% CIs 3.2-4.3) and 3.1 months (95% CIs 1.3-4.8) in the ICC group. Of the patients who had hepatic and extrahepatic progression dates recorded, these occurred at the same time in 81% and 82% of CRC and ICC patients, respectively; extrahepatic progression occurred before hepatic progression in 16% and 9% of CRC and ICC patients, respectively. Subgroup analyses identified covariates associated with a survival benefit in the CRC group: absence of extrahepatic disease, fewer liver tumours, smaller tumour to liver volume percentage, and being male.

HRQoL measured using EQ-5D-5L and EQ-VAS remained relatively high and constant between baseline and follow-up time points in the CRC group. A statistically significant reduction in HRQoL was observed between baseline and 3-months after SIRT but this was small and not clinically relevant. Methodological weaknesses meant that reliable conclusions about the impact of SIRT on patients' quality of life cannot be drawn from this study.

Severe complications on the day of treatment (no grade was recorded in the registry) were reported in 11 CRC patients (3%) and 1 ICC patient (2%). During the follow-up period 36% of CRC patients experienced an adverse event, of which 8% of the events were grade ≥3. In the ICC cohort, 49% of patients experienced an adverse event during the follow-up period, or which 7% were grade ≥3. The most frequently reported adverse events were mild (grade 1-2) fatigue and abdominal pain in both cohorts.

1.5.3 Discussion

This large, pragmatic, observational study is likely to reflect real-life practice in the NHS but is limited by the absence of a comparator treatment group. OS, PFS, and LPFS results from the CRC cohort are within the lower range of previously published estimates. The reliability of the study's findings is limited by high levels of missing data for certain outcomes, the absence of external data validation (in the form of triangulation with routinely collected data or against source documents), and

variability in how outcomes were measured and treatment techniques arising from the absence of a research protocol.

1.6 Published cost-effectiveness evidence on SIRT

A systematic review of economic literature on the cost-effectiveness of SIRT yielded 144 studies, of which one was relevant and was included in the review (Pennington et al. 2015). This modelled the cost-effectiveness of SIRT compared to BSC in patients with unresectable, chemotherapy-refractory CRC. The model demonstrated a total cost of £35,487 for SIRT and £12,730 for BSC; the difference was driven primarily by the initial cost of the SIRT procedure and the monthly costs for monitoring and treatment during the additional survival time in SIRT patients. The model calculated an increase in quality adjusted life years (QALYs) in the SIRT group of 0.81 compared to BSC (1.50 vs 0.69), and the improved survival resulted in a cost per QALY gained (or incremental cost-effectiveness ratio [ICER]) of £28,216. The model used an appropriate structure and described most assumptions. The lack of high quality comparative evidence limits the reliability of the model results. The overall survival time used for SIRT patients was longer than in alternative studies, and this is likely to favour SIRT. Sensitivity analysis was carried out to test the robustness of the model's results to changes in key inputs, although the cost of SIRT (another key driver) was inadequately explored. The choice of inputs and ranges used for sensitivity analysis may underestimate the overall cost per QALY and ICER and the uncertainty reported in the model. Alternative approaches used in external assessment centre model highlight the impact of these choices.

1.7 *De novo* cost-effectiveness model of SIRT compared to best supportive care by the external assessment centre

1.7.1 Methods

A new model was created by the external assessment centre to estimate the cost-effectiveness of SIRT compared with BSC in patients with unresectable, chemotherapy-refractory CRC. The SIRT CtE registry data, published studies, and clinicial opinion were used as sources of model inputs. The model used a 3-state partitioned survival analysis. Kaplan-Meier curves from the SIRT CtE registry data for OS and PFS were extrapolated and hazard ratios were taken from available published comparative studies to create a survival curve for the BSC arm of the model. A SIRT procedure cost of £21,870, based on NHS England tariff, was used. Costs for chemotherapy, patient monitoring, and treating adverse events were applied to both SIRT and BSC arms. Published utility values were applied to the progression-free and progressed states.

1.7.2 Results

The ICER for SIRT was £85,350 in the base case of the external assessment centre model. Treatment with SIRT resulted in an increase in QALYs of 0.32 (0.58 vs 0.26). The model showed that SIRT was £27,406 more expensive than BSC (£31,028 vs £3,623 discounted costs). This was primarily due to high initial procedure costs in the SIRT arm. The cost of the SIRT procedure and the survival time were the main drivers in the model. Probabilistic sensitivity analysis showed that all simulations

resulted in additional benefits in QALYs from SIRT compared to BSC for additional costs. From 3,000 simulations, 0.7% fell under a £30K willingness to pay threshold and 11.0% fell under the £50K threshold.

1.7.3 Discussion

The *de novo* cost-effectiveness model by the external assessment centre demonstrates that SIRT is unlikely to be considered cost effective in the UK (by the usual threshold used by NICE) when the technology is used in patients with CRC which has failed standard available therapies. The ICER for SIRT compared to BSC may be lower when used in patients with a longer life expectancy where the initial procedure cost is spread over a longer period. The model was limited by the absence of a control group in the SIRT CtE registry data. The model uses a hazard ratio which in turn assumes clinical effectiveness of SIRT (a QALY benefit at additional cost). This may not be a reliable assumption.

The higher base case ICER in the current *de novo* model (£85K) compared to Pennington et al. (£28K) can be attributed to a higher cost for the SIRT procedure and shorter OS estimate used in the *de novo* model.

There is inadequate data to make a reliable conclusion about the generalisability of the model to the ICC population.

2 Scope & project management

2.1 Project objective

To evaluate the clinical and cost-effectiveness of selective internal radiation therapy (SIRT) in treating patients with:

1. unresectable, chemotherapy-refractory, metastatic colorectal cancer (mCRC) in the liver, or
2. unresectable, chemotherapy-refractory, primary intrahepatic cholangiocarcinoma (ICC).

2.2 Project scope

The scope for the SIRT CtE evaluation is outlined below (Table 2.1).

Table 2.1. Scope for SIRT CtE project evaluation

Intervention	Selective internal radiation therapy
Population	1. People with unresectable, liver-dominant, metastatic colorectal cancer which has progressed following at least two lines of standard chemotherapy (i.e. irinotecan and oxaliplatin based chemotherapy) or those for whom standard chemotherapy is not suitable. 2. People with unresectable intrahepatic cholangiocarcinoma which has progressed following at least one line of standard chemotherapy or those for whom standard chemotherapy is not suitable.
Comparators	Best supportive care (this may include active symptom management using chemotherapy)
Outcomes	The outcome measures to be considered include: • overall survival (primary outcome) • progression-free survival • liver-specific progression free survival • response rates • adverse effects of treatment • health-related quality of life
Economic analysis	In line with the NICE reference case, a cost-effectiveness modelling approach has been selected with incremental cost per quality-adjusted life year (QALY) as the key outcome measure. The model will compare SIRT to best supportive care. Due to a paucity of evidence relevant to the ICC population, cost-effectiveness modelling will be carried out for the colorectal cancer population only.

2.3 Project background

Commissioning through Evaluation (CtE) is a NHS England (NHSE) programme which enables new treatments with limited evidence to be commissioned in a small number of centres with a planned evaluation. In 2013, SIRT was selected for evaluation under the CtE programme in two patient populations. Ten centres in England were appointed to undertake a total of approximately 165-220 procedures each year over approximately 3 years. Each centre collected data from SIRT procedures

conducted as part of the CtE project onto a registry hosted by the British Society for Interventional Radiologists (BSIR). The ten centres were:

- Cambridge University Hospitals NHS Foundation Trust
- Kings College Hospital NHS Foundation Trust
- Leeds Teaching Hospitals NHS Trust
- Newcastle-upon-Tyne Hospitals NHS Trust
- Nottingham University Hospitals NHS Trust
- Oxford University Hospitals NHS Foundation Trust
- The Christie NHS Foundation Trust
- The Royal Free London NHS Foundation Trust
- University Hospital Southampton NHS Foundation Trust
- University Hospitals Birmingham NHS Foundation Trust

NICE was commissioned to undertake the evaluation of the SIRT CtE project and appointed one of its external assessment centres, Birmingham & Brunel Consortium, to lead this work. In April/May 2015, a different centre, Cedar (Cardiff & Vale University Health Board & Cardiff University) was reallocated the evaluation project.

Cedar's role was to independently evaluate the SIRT CtE project in order to answer the following questions from NHS England:

1. Does treatment with SIRT for the clinical indications covered within the CtE scheme increase overall survival?
2. Does treatment with SIRT for the clinical indications covered within the CtE scheme increase liver and wider progression free survival?
3. What is the patient experience of treatment with SIRT for the clinical indications covered within the CtE programme?
4. What is the actual cost, and relative cost-effectiveness, of treatment with SIRT for the clinical indications covered within the CtE programme?
5. Does the data suggest any differential benefit for particular cohorts of patients within the wider clinical indications covered within the scheme?
6. Are there any factors from the experience of provision within centres participating in the scheme that should be taken into account in terms of future service provision, should the service become routinely commissioned by the NHS?
7. Are there any research findings that have become available during the course of the CtE scheme that should be considered alongside the evaluative findings of the CtE scheme?

3 Background

3.1 Metastatic colorectal cancer

Colorectal cancer includes cancers of the colon (large bowel), rectum, and appendix. Most colorectal cancers are adenocarcinomas. Metastatic CRC is TNM (tumour node metastases) stage IV or Dukes' D stage, and is also referred to as advanced colorectal cancer. CRC may be classified as TNM stage IVA where the metastasis is confined to one organ or site, or TNM stage IVB where there are metastases in more than one organ/site or the peritoneum. Approximately 28% of patients diagnosed with CRC are at TNM stage IV. The most common metastatic sites are the regional lymph nodes, liver, lungs, and peritoneum.

CRC is the third most common cancer in the UK and in 2014 there were 41,265 new cases of bowel cancer diagnosed (Cancer Research UK 2017). The lifetime risk of developing CRC is approximately 1 in 18 for men and 1 in 21 for women in England and Wales (NICE 2014a). In 2014, 15,903 people died from bowel cancer in the UK; 80% were in people aged 65 and over. The 5 year survival of patients diagnosed with TNM stage IV CRC is 3%.

A key risk factor for CRC is age, and 90% of bowel cancer cases occur in people aged 60 or over (NHS Choices 2016b). Diet, weight, activity levels, alcohol, smoking, and family history are other risk factors for CRC.

3.1.1 Current care pathway for advanced metastatic colorectal cancer

NICE recommends that control of symptoms should be the priority for managing mCRC (NICE 2014a). This may involve the use of surgery, chemotherapy, radiotherapy and supportive care. Resection of the primary or metastatic tumours is considered where possible but the majority (70-80%) of patients are unsuitable for resection due to clinical or technical reasons such as severe co-mobidities or unresectable extra-hepatic disease (Zampino et al. 2016).

Systemic chemotherapy is the first choice treatment for unresectable metastatic disease. Locoregional therapies such as transarterial chemoembolisation (TACE), hepatic artery infusion (HAI) chemotherapy, ablative therapies, and SIRT, may also be considered.

NICE recommends one of the following chemotherapy combinations as first-line treatments for CRC (NICE 2014a):

- FOLFOX (folinic acid plus fluorouracil plus oxaliplatin) as first-line treatment then single agent irinotecan as second-line treatment or
- FOLFOX as first-line treatment then FOLFIRI (folinic acid plus fluorouracil plus irinotecan) as second-line treatment or
- XELOX (capecitabine plus oxaliplatin) as first-line treatment then FOLFIRI (folinic acid plus fluorouracil plus irinotecan) as second-line treatment.

Chemotherapy may be combined with biological agents such as EGFR (epidermal growth factor receptor) inhibitors (cetuximab or panitumumab) or VEGF (vascular endothelial growth factor) inhibitors (bevacizumab). NICE recommends raltitrexed only for patients with advanced colorectal cancer who are intolerant to 5‑fluorouracil and folinic acid, or for whom these drugs are not suitable.

For patients who have progressed following standard first and second line therapies for advanced mCRC the aim of third line treatments is to prolong life, improve symptoms and maintain quality of life. Currently there are limited options available for patients with chemotherapy refractory advanced mCRC.

In 2016, NICE recommended trifluridine-tipiracil for adults who have had previous treatment with available therapies including fluoropyrimidine-, oxaliplatin- or irinotecan-based chemotherapies, anti-vascular endothelial growth factor agents and anti-epidermal growth factor receptor agents, or when these therapies are not suitable[1] (NICE 2016). NICE's recommendation was based on two randomised controlled trials comparing trifluridine-tipiracil to placebo plus best supportive care in patients who had mCRC which had progressed following at least two previous lines of standard chemotherapy. Compared with placebo, trifluridine–tipiracil increased median overall survival by 2.4 months (Yoshino et al. 2012) and by 2.0 months (Mayer et al. 2015). The committee considered this increase in survival to be small but clinically meaningful.

According to the NICE pathway for advanced mCRC, subsequent treatment options after trifluridine-tipiracil are supportive and palliative care (Figure 3.1).

Bevacizumab, cetuximab and panitumumab are not recommended by NICE at third line or beyond (NICE 2012) and were removed from the cancer drugs fund (CDF) approved list on 4 November 2015 (source: NICE committee papers for TA405). Regorafenib is licensed for patients with mCRC who have been treated with standard therapies (or for whom these are unsuitable) but is not recommended by NICE because of a non-submission of evidence by the manufacturer (NICE 2015).

3.1.2 Number of patients with unresectable chemotherapy-refractory mCRC in the UK

In the manufacturer submission for the NICE technology appraisal TA405 (NICE 2016) they estimate that 2,600 patients each year would reach the stage of third-line therapy for mCRC and be motivated to receive further treatment (England only). The sponsor acknowledged that a significant proportion of these patients may opt to enter clinical trials. Importantly, the evidence review group noted that this estimate which is based partly on clinical opinion may be unreliable. The population eligible to receive SIRT in a chemotherapy-refractory setting may be further reduced because only patients with liver-dominant mCRC would be suitable. Further technical considerations and the development of other third-line therapies approved by NICE (e.g. trifluridine-tipiracil) may also reduce the population eligible for SIRT in a chemotherapy-refractory setting.

[1] NICE recommend this therapy only when the company provides trifluridine–tipiracil with the discount agreed in the patient access scheme

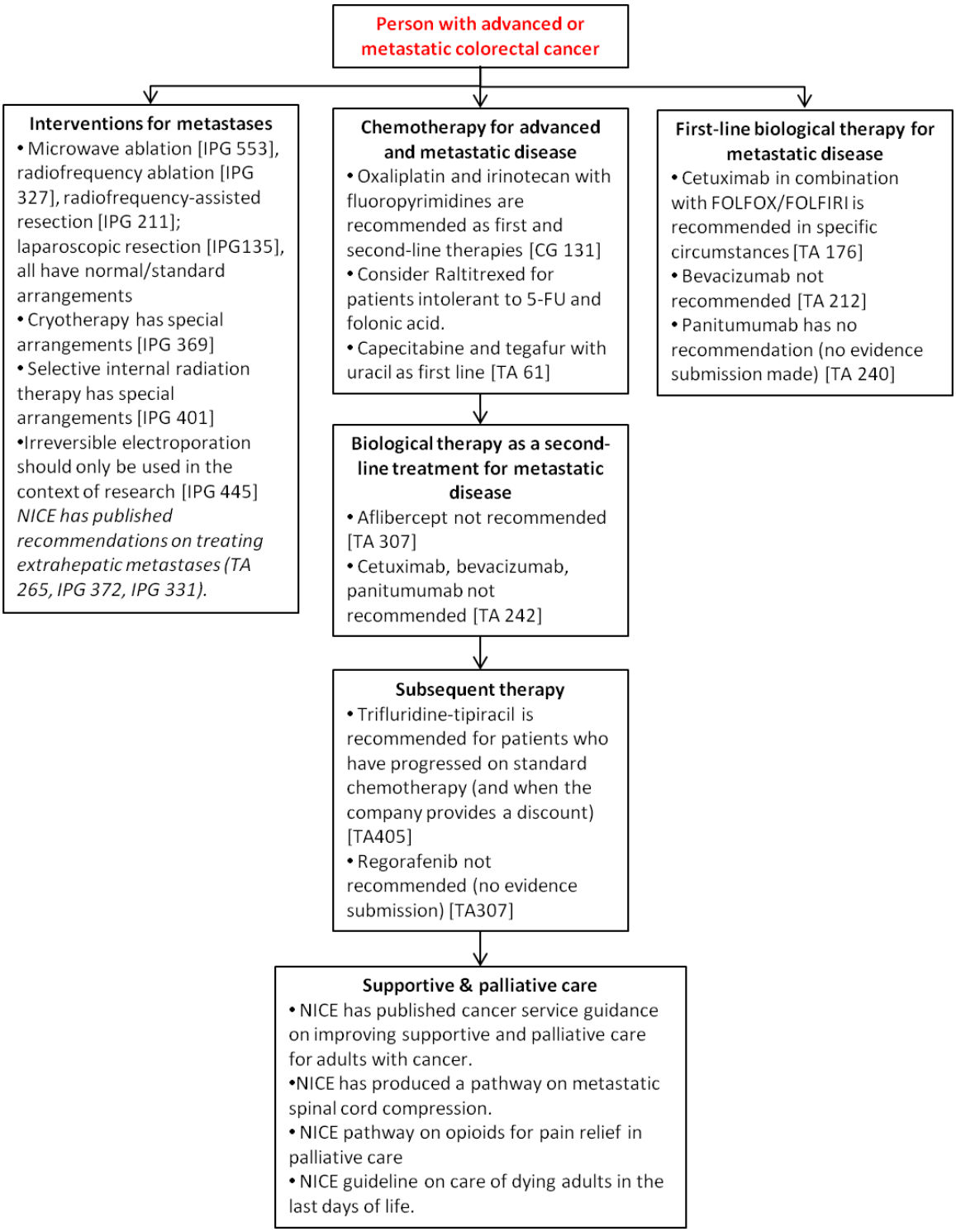


Figure 3.1 Treatment pathway for patients with advanced and metastatic colorectal, based on NICE guidance and adapted from NICE pathways.

3.2 Intrahepatic cholangiocarcinoma

Cholangiocarcinomas (bile duct cancers) are primary liver cancers which arise from the epithelial cells of the bile ducts. These cancers are rare but are often lethal due to advanced stage at presentation. Most cholangiocarcinomas are too advanced for curative survival resection. ICCs can originate from either small intrahepatic ductules (peripheral cholangiocarcinomas) or large intrahepatic ducts proximal to the bifurcation of the right and left hepatic ducts. The majority of cholangiocarcinomas (>90 percent) are adenocarcinomas, squamous cell carcinoma comprise most of the remaining cases .

Fewer than 1,600 people in Great Britain (Northern Ireland figures not available) are diagnosed with ICC each year. The 5 year survival rate for resectable ICC is between 20 and 40%; the 5 year survival rate for metastasised unresectable ICC is approximately 2% (Cancer Research UK 2015). Risk factors for bile duct cancer include primary sclerosing cholangitis, bile duct abnormalities (e.g. fibropolycystic liver disease), biliary stones (hepatolithiasis), chronic liver disease (cirrhosis and viral infection), infection with a liver fluke parasite, exposure to certain chemicals and toxins (e.g. Thorotrast)(NHS Choices 2016a). Rates of ICC have been rising in Western countries which may be explained by factors such as improved detection and diagnosis, misclassification, migration, increasing burden of chronic liver disease, and the potential role of environmental toxins (Valle et al. 2016).

3.2.1 Current care pathway for intrahepatic cholangiocarcinoma

Surgical resection with clear margins is the only potentially curative approach for patients with ICC. Most patients (>65%) however are diagnosed with non-resectable disease and have only palliative chemotherapy and supportive care as options (Bridgewater et al. 2014; Lamarca et al. 2014a; Valle et al. 2016). NICE has not produced clinical guidelines on the treatment of cholangiocarcinoma but has interventional procedures guidance (NICE 2005; NICE 2013b; NICE 2013c). The standard options for palliative treatment include chemotherapy, surgical bypass of the bile duct or the insertion of a stent using surgical, endoscopic or percutaneous techniques (NICE 2013b).

Patients with unresectable ICC may also be suitable for loco-regional therapies such as radiation therapy, TACE, transarterial chemoinfusion (TACI), radiofrequency ablation, and SIRT. The evidence base for loco-regional therapies in ICC is weak and these approaches are not established (Bridgewater et al. 2014).

For patients with advanced and inoperable ICC, cisplatin and gemcitabine has been demonstrated as an effective first line systemic treatment. The UK advanced biliary cancer 02 (ABC-02) clinical trial demonstrated a survival advantage of CisGem over gemcitabine alone (11.7 months vs 8.1 months; HR 0.64, 95% CI 0.52-0.80; p<0.001) and established CisGem as a reference regimen (Valle et al. 2010). Oxaliplatin is considered to be an appropriate alternative to cisplatin

There is no randomised controlled trial evidence supporting the use of second-line chemotherapy for patients who have progressed following first line chemotherapy. Currently active symptom

control, including management of biliary tract obstruction and infection and other symptoms arising from tumour progression, is the standard of care (Bridgewater et al. 2014; Lamarca et al. 2014a).

In a systematic review by Lamarca et al. (2014) the authors conclude that despite a paucity of quality evidence, second-line chemotherapy in advanced biliary cancers (including ICC) may be of potential benefit in selected patients such as those with good performance status. A phase III RCT (ABC-06 NCT01926236) is underway in the UK comparing FOLFOX chemotherapy to active symptom control which will elucidate the role of second line chemotherapy in advanced biliary cancer.

3.2.2 Number of patients with unresectable chemotherapy-refractory ICC in the UK

Approximately 1,600 people are diagnosed with ICC in England, Wales, and Scotland each year. Of these 60-70% (960-1120 people) are unsuitable for resection (TNM Stage III or IV) (Bridgewater, et al. 2014) and would be offered first-line chemotherapy. Of these, approximately 15% (144-168) may be suitable for second line treatments; this value is based on the number of patients in the ABC-02 trial who progressed to second-line treatment (Valle et al. 2010). It is unclear how many of these patients would meet the eligibility criteria for SIRT.

3.3 Selective internal radiation therapy

SIRT, also called transarterial radioembolisation (TARE) or radioembolisation (RE), is a form of intra-arterial brachytherapy used to treat tumours in the liver. These may be primary tumours (e.g. from ICC or hepatic cholangiocarcinoma) or metastatic tumours from primary cancers such as CRC. SIRT involves delivering microspheres containing a beta-emitting radionuclide, such as yttrium-90 (Y-90), directly into the tumour via the hepatic artery (Giammarile et al. 2011). This is carried out using a percutaneous transarterial approach. Microspheres are delivered preferentially to the tumour, limiting radiation damage to healthy surrounding tissue.

During the SIRT procedure, radiolabeled microspheres are infused into the hepatic artery supplying the tumour via a microcatheter which is usually accessed through the femoral artery. SIRT can be applied to the whole liver in one session through infusion in the right hepatic artery followed by infusion in the left hepatic artery, or to separate lobes a few weeks apart. This choice depends on the patient's liver function, tumour burden and prior chemotherapy exposure. The procedure is performed under local anaesthesia and oral or intravenous analgesia may be required. It takes about 1 hour and is carried out under X-ray guidance and patients usually stay in hospital for 1 to 2 days after the procedure.

A multidisciplinary team composed of specialists in interventional and diagnostic radiology; medical, radiation and surgical oncology; transplant surgery; nuclear medicine; hepatology; medical physics and radiation safety is necessary to provide a SIRT service.

3.3.1 Pre-SIRT work-up procedures

Before SIRT is undertaken, pre-treatment work-up and planning is carried out. Patients undergo general health checks, liver function tests, specialist imaging techniques and hepatic arteriography.

Selective coil embolisation of arteries to the stomach and duodenum is required in some patients to limit the delivery of microspheres outside the liver. The procedure is carried out under local anaesthesia in an angiography suite by an interventional radiologist. A trans-femoral catheter is placed under X-ray guidance to enable selective catheterisation of the hepatic artery.

After embolisation, technetium-99m labelled macro-aggregated albumin (MAA) is injected through the catheter with the tip positioned at the level where the microspheres will be delivered and a nuclear medicine scan is done. This maps the distribution of the isotope in the liver, to determine the extent of arteriovenous shunting to the lungs, and to ensure that there is no extrahepatic uptake of the isotope. Patients may need an additional pre-SIRT embolisation procedure if there is evidence of extra-hepatic uptake. Although treatment planning aims to selectively deliver microspheres to the tumour, any SIRT procedure will invariably result in some degree of irradiation of normal liver tissue.

3.3.2 SIRT medical devices

Two Y-90 microspheres devices are currently CE marked for SIRT in liver tumours, SIR-Spheres (Sirtex Medical) and TheraSphere (Biocompatibles UK; Table 3.1). A third medical device, QuiremSpheres (Quirem Medical, The Netherlands), was recently CE marked for use in SIRT and is available in the UK. This device uses poly-L-lactic acid microspheres containing holmium-166. This device was not available in the UK when the SIRT CtE project started and therefore has not been included further in this report.

Table 3.1. Characteristics of SIRT Y-90 microspheres

Characteristics	SIR-Spheres	TheraSphere
Manufacturer	Sirtex Medical	Biocompatibles UK
Material	Resin	Glass
Radionuclide	Yttrium-90	Yttrium-90
Diameter	20-60 µm	20-30 µm
Specific gravity	1.6 g/dL	3.6 g/dL
Activity per particle	40-70 Bq	2500 Bq
Average number of microspheres per vial	40-80 million	1.2–8 million

(Adapted from Giammarile et al. 2011)

3.3.2.1 SIR-Spheres

SIR-Spheres are sterile, single-use, resin microspheres containing yttrium-90. They are supplied at 3 GBq Y-90 per vial in 5 ml water for injection in a shielded shipping vial. Each vial contains 40–80 million microspheres, ranging from 20–60 micrometres in diameter (median diameter 32.5 micrometres). The maximum range of beta emission in tissue is 11 mm with a mean of 2.5 mm. A typical treatment with SIR‑Spheres consists of infusing 1.4–2.0 GBq Y-90 (30–40 million resin microspheres), into the hepatic artery at the site of the tumour. The dose delivered to the patient's liver is calculated through the body surface area (BSA) method or through the partition model method. The dose of beta radiation needed by the patient is used to calculate the volume of SIR‑Spheres needed.

SIR-Spheres are supplied with the following accessories:

- 1 single use SIR-Spheres delivery system
- a reusable acrylic delivery box
- v-vial
- v-vial holder.

SIR-Spheres are administered with the delivery system, using water for injection or 5% glucose to pulse push. Another syringe containing contrast medium can be connected to the delivery system, allowing intermittent contrast medium injection to assess and maintain forward flow throughout. The microspheres are infused into the delivery catheter from the v-vial using standard 10 ml or 20 ml syringes (Giammarile et al. 2011).

3.3.2.2 TheraSphere

TheraSphere consists of sterile, single–use, glass microspheres containing Y-90 as an integral component of the glass matrix. The steam sterilised microspheres have a mean diameter range of 20–30 micrometres and a specific activity of 2,500 Bq per microsphere at calibration. They are supplied in 6 dose sizes: 3, 5, 7, 10, 15 or 20 GBq in 0.6 ml pyrogen-free water supplied in a 1 ml vial, enclosed in an acrylic shield. Custom dose sizes are also available in increments of 0.5 GBq between 3 and 20 GBq. A single treatment with TheraSphere contains 1.2–8 million microspheres. The recommended dose to the liver is 80 Gy to 150 Gy. The amount of radioactivity needed to deliver the desired dose (in Gy) to the liver is calculated from liver volume converted to liver mass.

TheraSphere is supplied with the following accessories:

- One single-use TheraSphere administration set which includes a disposable tubing set and 1 empty sterile vial.
- One reusable non-sterile administration accessory kit (supplied to each site), including an acrylic box base, top shield, removable side shield and bag hook.

The administration set and administration accessory kit are used to deliver the microspheres in a volume of 60 ml saline (3 × 20 ml syringes).

3.4 Position of SIRT in treatment pathway

Currently, SIRT is not routinely commissioned in England for any indication (NHS England 2013). Before the CtE project began, SIRT was locally commissioned.

3.4.1 Colorectal cancer

The SIRT CtE study is designed to evaluate the efficacy of SIRT in patients with CRC who have previously been treated with at least two lines of standard chemotherapy (typically, oxaliplatin and irinotecan with fluoropyrimidines) or unless the patient has a specific contraindication to chemotherapy or cannot tolerate either regimen. This would position SIRT at an equivalent point in the care pathway as trifluridine-tipiracil which is recommended for adults who have had previous

treatment with available therapies including fluoropyrimidine-, oxaliplatin- or irinotecan-based chemotherapies, anti-vascular endothelial growth factor agents and anti-epidermal growth factor receptor agents, or when these therapies are not suitable (Figure 3.2). SIRT as a first line treatment for colorectal cancer has been evaluated by the SIRFLOX, FOXFIRE and FOXFIRE global trials, as a maintenance therapy by the SIR-step trial, and as a second line therapy by the EPOCH trial, respectively (see Section 6).

3.4.2 Intrahepatic cholangiocarcinoma

SIRT as a first line treatment for ICC is currently being evaluated by the SIRCCA clinical trial (see Section 6). The SIRT CtE study is designed to evaluate the efficacy of SIRT in patients who have previously been treated with standard chemotherapy (typically cisplatin and gemcitabine) or patients with a specific contraindication to chemotherapy.

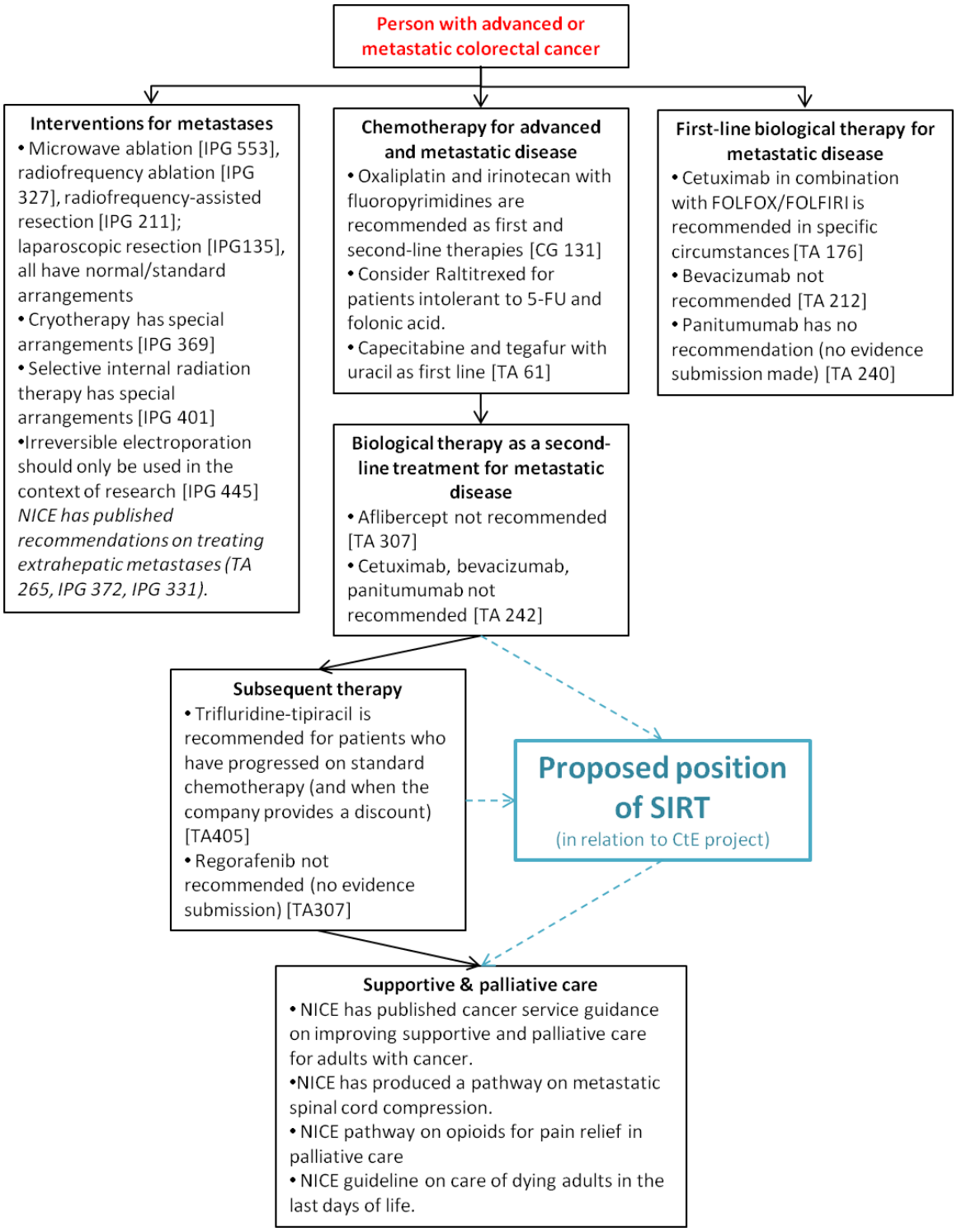


Figure 3.2. Proposed position of SIRT in the current care pathway for patients with advanced and metastatic colorectal cancer

4 Systematic review: Efficacy of SIRT for unresectable chemotherapy-refractory CRC liver metastases, and unresectable ICC

4.1 Summary

The purpose of this review was to systematically review and summarise the evidence on the efficacy of SIRT in patients with unresectable, liver-dominant, chemotherapy refractory CRC or ICC. The primary outcome was OS. A systematic literature search was conducted of Medline, EMBASE, Cochrane library, Scopus and EconLit and retrieved a total of 1,170 articles. Methodological weaknesses and considerable heterogeneity across included studies were identified.

Colorectal cancer liver metastases: Three systematic reviews and 24 primary studies were selected for inclusion in this review. Twenty-one studies were non-comparative (14 retrospective, 7 prospective) and three were comparative (2 retrospective observational, 1 randomised controlled trial). There was some heterogeneity across included studies in several prognostic factors.

Two retrospective comparative studies found statistically significant improvements in OS when SIRT was compared to standard therapy (11.9 vs 6.6 months [HR: 0.5]; 8.3 vs 3.5 months [HR: 0.26]). No statistically significant improvement in OS was observed in a small RCT comparing fluorouracil chemotherapy alone with SIRT plus chemotherapy (7.3 months vs 10.0 months [HR: 0.92]). Patients in the control arm were permitted to cross over to receive SIRT which may confound the OS estimate. PFS and LPFS were improved in the SIRT arm of the RCT (PFS 4.5 vs 2.1 months [HR: 0.51; p=0.03]; LPFS 5.5 vs 2.1 months [HR: 0.38; p=0.003]). No significant difference in severe adverse event rates was observed in the RCT. The most common adverse events in patients treated with SIRT in comparative studies were abdominal pain, fatigue, and nausea.

OS was reported in all 23 comparative and non-comparative studies and ranged from 6.0 to 12.7 months (weighted mean 9.6 months [95% CIs 8.9-10.4]). In a subset of 12 studies which reported OS in patients who had received at least two previous lines of chemotherapy, OS ranged from 7.0 to 11.6 months (weighted mean 9.1 months [95% CIs 8.4-9.7]). Median PFS ranged from 2.8 to 9.2 months in 9 studies (PFS weighted mean 4.0 months); LPFS was reported in 8 studies and ranged from 2.0 to 9.0 months (LPFS weighted mean 4.4 months). Survival proportions at 12 months ranged from 24% to 50% in 9 studies; survival at 24 months ranged from 0% to 25% in 6 studies. One study had health related quality of life (HRQoL) as an outcome although reporting was poor; anxiety levels, but not depression, reduced following SIRT. Results from this review were similar to those reported in three recent systematic reviews.

Intrahepatic cholangiocarcinoma: Two systematic reviews and 10 non-comparative primary studies comprising a total of 247 patients were included in this review. Median OS ranged from 9.0 to 22.0 months (weighted mean 15.3 months [95% CIs 12.0-18.7]). Median progression free survival was not reported in any of the studies. Survival proportions were reported in 4 studies, with survival at 12

months reported as between 33% and 68%. No studies reported HRQoL as an outcome. Results in this review were similar to those reported in two systematic reviews.

Discussion: The single arm, observational design of the majority of studies in this area can provide important insights into safety and technical success; but limited evidence on the efficacy and effectiveness of SIRT. There is a substantial risk of unreliable outcome measures such as survival and disease response. Retrospectively matched comparative studies risk bias from imbalanced prognostic factors, poor standardisation of control arm treatments, and variability in outcome measures. Such studies risk producing unrelaible effect sizes and should be interpreted with caution.

This review provides insights which are important to the SIRT CtE project. This review highlights the shortage of comparative studies, particularly prospectively designed studies such as RCTs. The impact of SIRT on patients' quality of life is an under-researched area.

Conclusions: This systematic review showed that patients with unresectable, chemotherapy-refractory CRCLM treated with SIRT live an average of 9.6 months. Two retrospective studies showed that SIRT confers a survival advantage of approximately 5 months. Limited available evidence suggests that SIRT delays overall progression and liver-specific progression. Evidence on the impact of SIRT on patients' quality of life is unreliable. Most studies on SIRT are observational with a substantial risk of bias. Patients with unresectable ICC treated with SIRT live between 9 and 22 months. There is no comparative evidence on whether SIRT improves survival in this population, and no evidence on progression free survival. Prospective and comparative studies (including measurement of HRQoL) are needed.

4.2 Introduction

This review aims to provide an overview of published evidence on the efficacy or effectiveness[2] of SIRT as a treatment for unresectable, liver dominant, chemotherapy-refractory CRCLM or unresectable ICC (i.e. populations which match those treated under SIRT CtE).

The methods used to select studies were the same across both CRCLM and ICC populations and have been presented together in Section 4.3. The results for each population have been presented separately in Section 4.4 (CRC) and Section 4.5(ICC).

4.3 Methods

4.3.1 Literature search

A systematic review of the evidence on the efficacy of SIRT for treating unresectable CRCLM or ICC was conducted. The searches conducted for the NICE interventional procedure overviews on SIRT (NICE 2013a; NICE 2013b) were reviewed and updated or adapted where necessary. As the searches for the interventional procedure overviews covered the period to February 2011, searches for this review were updated to cover the period January 2011 to January 2017.

A strategy was developed in Ovid Medline (see Appendix 2) and was adapted to the following databases: Medline In-Process; Embase; Cochrane Library (components: CDSR, Other reviews, CENTRAL, NHS EED); EconLit; Scopus; Pubmed (epub ahead of press only). No language restriction was applied. Results of all searches were combined in a Reference Manager 12 database together with the references of studies included in both the IPOs. The reference lists of any relevant systematic reviews were checked for additional studies.

4.3.2 Study selection

After de-duplication, one reviewer (HM or JW) selected publications that were considered relevant based on titles or abstracts using the inclusion and exclusion criteria presented in Tables 4.1 and 4.2. In a second selection round, an independent reviewer (JW) looked at full text articles and selected studies to be included in the review. Uncertainties were discussed and agreed upon between two reviewers (HM and JW).

The review search yielded 1,170 potentially relevant studies (Figure 4.1), 179 were retained for assessment of eligibility at full-text. Following this assessment 54 were retained for quality assessment and data extraction.

[2] In this instance the terms efficacy and effectiveness have been used interchangeably because the evidence does not adequately distinguish the terms.

Table 4.1 Inclusion and exclusion criteria for study selection of unresectable CRC

Inclusion	Exclusion
• Patients with unresectable CRCLM • Treatment with yttrium-90 SIRT • Data on OS	• Predominantly chemotherapy-naive patients (where SIRT is used as a first line treatment) AND results not stratified on number of previous lines of chemotherapy • Sample size <30 • CRC patients are not analysed separately • Animal studies • Non-English language • Conference abstracts

Table 4.2 Inclusion and exclusion criteria for study selection of ICC

Inclusion	Exclusion
• Patients with unresectable ICC • Treatment with yttrium-90 SIRT • Data on OS	• Only chemotherapy-naive patients (where SIRT is used as a first line treatment) • Sample size <10 • ICC patients are not analysed separately • Animal studies • Non-English language • Conference abstracts

4.3.3 Quality Assessment

Following study selection, systematic reviews were assessed with the SURE (2013) critical appraisal checklist for systematic reviews and comparative studies were assessed using the SURE checklist for RCT and other experimental studies. Non-comparative studies were assessed using a series of questions derived from checklists for observational studies that were deemed applicable to non-comparative studies, sources included the CASP checklist for Cohort Studies and Chan and Bhandari (2011). Assessment was performed by either HM or JW.

4.3.4 Data Extraction

The following data were extracted by one reviewer (HM or JW) from the selected studies: study design, technology, concurrent therapy, patient characteristics (including number of previous chemotherapy lines, previous liver directed therapy, and proportion of patients with limited extra hepatic metastases). In a cohort of mixed primary origin, only CRCLM or ICC data were extracted. The primary outcome was median OS. Secondary outcomes were PFS, LPFS, HRQoL and tumour response rates.

4.3.5 Statistical methods

Meta-analysis was not conducted due to high heterogeneity between studies, a lack of RCTs and comparative study designs. A pooled analysis was performed on studies reporting median OS, PFS, and LPFS to present a weighted mean of medians. Weight was applied based on the number of participants in each study. Pooled confidence intervals were also calculated.

4.4 Results of systematic review - colorectal cancer

4.4.1 Objective of current review

The purpose of this review was to provide an updated overview of the efficacy of SIRT in patient with unresectable CRCLM. The focus was on patients who are refractory to chemotherapy and are receiving SIRT following progression on at least two lines of chemotherapy.

4.4.2 Selected studies

The systematic literature search yielded 1,170 potentially relevant studies (Figure 4.1). Thirty-five primary studies were selected for full data extraction. Eight primary studies were subsequently excluded because of a high likelihood of patients being included in later publications (Chua 2011; Fendler et al. 2013; Kennedy et al. 2006; Lewandowski 2014; Mulcahy et al. 2009; Sato et al. 2008; Shady et al. 2016a; Shady et al. 2016b). Three systematic reviews, 3 comparative studies, and 21 non-comparative studies were included in this review (Table 4.3).

Table 4.3. Studies included in this review (CRC population)

Study types	Studies included in this review
Systematic reviews	3 studies: Rosenbaum 2013; Saxena et al. 2014; Zacharias 2015
Comparative	3 studies: 1 RCT (Hendlisz et al. 2010), 2 retrospective comparative (Bester et al. 2012; Seidensticker et al. 2012)
Non-comparative	21 studies: 7 prospective (Benson 2013; Cosimelli et al. 2010; Golfieri et al. 2015; Jakobs 2017; Maleux et al. 2015; Rosenbaum et al. 2016; Saxena et al. 2015) 14 were retrospective(Cianni et al. 2009; Damm et al. 2016; Hickey et al. 2015; Jakobs et al. 2008; Janowski et al. 2017; Kalva et al. 2014; Kennedy et al. 2015; Lahti 2015; Lam et al. 2014; Sabet et al. 2015; Schmeel 2016; Schonewolf 2014; Smits 2013; Sofocleous 2015).

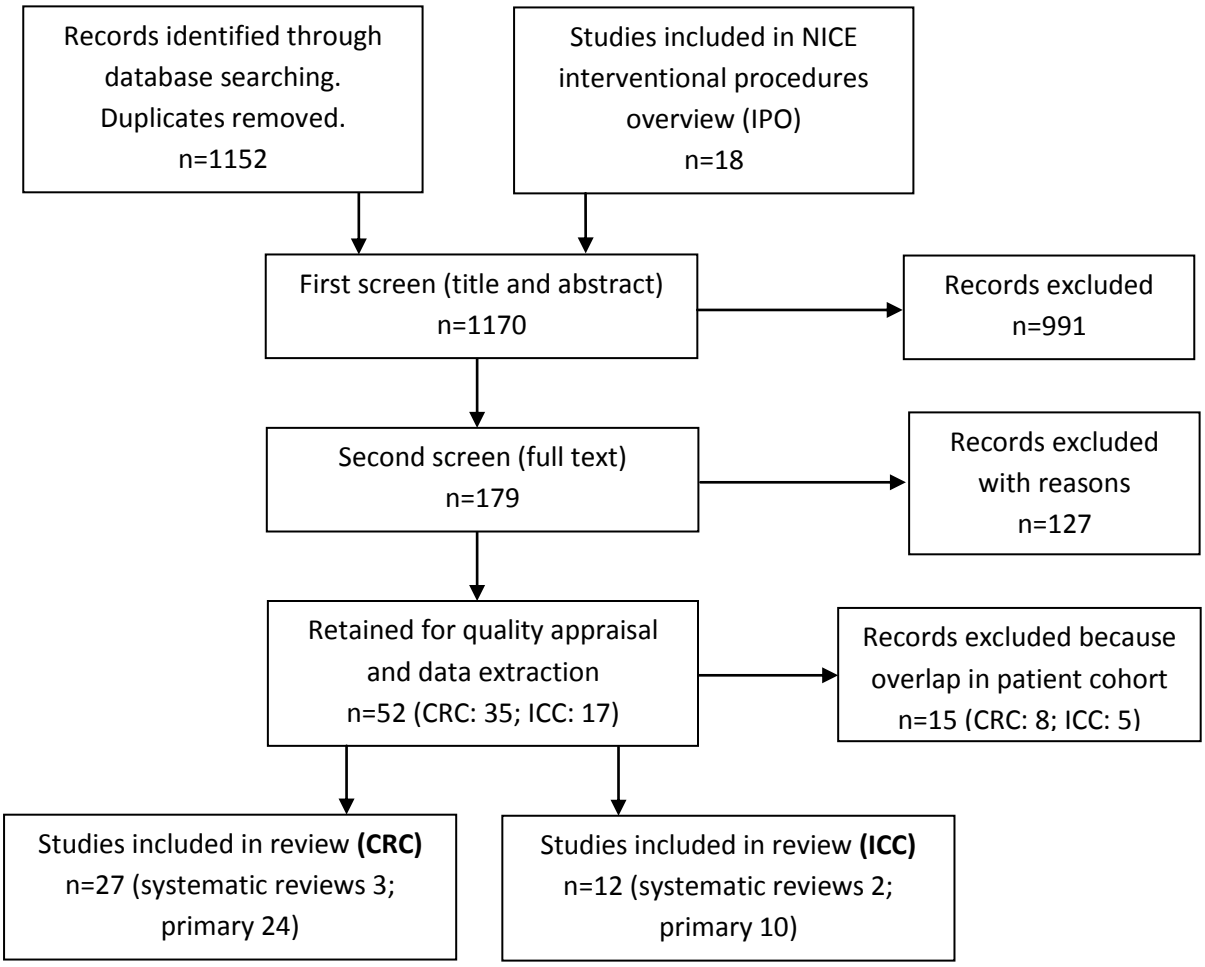


Figure 4.1. Flow diagram of selected studies

4.4.3 Previous systematic reviews

Ten reviews (including Health Technology Assessment reports) were identified and assessed for their relevance to this review. Three were recent (published since 2010) and relevant to this review and their findings have been summarised below (Rosenbaum 2013; Saxena et al. 2014; Zacharias 2015). There is substantial overlap in the studies included in the three systematic reviews.

Zacharias et al. (2015) systematic review

This review compared the effectiveness of hepatic artery based therapies (SIRT, HAI, and TACE) in patients with unresectable CRCLM. The authors searched only PubMed (May 2003-June 2013) with an appropriate range of search terms. Study selection criteria were clearly described, a flow diagram was included, and details of the authors' quality appraisal findings were published. The majority of included studies were observational.

The review included 24 SIRT studies (with 1,268 patients), 52 HAI studies (3,000 patients) and 14 TACE studies (1,038 patients). The majority of patients in the SIRT and TACE groups had received at least one prior line of chemotherapy (94% and 91% respectively).

Median OS was 11.4 months (95% CI 10.2-12.6) for SIRT, 16.0 months (95% CI 14.7-16.4) for HAI, and 21.0 (95% CI 20.6-22.4) for TACE as calculated by a random effects meta-analysis. For patients who had received at least one previous line of chemotherapy OS was 10.7 months (95% CI 9.5-12.0) for SIRT, 13.2 months (95% CI 12.2-14.2) for HAI, and 21.3 (95% CI 20.6-22.4) for TACE.

Response rates (percentage of patients showing a partial or complete response) for the three treatment strategies were 36% (95% CI 25-47) for SIRT, 48% (95% CI 42-54) for HAI, and 29% (95% CI 14-43) for TACE. Response rates were reduced in pre-treated patients: 32% (95% CI 24-39) for SIRT, 35% (95% CI 24-45) for HAI, and 28% (95% CI 7-48) for TACE.

Grade 3–4 toxicity was 55% in the HAI group, 26% in the SIRT group, and 17% in the TACE groups across all studies.

The volume and quality of evidence across the three modalities was different, and there is likely to be considerable heterogeneity in populations which could make these comparisons unreliable; for example patients treated with SIRT are more likely to be pretreated and more likely to have extra-hepatic disease. The authors conclude that the three liver directed therapies, SIRT, HAI, and TACE, are equally effective in patients with unresectable CRCLM. Relevance of the review to the SIRT CtE evaluation was limited because it included patients who had received ≤1 previous chemotherapy line.

Saxena et al. (2014) systematic review

This study reviewed the safety and efficacy (radiological response and survival outcomes) of SIRT in patients with unresectable, chemotherapy-refractory CRCLM. The authors searched MEDLINE and PubMed (1966-2012) with a limited range of search terms. Selection criteria were clearly explained, a flow diagram was presented, and critical appraisal results were reported. Twenty studies (with 979 patients) were included in the review. The median number of previous lines of chemotherapy was 3 (range 2-5.1), and a median of 20% (range 0-92%) of patients had undergone previous liver resection. The majority of included studies were observational.

Median OS was 12 months (range 8.3-36; reported in 11 studies; pooled analysis method not described). After SIRT treatment the median radiological response from 16 studies was as follows: complete response 0% (range 0-6%), partial response 31% (range 0-73%), stable disease 40.5% (range 17-76%), progressed disease 17.5% (range 6-50%). Median LPFS reported in 6 studies was 9 months (range 6-16). Median PFS reported in 8 studies was 4.9 months (range 3.4-9.3).

The overall median acute toxicity rate was 40.5% (range 11-100%). Most cases were mild (grade 1 or 2) and resolved without intervention. The most common toxicities were fatigue (median 38.5%), abdominal pain (median 16%), and nausea/vomiting (median 19%).

The authors also summarised statistically significant and non-significant prognostic factors and reported that number of previous lines of chemotherapy (≥3), poor radiological response, extra-hepatic disease, and extensive liver disease (≥25%) were the factors most commonly associated with poorer overall survival. These findings were derived from five studies (Chua 2011; Jakobs et al. 2008; Mulcahy et al. 2009; Nace 2011; Stubbs et al. 2006).

The authors conclude that SIRT is a safe and effective treatment for CRCLM in the salvage setting.

Rosenbaum et al. (2013) systematic review

This study reviewed tumour response and survival data in patients with unresectable and chemorefractory with CRCLM. The authors searched a range of databases (December 2001 – September 2012) with an appropriate range of search terms. Selection criteria were clearly reported with a flow diagram was presented. Critical appraisal results were reported. The authors presented a forest plot of survival proportions at 12 months but did not calculate pooled statistics for any outcomes due to heterogeneity between studies. Twenty-six publications were included. The authors separated studies which report on SIRT as monotherapy (13 studies; 901 patients) and SIRT in combination with systemic or intrahepatic chemotherapy (13 studies; 472 patients).

For SIRT as monotherapy, median OS ranged from 8.3 to 15.2 months (reported in 11 studies; no pooled analysis was conducted). Survival proportions at 12 months after treatment ranged from 37% to 59%. Tumour response rates (complete and partial response) ranged from 18% to 46% (from 10 studies). Disease control rates (complete, partial response, and stable disease) ranged from 29% to 90%. PFS ranged from 3.9 to 9.2 months (from 6 studies)

For SIRT in combination with chemotherapy, median OS ranged from 10.0 to 29.4 months (reported in 10 studies). Survival proportions at 12 months after treatment ranged from 43% to 74%. Tumour response rates ranged from 8% to 90% (from 11 studies). Disease control rates ranged from 59% to 100%.

Adverse events and toxicities were not reported in the review.

The authors conclude that approximately 50% of CRCLM salvage patients survive more than 12 months after SIRT treatment as monotherapy or in combination with chemotherapy.

4.4.4 Results from comparative studies (CRC)

Three comparative studies were identified (Bester et al. 2012; Hendlisz et al. 2010; Seidensticker et al. 2012) with a total of 355 patients (of which 274 were treated with SIRT) (Tables 4.4 and 4.5).

Hendlisz et al. (2010) was an open-label, multi-centre (Belgium) randomised phase III trial comparing fluorouracil (FU) protracted intravenous infusion (n=23) to SIRT plus intravenous FU (n=21). Ten patients in the control arm with documented progression were permitted to cross over to receive SIRT. Patients were followed up for a median of 24.8 months. The primary outcome of this trial was LPFS and a significant improvement in the SIRT group was reported (5.5 vs 2.1 months; HR 0.38 (95% CIs 0.28-0.94); p=0.003). An improvement in PFS was also shown in SIRT patients 4.5 vs 2.1 months

(HR 0.51 (0.28-0.94); p=0.03). There was a non-significant improvement in OS in the SIRT arm (10.0 vs 7.3 months; HR 0.92 [95% CIs 0.47-1.78]; p=0.80). Toxicity analysis showed no significant difference in the proportion of patients who had grade 3 or 4 toxicities (6 patients in FU group; 1 patient in SIRT group; p=0.10). The authors used time to liver progression (TTLP) and time to progression (TTP), but the description provided indicated that PFS and LPFS are in fact reported[3]. Hendlisz et al. was the highest quality study included in this review and demonstrated the difficulties in detecting large enough differences in OS so as to be statistically significant. The study may be subject to performance bias due to the open-label design, and cross-over of patients may obscure differences between the arms (Tables 4.4 and 4.5).

Bester et al. (2012) was a single-institution (Australia), retrospective comparative study comparing SIRT therapy (n=224) with conventional therapy/supportive care (n=29) in patients with unresectable and chemotherapy-refractory, liver dominant CRCLM (Table 4.4). The study also included patients with non-CRC primary cancers and some analyses were not stratified for CRC. Patients in the standard care arm were selected from a population who were assessed for SIRT eligibility but were considered unsuitable due to anatomical contraindications or refusal of consent; they were provided with conservative treatment of continued supportive care. Some baseline characteristics were presented separately for CRC patients treated with SIRT. Baseline characteristics for the CRC-only patients who received standard care were not reported therefore differences could not be assessed. The study reports that 85% of patients were ECOG performance status 0, and 14% of patients treated with SIRT were chemotherapy naive. Length of follow-up was not reported. OS was improved in the SIRT group compared to standard care (11.9 vs 6.6 months; HR: 0.5; log rank test p=0.001; Table 4.5). Adverse events occurred in 22% of patients immediately after SIRT, which were minor abdominal pain, nausea, and vomiting. The authors report that at the 1-month follow-up after SIRT, adverse events were minor and easily medically managed, including once case of radiation induced liver disease (RILD). Adverse events in the supportive care arm were not reported. The retrospective and non-randomised nature of this study means that there is substantial risk of bias from inadequately matched prognostic factors, allocation bias, poorly defined standard care regimens, and heterogeneity in outcome measures across the arms (Tables 4.4 and 4.5).

Seidensticker et al. (2012) was a multi-centre (Germany), retrospective comparative study comparing SIRT therapy (n=29) with a matched cohort of patients receiving BSC (n=29). BSC patients were matched on several criteria (prior treatment, tumour burden, liver involvement, synchronous/matachronous metastases, alkaline phosphatase (ALP) change, and carcinoembryonic antigen levels). The authors report that the groups were well-matched for baseline parameters. Patients treated with SIRT had a longer overall survival compared with BSC (8.3 vs 3.5 months; HR 0.26 [95% CIs 0.15-0.48]; p<0.001). Some patients treated with SIRT (31%) went on to receive chemotherapy. PFS was 5.5 months in the SIRT arm and 2.1 months in the BSC arm. The same issues of bias as described for Bester et al. (2012) apply to this study (Tables 3.4 and 3.5). Adverse events of mild abdominal pain and nausea occurred after SIRT in 48% patients. Three cases of grade 3 RILD were reported. Adverse events in the comparator arm were not reported.

[3] Typically, dead patients are censored in PFS, whilst they are excluded in TTP.

Table 4.4. Patient characteristics of comparative studies of SIRT in patients with chemotherapy-refractory, unresectable metastatic colorectal cancer

Author & year	Sample size	Country (study period)	Intervention	Comparator	Study type	Population	Key QA issues	Male	Age (years)	Previous chemo lines	Chemo-naive patients	EHM
Bester et al. 2012	**224 SIRT 29 SC**	Australia (2006-2011)	SIRT (SIR-spheres)	SC not defined	Retrospective comparative	Unresectable, liver only/dominant, CRCLM, chemotherapy-refractory or anticipated poor response.	Retrospective design limits reliability, and comparability between groups. Small patient numbers in SC group. Baseline demographics for SC group (and for some measures, SIRT also) were not presented for CRC group only. 85% of SIRT group were ECOG 0, the performance status for SC group not was reported. Number of previous chemotherapy lines not reported. AEs not reported for SC group. Survival was calculated from the date of SIRT procedure, and for SC group from time patients were consulted at clinic for SIRT eligibility. SC patients selected on the basis of anatomical ineligibility for SIRT, or refusal of consent. The authors state the groups were comparable.	63% SIRT 69% SC (incl. non-CRC)	67 SIRT 66 SC (incl. non-CRC) median	86% SIRT: ≥1 92% SC: ≥1 (incl. non-CRC)	14% SIRT 8% SC (incl. non-CRC)	38% SIRT 33% SC (incl. non-CRC)
Seidensticker et al. (2012)	**29 SIRT 29 SC**	Germany (2005-2008)	SIRT (SIR-spheres)	BSC – palliative care with intent to maximise quality of life	Matched-pair retrospective	Unresectable, liver dominant CRCLM, chemotherapy-refractory or refused.	Retrospective design limits reliability, and comparability between groups. Small patient numbers. Consecutive patient enrolment. SIRT patients matched to cohort of patients who received BSC only. 31% SIRT patients also received chemotherapy following SIRT. Unclear whether BSC patients also received chemotherapy. Matching process described. OS measured from date of previous progression to death (although unclear in description). PFS measured from previous progression to further progression. Progression measurement in BSC arm at discretion of treating clinician (imaging not mandatory), whereas RECIST used in SIRT group. Both groups were ECOG 0-2 and equal median (equivalent Karnofsky score). AEs not reported for BSC group.	76% SIRT 79% BSC	Mean: 62 SIRT 61 BSC	Median: 3 SIRT, 5 BSC 0% SIRT, 0% BSC: 1 previous line 28% SIRT, 24% BSC: 2 lines 31% SIRT, 38% BSC:3 lines 41% SIRT, 38% BSC: ≥4	0% SIRT, 0% BSC	48% SIRT, 48% BSC
Hendlisz et al. (2010)	**21 SIRT + FU 23 FU alone**	Belgium (2004-2007)	SIRT (SIR-spheres) plus FU chemotherapy	FU alone	Randomised controlled trial	Unresectable, liver dominant CRCLM, chemotherapy-refractory or intolerant to standard chemotherapy. ECOG 0-2.	Higher quality study, although small patient numbers and open label design limit reliability. Ten FU alone patients crossed over to SIRT arm which confounds survival estimates. 9 patietns in SIRT group received further therapy after SIRT. Majority of patients in both arms were ECOG 0 (71% SIRT+FU, 74% FU). RECIST criteria used to document progression in both groups. Time	48% SIRT + FU, 78% FU	Median: 62 SIRT + FU, 62 FU	NR	0% SIRT + FU, 0% FU	0% both groups

							to progression (TTP) defined as time to progression or death or loss to follow-up.					

AE, adverse event; BSC, best supportive care; CRC, colorectal cancer; CRCLM, colorectal cancer liver metastases; ECOG, Eastern Cooperative Oncology Group; EHM, extrahepatic metastases; FU, fluorouracil; NR, not reported; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria In Solid Tumors; SC, standard care; TTP, time to progression.

Table 4.5. Survival and tumour response results from comparative studies of SIRT in patients unresectable metastatic colorectal cancer

Author & year	Sample size	Median overall survival (months; 95% CI)	Median follow-up (months; 95% CI)	Median LPFS (months; 95% CIs)	Median PFS (months; 95% CIs)	Survival				Tumour response (RECIST criteria)			
						6 months	12 months	24 months	36 months	Complete response (CR)	Partial response (PR)	Stable disease (SD)	Progressive disease (PD)
Bester et al. (2012)	**224 SIRT 29 SC**	11.9 (10.1-14.9) SIRT, 6.6 (CIs NR) SC, Log rank p=0.001 HR estimate 0.5	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Seidensticker et al. (2012)	**29 SIRT 29 SC**	8.3 (NR) SIRT, 3.5 (NR) BSC, HR 0.26 (0.15-0.48), p<0.001	NR	NR	5.5 (NR) SIRT, 2.1 (NR) BSC	64% SIRT, NR for BSC	24% SIRT, 0% BSC	NR	NR	0% SIRT, NR for BSC	41% SIRT, NR for BSC	17% SIRT, NR for BSC	38% SIRT, NR for BSC
Hendlisz et al. (2010)	**21 SIRT + FU 23 FU alone**	10 (NR) SIRT + FU, 7.3 (NR) FU HR 0.92 (0.47-1.78), p=0.80	24.8 (range 2-41)	5.5 (NR) SIRT + FU, 2.1 FU (NR) HR 0.38 (0.20-0.72) p=0.003	4.5 (NR) SIRT + FU, 2.1 (NR) FU HR 0.51 (0.28-0.94) p=0.03	NR	NR	NR	NR	0% SIRT + FU, 0% FU	10% SIRT + FU, 0% FU (p=0.22)	76% SIRT + FU, 35% FU (p=0.001 for PR + CR)	10% SIRT + FU, 61% FU

BSC, best supportive care; CI, confidence interval; FU, fluorouracil; HR, hazard ratio; LPFS, liver-specific progression free survival; NR, not reported; PFS, progression-free survival; SC, standard care.

4.4.5 Results from non-comparative primary studies (CRC)

Overall, 23 studies comprising 2,517 patients treated with SIRT were included in the non-comparative section of this review (Table 4.6). Two comparative studies (only data from SIRT patients) and 21 non-comparative studies were included. The results from Bester et al. (2012) were not included in the main non-comparative data extraction table because patients treated with SIRT were also included in Saxena et al. (2015). There is a risk that some of the 61 CRC patients in Benson et al. (2013) are also included in Hickey et al. (2015)[1]. Six large studies with more than 100 patients were included, the largest of which included 606 patients. Nine studies were conducted in the US, 13 in Europe, and 1 in Australia (Table 4.6).

All studies included patients with chemotherapy-refractory, unresectable CRCLM (although one study did not clearly define the hepatic tumours as unresectable). Studies enrolled patients with either liver-only (no extrahepatic metastases) or liver-dominant metastases (four studies did not report whether patients had liver-dominant metastases). Five studies did not report the percentage of patients with extra-hepatic metastases but described the population as liver dominant. The majority of studies included only chemotherapy refractory patients (i.e. patients' disease had progressed following at least one line of chemotherapy) or they were intolerant to chemotherapy. Only two studies did not report any information on the number of previous lines of chemotherapy administered to CRC patients (Hendlisz et al. 2010; Smits et al. 2013), but these described the patient population as chemotherapy refractory and therefore were included in this review. Two studies reported that a small proportion of chemotherapy naive patients were included: Hickey et al. (2015) had 3% and Kennedy et al. (2015) had 6%. Fifteen studies reported previous liver-directed therapies including resection, ablation, HAI, or TACE (7 studies did not report this) (Table 4.6). Nine studies included patients with an ECOG (Eastern Cooperative Oncology Group) performance status of 0-2, three studies included patients with ECOG status 0-1, 2 studies included patients with an ECOG status of 0-3, and nine studies did not report ECOG performance status range as an inclusion criteria.

Twelve studies reported the proportion of patients who required more than 1 SIRT procedure (one of these reported the median number of sessions required per patient). Of the studies which reported this outcome, the proportion of patients who required ≥2 SIRT sessions ranged from 3% to 55%).

Median length of follow-up was reported in 12 of the 23 studies and ranged from 2.9 to 31.2 months (Table 4.7).

Overall survival

OS was reported in all 23 studies from a total of 2,517 patients. The pooled OS estimate from the included studies was 9.6 months (weighted mean; 95% CIs 8.9-10.4) and ranged from 6.0 to 12.7 months (Table 4.7).

In order to focus on a chemotherapy-refractory population which would more closely represent the SIRT CtE cohort (i.e. to exclude chemotherapy-naive patients and patients who had failed only 1 line

[1] although this was not confirmed when the author was contacted

of chemotherapy), OS from studies in which patients who received at least 2 previous lines of chemotherapy were presented (Table 4.8). Twelve studies were identified in which the cohort was ≥95% patients who had failed ≥2 previous lines of chemotherapy, or presented such patients in a subgroup analysis. A total of 1258 patients were reported in these studies. The pooled OS was 9.1 months (95% CIs 8.4-9.7), and the range across these studies was 7.0 to 11.6 months (Table 4.8).

Progression-free survival (PFS)

PFS was reported in 9 studies (437 patients) and ranged from 2.8 to 9.2 months (weighted mean 4.0 months). LPFS was reported in 8 studies (376 patients) and ranged from 2.0 to 9.0 months (weighted mean 4.4 months) (Table 4.7).

Tumour response

Tumour response rates measured using the RECIST criteria were reported in 12 studies (although 2 studies did not report the category of progressive disease). Complete response (CR) rates ranged from 0% to 5% in patients treated with SIRT; partial response (PR) rates ranged from 5% to 41%; stable disease (SD) rates ranged from 17% to 86%; progressive disease (PD) rates ranged from 10% to 44% (Table 4.7).

Survival proportion

Survival proportions at 12 and 24 months were reported in 9 and 6 studies respectively. Survival at 12 months ranged from 24% to 50%, and survival at 24 months ranged from 0% to 25% (Table 4.7).

Quality of life

One study included in the review reported quality of life as an outcome (Cosimelli et al. 2010). Patients were assessed prior to SIRT and 6 weeks after treatment using disease-specific quality of life tools EORTC QLQ C30, EORTC QLQ CR38, EORTC QLQ LMC-21), and the hospital anxiety and depression evaluation scale (HADs). Patient satisfaction was also assessed using EORTC QLQ SAT-32. Results from these assessments were poorly reported. The authors state that 14 of 50 patients were not adversely affected by SIRT but do not state by which measure. Patients reported a mean HADs score of 8 for anxiety and 9 for depression before SIRT treatment which indicated a “borderline abnormal” score. Six weeks after SIRT, patients’ anxiety levels were significantly reduced ($P<0.01$); with no significant change in depression score.

Table 4.6. Patient demographics from 23 studies on SIRT (non-comparative data only presented) – colorectal cancer population

Author & year	Sample size[1]	Country (study period)	Y-90 technology	Study type	Population	Key QA issues	Male	Age (mean)	Previous chemo lines	Chemo-naive patients	EHM	Previous liver-directed therapy	Multiple SIRT procedures
Jakobs et al. (2017)	**104**	Germany (no dates)	SIR-spheres	Prospective non-comparative	Unresectable, liver dominant CRCLM, chemotherapy-refractory. ECOG not reported.	Number of previous lines not reported in detail. Consecutive recruitment. Previous liver-directed therapies not described. PFS not reported.	70%	64	All patients progressed following FU, IRI, and OXA. 46% had prior BEV or CET	0%	55%	NR	NR
Damm et al. (2016)	**106**	Germany (2006-2010)	SIR-spheres	Retrospective non-comparative	Unresectable, liver dominant CRCLM, chemotherapy-refractory. ECOG not reported.	Includes patients who have failed 1 previous line of chemo.	66%	63 (median)	Median 3 lines (range 1-5) 8%: 1 previous line 33%: 2 32%: 3 26%: ≥4	0%	28%	28% resection or ablation	Median 2 sessions per patient (range 1-5)
Janowski et al. (2016)	**58**	USA (2011-2015)	SIR-spheres	Retrospective non-comparative	Unresectable, CRCLM, chemotherapy-refractory. Mostly ECOG 0-2.	Includes patients who have failed 1 previous line of chemo. Not reported whether metastases were liver dominant.	50%	56 median	Median 2 lines (range 1-5) 21%: 1 previous line 50%: 2 2%: ≥3	0%	67%	NR	55%: 2 sessions
Rosenbaum et al. (2016)	**42**	Netherlands (no dates)	SIR-spheres	Prospective non-comparative	Unresectable, CRCLM, chemotherapy-refractory. ECOG 0-2.	Includes patients who have failed 1 previous line of chemo. Includes patients where EHM may not be liver dominant.	69%	62	36%: 1 previous line 38%: 2 26%: ≥3	0%	29%	12% segmentectomy; 10% ablation; 7% hemihepatectomy; 3% other.	4%: 2 sessions
Schmeel et al. (2016)	**44**	Germany (no dates)	Both	Retrospective non-comparative	Unresectable, liver predominant CRCLM, chemotherapy-refractory. ECOG not reported.		61%	61	All had at least 2 lines of IRI and OXA.	0%	44%	0% local intrahepatic therapies	23%: ≥2 sessions
Hickey et al. (2015)[2]	**531**	USA (2001-2014)	TheraSphere	Retrospective non-comparative	Unresectable, liver dominant CRCLM, progressed on chemo and loco-regional therapy. ECOG 0-2.	Includes patients who have failed 0 & 1 previous lines of chemotherapy	59%	NR	41% had 1-2 previous cytotoxic drugs (5FU, OXA, or IRI); 56% had 3 previous drugs	3%	38%	18% resection; 14% ablation; 4% TACE	NR
Saxena et al. (2015)[3]	**302**	Australia (2006-2013)	SIR-spheres	Prospective non-comparative	Unresectable, liver dominant CRCLM, chemotherapy-refractory. ECOG 0-3.	Majority of patients failed 1 line previous chemotherapy, Subgroup analysis for 2 lines and >3 lines	65%	64	53%: 1 previous line 30%: 2 17%: ≥3	0%	41%	27% resection; 4% ablation; 0.7% TACE	NR

[1] CRC patient receiving SIRT

[2] Includes data from patients reported in Lewondowski 2014; Mulcahy 2009; Sato 2008.

[3][3] Includes data from patients reported in Bester 2012; Chua 2011

Author & year	Sample size[1]	Country (study period)	Y-90 technology	Study type	Population	Key QA issues	Male	Age (mean)	Previous chemo lines	Chemo-naive patients	EHM	Previous liver-directed therapy	Multiple SIRT procedures
Kennedy et al. (2015)[1]	**606**	USA (2002-2011)	SIR-spheres	Retrospective non-comparative	Unresectable, liver dominant CRCLM, progressed on ≥1 previous line of chemotherapy. ECOG 0-3.	Includes patients who have failed 0 & 1 previous lines of chemotherapy, although results have been stratified	62%	62	Median 2 lines (range 0-6) 6%: chemo naive 35%: 1 previous line 32%: 2 27%: ≥3	6%	35%	28% resection/ ablation; 6% HAI/ TACE/TAE	Median of 2 sessions.
Sabet et al. (2015)	**51**	Germany (NR)	TheraSphere & SIR-sphere	Retrospective non-comparative	Unresectable, liver dominant CRCLM, chemotherapy-refractory. ECOG ≥1 26%; ECOG <1 75%.	Focus of study is prognostic factors	65%	61	All patients progressed on ≥2 previous lines of chemotherapy	0%	49%	NR	NR
Golfieri et al. (2015)	**52**	Italy (2005-2011)	SIR-spheres	Prospective non-comparative	Unresectable, liver dominant CRCLM, chemotherapy-refractory. ECOG 0-1.	Choi criteria used to assess tumour response. (13% received chemo after SIRT)	77%	63	5%: 1 previous line 49%: 2 46%: ≥3	0%	23%	48% resection; 2% HAI	NR
Sofocleous et al. (2015)	**53**	USA (2009-2013)	SIR-spheres	Retrospective non-comparative	Unresectable, liver dominant CRCLM, chemotherapy-refractory. ECOG 0-2.	Not clear how many patients received only 1 previous line. Majority of patients received treatment after SIRT.	57%	54 (median)	All patients heavily pretreated 28%: ≥3 previous lines	NR	77%	49% liver surgery; 29% HAIP	34%: 2 sessions
Lahti et al. (2015)	**104**	USA (2007-2014)	SIR-spheres	Retrospective non-comparative	Unresectable, liver dominant CRCLM, chemotherapy-refractory (SIRT used as 3rd line therapy). ECOG 0-2.	Focus on KRAS status. 51% patients received chemotherapy after SIRT	67%	63 (median)	Median 5 previous chemotherapy agents (range 1-8) 15%: 1 previous line 85%: ≥2	0%	NR	32% resection; 16% HAI; 9% TACE	NR
Maleux et al. (2015)	**71**	Belgium (2005-2014)	SIR-spheres	Prospective non-comparative	Unresectable, liver dominant CRCLM, chemotherapy-refractory. ECOG 0-1.		72%	62.5	38%: 2 previous lines 62%: 3	0%	31%	14% resection; 8% ablation	0%
Kalva et al. (2014)	**45**	USA (2005-2011)	SIR-spheres	Retrospective non-comparative	CRCLM which failed at least 1 previous line of chemotherapy. ECOG 0-2.	Does not report whether tumours were resectable. Includes patients with just previous chemotherapy line. Includes patients where EHM may not be liver dominant.	53%	67 (median)	All patients received chemotherapy before SIRT. Ranged from 1-9 prior regimens, median 3.	0%	64%	13% ablation; 4% radiotherapy; 13% TACE	11%: 2 sessions
Lam et al. (2014)	**45**	USA (2004-2011)	SIR-spheres	Retrospective non-comparative	Unresectable (probably), liver dominant CRCLM, salvage setting. ECOG 0-1.	All patients termed salvage but not clear how many previous lines. Focus on dosimetry. Not clear whether extrahepatic mets present.	53%	58	98% pts had previous chemotherapy	NR (2%?)	NR	38% resection; 24% ablation; 2% TAE	NR

[1] Includes data from patients in Kennedy et al. 2006

Author & year	Sample size[1]	Country (study period)	Y-90 technology	Study type	Population	Key QA issues	Male	Age (mean)	Previous chemo lines	Chemo-naive patients	EHM	Previous liver-directed therapy	Multiple SIRT procedures
Schonewolf et al. (2014)	**30**	USA (2007-NR)	SIR-spheres	Retrospective non-comparative	Unresectable, liver dominant CRCLM, failed 1, 2, or 3 previous chemotherapy lines. ECOG not reported.		60%	61	Mean 2.1 (range 0-5)	0% (1 patient?)	NR	13% ablation	53%: sequential sessions
Benson et al. (2013)	**61**	USA (2007-2009)	TheraSphere	Prospective non-comparative	Unresectable, liver dominant metastases of mixed primaries (results stratified). Disease progression under standard treatment. ECOG 0-2.	Demographics not stratified for CRC. 1 chemotherapy-naive patient included. Potential overlap in patients with Hickey et al. (2015) study. Company is a co-author.	NR	NR	2%: 0 previous lines 39%: 1 previous line 59%: ≥2	2%	NR (not stratified)	NR	NR
Smits et al. (2013)	**30 (CRC patients part of a larger cohort)**	Netherlands (2009-2012)	SIR-spheres	Retrospective non-comparative	Unresectable, liver dominant metastases of mixed primaries (results stratified). Disease progression with systemic treatment or contraindicated. ECOG not reported.	Demographics not stratified for CRC. Previous lines of chemotherapy not reported for CRC cohort.	NR	NR	NR	NR	NR	NR	17%: sequential sessions
Seidensticker et al (2012)	**29 (pairs)**	Germany (2005-2008)	SIR-spheres	Retrospective **comparative**	Unresectable, liver dominant CRCLM, chemotherapy-refractory or refused. ECOG 0-2.	Comparative study comparing SIRT with standard care. 31% pts received chemotherapy after SIRT	76% SIRT only	62 for SIRT only	Median 3 0%: 1 previous line 28%: 2 31%:3 41%: ≥4	10%	48%	24% resection; 3% ablation; 3% TACE; 14% brachytherapy	31%: sequential sessions
Cosimelli et al. (2010)	**50**	Italy (NR)	SIR-spheres	Prospective non-comparative	Unresectable, liver dominant CRCLM, chemotherapy-refractory. ECOG 0-2.	28% pts received chemotherapy after SIRT	74%	64	0%: 1 previous line 0%: 2 24%:3 76%: ≥4	0%	22%	24% resection	3%: 2 sessions
Hendlisz et al. (2010)	**21 (SIRT patients)**	Belgium (2004-2007)	SIR-spheres	Randomised controlled trial	Unresectable, liver dominant CRCLM, chemotherapy-refractory or intolerant to standard chemotherapy. ECOG 0-2.	Compared FU infusion alone to FU+SIRT. Patients on FU alone permitted to cross over to SIRT arm. Previous chemotherapy was not reported.	48%	62 (median)	NR	0% (probably)	0% (exclusion)	0% TAE; 0% HAI	NR
Cianni et al. (2009)	**41**	Italy (2005-2008)	SIR-spheres	Retrospective non-comparative	Unresectable, liver dominant CRCLM, chemotherapy-refractory. Median ECOG 0.7.	Previous number of chemotherapy lines not reported	73%	61	Text suggest at least 3 but not clear	0%	10%	NR	17%: 2 sessions

Author & year	Sample size[1]	Country (study period)	Y-90 technology	Study type	Population	Key QA issues	Male	Age (mean)	Previous chemo lines	Chemo-naive patients	EHM	Previous liver-directed therapy	Multiple SIRT procedures
Jakobs et al. (2008)[1]	**41**	Germany (2003-2007)	SIR-spheres	Retrospective non-comparative	Unresectable, liver dominant CRCLM, failed currently available therapies. ECOG not reported.		73%	61	Mean 2.8 7%: 1 previous line 85%: 2	0% (not clear)	17%	29% resection; 20% ablation; 5% TACE	NR

BEV, bevacizumab; CRC, colorectal cancer; CET, cetuximab; CRCLM, colorectal cancer liver metastases; ECOG, Eastern Cooperative Oncology Group score; EHM, extrahepatic metastases; 5FU, fluorouracil; HAI(P), hepatic arterial infusion (pump); IRI: irinotecan; KRAS, Kirsten rat sarcoma (gene mutation), NR, Not reported; OXA, oxaliplatin; QA, quality appraisal; SIRT, selective internal radiation therapy; TAE, trans arterial embolisation; TACE, trans arterial chemo-embolisation; Y-90, yttrium-90.

[1] Includes data reported in Fendler 2013

Table 4.7. Survival and response statistics from 23 studies on SIRT (non comparative data only) – colorectal cancer population

Author & year	Sample size	Median OS (months; 95% CI)	Median follow-up (months; 95% CI)	Median LPFS (95% CIs)	Median PFS (months; 95% CIs)	Survival (months)				Tumour response (RECIST criteria)			
						6	12	24	36	CR	PR	SD	PD
Jakobs et al. (2017)	**104**	10.2 (7.8-13.0)	All died	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Damm et al. (2016)	**106**	6.7 (NR)	6.0 (range 1-48)	NR	3.5	NR	NR	NR	NR	NR	NR	NR	NR
Janowski et al. (2016)	**58**	6 (4.5-7.5)	NR	2 (0.3-3.7)	NR	NR	33%	NR	NR	0%	19%	43%	38%
Rosenbaum et al. (2016)	**42**	9.2 (6.1-12.4)	NR	NR	NR	71%	NR	NR	NR	0%	NR	NR	NR
Schmeel et al. (2016)	**44**	8 (6-10)	NR	NR	NR	NR	NR	NR	NR	0%	2%	86%	11%
Hickey et al. (2015)[1]	**531**	10.6 (8.8-12.4)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Saxena et al. (2015)[2]	**302**	10.5 (NR)	7.2 (0.2-72.8)	NR	NR	66%	42%	17%	13%	1%	37%	32%	28%
Kennedy et al. (2015)[3]	**606**	9.6 (9.0-11.1)	8.6 (0.1-77.7)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Sabet et al. (2015)	**51**	7 (5-8)	11.0 (±9)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Golfieri et al. (2015)	**52**	11.0 (8.0-14.0)	7.0	NR	NR	NR	NR	NR	NR	0%[4]	65%	18%	18%
Sofocleous et al. (2015)	**53**	12.7 (5.2-20.2)	15.0	4.7 (3.5-5.8)	NR	NR	50%	25%	NR	0% (12 wks)	7% (12 wks)	61% (12 wks)	33% (12 wks)
Lahti et al. (2015)	**104**	6.9 (5.4-8.4)	31.2	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Maleux et al. (2015)	**71**	8 (7-9)	NR	4	3	65%	30%	6%	NR	NR	NR	NR	NR
Kalva et al. (2014)	**45**	6.1 (4.9-9.1)	4.9 (range 7d – 4.7 y)	NR	NR	53%	29%	NR	NR	0%	2%	71%	13%[5]
Lam et al. (2014)	**45**	11.2 (NR)	2.9	NR	NR	NR	NR	NR	NR	0%	17% (includes CR)	46%	NR
Schonewolf et al. (2014)	**30**	9.4 (6.4-15.2)	7.0	NR	3.2 (1.1-7.2)	NR	NR	NR	NR	NR	NR	NR	NR

[1] Includes data from patients reported in Lewondowski 2014; Mulcahy 2009; Sati 2008.
[2] Includes data from patients reported in Bester 2012; Chua 2011
[3] Includes data from patients in Kennedy et al. 2006
[4] Choi criteria
[5] Excluding 7 patients who died before follow-up

Author & year	Sample size	Median OS (months; 95% CI)	Median follow-up (months; 95% CI)	Median LPFS (95% CIs)	Median PFS (months; 95% CIs)	Survival (months)				Tumour response (RECIST criteria)			
						6	12	24	36	CR	PR	SD	PD
Benson et al. (2013)	**61**	8.8 (6.6-11.9)	NR	3.0 (2.0-5.8)	2.9 (1.3-3.1)	NR	NR	NR	NR	0%	5%	53%	NR
Smits et al. (2013)	**30**	8.9 (6.9-10.9)	NR	3.0 (2.8-3.3)	2.8 (2.2-3.3)	NR	NR	NR	NR	NR	NR	NR	NR
Seidensticker et al (2012)	**29**	8.3 (NR)	NR	NR	5.5 (NR)	64%	24%	NR	NR	0%	41%	17%	38%
Cosimelli et al. (2010)	**50**	12.6 (7-18.3)	11.0	NR	3.7 (2.6-4.9)	85%	50%	19.5%	NR	2%	22%	24%	44%
Hendlisz et al. (2010)	**21**	10 (NR)	24.8	5.5 (NR)	4.5 (NR)	NR	NR	NR	NR	0%	10%	76%	10%
Cianni et al. (2009)	**41**	11.6 (NR)	NR	9	9.2	90%[1]	44%[12]	0%[12]	0%[12]	5%	41%	34%	20%
Jakobs et al. (2008)[2]	**41**	10.5 (1.3-38.3)	7.9	5.9 (NR)	NR	68%[12]	40%[12]	21%[12]	14%[12]	0%	17%	61%	10%
Summary (pooled results)	**2517**	**9.6 (8.9-10.4) n=2517**	-	**4.4 (3.6-5.2) n=376**	**4.0 (3.3-4.7) n=437**	-	-	-	-	-	-	-	-

CI, confidence intervals; CR, complete response; LPFS: liver-specific progression free survival; OS, overall survival; NR, not reported; PFS: progression free survival; PD, progressed disease; PR, partial response; RESIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

[1] Data taken from Saxena et al. (2014) systematic review

[2] Includes data reported in Fendler 2013

Table 4.8. Summary of overall survival estimates from 12 studies on patients who received ≥2 previous lines of chemotherapy [1]

Study author and year	n	OS in months (95% CIs)	Previous chemotherapy lines (from whole cohort or subgroup analysis)
Jakobs et al. (2017)	104	10.2 (7.8-13.0)	Data from whole cohort. All patients progressed following FU, IRI, and OXA.
Schmeel et al. (2016)	44	8.0 (6.0-10.0)	Data from whole cohort. All patients progressed following at least 2 lines of IRI and OXA.
Hickey et al. (2015)	295	9.2 (7.8-10.6)	Data from subgroup of patients (56%) who received 3 previous cytotoxic drugs (assumed to equate to ≥2 previous lines of chemotherapy).
Saxena et al. (2015)	91	10.5 (NR; 2 previous lines)	Data from subgroup of patients who received 2 previous lines (30%).
	52	5.6 (NR; ≥3 previous lines)	Data from subgroup of patients who received 2 previous lines ≥3 previous lines (17%)
		Weighted mean for ≥2 lines OS=8.7[2]	No combined analysis of ≥2 previous lines presented. Weights calculated from number of patients in subgroups.
Kennedy et al. (2015)	184	9.0 (7.8-11.0; 2 previous lines)	Data from subgroup of patients who received 2 previous lines (32%).
	158	8.1 (6.4-9.3; ≥3 previous lines)	Data from subgroup of patients who received ≥3 previous lines (27%)
		Weighted mean for ≥2 lines OS=8.6[1]	No combined analysis of ≥2 previous lines presented. Weights calculated from number of patients in subgroups.
Sabet et al. (2015)	51	7 (5-8)	Data from whole cohort: patients progressed on ≥2 previous lines (no further information on number of lines provided)
Golfieri et al. (2015)	52	11.0 (8.0-14.0)	Data from whole cohort (95%); patients progressed on ≥2 previous lines.
Maleux et al. (2015)	71	8 (7-9)	Data from whole cohort, patients progressed on ≥2 previous lines. 38% of patients received 2 previous lines, 62% progressed after 3 lines).
Benson et al. (2013)	36	7.4 (5.3-9.9)	Data from subgroup of patients (59%) who received ≥2 previous lines.
Seidensticker et al. (2012)	29	8.3 (NR)	Data from whole cohort: patients progressed on ≥2 previous lines (28% =2 lines, 31% =3 lines, 41% ≥4 lines).
Cosimelli et al. (2010)	50	12.6 (7-18.3)	Data from whole cohort: patients progressed on ≥3 previous lines (24% =3 lines, 74% ≥4 lines)
Cianni et al. (2009)	41	11.6 (NR)	Text suggests that whole cohort progressed on ≥3 previous lines but not clear.
Summary (pooled results)	**1258**	**Weighted mean OS: 9.1 months (95% CIs 8.4-9.7) Range: 7.0-12.6**	

FU, fluorouracil; IRI, irinotecan; OS, overall survival; OXA, oxaliplatin; NR, not reported.

[1] Studies in which ≥95% of patients received ≥2 previous lines of chemotherapy or those with subgroup analysis of patients who received ≥2 previous chemotherapy lines.
[2] Weights calculated from number of patients in subgroups.

4.5 Results of systematic review - intrahepatic cholangiocarcinoma

4.5.1 Objective of current review

The purpose of this review was to provide an updated overview of the efficacy of SIRT in patients with unresectable ICC. The focus was on patients who are refractory to chemotherapy, although studies with a high proportion of chemotherapy naive patients were also included because of a paucity of evidence.

4.5.2 Selected studies

Two systematic reviews and 10 primary studies were included in this review.

4.5.3 Previous systematic reviews (ICC)

Two systematic reviews (Al-Adra 2015; Boehm 2015) were identified and deemed to be relevant to this review (Table 4.9).

Table 4.9. Details of systematic reviews of SIRT for the treatment of ICC

Author (year)	Description of systematic review
Al-Adra (2015)	Systematic review of evidence for the treatment of unresectable ICCS with yttrium-90 micropsheres
Boehm (2015)	Systematic review and meta-anlysis on the comparative effectiveness of HAT- hepatic artery infusion (HAI), transcatheter arterial chemoembolization (TACE), drug-eluding bead TACE (DEB-TACE), and Yttrium90 radioembolization (Y-90) for unresectable ICC.

Al-Adra (2015) Systematic review

This review examined the treatment of unresectable ICCs with Y-90 SIRT. A good selection of databases covering the periods 2000 to 2013 were searched. Study selection criteria were well described and a flow diagram was included. However no quality assessment of studies was performed or considered. Twelve studies were included, 7 of these were conference abstracts and 3 had <10 participants. All the studies were non-comparative studies. Of the studies that were reported in full-text, Hyder et al. (2013) did not provide patient details for each intra-arterial therapy (IAT; 46/198 patients were SIRT) that was investigated, and Mouli et al. (2013) did not present OS for the whole group only by tumour morphology. Not all the studies reported the type of SIRT that was used.

The majority of patients had undergone previous treatment for their ICC; 54% had received chemotherapy and/or surgical resection (33%).

Weighted median OS was 15.5 months (range 7-22.2). Only 6 studies reported response rates (RECIST criteria or mRECIST/PERCIST), a weighted mean partial response was observed in 28% and stable disease in 54% of patients at 3 months.

The authors conclude that OS of patients with ICC after treatment with SIRT is higher than historical survival rates and is similar to those treated with systemic chemotherapy and/or trans arterial chemoemolization therapy. They report that the complication profile of SIRT is similar to that of other intra-arterial treatment modalities. The authors state that randomised controlled trials comparing systemic chemotherapy, TACE and local radiation are required to identify the optimal treatment modaility for unresectable ICC.

Boehm (2015) systematic review

This review examined the comparative effectiveness of hepatic artery based therapies, including Y-90 micropsheres, for unresectable ICCs. Only one database (PubMed) was searched to identify evidence from between 1990 and 2013; it would appear that all relevant studies have been included. Study selection criteria were described and a flow diagram was included; studies with < 10 patients were excluded. Quality assessment of the studies was performed and details provided. Five studies exploring the treatment of unresectable ICCs with SIRT were included; all were non-comparative studies. Four studies involved SIR-Spheres and one TheraSpheres. It is possible that 2 of the studies (Haug et al. 2011; Hoffamn et al. 2012) included overlapping patient populations. The authors of the review conducted a meta-analysis even though all the included studies were non-comparative studies and therefore subject to a high risk of bias and the patient populations were hetereogeneous. The forest plot of the meta-analysis indicates that there is hetereogeneity in the studies. Details of previous treatment regimens were not provided.

The median OS, using a random effects model, for SIRT was 13.9 months (95% CI 9.5 – 18.3). Overall response (partial or complete) was observed in 27.4% (95% CI 17.4 – 37.5) of patients and stable disease in 54.8% (95% CI 45.2 – 56.7) of patients.

Comparison of SIRT with other hepatic artery based therapies such as hepatic arterial infusion (HAI), transcatheter arterial chemoembolisation (TACE), drug-eluting bead TACE (DEB-TACE) were as follows. Median OS was highest for for HAI (22.8, 95% CIs 9.8–35.8) months versus SIRT (13.9, 95% CIs 9.5–18.3) months versus TACE (12.4, 95% CIs 10.9–13.9) months versus DEB-TACE (12.3, 95% CIs 11–13.5) months. The grade 3 or 4 toxicity (events per patient) was highest for HAI (0.35, 95% CIs 0.22–0.48) versus TACE (0.26, 95% CIs 0.21–0.32) versus DEB- TACE (0.32, 95% CIs 0.17–0.48).

The authors concluded that hepatic artery therapies appear promising for improving patient outcomes with unresectable ICC.

4.5.4 Results from primary studies (ICC)

Fifteen primary studies were selected for full data extraction, however 5 were subsequently excluded. The reasons for excluding the studies were as follows: Haug et al. (2011) possibly had an overlapping patient population with Hoffman et al. (2102) therefore the latter was retained as it had a slightly larger cohort; Hyder et al. (2013) did not provide patient details for each intra-arterial therapy that was investigated; (Mouli et al. 2013) did not present OS for the whole group; for Xing et al. (2016) it appeared that the patient population overlapped with Camacho et al. (2014), which was retained, was not specific for ICC and didn't report OS for the whole group; Rayer et al. (2015)

Overall 10 studies (Beuzit et al. 2016; Camacho 2014; Filippi et al. 2015; Hoffmann 2012; Ibrahim et al. 2008; Jia 2016; Mosconi et al. 2016; Rafi et al. 2013; Saxena et al. 2010; Soydal et al. 2016) comprising 247 patients were included in this review; all were non-comparative studies and therefore subject to a high risk of bias (Table 4.10). Five studies were prospectively conducted and five were retrospective.

The studies only included patients with unresectable ICC; one study did not report the percentage of patients with extra-hepatic metastases. Overall 78% of patients were chemotherapy-refractory (i.e. they had progressed following at least one previous line of chemotherapy). The number of lines of chemotherapy was not reported in any of the studies. Only Ibrahim et al. (2008) had a majority of chemo-naive patients, 71% (17/24). Eight studies reported previous liver-directed therapies with resection being the most common other therapies included ablation and TACE (Table 4.10).

Median or mean length of follow-up was reported in 7 of the 10 studies and ranged from 8.0 to (Table 4.11).

Overall survival

OS was reported in 9 studies with a total of 230 patients (Filippi et al. (2015) was excluded because only mean OS was reported). The weighted mean of median OS across 9 studies was 15.3 months (95% confidence intervals 12.0-18.7) with a range of 9.0 to 22 months (Table 3.11). The addition of the mean OS estimate from Filippi et al. (2015) to the pooled estimate did no alter the result.

Progression-free survival (PFS)

Median PFS was not reported in any of the studies (Table 3.11). Beuzit et al. (2016) presented a comparison of PFS between subgroups but did not report PFS for the entire cohort.

Tumour response

Tumour response rates measured using the RECIST criteria were reported in 8 studies (one study used the WHO criteria). Complete response rates were zero in all 8 studies; partial response rates ranged from 0% to 82.4%%; stable disease rates ranged from 17.6% to 71%; progressive disease rates ranged from 0% to 55% (Table 4.11).

Survival proportion

Survival proportions were reported in 4 studies. Survival at 12 months following SIRT treatment ranged from 33% to 68%, and survival at 24 months ranged from 20% to 27% (Table 4.11).

Health related quality of life

None of studies identified reported HRQoL or patient satisfaction as an outcome.

Table 4.10. Study details and patient demographics from 10 non-comparative studies of SIRT in unresectable intrahepatic cholangiocarcinoma

Author & year	Sample size (SIRT)	Country (study period)	Y-90 technology	Study type	Population	Key quality appraisal issues	Male	Age (mean years)	Chemo-naive patients	EHM	Previous liver-directed therapy	Number of SIRT procedures
Beuzit et al. (2016)	**45**	France (2010-2014)	TheraSphere	Retrospective, non-comparative	Unresectable, chemorefractory ICC. ECOG 0-2.	Includes chemotherapy naive patients.	53%	64 (median)	8%	0%	2% chemoembolisation; 4% ablation	22%: 2 session 4%: 3 sessions
Jia et al. (2016)	**24**	China & ?USA (2006-2015)	SIR-sphere	Retrospective, non-comparative	Unresectable, chemorefractory ICC. ECOG 0-1.	All patients had received first-line cisplatin and gemcitabine	33%	62	0%	13%	NR	13%:2 sessions
Mosconi et al. (2016)	**23**	Italy (2010-2015)	SIR-sphere	Retrospective, non-comparative	Unresectable ICC. ECOG 0-2.	Includes chemotherapy naive patients.	61%	65	48%	9%	17% TAC; 17% TAE; 44% resection; 26% lobectomy	13% repeated procedure
Soydal et al. (2016)	**16**	Turkey (2008 – 2014)	SIR-spheres	Retrospective, non-comparative	Unresectable ICC. ECOG not reported.	Follow-up time was to endpoint (death). Includes chemotherapy naive patients.	50%	55	44%	31%	13% resection; 6% TACE	NR
Filippi et al. (2015)	**17**	Italy (NR)	SIR-spheres	Prospective, non-comparative	Unresectable, chemorefractory ICC. ECOG 0-2.	Patient characteristics not fully reported for ICC as not stratified. Method of enrolment not reported. Follow-up time was to endpoint (24 months or death). Median OS not reported (only mean). Includes chemotherapy naive patients.	35%	59	12%	24%	24% resection	18%: sequential sessions
Camacho et al. (2014)	**21**	USA (2009 – 2012)	SIR-spheres	Prospective, non-comparative	Unresectable mass-like ICC refractory to standard chemotherapy. ECOG 0-2.	Patient characteristics not fully reported for ICC as not stratified. Follow-up time was to endpoint (death) but median not reported.	62%	63 (median)	0%	NR	48% resection (biliary surgery)	NR
Rafi et al. (2013)	**19**	USA (2002 – 2010)	SIR-spheres	Prospective, non-comparative	Unresectable ICC, refractory to standard chemotherapy. ECOG 0-2.	Follow-up time was to endpoint (death). Includes chemotherapy naive patients.	37%	63	0%	58%	21% TACE	16%: 2 sessions; 5% 3 sessions.
Hoffman et al. (2012)	**33**	Germany (2007 – 2010)	SIR-spheres	Retrospective, non-comparative	Unresectable ICC or chemorefractory liver metastases from ICC. ECOG 0-2.	Includes chemotherapy naive patients.	55%	65	18%	24%	36% resection; 6% ablation; 9% TACE	0%
Saxena et al. (2010)	**25**	Australia (2004 - 2009)	SIR-spheres	Prospective, non-comparative	Unresectable ICC. ECOG 0-2.	Method of enrolment not reported. Follow-up time was to endpoint (death). Includes chemotherapy naive patients.	52%	57	28% or 32% (discrepancy in paper)	48%	40% resection; 8% ablation; 8% TACE	NR
Ibrahim et al. (2008)	**24**	USA (NR)	TheraSphere	Prospective, non-comparative	Unresectable ICC. ECOG 0-2.	Method of enrolment not reported. Includes chemotherapy naive patients.	67%	68median	71%	33%	NR	38%: 2 sessions 25%: ≥3 sessions

ECOG, Eastern Cooperative Oncology Group; ICC, intrahepatic cholangiocarcinoma; NR, not reported.

Table 4.11. Survival and response statistics from non-comparative studies of SIRT in intrahepatic cholangiocarcinoma

Author & year	n	Median OS (months; 95% CI)	Median follow-up (months)	Median L PFS (months; 95% CIs)	Median PFS (months; 95% CIs)	Survival				Tumour response (RESIST criteria)			
						6 months	12 months	24 months	36 months	CR	PR	SD	PD
Beuzit et al. (2016)	**45**	19.0 (8.6-29.3)	NR	NR	NR	NR	NR	NR	NR	0% (best response)	13% (best response)	71% (best response)	16% (best response)
Jia et al. (2016)	**24**	9.0 (5.6-12.4)	11.3 (mean; range 3-36)	NR	NR	70%	33%	20%	20% (30 months)	0% (3 months)	36% (3 months)	46% (3 months)	18% (3 months)
Mosconi et al. (2016)	**23**	17.9 (14.3-21.4)	16 (range 2-52)	NR	NR	NR	68%	21%	NR	0% (3 months) 5% (mRECIST)	15% (3 months) 40% (mRECIST)	30% (3 months) 15% (mRECIST)	55% (3 months) 40% (mRECIST)
Soydal et al. (2016)	**16**	9.6 ±2.3 (5.1-14.2)	8.0 (3.2-27.6	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Filippi et al. (2015)	**17**	Mean OS 64.5 weeks (54.7-74.4)	NR	NR	NR	NR	NR	NR	NR	0	82%	18%	0
Camacho et al. (2014)	**21**	16.3 (7.2-25.4)	NR	NR	NR	NR	NR	NR	NR	0% (1 month for n=21) 0% (3 month for n=16)	5% (1 month for n=21) 0% (3 month for n=16)	57% (1 month for n=21) 63% (3 month for n=16)	38% (1 month for n=21) 38% (3 month for n=16)
Rafi et al. (2013)	**19**	11.5 (3.2-19.8) as stated in main text	15	NR	NR	67%	56%	17% (18 months)	NR	0% (at 3 months)	11% (at 3 months)	68% (at 3 months)	21% (at 3 months)
Hoffman et al. (2012)	**33**	22 (7.9–29.4)	10 (range 3.1-44)	NR	NR	NR	NR	NR	NR	0% (at 3 months)	36% (at 3 months)	52% (at 3 months)	15% (at 3 months)
Saxena et al. (2010)	**25**	9.3 (NR)	8.1 (range 0.4-56)	NR	NR	56%	40%	27%	13%	0	24%	48%	20%
Ibrahim et al. (2008)	**24**	14.9 (NR)	17.7	NR	NR	NR	NR	NR	NR	0% (WHO criteria; n=22)	27% (WHO criteria; n=22)	68% (WHO criteria; n=22)	5% (WHO criteria; n=22)

CI, confidence intervals; CR, complete response; EHM, extrahepatic metastases; ICC, intrahepatic cholangiocarcinoma; NR, Not reported; OS, overall survival; PD: progressed disease; PR, partial response; RESIST, Response Evaluation Criteria in Solid Tumors; QA, quality appraisal; SD, stable disease; SIRT, selective internal radiation therapy; TAE, trans arterial embolisation; Y-90, yttrium-90.

4.6 Discussion

4.6.1 Colorectal cancer population

Three comparative studies of SIRT in patients with unresectable, chemotherapy refractory CRCLM were identified in our literature search. Two retrospective studies compared SIRT to standard therapy (6.6 vs 11.9 months; 3.5 vs 8.3 months) and found statistically significant improvements in OS. In the case of Seidenticker et al. BSC patients were matched retrospectively on several matching criteria, and the authors report similar baseline characteristics. Like most retrospective studies, the results are subject to outcome measurement variability and poorer quality retrospective data collection methods. The date from which OS is calculated may not be comparable between groups and may result in bias in favour of the standard care arm. Bester et al. (2012) retrospectively compared survival outcomes in patients treated with SIRT with those from patients who were ineligible for SIRT. Whilst the authors of both studies made efforts to select a comparison group which did not have more advanced disease and was well matched to the SIRT group, retrospective and non-randomised studies such as Bester et al. and Seidensticker et al. are at risk of bias if important prognostic factors are inadequately matched between groups. Poor standardisation and definitions of BSC and standard care in comparative studies also limits interpretation and generalisability of their results. Zafar and colleagues (2008) point out that BSC is often at the discretion of the treating investigator.

The results of this systematic review on the efficacy of SIRT as a treatment for unresectable, chemotherapy-refractory CRCLM are in line with other recently published reviews. Median OS, the primary outcome of this review, in 23 included studies ranged from 6.0 to 12.7 months. A total of 2,517 patients were included, most of whom had unresectable, liver-dominant CRCLM. We excluded studies where a substantial proportion of the patients were chemotherapy naive.

A recent systematic review by Zacharias and colleagues (2015) reported a pooled OS of 10.7 months in unresectable CRCLM (in patients who had failed at least one previous line of chemotherapy). Saxena et al. (2014) reported a pooled median overall of 12 months across 11 studies. Whilst the patient population was described as unresectable, chemotherapy-refractory CRCLM, the authors included studies in which the number of previous lines of chemotherapy was not reported which may account for a higher OS estimate. Finally, Rosenbaum et al. (2013) reported a range of OS from 8.3 to 15.2 months in patients with unresectable, chemotherapy refractory CRCLM who received SIRT as monotherapy, and a range of 10.0-29.4 months in patients who received SIRT in combination with chemotherapy. This current review provides a useful update on the three previous reviews (searches in 2012 and 2013) because it captures several large studies published recently, including 6 studies with at least 100 patients. In addition, we have excluded small studies (n<30) and studies where previous chemotherapy is not reported. As such, we have produced a reliable review, noting the study design limitations, that includes the most recent evidence of SIRT for unresectable, chemotherapy refractory CRCLM.

We provided additional analyses in this review focusing on studies where OS results were presented for patients who had received at least two previous lines of chemotherapy. Weighted mean of median OS was 9.1 months (n=1258) in this group. Rosenbaum et al. points out that knowledge of

previous systemic treatments are important and encourage better reporting of this. The author states: "on one hand, heavily pretreated patients generally have more advanced disease and will possibly benefit less from [SIRT]. On the other hand, patients who have not yet received all standard available systemic treatment regimens may do so after [SIRT], thereby obscuring [its] survival benefit".

Improved HRQoL is often described as a potential benefit of SIRT. NICE's Interventional Procedures Guidance (IPG401) calls for more evidence on the impact of SIRT on HRQoL as well as OS. Only one study identified for this review used QoL as a secondary outcome measure (Cosimelli et al. 2010). The results of these assessments were poorly reported; a reduction in anxiety levels following SIRT was the only adequately described outcome. Two RCTs, Gray et al (2001) and Van Hazel et al. (2004) report quality of life as an outcome. These studies were excluded from this review because they included only chemotherapy-naive patients and therefore were not relevant to the CtE project.

This report is limited by a paucity of high quality comparative evidence. It relies in large part on single arm observational studies, the majority of which are retrospective. Such studies do provide important information on the safety and technical success of SIRT. This new review incorporates large datasets spanning many years from established SIRT groups in the US (Hickey et al. 2015;Kennedy et al. 2015) and Australia (Saxena et al. 2015), demonstrating widespread acceptance amongst specialists. However, the absence of a control group limits interpretation on the efficacy of SIRT in unresectable, chemotherapy refractory CRCLM. Heterogeneity across the studies in patient characteristics is also an issue.

Choice of primary outcome is key to producing evidence which is relevant to patients and commissioners. Some studies choose to report outcomes which rely on response assessment such as PFS, instead of OS. Tumour response as defined by RECIST criteria (Eisenhauer et al. 2009) is useful as a consistent measure for what happens to a tumour during therapy (Booth and Eisenhauer 2012). However, PFS may not correspond to a measurable improvement in survival or quality of life, which are arguably the most meaningful outcomes to patients. A recent standards document provided a useful guide to consistent outcome measurement and reporting in studies of SIRT, to enable better comparison and interpretation of results (Salem et al. 2011).

4.6.2 Intrahepatic cholangiocarcinoma population

There is a lack of high quality evidence evaluating the efficacy of SIRT for unresectable ICC; no comparative studies were identified for this review. This review includes studies included in two previous systematic reviews (Al-Adra 2015; Boehm 2015) as well as more recently published studies. Median OS, the primary outcome of this review, across 9 studies was used to calculate a weighted mean of median OS of 15.3 months (range: 9.0-22 months) from a total of 230 patients ; this is similar to that published in the other reviews [15.5 months from Al-Adra et al., 2015 and 13.9 months from Boehm et al., 2015]. It should be noted that there is heterogeneity between studies included in this review and therefore caution should be exhibited in using this value.

NICE's interventional procedure guidance (IPG459) calls for more evidence on the effect of SIRT on QoL in ICC patients. However, no studies were identified for this review which reported QoL as an outcome.

5 Literature review: survival estimates in patients with CRC and ICC treated with best supportive care

5.1 Summary

A rapid review was conducted to identify studies which report survival estimates from patients treated with BSC to provide context to non-comparative SIRT data.

Colorectal cancer: Seven randomised controlled trials were identified where BSC was the control treatment (1156 BSC patients). BSC tended to be poorly defined and varied by institution; usually BSC aims to provide palliative treatment without using investigational cancer therapies. Median OS across seven studies ranged from 2.4 months to 6.6 months (weighted mean 5.3 months). Median PFS ranged from 1 month to 7.3 months across five studies (weighted mean 3.2 months).

Intrahepatic cholangiocarcinoma: No studies were identified which reported overall survival in patients with chemotherapy-refractory ICC who received BSC. In the absence of relevant studies, a further non-systematic and directed search was conducted to identify useful information on survival. Extrapolated results indicated that patients with ICC following first-line progression survive approximately 4 months. A review of second line chemotherapy regimens in ICC patients reported an OS of 7.2 months.

Direct comparisons of SIRT data (from observational studies and the CtE study) with BSC data from higher quality RCTs are not appropriate and should interpreted with extreme caution. Differences in patient selection criteria, data collection methodologies, and outcome measurements are likely to produce differences in results between RCTs and observational studies.

5.2 Introduction

This section describes a literature review conducted to identify studies which report the survival of patients who have received best supportive care. This approach to gathering survival data from BSC-treated patients was chosen to provide context (not a direct comparison) in the CtE evaluation to the non-comparative data captured on the SIRT registry and to results from published non-comparative studies on SIRT. It is in recognition of the paucity of published comparative evidence on SIRT in both the CRC and ICC populations, and an absence of a comparator in the SIRT CtE registry. The patient populations have been chosen to reflect the eligibility criteria used to select patients to receive SIRT under the CtE arrangements.

5.2.1 Aim of rapid review

This rapid review was designed to identify studies which report median OS or median PFS in patients receiving BSC for chemotherapy refractory mCRC or ICC. Initial searches indicated that single arm studies on the effectiveness of BSC in this patient group are rare. As such a strategy was designed to encompass high quality comparative studies in which BSC was the control arm.

5.3 Methodology

A strategy was developed in Ovid Medline (Appendix 3) and was adapted to the following databases: Medline In-Process; Embase; Cochrane Library (components: CDSR, DARE, CENTRAL, NHS EED); EconLit; Scopus; Pubmed (epub ahead of press search only). Searches were performed in September 2016. The searches were restricted to English language and from 2006 onwards. After de-duplication, one reviewer (HM) selected publications that were considered relevant based on titles or abstracts using the inclusion and exclusion criteria presented in Table 5.1. In a second selection round, a different independent reviewer (JW) looked at full text articles and selected studies to be included in the review.

Following study selection, comparative studies were assessed using the SURE checklist for RCT and other experimental studies. The following data were extracted by one reviewer (JW) from the selected studies: study design, intervention and control, patient characteristics including number of previous chemotherapy lines. Outcomes of interest were OS and PFS.

A pooled analysis was performed on studies reporting median overall survival in patients treated with best supportive care in order to present a weighted mean of median overall survival figure. Weight was applied based on the number of participants in each study.

Table 5.1 Inclusion and exclusion criteria

	Include	Exclude
Population	Patients with chemotherapy refractory CRC who have progressed following at least two lines of chemotherapy (or are resistant or intolerant to standard chemotherapy including fluorouracil with oxaliplatin and irinotecan)	• Patients are candidates for resection/surgery • Majority of CRC participants have received 0 or 1 previous line of chemotherapy • Majority of ICC participants are

	OR Patients with unresectable, chemotherapy refractory (disease progression following at least one previous line of chemotherapy) ICC.	chemotherapy-naive
Intervention	*(In this case the intervention of interest was standard care which in most studies identified was actually the control arm)* • Best supportive care • Third line palliative chemotherapy	
Comparator	Any	
Outcomes	Only include studies which report overall survival or progression-free survival	• Studies which don't report over survival or progression-free survival
Study selection	• RCTs and prospective comparative studies • Systematic reviews • Prioritise UK and European studies and US	• Non-comparative studies (CRC only) • Retrospective studies (CRC only) • Observational studies (CRC only) • Sample size <50 in BSC arm • Non-English language • Conference proceedings • Animal studies

5.4 Results (CRC)

5.4.1 Selected studies

The systematic literature search yielded 362 potentially relevant studies (Figure 5.1) and 6 studies were identified from supplementary searching and input from clinical experts, 140 were retained for assessment of eligibility at full text. Two systematic reviews were identified and checked for additional primary studies not identified in our search (Hoyle et al. 2013a; Nielsen et al. 2014). Both systematic reviews were subsequently excluded because all primary studies were identified in this current review.

Ten studies were retained for quality assessment and data extraction. Two phase II RCTs were excluded at this stage (Caballero-Baños et al. 2016; Jia et al. 2015) because the BSC arm had fewer than 50 patients, and because BSC was not defined. Two retrospective cohort studies were also excluded at this stage because of their inferior study design (Bester et al. 2013b; Seidensticker et al. 2012). Both the studies compared SIRT with BSC and therefore were highly relevant to this topic. The results of these studies are reported in full in Section 4 of this report.

Seven RCTs (6 phase III studies and 1 phase II study) were included in this review of best supportive care survival (Grothey et al. 2013; Hickish et al. 2017; Jonker et al. 2007; Li et al. 2015;Mayer, van Cutsem et al. 2015; van Cutsem et al. 2007; Yoshino et al. 2012; Table 5.2). These studies had a total of 3,271 patients of whom 1,235 were randomised to receive placebo plus BSC. One study (Hickish

et al. 2017) included patients from the UK; three other studies were international and included patients in Europe.

All seven RCTs studied the efficacy of an investigational medicinal product (IMP) plus BSC against BSC alone or with a placebo. The IMPs in the intervention arms were regorafenib (an oral multi-kinase inhibitor), TAS-102 (an oral agent combining trifluridine and tipiracil hydrochloride), cetuximab, panitumumab (both monoclonal antibodies against epidermal growth factor receptor), and MABp1 (an antibody which targets interleukin 1α; Table 5.2).

In all studies, except Yoshino et al. (2012) where BSC was not defined, the control arm was BSC (with or without a placebo) which was described generally as best supportive care excluding investigational antitumour agents or antineoplastic chemotherapy, hormonal therapy or immunotherapy. In the case of Hickish et al. (2017), BSC also excluded immunosuppressive drugs or drugs that inhibit tumour necrosis factor α or interleukin 1; use of corticosteroids, megestrol, or stimulants, was restricted to events deemed medically necessary until the 8 week assessment was completed. In the case of Van Cutsem et al. (2007) BSC was defined as "best palliative care as per investigator" (Table 5.2).

The population across all seven studies included patients with chemotherapy refractory mCRC . Eligible patients had progressed following at least 2 previous lines of standard chemotherapy, which in most studies included fluoropyrimidine, irinotecan, and oxaliplatin, or were intolerant to standard chemotherapy. In the case of Grothey et al. (2013) and Jonker et al. (2007) a small number of patients had received only 1 previous line. Hepatic metastases were not an inclusion criteria in these studies. Only 2 studies reported the proportion of patients with hepatic metastases (58% and 67% in Yoshino et al. 2012; and 80% in Jonker et al. 2007). Three studies included patients with an ECOG performance status of 0 to1, three studies included patients with ECOG status 0 to 2, and one study included patients with ECOG status 1-2.

Median length of follow-up was reported in five studies and ranged from 6.1 months to 14.6 months (Table 5.3).

5.4.2 Overall survival

OS of patients in the BSC arm reported in the seven studies (n=1,156) was 5.3 months (weighted mean; 95% CIs 4.7-5.8) and ranged from 2.4 months to 6.6 months (Table 5.3).

In the study by Van Cutsem et al. (2007), 76% of patients randomised to the BSC subsequently crossed over the intervention arm to receive panitumumab, as such data from this trial may not provide a reliable estimate of survival for patients receiving only BSC. Patients randomised to receive BSC and placebo in Hickish et al. (2017) were also permitted to cross over, and the OS estimate in this group was based only on patients who did not cross over. As a result the OS estimate may be biased for shorter survival in the BSC group because these patients either progressed before the 8 week assessment or they chose not to continue to the open label phase of the study.

The pooled analysis was repeated with the Van Cutsem et al. (2007) and Hickish et al. (2017) omitted. The overall survival across the 5 studies was 5.2 months (range: 4.6 to 6.6 months).

5.4.3 Progression free survival

PFS was reported in five studies (neither Jonker et al. or Hickish et al. reported this outcome) and ranged from 1 month to 7.3 months (Table 5.3). The pooled analysis of median PFS across these studies was 3.2 months (weighted mean [95% CIs 2.9-3.5]). Following exclusion of Van Cutsem et al. data (because a majority of BSC patients crossed over to the intervention arm), the median PFS across four studies was 1.6 months (weighted mean) and the range was 1 month to 1.7 months.

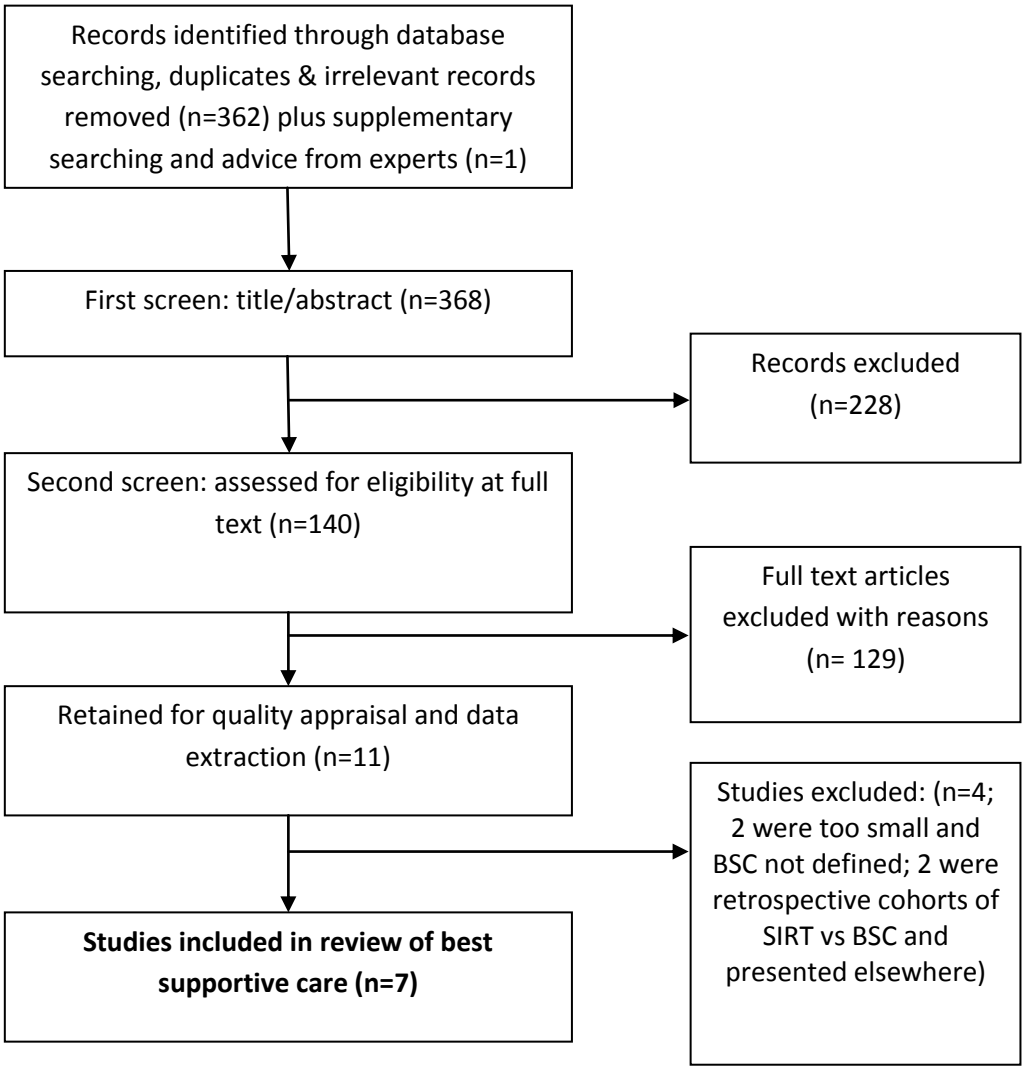


Figure 5.1. Flow diagram of selected studies (CRC population)

Table 5.2. Study details from 7 included studies reporting survival of CRC patients receiving best supportive care

Study	n (i)	n (c) (BSC)	Country & study period	Design	Population	Intervention	Control	Male	Age (median years)	Previous lines of chemotherapy (i/c)	QA issues & relevance to SIRT CtE
Hickish et al. (2017)	207 (OS data for 116)	102 (OS data for 23)	International (2014-2015)	RCT (phase III)	Chemotherapy refractory mCRC with multiple symptoms associated with poor outcomes. Patients received ≥2 previous lines including IRI, and OXA. ECOG 1-2.	MABp1 & BSC	BSC* & placebo (other drugs also excluded – see text)	62% (i), 58% (c)	64 (i), 63 (c)	2 lines: 27%/28%; 3 lines: 27%/32%; ≥4 lines: 44%/40%	Proportion of liver metastases not reported. OS and PFS not primary outcomes. OS available for only 23 patients in placebo group. Placebo patients were permitted to receive MABp1; OS data is only from placebo patients who progressed during first 8 weeks or elected not to continue. No independent review of imaging results. ECOG 0 patients excluded.
Li et al. (2015) CONCUR	136	68	China, HK, S Korea, Taiwan, Vietnam (2012-2013)	RCT (phase III)	Chemotherapy refractory mCRC. Patients received ≥2 previous lines including FP, IRI, and OXA. ECOG 0-1.	Regorafenib & BSC	BSC* & placebo	63% (i), 49% (c)	58 (i), 56 (c)	2 lines: 23%/21%; 3 lines: 24%/28%; ≥4 lines: 54%/51%	Proportion of liver metastases not reported. No European patients. No independent review of imaging results. ECOG 2 patients excluded.
Mayer et al. (2015) RECOURSE	534	266	International (2012-2013)	RCT (phase III)	Chemotherapy refractory mCRC. Patients received ≥2 regimens of standard chemotherapies. Must have received FP, IRI, OXA, BEV, (and CET or PAN if KRAS WT). ECOG 0-1.	TAS-102 & BSC	BSC* & placebo	61% (i), 62% (c)	63 (i), 63 (c)	2 lines: 18%/17%; 3 lines: 22%/20%; ≥4 lines 60%/63%.	Proportion of liver metastases not reported. 42% of patients received additional systemic therapy after participation in the trial. ECOG 2 patients excluded.

Grothey et al. (2013) CORRECT	505	225	International (2010-2011)	RCT (phase III)	Chemotherapy refractory mCRC. Patients had to have progressed on licensed standard therapies or have stopped due to side effects (including FP, IRI, OXA, BEV, and CET or PAN if KRAS WT). ECOG 0-1.	Regorafenib & BSC	BSC* & placebo	62% (i), 60% (c)	61 (i), 61 (c)	1 line: 3%/2%; 2 lines: 24%/23%; 3 lines: 25%/28%; ≥4 lines: 49%/47%.	Proportion of liver metastases not reported. Small minority received only 1 previous line. No independent review of imaging results. Some patients received anti-cancer treatments after progression. ECOG 2 patients excluded.
Yoshino et al. (2012)	112	57	Japan (2009-2010)	RCT (phase II)	Unresectable, chemotherapy refractory mCRC. Previous treatment of ≥2 standard chemotherapy regimens and were refractory or intolerant to FP, IRI, and OXA. ECOG 0-2.	TAS-102 & BSC	BSC & placebo (not defined)	57% (i), 49% (c)	63 (i) and 62 (c)	2 lines: 15%/23%; ≥3 lines: 85%/77%	Only 58% and 67% had liver metastases. Patients in both groups had subsequent cancer treatment. All patients were Japanese. BSC treatment not defined.
Jonker et al. (2012)	287	285	Canada & Australia (2003-2005)	RCT (phase III)	Chemotherapy refractory mCRC. ECGR positive. Disease progression on FP, IRI, and OXA, or contraindications. ECOG 0-2.	Cetuximab & BSC	BSC* (measures to provide palliation of symptoms and improve QOL)	65% (i), 64% (c)	63 (i) and 64 (c)	1 or 2 lines: 17%/19%; 3 lines: 38%/38%; 4 lines: 30%/25%; ≥5: 14%/18%	80% had liver metastases and study included some patients with 1 previous line of chemo. Trial not blinded. No independent review of imaging results. 7% of BSC pts subsequently received cetuximab. 28% (I) and 23% (c) of patients received anticancer treatment after disease progression.

Van Cutsem et al.	231	232	International (2004-2005)	RCT (phase III)	Chemotherapy refractory mCRC ECGR positive. Disease progression following last administration of FP, IRI, and OXA. ECOG 0-2.	Panitumumab & BSC	BSC (best palliative care per investigator)	63%	62	2 lines: 100%: 3 lines: 37%	76% of BSC pts crossed over to PAN. Proportion of pts with liver metastases not reported. Trial not blinded.

* best supportive care excluding investigational antitumour agents or antineoplastic chemotherapy, hormonal therapy or immunotherapy

BEV: bevacixumab; BSC: best supportive care; CI: confidence intervals; CET: cetuximab; ECOG: Eastern Cooperative Oncology Group; FP: fluoropyrimidine; HK: Hong Kong; IRI: irinotecan; KRAS WT: Kirsten Rat Sarcoma Viral Oncogene Homolog (Wild-type); OS: overall survival; OXA: oxaliplatin; PFS: progression free survival; PAN: pantiumumab; RCT: randomised controlled trial; TAS-102: a combination agent combining trifluridine and tipiracil hydrochloride.

Table 5.3. Survival statistics from included studies (CRC population)

Study	Year	n (i)	n (c)	Median follow-up (months)	Median OS intervention arm (95% CIs)	Median OS in BSC arm (95% CIs)	Difference in OS between groups	Median PFS intervention arm (95% CIs)	Median PFS control arm (95% CIs)	Difference in PFS between groups	AEs reported	QoL reported
Hickish et al.	2017	207 (OS 116)	102 (OS 23)	6.1	6.1 (IQR 4.4-7.2) n=116	2.4 (1.9-3.2) [1] n=23	Log rank p=0.0002	NR	NR	NR	Y	Y
Li et al. (CONCUR)	2015	136	68	7.4	8.8 (7.3-9.8)	6.3 (4.8-7.6)	HR 0.55 (95% CI 0.40-0.77; p=0.00016)	3.2 (2.0-3.7)	1.7 (1.6-1.8)	HR 0.31 (95% CI 0.22-0.44; p<0.0001)	Y	Y
Mayer et al. (RECOURSE)	2015	534	266	11.8	7.1 (6.5-7.8)	5.3 (4.6-6.0)	HR 0.68 (95% CI 0.58-0.81; p<0.001)	2.0 (1.9-2.1)	1.7 (1.7-1.8)	HR 0.48 (95% CI 0.41-0.57; p<0.001)	Y	N
Grothey et al. (CORRECT)	2013	505	225	NR	6.4 (IQR 3.6-11.8)	5.0 (IQR 2.8-10.4)	HR 0.77 (95% CI 0.64-0.97; p=0.0052)	1.9 (IQR 1.6-3.9)	1.7 (IQR 1.4-1.9)	HR 0.49 (95% CI 0.42-0.58; p<0.0001)	Y	Y
Yoshino et al.	2012	112	57	11.3	9.0 (7.3-11.3)	6.6 (4.9-8.0)	HR 0.56 (95% CI 0.39-0.81)	2.0 (1.9-2.8)	1.0 (1.0-1.0)	HR 0.41 (95% CI 0.28-0.59; p<0.0001)	Y	N
Jonker et al.	2007	287	285	14.6	6.1m (NR)	4.6 (NR)	HR: 0.77 (95% 0.64-0.92; p=0.005)	NR	NR	HR 0.68 (95% CI 0.65-0.95; p=0.01)	Y	Y
Van Cutsem et al.	2007	231	232	8.1	6.3 (from 193d (NR))	6.0 (from 184d (NR))	HR 1.00 (95% CI 0.82-1.22; p=0.81)	8 (7.9-8.4)	7.3 (7.1-7.7)	HR 0.54 (95% CI 0.44-0.66; p<0.0001)	Y	Y[2]

AEs: adverse events: CI: confidence intervals; HR: hazard ratio; IQR: interquartile range; NR: not reported; OS: overall survival; PFS: progression free survival; QoL: quality of life.

[1] Placebo patients were permitted to cross-over to receive MABp1. Only placebo patients who did not cross-over were included in the survival analysis. These are patients that either progressed prior to the 8 week assessment or elected not to continue to the open label phase of the trial. The authors point out that there is a high risk of bias in the survival estimated of the placebo group for this reason.

[2] Quality of life outcomes reported in Odom et al (2011) and Siena (2007)

5.5 Results (ICC)

The systematic literature search yielded 753 potentially relevant studies. None of the identified studies met the inclusion criteria (Table 5.1).

5.5.1 Additional literature

Given the absence of studies on chemotherapy-refractory ICC patients receiving best supportive care, a directed search of reviews which report the efficacy of second-line therapies in ICC patients was conducted to capture any useful information which may be presented in the discussion about the expected length of survival in patients receiving BSC.

A systematic review of second-line chemotherapy in advanced ICC was conducted by Lamarca et al. (2014a). No comparative studies were identified and no studies of best supportive care were included. Twenty-five studies were included with a total of 761 patients. The mean OS was 7.2 months (95% CIs 6.2-8.2) and PFS was 3.2 months (95% CIs 2.7-3.7).

The authors of this review did not present any definitive data on OS in patients who receive BSC following progression on first line chemotherapy. However the authors extrapolated the results from an important trial of first-line chemotherapy to estimate the survival of patients following progression after which best supportive care was administered. Lamarca et al. (2014) estimated a 4 month duration of overall survival in patients treated with BSC who have progressed following first-line chemotherapy. This estimate should be interpreted cautiously as it has been secondarily extrapolated.

Bridgewater et al. (2014) presented guidelines for the management of ICC. Their recommendation is that there is no significant evidence that further chemotherapy beyond progression of first-line chemotherapy improves survival. The authors report overall survival from two phase II non-comparative studies of second-line chemotherapy: 4.1 months (Oh et al. 2011) and 6.7 months (Lee et al. 2009).

A phase III randomised controlled trial comparing FOLFOX to active symptom control (ASC) is currently underway (ABC-06 trial; Lamarca et al. 2014b) which will provide valuable information on both the overall survival of patients receiving ACS and any survival benefit from second line chemotherapy. The sample size for ABC-06 trial is based on an improvement from 4 months in the ASC arm to 6.3 months in the FOLFOX arm.

5.6 Discussion

5.6.1 Colorectal cancer population

The results of this rapid review on the length of survival in advanced, chemotherapy refractory mCRC patients receiving BSC demonstrate fairly consistent results across seven high quality RCTs. Patients in the control arm of interventional clinical trials in the salvage setting receiving BSC (with or without a placebo) had a median overall survival of between 2.4 months and 6.6 months. The low OS estimate of 2.4 months observed in Hickish et al. (2017) is likely to be a reflection of the inclusion

criteria which aimed to recruit patients showing multiple symptoms associated with poor outcomes including an ECOG performance status of 1 or 2. In addition, the OS estimate may be biased to shorter survival because this was a subgroup who had progressed or chose not to cross-over to the intervention arm. Conversely, Van Cutsem et al. (2007) included patients who had crossed over in the OS estimate which may bias the result in favour of longer survival in BSC patients. Following exclusion of these studies the median OS remained at 5.3 months (range 4.6 to 6.6 months).

Patients participating in the six studies included in this review were similar to those in the CtE population in that they had failed at least 2 previous lines of standard chemotherapy as treatment for mCRC. The ECOG performance status for the SIRT CtE cohort was 0-2; the 7 studies presented in this review also include patients captured in this range. Three studies include patients within the ECOG range of 0-2, three studies have an ECOG range of 0-1, and one has a range of 1-2. However, one important difference is that the presence of unresectable liver metastases was not an inclusion criterion for the BSC studies. Only two studies reported the proportion of liver metastases. The impact of this difference in the patient populations is uncertain.

The results from this review may provide context to survival estimates from studies of SIRT used in the salvage setting, most of which are non-comparative. The SIRT CtE registry results also lacks comparative data. Direct comparison of results from single arm SIRT studies or the SIRT registry to survival estimates for BSC reported here is not appropriate. Survival and progression outcomes from patients who received BSC as part of tightly controlled clinical trials should be interpreted cautiously in the context of data gathered from patients who received SIRT as part of the CtE project (which was set up as a service evaluation) and in the context of lower quality observational studies. It is risky to compare data from studies which are substantially different in terms of study design, eligibility criteria, patient selection, geographical and temporal setting, outcome assessments, and length of follow-up.

BSC is often poorly defined in clinical trials (Zafar et al. 2008); it varies across trials and in many cases is at the discretion of the investigator. Commonly the intention of BSC in trials is to provide palliative care for symptom control whilst excluding the use of antineoplastic agents. Variation in the definition of BSC and how it is administered is likely to be present in the studies included in this review. Furthermore, BSC from these studies may differ from the care typically provided to such patients in the UK which limits the generalisability of these results to the NHS setting.

5.6.2 Intrahepatic cholangiocarcinoma population

The results of this review demonstrated the paucity of evidence on the efficacy of second line treatments for ICC, including best supportive care or active symptom control. No studies have directly studied the survival of patients receiving BSC. Authors of one review have estimated overall survival in BSC patients as 4 months. Such an estimate from a secondary extrapolation of trial data should be viewed very cautiously.

For patients who receive second line chemotherapy, overall survival is reported as 7.2 months in a recent review. However, these patients may well be selected for continuing treatment due to their better performance status and prognosis. Their comparability to the SIRT CtE cohort is unclear and should be interpreted very cautiously.

6 Review of ongoing or recently completed clinical trials

6.1 Summary

Nine ongoing or recently completed and unpublished studies were identified which were relevant to the SIRT CtE evaluation. Of these, 7 were RCTs and 2 were registries. No studies were identified which matched the CtE population in patients with CRC or ICC.

The generalisability of the identified RCTs to the SIRT CtE project will be limited because of the difference in population and study design.

Results have recently been published in abstract form from the SIRFLOX, FOXFIRE, and FOXFIRE-Global RCTs. These trials assessed whether the addition of SIRT to radiosensitising chemotherapy in chemotherapy-naive patients conferred additional benefits in the first-line setting. No improvement in OS, PFS, or HRQoL was observed, but the SIRT group showed significantly improved LPFS and response rates. Patients treated with SIRT in combination with chemotherapy experienced more severe adverse events than patients treated with chemotherapy alone. Generalisability of these results in generally chemotherapy-sensitive patients to the CtE decision problem is limited since the CtE population is chemotherapy-refractory or chemotherapy-intolerant.

The two registry studies were CIRT and RESIN. CIRT is sponsored by the Cardiovascular and Interventional Radiological Society of Europe (CIRSE) and collects data, including QoL (using a disease-specific tool), on patients receiving SIRT for liver tumours of any primary origin. RESIN is a US-based registry with tumour response as the primary outcome.

6.2 Introduction

The purpose of this section is to collate information about ongoing (or recently completed) studies which are potentially relevant to the evaluation of the SIRT CtE evaluation but which have not been published. Studies with populations different to that of CtE have been included as these provide useful context to the evidence directly relevant to CtE.

6.3 Search method

Three publically accessible clinical trial registries were searched (Table 6.1). Studies on patients with CRCLM or ICC treated with SIRT, and with outcomes relating to the efficacy of SIRT were considered relevant. The review focused on comparative studies or those with a registry design.

Table 6.1. Clinical trial registries searched

	ClinicalTrials.gov	ISRCTN	WHO International Clinical Trials Registry Platform
Search date	1st Feb 2016 and updated on 19th January 2017	28th April 2016 and updated on 19th January 2017	28th April 2016 and updated on 19th January 2017
Search terms	*Yttrium OR Therasphere OR SIR-spheres OR Selective internal radiotherapy OR Selective internal radiation therapy*	*Yttrium OR Therasphere OR SIR-spheres OR Selective internal radiotherapy OR Selective internal radiation therapy*	**In title:** *Yttrium OR Therasphere OR SIR-spheres OR Selective internal radiotherapy OR Selective internal radiation therapy*; **Condition:** *cancer.*
Studies retrieved	261 clinical trial entries, or which 42 were potentially relevant	One additional relevant trial	83 clinical trial entries, of which 4 were potentially relevant

6.4 Results

6.4.1 Relevant ongoing or recently published clinical trials

Published clinical trials were excluded from the list of relevant studies as these were captured during the systematic review of SIRT efficacy in Section 4. Nine relevant ongoing/unpublished clinical trials were identified (Table 6.2).

The 9 relevant studies were comprised of 7 RCTs and 2 prospective, observational registry studies. The registry studies were non-comparative but were considered important because of similarities in methodology and study design to the SIRT CtE project.

The remaining 11 studies were considered not to be of high relevance because they were non-comparative, or had been withdrawn prior to recruitment. These are presented in Appendix 4.

SIRFLOX

Full title: FOLFOX Plus SIR-SPHERES MICROSPHERES Versus FOLFOX Alone in Patients With Liver Mets From Primary Colorectal Cancer (NCT00724503)

The SIRFLOX trial has been completed and published by van Hazel and colleagues (2016) (Van Hazel et al. 2004), see summary below. This publication does not report OS. This trial has been included here because its data will contribute to the FOXFIRE-global pooled analysis of overall survival.

SIRFLOX was an international, multi-centre, open-label, RCT in chemotherapy-naïve pts with non-resectable, liver only or liver dominant mCRC (Gibbs et al. 2014). The trial compared standard chemotherapy (mFOLFOX6: 5-fluorouracil, leucovorin and oxaliplatin) plus SIRT (SIR-spheres) to chemotherapy alone (bevacizumab was allowed at the discretion of the treating investigator). The primary outcome was progression free survival (PFS). Secondary outcomes included PFS in the liver, overall survival (OS), tumour response rate (liver and any site), health-related quality of life (HRQoL); toxicity and safety; and liver resection rate.

The trial was sponsored by Sirtex Medical (the manufacturer of SIR-spheres) and was conducted in sites in USA, Europe, Australia, New Zealand and the Middle East. No UK sites were involved in this trial. A total of 530 patients were recruited to the study.

FOXFIRE (UK Only)

Full title: An open-label randomised phase III trial of 5-Fluorouracil, OXaliplatin and Folinic acid +/- Interventional Radio-Embolisation as first line treatment for patients with unresectable liver-only or liver-predominant metastatic colorectal cancer (ISRCTN83867919)

FOXFIRE is a UK-based, multi-centre, open-label, RCT in patients with non-resectable, liver only or liver dominant mCRC who have not received chemotherapy for metastatic disease (Dutton et al. 2014). The trial compares standard chemotherapy (OxMdG: 5-fluorouracil, oxaliplatin and folinic acid) with SIRT (SIR-spheres) to chemotherapy alone. OxMdG is equivalent in drug doses to FOLFOX but uses a different delivery regimen with regard to the sequencing of drugs. The primary outcome is OS. Secondary outcomes include PFS, liver-specific PFS, patient-reported outcomes, safety, response rate, resection rate and cost-effectiveness. Patient-reported outcomes are assessed using the generic EORTC Quality of Life Questionnaire (QLQ-C30) and disease specific EORTC QLQ-LMC21. Health economic outcomes will be based upon utilities measured by EQ-5D and collection of health economic data including costs of chemotherapy and SIRT, hospital visits, imaging, surgical procedures, and in-patient lengths of stay.The trial is sponsored by the University of Oxford and is funded by Cancer Research UK. A total of 26 UK sites recruited a final total of 364 patients. The overall trial end date is October 2016.

FOXFIRE-Global

Full title: FOLFOX6m Plus SIR-Spheres Microspheres vs FOLFOX6m Alone in Patients With Liver Mets From Primary Colorectal Cancer (FOXFIREGlobal) (NCT01721954)

FOXFIRE-Global is an international, multi-centre, open-label, RCT in chemotherapy-naïve pts with non-resectable, liver only or liver dominant mCRC. The trial compares standard chemotherapy (mFOLFOX6) with SIRT (SIR-spheres) to chemotherapy alone (bevacizumab is allowed). The primary

outcome is overall survival. FOXFIRE-Global study has been designed so that it may be combined with the SIRFLOX and FOXFIRE studies, allowing for the pooling of the 3 study's data on safety and efficacy outcomes, with the combined studies powered for overall survival.

The trial is sponsored by Sirtex Medical (the manufacturer of SIR-spheres) and was conducted in sites in USA, Europe, Australia, New Zealand and the Middle East. No UK sites are involved in this trial. Enrolment to the FOXFIRE-Global trial is complete (estimated at 200 patients).

Pooled analysis of SIRFLOX, FOXFIRE, and FOXFIRE-global

The planned combined analysis of overall survival from SIRFLOX, FOXFIRE, and FOXFIRE-Global (FF-SF-FFG) was recently published as a conference abstract (Sharma et al. 2017). The analysis included 1,103 chemotherapy-naive mCRC patients. This evaluated whether the addition of SIRT to radiosensitising, first-line chemotherapy patients conferred additional benefits to first-line chemotherapy alone. Median follow-up was 43.3 months. A full quality appraisal has not been possible because this has been published as a conference abstract. The full paper is currently in press.

In the published conference abstract, no difference in OS (HR 1.04; 95% CIs 0.90-1.19; p=0.609) or PFS (HR 0.90; 95% CI 0.79-1.02; p=0.108) was observed between the groups (chemotherapy-alone versus chemotherapy plus SIRT). LPFS was improved in the SIRT group (HR: 0.51; 95% CIs 0.43-0.62; p<0.001), as was the objective response rate (p=0.001). Severe adverse events were more common in the SIRT group (p=0.009) and no difference in HRQoL (measured using EQ-5D) was observed between the arms at 6, 12, or 24 months. Unpublished overall survival results from subgroup analyses indicate that patients with a primary tumour originating within the right side of the bowel may benefit significantly more from the addition of SIRT to chemotherapy, compared to other patients (University of Oxford website, 2017). Generalisability of these results in generally chemotherapy-sensitive patients to the CtE decision problem is limited since the CtE population is chemotherapy-refractory or chemotherapy-intolerant.

EPOCH

Full title: Efficacy Evaluation of TheraSphere Following Failed First Line Chemotherapy in Metastatic Colorectal Cancer (NCT01483027)

EPOCH is an international, multi-centre, open-label, RCT in patients with liver-only mCRC of the liver who have failed first-line chemotherapy (Karpf et al. 2014). The trial compares standard chemotherapy (oxaliplatin or irinotecan based) plus SIRT (TheraSphere) with chemotherapy alone. The primary outcome is PFS and secondary outcomes are OS, tumour response, time to symptomatic progression, hepatic PFS, and quality of life (assessed using the disease specific tool, FACT-C).

The trial, which is sponsored by BTG International UK Ltd (manufacturer of TheraSphere), is being conducted across several countries including 6 sites in the UK. The target enrolment is 340 patients, and is due to complete in late 2018/early 2019.

SIR-Step trial

Full title: Comparing HAI-90Y (SIR-spheres) + Chemotx LV5FU2 Versus Chemotx LV5FU2 Alone to Treat Colorectal Cancer (NCT01895257)

SIR-step is a Belgian, multicentre, open-label, RCT in patients with dominant or exclusive and unresectable liver mCRC controlled after 3-6 months of chemotherapy induction. The trial aims to evaluate a maintenance strategy comparing SIRT (SIR-spheres) plus continuing simplified chemotherapy (LV5FU2) with/without targeted therapy (bevacizumab or cetuximab) versus continuing simplified chemotherapy with/without targeted therapy alone. The primary outcome is time to first progression (TTP1). Secondary outcomes are time to global progression (TTP1 + TTP2), Time to second progression (TTP2), TTP1 liver only, PFS, OS, safety, resection rate, quality of life (QoL).

The trial is sponsored by Antwerp University and is being conducted in sites in Belgium. Enrolment is ongoing and aim is to recruit 162 patients. The study is due to complete in December 2018.

Selective Internal Radiotherapy (SIRT) Versus Transarterial Chemoembolisation (TACE) for the Treatment of Cholangiocellular Carcinoma (CCC)

This is a pilot randomised controlled trial (NCT01798147) at a single centre in Germany in chemotherapy naive patients with unresectable, liver-only ICC (Kloecker et al. 2014). The trial compares doxorubicin drug-eluting bead trans arterial chemo-embolization (DEB-TACE) to SIRT (SIR-spheres). The primary outcome measure is PFS. Secondary outcomes include OS and TTP. The target study population is 24 patients, 12 patients in each group. The trial is sponsored by Johannes Gutenberg University Mainz and is due to complete October 2016. The status of this trial is unknown as details on ClinicalTrials.gov have not been updated in at least 2 years.

CIRT registry

The CIRT registry (NCT02305459) was started in 2014 and is due to complete in 2019-20. The registry is a European-wide registry that aims to prospectively collect data on SIR-Spheres therapies. It is sponsored by the Cardiovascular and Interventional Radiological Society of Europe (CIRSE). The registry will collect data on patients receiving SIRT for liver tumours of any primary origin, and does not collect comparative data. It appears from the information available on the study website that SIRTEX medical are involved but the arrangements are not described.

RESIN registry

The RESIN registry (NCT02685631) was initiated in 2015 and is due to complete in 2020/21. The study is sponsored in the US by Vanderbilt University/Ingram Cancer. The study aims to collect data from 400 patients treated with Yttrium-90 SIRT; the available information does not specify a primary cancer type. The registry does not appear to collect data from comparator patients. The primary outcome measure is tumour response (modified Response Evaluation Criteria in Solid Tumors (mRECIST) or European Association for Study of Liver Cancer (EASL)). Secondary outcomes are Treatment related toxicity assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE v4), overall survival, and time to progression. According to a press release from Vanderbilt University, the RESIN registry is a collaboration with 6 medical centres and SIRTEX medical.

SIRCCA study

Full title: SIRT Followed by CIS-GEM Chemotherapy Versus CIS-GEM Chemotherapy Alone as 1st Line Treatment of Patients With Unresectable Intrahepatic Cholangiocarcinoma (NCT02807181)

SIRCCA is an international, multi-centre, open-label RCT in patients with unresectable ICC. The trial compares the effect of SIRT prior to chemotherapy (cispaltin-gemcitabine) with chemotherapy alone. The primary outcome is survival at 18 months following randomisation. Secondary outcomes include liver-specific PFS, PFS, response rate, overall survival, surgery and resection rate, AEs and safety. The trial aims to recruit 180 patients. The trial is sponsored by Sirtex Medical.

6.5 Relevance of identified studies to the SIRT CtE project

No studies were identified which match the CtE population in the third-line colorectal cancer population.

The populations in FOXFIRE, SIRFLOX, and FOXFIRE-Global are chemotherapy-naive and SIRT is being added to first-line therapy. The applicability of the FF-SF-FFG combined analysis to the CtE evaluation is limited due to differences in the eligibility criteria. The FF-SF-FFG analysis was evaluating whether SIRT provided an additional benefit to chemotherapy. Generalisability of these results in generally chemotherapy-sensitive patients to the CtE decision problem is limited since the CtE population is chemotherapy-refractory or chemotherapy-intolerant. Since cross-over in subsequent lines of therapy cannot be controlled in a first-line study, a survival advantage may be difficult to detect in a controlled prospective study with this design.

In EPOCH, SIRT is used as a second-line treatment, and in SIR-step patients have not progressed following their first-line of chemotherapy. The generalisability of the results from the RCTs to the SIRT CtE project is limited because of the difference in population. In addition, these clinical trials will recruit a more homogenous population compared to the SIRT CtE project, and the treatment and observations will be more “protocolised” which may impact on the results.

The SIRCCA study is of interest, but appears to use SIRT in chemo-naive patients (prior to chemotherapy) and therefore is of limited relevance to the SIRT CtE project.

The CIRT registry may contain data from UK sites. Of particular interest is measurement of quality of life using disease-specific quality of life tools.

Table 4.2. Clinical trials relevant to the evaluation of SIRT CtE study

Identifier	Title	Acronym	Status	Enrolment	Design	Start date	Estimated completion date	Primary Completion Date	Outcome measures	Population	Relevance	Location
NCT00724503	FOLFOX Plus SIR-SPHERES MICROSPHERES Versus FOLFOX Alone in Patients With Liver Mets From Primary Colorectal Cancer (Gibbs et al. 2014)	SIRFLOX	Part-published	518	RCT	2006	2018	2017	PFS	CRC	Different population (chemo naive)	International
ISRCTN83867919	FOXFIRE: an open-label randomised phase III trial of 5-Fluorouracil, OXaliplatin and Folinic acid +/- Interventional Radio-Embolisation as first line treatment for patients with unresectable liver-only or liver-predominant metastatic colorectal cancer (Dutton et al. 2014)	FOXFIRE (UK only)	Part-published	364 (final)	RCT	2008	2016	2016	OS, PFS, safety and toxicity, costs, QoL, response rate, resection rate	CRC	Different population (chemo naive)	UK
NCT01798147	Selective Internal Radiotherapy (SIRT) Versus Transarterial Chemoembolisation (TACE) for the Treatment of Cholangiocellular Carcinoma (CCC) (Kloeckner et al. 2014)		Status unknown	24	RCT	2011	2016	2016	PFS, OS, TTP	ICC	Different population (chemo naive)	Germany
NCT01483027	Efficacy Evaluation of TheraSphere Following Failed First Line Chemotherapy in Metastatic Colorectal Cancer (Karpf 2015)	EPOCH	Recruiting	340	RCT	2012	2019	2018	PFS	CRC	Different population (2nd line)	International (incl UK)
NCT01721954	FOLFOX6m Plus SIR-Spheres Microspheres vs FOLFOX6m Alone in Patients With Liver Mets From Primary Colorectal Cancer	FOXFIRE Global	Part-published	200	RCT	2013	2019	2017	POS, PFS	CRC	Different population (chemo naive)	International
NCT01895257	Comparing HAI-90Y (SIR-spheres)+Chemotx LV5FU2 Versus Chemotx LV5FU2 Alone to Treat Colorectal Cancer	SIR-Step trial	Recruiting	162	RCT	2013	2018	2017	TTP, PFS, safety, resection rate, QoL, OS	CRC	Different population (mCRC controlled after 3-6m chemotherapy)	Belgium
NCT02305459	CIRSE Registry for SIR-Spheres Therapy	CIRT	Recruiting	1200	Prospective observational	2014	2020	2019	QoL	CRC	Alternative registry	Austria
NCT02685631	Yttrium Y 90 Resin Microspheres Data Collection in Unresectable Liver Cancer: the RESIN Registry	RESIN	Recruiting	400	Prospective observational	2015	2021	2020	Response rate, toxicity, OS, TTP	Mixed	Alternative registry	USA
NCT02807181	SIRT Followed by CIS-GEM Chemotherapy Versus CIS-GEM Chemotherapy Alone as 1st Line Treatment of Patients With Unresectable Intrahepatic Cholangiocarcinoma	SIRCCA	Not yet open for recruitment	180	RCT	2016	2019	2019	Survival at 18m, PFS, response rate, OS	ICC	Yes (unresectable ICC)	International (incl UK)

CRC, colorectal cancer; ICC, intrahepatic cholangiocarcinoma; mCRC, metastatic colorectal cancer; OS, overall survival; PFS, progression free survival; QoL, quality of life; RCT, randomised controlled trial; TTP, time to progression

7 Evaluation of SIRT CtE registry study

7.1 Summary

Methods: The SIRT CtE registry study was a single-arm, observational, service evaluation study to evaluate SIRT in ten NHS centres in England. Patients who met the inclusion criteria were eligible to receive SIRT as part of the CtE scheme and were treated between December 2013 and March 2017. Data were collected prospectively onto a registry and were extracted for analysis in early March 2017. Patients treated most recently had very short follow-up periods. The median time to follow-up was 14.3 months. Overall survival was the primary outcome. Patients who did not have a date of death were censored at the latest point they were known to be alive, and patients missing this information were excluded from the analysis. Secondary outcomes were PFS, LPFS, HRQoL, procedural complications, and adverse events during follow-up. The two populations were adults with: i) unresectable, chemotherapy-refractory CRCLM; ii) unresectable, chemotherapy-refractory primary ICC.

Results: A total of 399 patients with CRC and 61 with ICC were included in the analysis. Most of these patients had an ECOG performance status of 0 or 1. In the CRC group, most patients did not show evidence of extrahepatic metastatic disease and had received two previous lines of chemotherapy. Most ICC patients had received 1 or 2 lines of chemotherapy prior to SIRT. In both cohorts most patients had a single SIRT procedure of palliative intent. Patients required hospitalisation for 1 or 2 nights for their SIRT procedure; a minority of patients received concomitant chemotherapy (35% in CRC cohort; 12% in ICC cohort) with SIRT. Some patients also received chemotherapy following SIRT.

Survival statistics were as follows:

Outcome (median in months)	CRC cohort (95% CIs)	ICC cohort (95% CIs)
OS from first SIRT procedure to death	7.6 (6.9-8.3) (240 events)	8.7 (5.3-12.1) (33 events)
PFS from first SIRT procedure to earliest date of hepatic or extrahepatic disease progression (or death)	3.0 (2.8-3.12) (331 events)	2.8 (2.6-3.1) (47 events)
LPFS survival from first SIRT procedure to earliest date of hepatic disease progression (or death)	3.7 (3.2-4.3) (300 events)	3.1 (1.3-4.8) (46 events)

In subgroup analyses of the CRC group, patients with no extrahepatic disease showed a statistically significant longer overall survival compared with those with extrahepatic metastases; patients with fewer liver tumours survived longer than patients with more liver tumours; patients with smaller tumour to liver volume percentages also survived longer; and males had a longer OS than females.

HRQoL measured using EQ-5D-5L and EQ-VAS remained relatively high and constant between baseline and follow-up time points (between 0.80 and 0.85 of a maximum of 1) in the CRC group. A

statistically significant reduction in HRQoL was observed from baseline to 3-months after SIRT but this was small (0.042 point change on a scale of approximately 0-1) and did not reach a minimally important difference threshold. Measurement time points and methodology were variable across sites with high levels of missing data; robust conclusions regarding the impact of SIRT on patients' quality of life cannot be drawn.

Severe complications on the day of treatment were reported in 11 CRC patients (3%) and 1 ICC patient (2%). During the follow-up period 36% of CRC patients experienced an adverse event, of which 8% of the events were grade ≥3. In the ICC cohort, 49% of patients experienced an adverse event during the follow-up period, or which 7% were grade ≥3. The most frequently reported adverse events were mild (grade 1-2) fatigue and abdominal pain in both cohorts. No severe cases of radiation induced liver disease were recorded in either cohort. The most common abnormal laboratory value events were raised aspartarte aminotransferase and raised alanine aminotransferase. In the CRC cohort, 5% of laboratory events were grade ≥3, and 4% in the ICC cohort.

Discussion: Results were within the range of previously published survival estimates of OS. The CtE CRC cohort was comparable to that presented in a published retrospective comparative study which demonstrated a statistically significant survival benefit of 5 months from SIRT compared to best supportive care. The paucity of published evidence from ICC patients makes interpretation and contextualisation of the CtE data even more challenging.

This large, pragmatic, observational design is likely to reflect real-life practice in the NHS but is limited by the absence of a comparator treatment. Other limitations were that data were missing for most variables and reported data were not externally validated. Progression was recorded only at scheduled clinical assessments that took place in intervals of 2 to 3 months. Estimation of PFS with such interval-censored data is less reliable than if the dates of progression were exact.

In the absence of comparator data, conclusions regarding a survival benefit from SIRT cannot be reliably drawn. Randomised controlled trials are required to distinguish the effects of treatment from the influence of prognostic factors, both known and unknown. Such studies are required to support the suggestion of a survival benefit from SIRT reported from this and other observational studies.

Conclusions: The present study reports overall survival in chemotherapy-refractory CRC and ICC patients treated with SIRT. Severe adverse events following SIRT were rare. The impact of SIRT on patients' HRQoL was not informed by this study. Survival estimates align with previously published observational studies. Existing evidence is not reliable enough in the ICC group to make a similar statement. Studies with observations from patients having received a comparator treatment are needed to inform the debate on the clinical effectiveness of SIRT.

7.2 Methods

7.2.1 Study design

Between December 2013[1] and February 2017 patients were treated with SIRT for liver tumours as part of a prospective, observational, non-comparative, service evaluation study. This project was part of NHS England's CtE program, where new treatments were commissioned in the NHS with a planned evaluation. The aim was to gather clinical and cost-effectiveness data on SIRT to inform a commissioning decision. The project was considered to be service evaluation and did not go through scientific review, ethical or global governance approvals. Institutional approval for the service evaluation at each of the sites providing SIRT was the responsibility of the clinical team at each site. SIRT was considered standard care at the provider centres and patient consent was sought using the sites' established processes. The SIRT procedure (including related care) and data submission activities were funded by NHSE through the CtE scheme. Pseudonymised data relating to patient characteristics, treatment planning, the SIRT procedure, safety and adverse events, imaging results, survival, and HRQoL were prospectively collected by the clinical teams and submitted to a pre-existing online SIRT registry (hosted by the British Society of Interventional Radiology [BSIR]). This service evaluation project did not have a centralised protocol and was not prospectively registered on a clinical trials database.

All patients who received a SIRT procedure until the end of February 2017 were included in the analysis. Data were extracted from the registry for analysis on 5th March 2017; therefore patients had unequal lengths of follow-up. Patients treated in the 2 to 3 months preceding the data extraction date may be missing most follow-up data. Patients continued to be treated under the CtE scheme until the end of March 2017; patients treated in the final month were not included in the analysis due to constraints on the evaluation timeline.

Patients were treated at the following ten NHS institutions in England: Cambridge University Hospitals NHS Foundation Trust, Kings College Hospital NHS Foundation Trust, Leeds Teaching Hospitals NHS Trust, Newcastle-upon-Tyne Hospitals NHS Trust, Nottingham University Hospitals NHS Trust, Oxford University Hospitals NHS Foundation Trust, the Christie NHS Foundation Trust, the Royal Free London NHS Foundation Trust, University Hospital Southampton NHS Foundation Trust, University Hospitals Birmingham NHS Foundation Trust.

7.2.2 Population

Two populations were eligible to receive SIRT under the CtE funding arrangements in the UK National Health Service (NHS): i) adults with unresectable, chemotherapy refractory, colorectal cancer (CRC) liver metastases; ii) adults with unresectable, chemotherapy refractory intrahepatic cholangiocarcinoma (ICC).

The eligibility criteria established by NHSE for inclusion in the SIRT CtE cohort for the two populations were as follows. For the metastatic CRC (mCRC) population: i) histologically confirmed

[1] The SIRT CtE project started proper in Dec 2013 however the registry holds 4 cases which occurred before this date (3 patients from Southampton and 1 from Cambridge).

carcinoma with liver-specific or liver-dominant metastases not amenable to curative liver surgical resection; ii) unequivocal and measurable CT evidence of liver metastases which are not treatable by surgical resection or local ablation with curative intent at the time of CtE entry; iii) no clinical trial of SIRT available as alternative treatment; iv) WHO performance status of 0–2; v) life expectancy > 3 months; vi) evidence of clinical progression during or following both oxaliplatin-based and irinotecan-based chemotherapy, unless the patient has a specific contraindication to chemotherapy or did not tolerate either regimen; vii) adequate haematological and hepatic function as follows: serum bilirubin ≤ 1.5 x ULN; absolute neutrophil count > 1.5 x 10^9/L, platelets > 100 x 10^9/L; albumin ≥ 30 g/L; viii) having the primary colorectal tumour in situ was not a exclusion criterion; ix) patients were permitted to have limited extra-hepatic disease that was not life threatening nor a cause for significant morbidity if the liver metastases could be controlled with locally direCtEd therapy, e.g. lung metastases, multiple lymph nodes or low-volume peritoneal disease; x) no central nervous system metastases or bone metastases; xi) no evidence of ascites, cirrhosis or portal; xii) no previous portal venous embolisation or previous chemo-embolisation; xiii) no previous radiotherapy to the upper abdomen or the right lower thorax; xiv) female patients were either post-menopausal or using an acceptable method of contraception and were not pregnant or breast-feeding; xv) male patients, if sexually active with a pre-menopausal partner, had to be using an appropriate method of contraception.

For the ICC population the same eligibility criteria were used except that there should be evidence of clinical progression during or following standard chemotherapy, unless the patient has a specific contraindication to chemotherapy. Unlike the mCRC population the type of chemotherapy and number of lines was not limited. Standard chemotherapy in this group would usually comprise one line of a combination of cisplatin and gemcitabine.

7.2.3 Procedures

Two brands of CE-marked active implantable medical devices were used to carry out the SIRT procedure: i) SIR-spheres (Sirtex Medical Ltd, Australia) use resin microspheres; ii) TheraSphere (Biocompatibles UK Ltd, UK) use glass microspheres. Both were Y-90 microspheres although this was not specified under the CtE funding arrangements[1].

The service evaluation design meant that each site followed their local process for undertaking SIRT procedures. All patients received a hepatic arteriogram and a liver-to-lung breakthrough nuclear medicine scan to ensure suitability for receiving this procedure, and to plan the delivery of the Y-90 microspheres. Selective coil embolisation of arteries to the stomach, duodenum or other visceral structures may be carried out to limit the delivery of microspheres outside the liver. Dosing of SIR-spheres and TheraSpheres was carried out as per manufacturer instructions. For SIR-spheres the dose was calculated through the body surface area (BSA) method or through the partition model method. For TheraSpheres the dose to the liver was calculated from liver volume converted to liver mass. A technical description of the SIRT procedure is provided in Section 3.

[1] A third medical device, QuiremSpheres (Quirem Medical, The Netherlands), is now CE-marked and became available after the start of the SIRT CtE project. No patients in the SIRT CtE study were treated using QuiremSpheres.

Administration of concomitant chemotherapy and post-SIRT chemotherapy was at the discretion of the treating clinician.

As is standard practice in the UK, sites were expected to follow patients up every 2 to 3 months after their SIRT procedure until progression was detected (and later for survival data). Follow-up appointments would usually consist of an abdominal CT scan (plus chest and/or pelvis in patients with extrahepatic disease), and in some cases an MRI or PET scan was also carried out. In addition, sites invited patients to complete the generic HRQoL questionnaire, EQ-5D-5L (Herdman et al. 2011), prior to SIRT and every three months until progression. Follow-up assessments after progression were occasionally recorded in the registry. Throughout the follow-up period adverse events were assessed and recorded.

7.2.4 Data collection and data analysis

The pathway for data collection in a typical case in the SIRT CtE study is presented in Figure 7.1. Data were collected by the clinical teams at each site using their established processes and subsequently entered into the SIRT registry hosted by the BSIR (available at https://sirtregistry.co.uk/). At the study end, pseudonymised data from CtE cases were added to the registry. A full list of fields within the SIRT registry are provided in Appendix 5. All patient identifiers were replaced by a unique patient identifier. The final anonymised dataset was extracted from the registry by BSIR on 5th March 2017 and sent to an independent research group, Cedar (Cardiff and Vale University Health Board), for analysis. Data were only collected on patients who received SIRT and no comparator data were available. Details of patients who received a work-up procedure but were ultimately ineligible for SIRT were not included. It was not possible to carry out external validation/triangulation of data entered onto the registry by clinical teams because of the anonymous nature of the dataset.

Due to time constraints, there was no follow-up phase of the study after the last SIRT treatment. In order to maximize procedural data all patients who received a SIRT procedure were included in the analysis regardless of the duration of follow-up. As such, patients had unequal follow-up periods, and patients treated most recently would be missing some or all follow-up data. Missing data proportions were reported for all outcomes. Patients with a missing diagnosis or missing SIRT administration date were excluded from the analysis. Data from the CRC and ICC cohorts have been presented and analysed separately. No data from a comparator group was collected.

Date of death was recorded in the SIRT registry by clinical teams using locally accessible data; at some sites date of death was obtained or validated using the NHS Spine portal where electronic records of patient information are accessible. OS was defined as the duration from the first SIRT procedure until death from any cause. Patients with no date of death recorded were right censored at the date at which they were lost to follow-up (LTFU) date. LTFU date was captured using the most recent date of imaging, or EQ-5D-5L administration, or follow-up visit, or chemotherapy administration, and in some cases sites specifically recorded the most recent date the patient was known to be alive. Patients with no date of death, no LTFU date, or a date of death prior to SIRT were excluded from OS analysis. Survival proportions at 3, 6, 12, 24, and 36 months were reported for patients for whom this data was available (for those most recently recruited these data were unavailable).

Hepatic and extrahepatic tumour response assessments were carried out locally by a radiologist and recorded separately in the SIRT registry. It is the standard practice to discuss treatment response in the multidisciplinary team meeting. Blinded assessment or validation by another radiologist was not routinely carried out. The evaluation criteria were noted in the registry (usually as the response evaluation criteria for solid tumours (RECIST) (Eisenhauer et al. 2009)). PFS was defined as the duration from the first SIRT administration to the earliest date of detection of progressive disease (PD; either hepatic or extrahepatic) by CT, MRI, or PET scan, or to the date of death from any cause if progression was not recorded. Patients with no PD recorded were censored at the most recent date of non-progression (complete response (CR) or partial response (PR) or stable disease (SD)). Cases where no imaging results were recorded were excluded from this analysis.

LPFS was defined as the duration from the first SIRT administration to the date of progression in the liver or death from any cause. Patients with no PD in the liver were censored at the most recent date of non-progression in the liver. Cases with no hepatic imaging results were excluded from this analysis.

A range of baseline and procedural parameters were recorded in the registry (Appendix 5) including haematologic, liver function, and blood biochemistry tests. Baseline albumin laboratory values were excluded if they were <15 g/L as these were assumed to be data entry errors (probably due to confusion of the unit of measurement). The following data were categorised: age at time of SIRT was categorised into <65 years and ≥65 years; number of liver tumours was categorised into 1-5, 6-10, >10, and uncountable; number of previous chemotherapy lines was categorised into 1, 2, 3, ≥4.

Prior chemotherapy regimens were recorded in a free text field. A search of regimen synonyms was carried out to count the number of patients who received each type of chemotherapy prior to their SIRT administration and concomitantly to SIRT.

The percentage tumour volume to liver volume was recorded for either the whole liver, or for right and left lobes separately. Where a whole liver measurement was absent, right and left values were added to produce a proxy for a whole liver measurement. Similarly, prescribed activity (from the Y-90 microspheres) was recorded separately for the whole liver, and for right and left lobes. Prescribed activity was recorded in the registry using GBq as the unit of measurement, however some very high values were also recorded which were likely to be erroneous having been measured in MBq. Therefore any prescribed activity of >100 units was converted using a 0.001 conversion factor. Prescribed activity was also presented separately for the two brands of yttrium-90 microscpheres (SIR-spheres or TheraSphere).

Severe complications that occurred during the treatment[1] and subsequent AEs were recorded. AEs were graded; the criteria used for grading was not prescribed although it was assumed that most centres would use the Common Terminology Criteria for Adverse Events (CTCAE) system. The SIRT registry recorded the following AEs using a check box: abdominal pain, fatigue, fever, nausea, vomiting, gastritis, gastrointestinal (GI) ulcer, radiation-induced liver disease (RILD), radiation pneumonitis, radiation cholecystitis, radiation pancreatitis. The registry recorded the following

[1] The registry did not record a grade for day-of-treatment complications; instead the question was worded as "were any severe day of treatment complications experienced?"

abnormal laboratory results using a check box: hypoalbuminemia, hyperbilirubinemia, alanine aminotransferase (ALT) increased, aspartarte aminotransferase (AST) increased, INR increased, neutrophil count decreased, platelet count decreased. The registry also had an “other” category for free-text entries for both adverse events and abnormal laboratory results. Date and grade (grading system not specified in registry) were also recorded.

The total number of all-causality AEs and total number of AEs of grade 3 or above were calculated by counting all recorded AEs in each follow-up entry on the registry. Common events recorded in the “other” category were presented; and all grade ≥3 events recorded in the “other” category were presented individually. The total number of all-causality abnormal laboratory results and total number of grade 3 or above laboratory events were counted from each follow-up entry on the registry.

Incidents or complaints related to the radioactive microsphere product used in the procedure were recorded in the registry. The following question was used to capture this information “was there a product incident or complaint associated with the treatment?”.

EQ-5D-5L and EQ-VAS data were collected on the registry. EQ-5D-5L is a patient reported outcome measure which consists of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Respondents rate their level of severity for each dimension using a five-point ordinal scale. The responses are converted to an index score between 0 and 1 (Herdman et al. 2011). The EQ-VAS (visual analogue score) forms the second part of the questionnaire in which patients are asked to mark their health status today on a scale between 0 and 100 (0 corresponds to "the worst health you can imagine", and 100 corresponds to "the best health you can imagine"). EQ-5D-5L and EQ-VAS scores were grouped according to time elapsed since SIRT administration (Table 7.1).

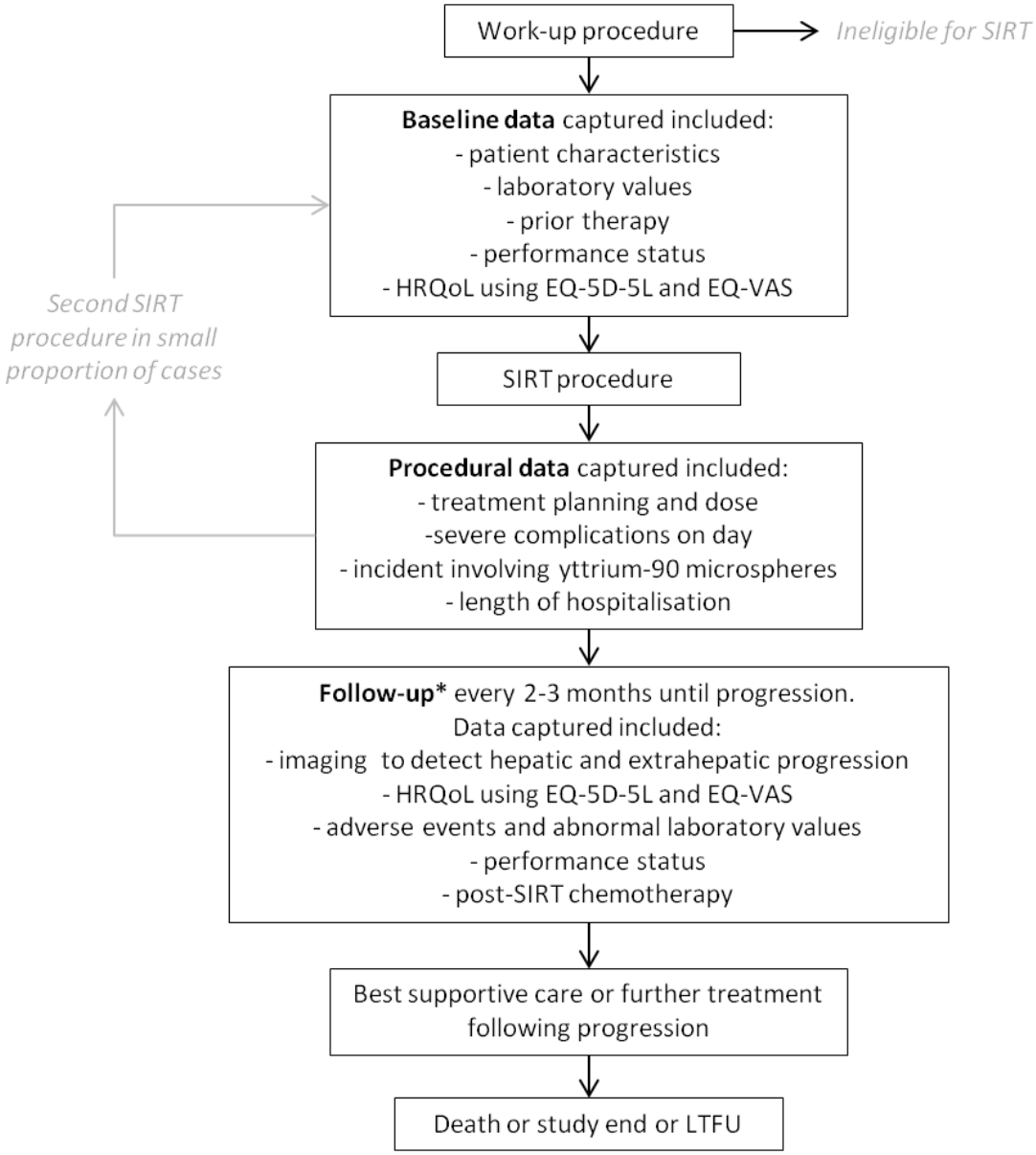
Table 7.1 Categorisation of EQ-5D-5L and EQ-VAS scores according to time elapsed since SIRT procedure.

Time since SIRT procedure when EQ-5D-5L and EQ-VAS were measured	Time point group
0-60 days prior to SIRT	Baseline
60 to 120 days after SIRT	3-month follow-up
150-210 days after SIRT	6-month follow-up
240-300 days after SIRT	9-month follow-up
12 months (± 3 months)	12-month follow-up
24 months (± 6 months)	24-month follow-up

7.2.5 Statistical analysis

All statistical analyses were conducted in IBM SPSS Statistics version 21.0.0.0 (IBM Corp. Armonk, NY) or R (R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org/). Descriptive statistics (mean, median, standard deviation (SD), interquartile range (IQR), range, 95% confidence intervals) for continuous variables were reported as appropriate. Frequency counts were calculated for qualitative variables. For each statistical comparison, p-value and confidence intervals were reported. P-values at <0.05 were considered statistically significant and all tests were two-sided.

OS, PFS, and LPFS were estimated using the Kaplan-Meier analysis (Kaplan and Meier 1958). Survival curves were presented with 95% confidence intervals (CIs) and numbers at risk displayed. Application of competing risk analysis was not considered to be appropriate. Potentially important baseline covariates were tested to identify statistically significant prognostic factors associated with survival in the CRC cohort using the pairwise log-rank test. The sample size was too small to analyse subgroups in the ICC cohort. Hazard ratios (HRs) for baseline covariates were estimated for overall survival by univariate Cox proportional hazards models. The following covariates were selected: number of previous lines of chemotherapy (categories: 0, 1, 2, 3, ≥4), ECOG performance status (categories: 0, 1, 2), age (either as continuous or categories: <65 years, ≥65 years), sex, primary tumour *in situ* or not, prior biological therapy (including bevacizumab, cetuximab, aflibercept, panitumumab), presence of extrahepatic metastases (categories: yes, no), extent of liver involvement (continuous or categories: <25%, 25-50%, >50%), prior liver surgery (categories: yes, no), number of liver tumours (categories: 1-5, 6-10, >10). The reverse Kaplan-Meier method was used to calculate median follow-up time (this is a more robust method whereby the event indicator in the Kaplan-Meier survival curve is reversed) (Schemper and Smith 1996). Survival proportions were taken from the Kaplan-Meier life tables at 6, 12, 24, and 36 months. Comparisons of EQ-5D-5L/VAS scores from baseline to follow-up time points were calculated using a paired samples Student's T-test (pre – post SIRT scores). Negative change scores indicate an improvement in HRQoL following SIRT.



*Components of follow-up were not necessarily measured at the same time or frequency. Some or all of follow-up components may be missing, particularly in patients with short follow-up period due to study closure. Some patients received follow-up after progression. Further treatment (e.g. chemotherapy) during or after SIRT was at the treating clinician's discretion.

HRQOL, health-related quality of life; LTFU, lost to follow up; VAS, visual analogue scale.

Figure 7.1. Typical pathway and data collection process for patients in the SIRT CtE study.

7.3 Results

A total of 514 patients were treated under the scheme until close of data entry at the end of February 2017 (self reported numbers). A total of 474 patients were added to the SIRT registry, of which 460 were valid data entries[1] (cases with missing or ineligible diagnoses were excluded, and cases with no SIRT procedure date were also excluded). A total of 399 (87%) valid cases were in the CRC cohort and 61 (13%) in the ICC cohort. Across the 10 SIRT centres in England, the numbers of patients treated ranged from 15 to 120 (Table 7.2).

Table 7.2 Number of patients treated and entered onto the registry from each of the 10 SIRT CtE provider centres in England by diagnosis type and total (ordered by total number of patients treated)

Name of SIRT CtE provider hospital in England	Number of patient entries[2] added to the registry (%)		
	CRC	ICC	Total
Churchill Hospital (Oxford)	108 (27%)	12 (20%)	**120 (26%)**
Christie's Hospital (Manchester)	63 (16%)	16 (26%)	**79 (17%)**
Royal Free Hospital (London)	47 (12%)	10 (16%)	**57 (12%)**
Nottingham City Hospital (Nottingham)	47 (12%)	5 (8%)	**52 (11%)**
Freeman Hospital (Newcastle)	29 (7%)	6 (10%)	**35 (8%)**
Southampton General Hospital (Southampton)	35 (10%)	1 (3%)	**36 (8%)**
Addenbrooke's Hospital (Cambridge)	28 (7%)	5 (8%)	**33 (7%)**
Queen Elizabeth Hospital (Birmingham)	18 (5%)	1 (2%)	**19 (4%)**
King's College Hospital (London)	12 (3%)	2 (3%)	**14 (3%)**
St James's Hospital (Leeds)	12 (3%)	3 (5%)	**15 (3%)**
Total	**399 (100%)**	**61 (100%)**	**460 (100%)**

Baseline characteristics and prior treatments

Patients in the CRC cohort were 67% male and 33% female; they had a median age of 66 years. In the ICC cohort, 53% were male and 48% were female; the median age was 64 years (Table 7.3). Most patients had an ECOG performance score of 0 or 1 (93% CRC cohort; 91% ICC cohort) and the majority did not have extrahepatic metastatic disease (60% CRC; 59% ICC). Almost all patients had received prior systemic chemotherapy or biologics (98% CRC; 92% ICC). Most patients in the CRC cohort had received 2 or 3 lines of prior chemotherapy (78%) consisting predominantly of fluoropyrimidine-, oxaliplatin- or irinotecan-based regimens[3]. In the ICC cohort most patients had received 1 or 2 lines (81%) consisting mostly of cisplatin and gemcitabine (Table 7.3). Most patients had not received prior hepatic procedures (72% CRC; 84% ICC). The median duration from primary diagnosis to the first SIRT procedure was 2.1 years in the CRC cohort and 1.1 years in the ICC cohort.

[1] Patients treated within the final weeks of the project were not added to the registry because time constraints meant that the data cut-off was before the procedures were undertaken.
[2] Only valid entries included; cases with no diagnosis or no SIRT procedure date were excluded.
[3] Patients who were intolerant to standard chemotherapy were eligible to receive SIRT which may explain the 9% of CRC patient who received only one previous line of chemotherapy. This cannot be verified using data collected in the SIRT registry.

In the CRC group, the median time from diagnosis of metastatic disease to SIRT was 1.8 years. Very few patients had ascites or liver cirrhosis (Table 7.3).

Table 7.3. Baseline patient characteristics of CRC and ICC cohorts treated with SIRT

Parameter	Data from CRC cohort	Data from ICC cohort
Total	n=399	n=61
Age at time of procedure (years)	n=398 Median 66 (IQR 57-72) Mean 64 (SD 12)	n=61 Median 64 (IQR 55-72) Mean 62 (SD 12)
Age (<75 years / ≥75 years)	333 (84%) / 65 (16%)	53 (87%) / 8 (13%)
Male/Female (%)	133 (33%)/266 (67%)/133 (33%)	32 (53%)/29 (48%)
Baseline ECOG score		
0-Fully Active	201 (50%)	32 (53%)
1-Restricted	170 (43%)	23 (38%)
2-Ambulatory	13 (3%)	2 (3%)
3-Capable	1 (0.3%)	0
Missing	14 (4%)	4 (7%)
Limited extrahepatic disease		
Yes	159 (40%)	22 (36%)
No	236 (60%)	36 (59%)
Missing	0	3 (5%)
Location of metastatic disease[1]		
Lung	106	8
Lymph nodes	40	14
Bone	2	0
Brain	0	0
Other	32	4
Primary tumour resected		
Yes	226 (57%)	0
No	123 (31%)	2 (3%)
Missing	50 (13%)	59 (97%)
Time from primary diagnosis to SIRT procedure (years)	n=321 Median 2.1 (IQR 1.5-3.2)	n=53 Median 1.1 (IQR 0.7-1.4)
Time from metastatic diagnosis to SIRT procedure (years)	n=313 Median 1.8 (IQR 1.2-2.6)	N/A
Prior systemic chemotherapy (including biologics)		
Yes	391 (98%)	56 (92%)
No	8 (2%)	3 (5%)
Missing	0	2 (3%)
Number of previous chemotherapy lines		
1	34 (9%)	40 (66%)
2	222 (56%)	9 (15%)
3	87 (22%)	1 (2%)
≥4	34 (9%)	2 (3%)
Missing	22 (6%)	9 (15%)
Prior chemotherapy received (including biologics)[1]		

[1] Multiple tumour locations permitted.

Fluoropyrimidine-based	282 (71%)	3 (5%)
Oxaliplatin	303 (76%)	5 (8%)
Irinotecan	302 (76%)	-
Capacitabine	155 (39%)	2 (3%)
Cisplatin	-	48 (79%)
Gemcitabine	-	49 (80%)
Bevacizumab	119 (30%)	-
Cetuximab	109 (27%)	-
Aflibercept	25 (6%)	-
No chemotherapy recorded	53 (13%)	11 (18%)
Prior adjuvant therapy[2]		
Yes	85 (21%)	3 (5%)
No	303 (76%)	55 (90%)
Missing	11 (3%)	3 (5%)
Prior hepatic procedures		
Yes	110 (28%)	9 (15%)
No	289 (72%)	51 (84%)
Missing	0	1 (2%)
Portal vein thrombosis		
Patent	390 (98%)	55 (90%)
Lobar thrombosis	3 (1%)	2 (3%)
Segmental thrombosis	3 (1%)	2 (3%)
Missing	3 (1%)	2 (3%)
Ascites		
Yes	3 (1%)	4 (7%)
No	394 (99%)	55 (90%)
Missing	2 (0.5%)	2 (3%)
Cirrhosis		
Yes	0	0
No	397 (100%)	59 (97%)
Missing	2 (0.5%)	2 (3%)

ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; N/A, not applicable; SD, standard deviation.

Treatment and procedure

In the CRC cohort, 29% of patients had 1-5 tumours, 13% had 6-10 tumours, and 44% had >10 tumours. In the ICC cohort, 51% of patients had 1-5 tumours, 15% had 6-10 tumours, and 21% >10 tumours. Most patients had bilobar tumours (76% CRC; 64% ICC). Median bilirubin values prior to SIRT were 9.0 µmol/L (IQR 6.0-12.0) in the CRC cohort and 8.0 µmol/L (IQR 5.3-11.8) in the ICC cohort. Median baseline albumin values prior to SIRT were 37.0 g/L (IQR 33.0-41.0) in the CRC cohort and 38.0 g/L (IQR 33.5-42.5) in the ICC cohort (Table 7.4). Arteries were embolised during the work-up procedure in 52% of CRC patients and 34% in ICC patients. In the majority of patients (72% CRC; 56% ICC) the intent of the SIRT procedure was palliative (high levels of missing data was an issue for this measure).

[1] Only chemotherapy drugs reported in at least 2% of patients are presented.
[2] 29 patients had dates for prior adjuvant therapy (median 32 [IQR 20-38] months prior to SIRT).

Most CRC patients received SIRT as a single procedure targeting the whole liver (52% split microsphere administration; 17% single microsphere administration) or the right lobe (15%). A small proportion (3%) of CRC patients had sequential lobes treated in two (or more) sessions[1]. In the ICC cohort, 52% of patients received SIRT as a single procedure targeting the whole liver (26% split administration; 26% single administration). Within the ICC cohort, 8% of patients received two sessions (Table 7.4).

The majority of SIRT procedures were conducted using the resin Y-90 microspheres, SIR-spheres (86% of CRC cases; 74% of ICC cases). The remaining procedures were carried out using glass Y-90 microspheres, TheraSpheres (by BTG). Mean prescribed activity was 2.00 GBq (SD 2.22) for CRC patients and 2.38 GBq (SD 3.03) for ICC patients. The median overall tumour to liver volume ratio was reported for 270 (68%) CRC patients as whole liver measurements, and 32 (52%) ICC cases. The median tumour to liver volume ratio was 15% (IQR 7-27%) in the CRC cohort, and 17% (IQR 8-27%) in the ICC cohort. Most patients had a hospital stay of 1 night (CRC 66%; ICC 66%) or 2 nights (CRC 22%; ICC 23%) for their SIRT procedure (Table 7.4).

Chemotherapy was delivered concomitantly with SIRT in 35% of CRC cases (predominantly 5-FU and oxaliplatin) and 12% of ICC cases. Post-SIRT, a minority of cases went on to receive further chemotherapy during their follow-up phase (22% of CRC cases; 15% of ICC cases)[2] (Table 7.4).

Table 7.4 Treatment planning and procedure in the CRC and ICC cohorts

Parameter	Data from CRC cohort	Data from ICC cohort
Location of liver tumour(s)		
Bilobar	304 (76%)	39 (64%)
Left	28 (7%)	0
Right	59 (15%)	17 (28%)
Missing	8 (2%)	5 (8%)
Number of liver tumours		
1-5	114 (29%)	31 (51%)
6-10	52 (13%)	9 (15%)
>10	174 (44%)	13 (21%)
Uncountable	33 (8%)	3 (5%)
Missing	26 (7%)	5 (8%)
Bilirubin (µmol/L) prior to SIRT	n=384 Mean 10.3 (SD 6.3) Median 9.0 (IQR 6.0-12.0)	n=60 Mean 9.3 (SD 5.5) Median 8.0 (IQR 5.3-11.8)
Albumin (g/L) prior to SIRT	n=359[3] Mean 36.5 (SD 6.0) Median 37.0 (IQR 33.0-41.0)	n=57[4] Mean 38.1 (SD 5.7) Median 38.0 (IQR 33.5-42.5)
Arteries embolized before SIRT therapy		
Yes	208 (52%)	21 (34%)

[1] This measure may be an underestimate because of inconsistencies in recording within the registry.
[2] This estimate may be unreliable due to missing follow-up entries due to repatriation of patients to their referring centres.
[3] 29 cases excluded because data error suspected (entries below 15 g/L were excluded as we assumed this was a data entry error due to unit ambiguity in the registry).
[4] 3 cases excluded as entries below 15 g/L albumin.

No	108 (27%)	22 (36%)
Missing	83 (21%)	18 (30%)
Intent of SIRT procedure		
Palliative	289 (72%)	34 (56%)
Down-staging	7 (2%)	1 (2%)
Bridge to surgery	1 (0.3%)	0
Missing	102 (26%)	26 (43%)
SIRT procedure target/type		
Whole liver (split administration in single session)	206 (52%)	16 (26%)
Whole liver (single catheter)	68 (17%)	16 (26%)
Whole Liver (sequential lobar/ two sessions)	13 (3%)	5 (8%)
Right lobe	61 (15%)	16 (26%)
Left lobe	20 (5%)	0
Segmental	20 (5%)	6 (10%)
Missing	11 (3%)	2 (3%)
Number of administrations		
1	172 (43%)	29 (48%)
2	101 (25%)	11 (18%)
3	9 (2%)	1 (2%)
Missing	117 (29%)	20 (33%)
SIRT microsphere brand		
SIR-spheres (resin)	343 (86%)	45 (74%)
TheraSphere (glass)	53 (13%)	16 (26%)
Missing	3 (0.8%)	0
Liver measured as whole or lobes		
Whole	120 (30%)	33 (54%)
Right and left separately	255 (64%)	23 (38%)
Missing	24 (6%)	5 (8%)
Percentage tumour to liver volume (whole liver measurements only)	n=270 Mean 18.9 (SD 15.1) Median 15.0 (IQR 7.0-27.3)	n=32 Mean 19.0 (SD 14.6) Median 17.0 (IQR 8.2-26.7)
Percentage tumour to liver volume (whole liver measurements, measurements where left and right are combined[1])	n=341 Mean 21.1 (SD 18.5) Median 15.0 (IQR 7.0-30.0)	n=46 Mean 20.3 (SD 15.9) Median 17.0 (IQR 8.0-28.5)
Prescribed activity (GBq)[2]	n=308 Mean 2.00 (SD 2.22) Median 1.70 (IQR 1.30-2.05)	n=42 Mean 2.38 (SD 3.03) Median 1.63 (IQR 1.30-2.16)
Prescribed activity (GBq) for SIR-spheres	n=271 Mean 1.74 (SD 2.13) Median 1.64 (IQR 1.28-1.93)	n=31 Mean 1.51 (SD 0.43) Median 1.50 (IQR 1.19-1.79)
Prescribed activity (GBq) for TheraSphere	n=34 Mean 4.18 (SD 1.71)	n=11 Mean 4.85 (SD 5.29)

[1] Advice from two clinicians was that right and left lobe measurements can be added to produce a whole liver measurement, however there is uncertainty about how these fields were interpreted by sites.
[2] Values of >100 were assumed to be in MBq and were converted to GBq.

	Median 3.91 (3.45-5.31)	Median 2.81 (IQR 2.03-5.34)
Length of stay in hospital following SIRT procedure		
1 night	265 (66%)	40 (66%)
2 nights	87 (22%)	14 (23%)
3 nights	12 (3%)	1 (2%)
4 nights	8 (2%)	2 (3%)
>4 nights	10 (3%)	2 (3%)
Concomitant chemotherapy administered with SIRT		
Yes	141 (35%)	7 (12%)
No	242 (61%)	52 (85%)
Missing	16 (4%)	2 (3%)
Concomitant chemotherapy received[1]		
5-FU	99 (25%)	5 (8%)
Oxaliplatin	31 (8%)	4 (7%)
Irinotecan	24 (6%)	1 (2%)
Capacitabine	9 (2%)	0
Cisplatin	0	1 (2%)
Cetuximab	7 (2%)	0
Post-SIRT chemotherapy received during follow-up		
Yes	89 (22%)	9 (15%)
No	214 (54%)	37 (61%)
Missing	96 (24%)	15 (25%)

IQR, interquartile range; N/A, not applicable; SD, standard deviation.

7.3.1 Follow-up visits

Using reverse Kaplan-Meier estimator (Schemper & Smith 1996), patients were followed up for a median of 14.3 months (95% CIs 9.2-19.4) in the CRC cohort, and for 13.9 months (95% CIs 9.6-18.1) in the ICC cohort. Reverse KM is a more robust method than the simple median among patients with censored data (3.9 months [IQR 2.8-6.4] and 5.1 months [IQR 2.9-10.8]) for the CRC and ICC cohorts, respectively [2].

In the entire study cohort, a total of 388 patients (84%) had at least 1 follow-up visit; the majority of patients had 1 or 2 follow-up visits (Table 7.5). The median number of days between the first SIRT procedure and the first follow-up visit was 71 days (IQR 33-71).

Imaging scans were recorded separately from follow-up visits in the registry. A total of 367 patients (80%) had at least one imaging scan recorded in the registry; and the majority had 1 or 2 imaging scans (Table 7.5). The median number of days between the first SIRT procedure and the first imaging visit was 78 days (IQR 67-88).

[1] Only chemotherapy drugs reported in at least 2% of patients are presented

[2] The simple median of follow-up time from censored patients systematically underestimates the follow-up period because "longer follow-up times have a higher likelihood of being unavailable because of intermittent deaths than short individual follow-ups". Using reverse Kaplan-Meier estimator, "the unobservable follow-up time of a deceased patient is interpreted as the follow-up time that potentially would have been observed had that patient not died" (Shemper & Smith, 1996).

Table 7.5 Number of follow-up visits and visits for imaging scans recorded for patients from the entire study cohort

Number of visits	Number of patients (n=460 entire cohort)	
	Follow-up visits	Imaging scan visits
0	72 (16%)	93 (20%)
1	166 (36%)	195 (42%)
2	102 (22%)	111 (24%)
3	78 (17%)	36 (8%)
4	22 (5%)	14 (3%)
At least 5	20 (4%)	11 (2%)

7.3.2 Overall survival

At the conclusion of the study, 240 (60%) CRC deaths were recorded and 33 (54%) deaths in the ICC cohort. A total of 139 (35%) of CRC patients and 23 (38%) of ICC patients were censored at their last recorded follow-up date. The survival status of 20 CRC patients and 5 ICC patients were not established (missing data) (Table 7.6).

Table 7.6. Number of events recorded in CRC and ICC cohorts for OS, PFS, and LPFS. Numbers of patients with missing and censored data also shown.

Measure	Number of events in CRC cohort (n=399)			Number of events in ICC cohort (n=61)		
	Event recorded	Censored	Missing	Event recorded	Censored	Missing
OS	240 (60%)	139 (35%)	20 (5%)	33 (54%)	23 (38%)	5 (8%)
PFS	269 (67%) progressed 62 (16%) died	24 (6%)	41 (10%)	40 (66%) progressed 7 (11%) died	7 (11%)	7 (11%)
LPFS	209 (52%) progressed 91 (23%) died	53 (13%)	46 (12%)	33 (54%) progressed 13 (21%) died	8 (13%)	7 (11%)

CRC, colorectal cancer; ICC, intrahepatic cholangiocarcinoma; LPFS, liver-specific progression-free survival; OS, overall survival; PFS, progression-free survival

In the CRC cohort, median OS was 7.6 months (95% CIs 6.9 – 8.3) (Table 7.7; Figure 7.2). The survival rates for the CRC cohort were 92% at 3 months post-SIRT, 83% at 6 months, 30% at 12 months, and 7% at 24 months. No patients survived to 36 months in either cohort. The reason for death was not recorded for 69% of CRC patients and 67% of ICC patients; this high proportion of missing data made this measure unreliable.

In the ICC cohort, median OS was 8.7 months (95% CIs 5.3-12.1) (Table 7.2; Figure 7.3). Survival proportions for the ICC cohort were 89% at 3 months post SIRT, 85% at 6 months, 37% at 12 months, and 7% at 24 months. No patients survived to 36 months in either cohort (although some were censored).

The impact of short follow-up periods was evaluated in a restricted cohort of patients treated prior to 28th Feb 2016 (1 year before study closure). In this restricted cohort, median overall survival was 7.8 months (95% CIs 7.1-8.5) in 238 CRC patients (82% died, 18% censored), and 8.7 months (95% CIs

5.2-12.2) in 40 ICC patients (73% died, 28% censored). These results indicate that the survival estimates are robust to changes in the distribution of follow-up period.

Table 7.7. Summary of survival outcomes for CRC and ICC populations

Outcome (median)	CRC cohort	ICC cohort
Overall survival (months)	7.6 (95% CIs 6.9 – 8.3)	8.7 (95% CIs 5.3-12.1)
Progression free survival (months)	3.0 (95% CIs 2.8-3.12)	2.8 (95% CIs 2.6-3.1)
Liver-specific progression free survival (months)	3.7 (95% CIs 3.2-4.3)	3.1 (95% CIs 1.3-4.8)

CRC, colorectal cancer; ICC, intrahepatic cholangiocarcinoma.

7.3.3 Progression free survival

Progression was observed in a total of 269 (68%) CRC patients and 40 (66%) ICC patients. The RECIST criteria were used to document progression in 85% of scans in the CRC group (14% did not record the criteria); in the ICC cohort RECIST was used in 94% of scans. A total of 331 (84%) CRC patients and 47 (77%) ICC patients were recorded as having progressed or died (Table 7.6). In total, 24 (6%) CRC patients and 7 (12%) ICC patients were censored at the last imaging date when no progression was recorded. Median PFS was 3.0 months (95% CIs 2.8-3.1) in the CRC cohort (Table 7.7; Figure 7.4). Median PFS was 2.8 months (95% CIs 2.6-3.1) in the ICC cohort (Table 7.7; Figure 7.4).

7.3.4 Liver-specific progression free survival

A total of 209 (52%) hepatic progression events were recorded in the CRC cohort, and 33 (54%) in the ICC cohort (Table 7.6). In the LPFS analysis for the CRC cohort 299 (75%) events (hepatic progression or death) were recorded, 53 (13%) patients were censored, and 43 (11%) were excluded. The median LPFS in the CRC cohort was 3.7 months (95% CIs 3.2-4.3) (Table 7.7; Figure 7.4). In the ICC cohort, 75% patients progressed or died, 13% were censored, and 11% were excluded. The median LPFS was 3.1 months (95% CIs 1.3-4.8) in the ICC group (Table 7.7; Figure 7.5).

In the CRC group, 153 patients had dates recorded for both hepatic progression and extrahepatic progression. Of these, hepatic and extrahepatic progression was recorded on the same date in 124 patients (81%); extrahepatic progression occurred before hepatic progression in 24 patients (16%); and hepatic progression occurred prior to extrahepatic progression in 5 patients (3%). In the ICC group, 22 patients had dates recorded for both intra- and extrahepatic progression. In 18 patients (82%) these dates were the same, in 2 patients (9%) extrahepatic progression occurred first, and in 2 patients (9%) hepatic progression occurred first.

7.3.5 Subgroup analysis (overall survival)

Subgroup analysis identified four covariates that resulted in a statistically significant difference in median overall survival in the CRC cohort. No subgroup analyses were carried out on the ICC cohort because of the small sample size. OS in the CRC group differed significantly between patients who had extrahepatic metastasis and those who did not (log-rank test, p-value=0.021); the HR was 0.74 (95% CIs 0.57-0.96; univariate Cox proportional hazards p-value=0.022) (Table 7.8; Figure 7.6). OS

also differed significantly between the categories of number of liver tumours (log-rank test, p-value=0.008); the HR was 1.67 (95% CIs 1.06-2.62; p=0.027) when the group of 6-10 tumours was compared to the reference group of 1-5 tumours; the HR was 1.61 (95% 1.17-2.21) when the group of >10 tumours was compared to the reference group (Figure 7.7). OS was longer in males compared to females (log-rank test, p-value=0.012); the HR was 1.389 (95% CIs 1.073-1.800; p=0.013) (Figure 7.8). OS was also related to the percentage tumour to liver volume measurements at baseline (log rank test, p<0.001); the HR was 1.955 (95% CIs 1.424-2.685) comparing the category of tumour to liver volume >25% to 50% with the reference category of ≤25%; the HR was 2.994 (1.791-5.005) when the category of >50% was compared to the reference category (Figure 7.9). No significant difference in survival was observed using the covariates of prior chemotherapy lines, ECOG performance status, age, and prior liver procedures (Table 7.8).

7.3.6 Health related quality of life

Measurement of changes in HRQoL from baseline to follow-up was hindered by high levels of missing data at all follow-up periods. In the CRC cohort, only 32% of patients had an EQ-5D-5L measurement at 3 months which dropped further to 3% at 12 months. Reasons include short follow-up of recently treated patients, poor implementation of the EQ-5D-5L measurement tool across sites, and anecdotal reports of challenges in recruiting patients to participate.

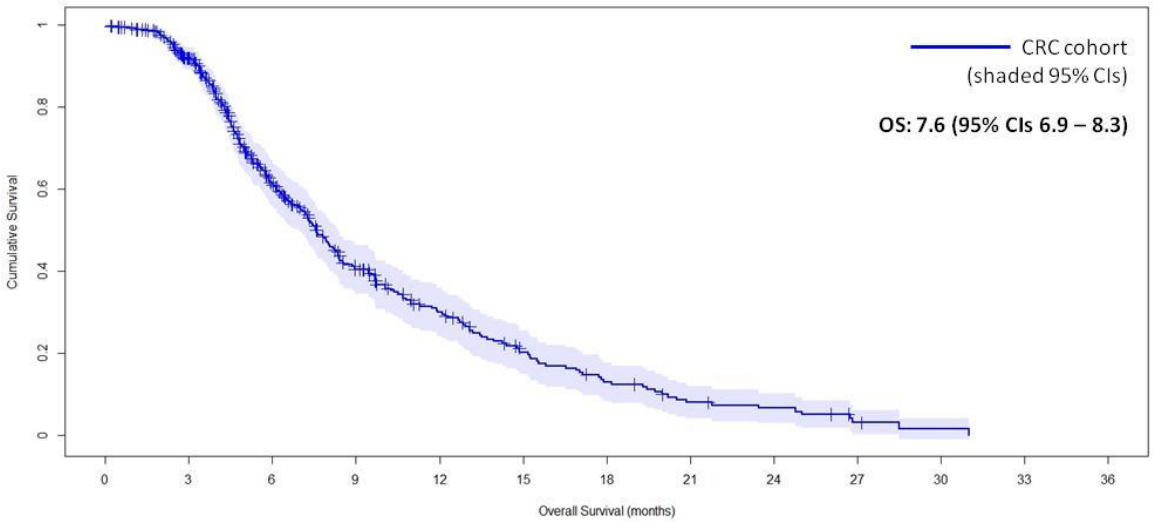
The available data showed that EQ-5D-5L remained relatively constant across time points from baseline (0-60 days prior to SIRT) to 12 months (±3 months) post SIRT in the CRC population where scores ranged from the highest value of 0.832 at baseline to 0.743 at 12 months post SIRT (Figure 7.10). The overall health scores (EQ-VAS) ranged from the highest value of 80 at 9 months post-SIRT to 69 at 12 months post SIRT. There was only one reported score at 24 months post SIRT for both EQ-5D-5L and EQ-VAS scores in the CRC group.

In the ICC cohort EQ-5D-5L scores were only reported at baseline and 3 months post-SIRT (Figure 7.11); EQ-5D-5L scores were 0.810 and 0.836 respectively. Overall health scores using the EQ-VAS scale were 75 at baseline and 77 at 3 months post SIRT.

A small but statistically significant reduction in EQ-5D-5L-measured HRQoL was reported from baseline (score 0.85) to 3 months post-SIRT (score 0.81) in the CRC group: difference in score 0.042 (95% CIs 0.012-0.072); p=0.006 (Table 7.9). A similar reduction was observed in the overall health score measured by EQ-VAS from baseline (score 76.8) to 3 months post SIRT (score 73.7); the difference in scores was 3.05 (95% CIs 0.22-5.88; p=0.035) (Table 7.10). Changes in EQ-5D-5L scores and EQ-VAS from baseline to 6 months and 12 months post SIRT were not statistically significant. No patients had baseline and 24 month post SIRT scores. In the ICC population changes in EQ-5D-5L scores and EQ-VAS from baseline to 3 months post SIRT were not statistically significant (Tables 6.11 and 6.12). Too few patients had scores at 6, 12, and 24 months post SIRT to enable a comparison with baseline.

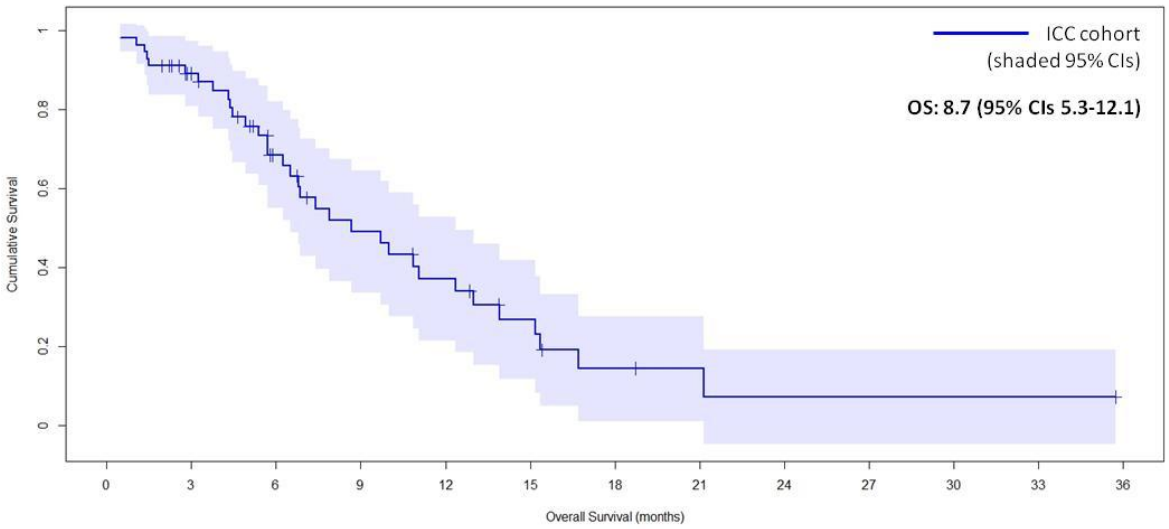
EQ-5D-5L scores were summarised separately prior to progression and after progression. The mean pre- and post-progression scores in the CRC cohort were 0.82 (SD 0.17; n=68) and 0.77 (SD 0.16; n=105), respectively. In the ICC cohort, the mean pre- and post-progression scores in the CRC cohort were 0.80 (SD 0.17; n=10) and 0.80 (SD 0.17; n=12), respectively.

Figure 7.2. Kaplan-Meier curve of overall survival following SIRT in the CRC cohort (95% CIs shown shaded; numbers at risk at 3 month intervals displayed)



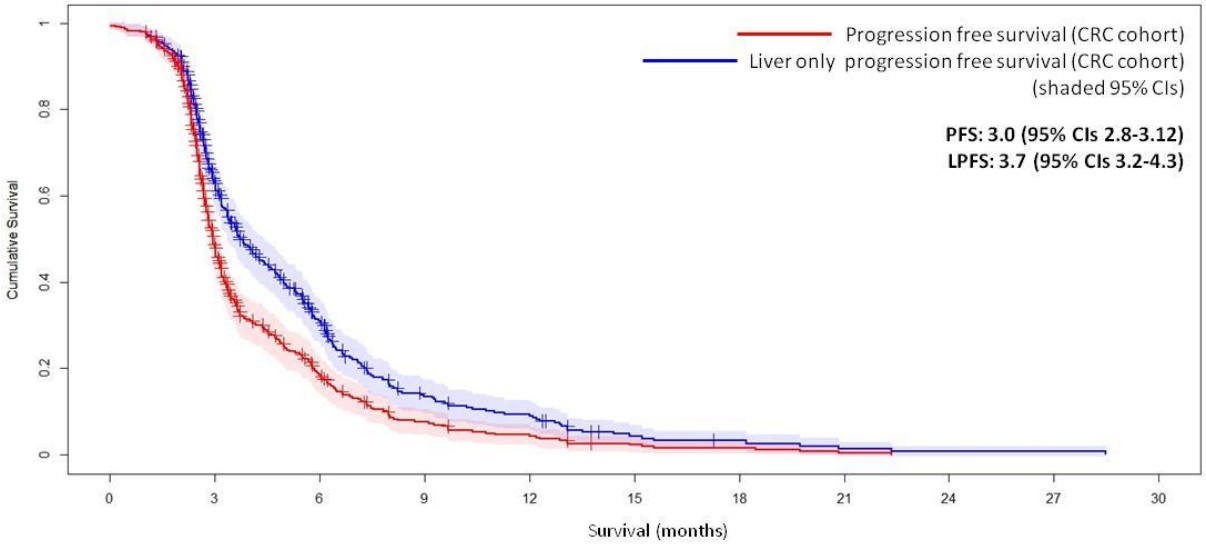
Months	0	3	6	9	12	15	18	21	24	27	30	33	36
Number at risk	379	302	163	92	61	37	22	12	9	3	1	0	0

Figure 7.3. Kaplan-Meier curve of overall survival following SIRT in the ICC cohort (95% CIs shown shaded; numbers at risk at 3 month intervals displayed)



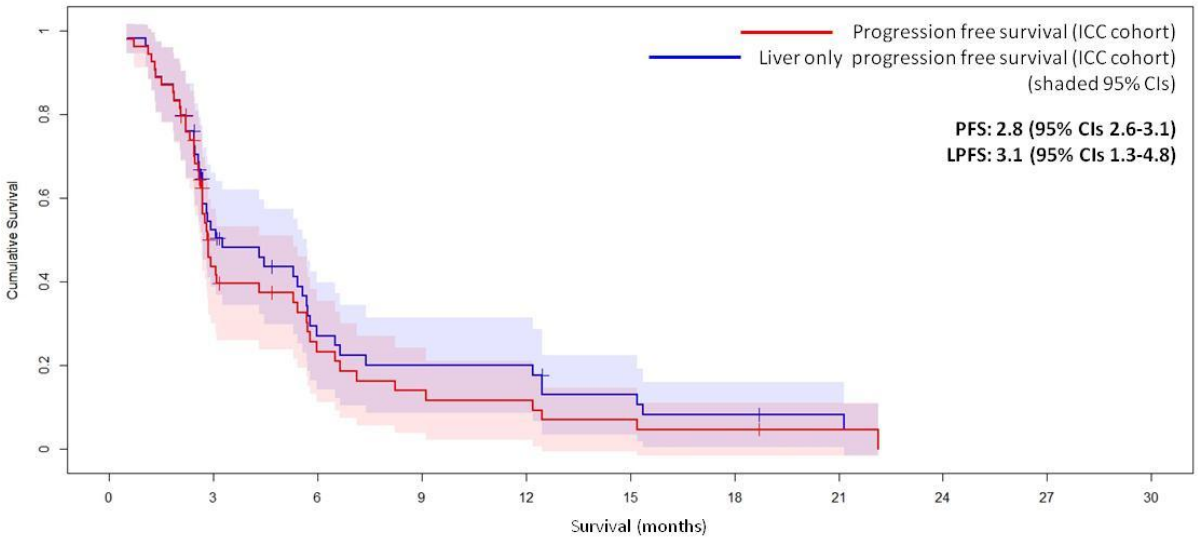
Months	0	3	6	9	12	15	18	21	24	27	30	33	36
Number at risk	56	43	26	17	12	7	3	2	1	1	1	1	0

Figure 7.4. Kaplan-Meier curve of progression free survival and liver only progression free survival in patients with metastatic colorectal cancer following SIRT (95% CIs shown shaded; numbers at risk 3 at month intervals displayed)



Months	0	3	6	9	12	15	18	21	24	27	30
Number at risk (PFS)	354	157	59	23	14	6	4	1	0	0	0
Number at risk (LPFS)	352	196	88	35	24	8	5	2	1	1	0

Figure 7.5. Kaplan-Meier curve of progression free survival and liver only progression free survival in patients with intrahepatic cholangiocarcinoma following SIRT (95% CIs shown shaded; numbers at risk at 3 month intervals displayed)



Months	0	3	6	9	12	15	18	21	24	27	30
Number at risk (PFS)	54	21	10	6	5	3	2	1	0	0	0
Number at risk (LPFS)	54	25	11	8	8	5	3	2	0	0	0

Table 7.8. Kaplan-meier analysis and univariate Cox proportional hazards model of survival by baseline characteristics in the colorectal population (statistically significant p-values in bold)

Subgroup	n (pts)	n (events)	Median OS in months	OS 95% CI	Hazard ratio (95% CIs)	p-value
Number of lines of previous chemotherapy (including biologics); log-rank test p=0.098						
*1 line**	32	19	11.3	4.9-17.6	Ref	Ref
2 lines	210	127	7.0	6.2-7.8	1.506 (0.926-2.448)	0.099
3 lines	85	58	8.9	6.7-11.2	1.143 (0.680-1.921)	0.614
≥4 lines	33	27	7.3	5.1-9.4	1.732 (0.959-3.127)	0.069
Primary tumour in situ; log-rank test p=0.079						
Yes	117	82	7.4	6.0-8.7	1.282 (0.973-1.689)	0.077
No	217	136	8.9	7.4-10.3	Ref	Ref
Prior biologic therapy [1]; log-rank test p=0.783						
No	189	112	7.6	6.6-8.6	Ref	Ref
Yes	190	128	7.4	6.5-8.4	1.036 (0.803-1.338)	0.783
ECOG performance status; log-rank test p=0.180						
*0**	192	124	8.4	6.9-9.8	Ref	Ref
1	162	96	6.6	5.5-7.7	1.252 (0.956-1.640)	0.103
2	13	12	6.3	2.0-10.6	0.854 (0.465-1.567)	0.610
Presence of extrahepatic metastases; log-rank test **p=0.021**						
*Yes**	151	100	7.1	5.7-8.4	Ref	Ref
No	225	137	8.1	6.9-9.2	0.738 (0.568-0.957)	**0.022**
Age (continuous)					0.997 (0.985-1.008)	0.562
Age (categories); log-rank test p=0.316						
*<65 years**	172	113	8.2	6.9-9.5	Ref	Ref
≥65 years	206	126	7.4	6.4-8.3	1.140 (0.882-1.473)	0.317
Prior liver procedures; log-rank test p=0.114						
*Yes**	104	63	7.1	6.2-7.9	1.262 (0.944-1.685)	0.116
No	275	177	9.7	8.9-10.4	Ref	Ref
Number of liver tumours; log-rank test **p=0.008**						
*1-5**	107	58	11.3	8.7-13.8	Ref	Ref
6-10	50	28	6.7	3.8-9.5	1.666 (1.059-2.621)	**0.027**
>10	167	117	7.3	6.2-8.3	1.608 (1.171-2.208)	**0.003**
Sex ; log-rank test **p=0.012**						
Female	129	96	6.4	5.2-7.7	1.389 (1.073-1.800)	**0.013**
Male	250	144	8.2	7.2-9.2	Ref	Ref
Percentage tumour to liver volume (continuous)					1.023 (1.016-1.030)	**<0.001**
Percentage tumour to liver volume; log rank test **p<0.001**						
≤25%	226	135	9.4	8.0-10.9	Ref	Ref
>25% to 50%	80	57	5.3	4.4-6.2	1.955 (1.424-2.685)	**<0.001**
>50%	22	17	5.3	6.8-8.2	2.994 (1.791-5.005)	**<0.001**

*Reference category for univariate Cox regression analysis. ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; OS, overall survival.

[1] Includes bevacizumab, cetruximab, aflibercept.

Figure 7.6. Kaplan-Meier curve of OS in patients following SIRT (CRC cohort); results from patients with extrahepatic metastatic disease and patients without extrahepatic metastatic disease shown separately; hazard ratio (95% CIs) shown with p-value.

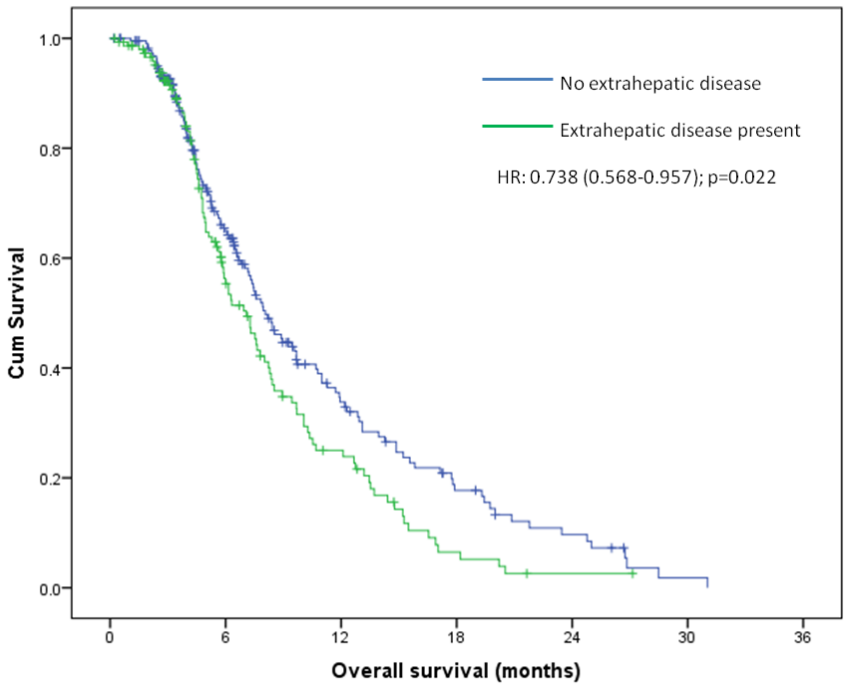


Figure 7.7. Kaplan-Meier curve of OS in patients following SIRT (CRC cohort); results from patients with 1-5 liver tumours, 6-10 liver tumours, or >10 liver tumours are shown separately; hazard ratio (95% CIs) shown with p-value.

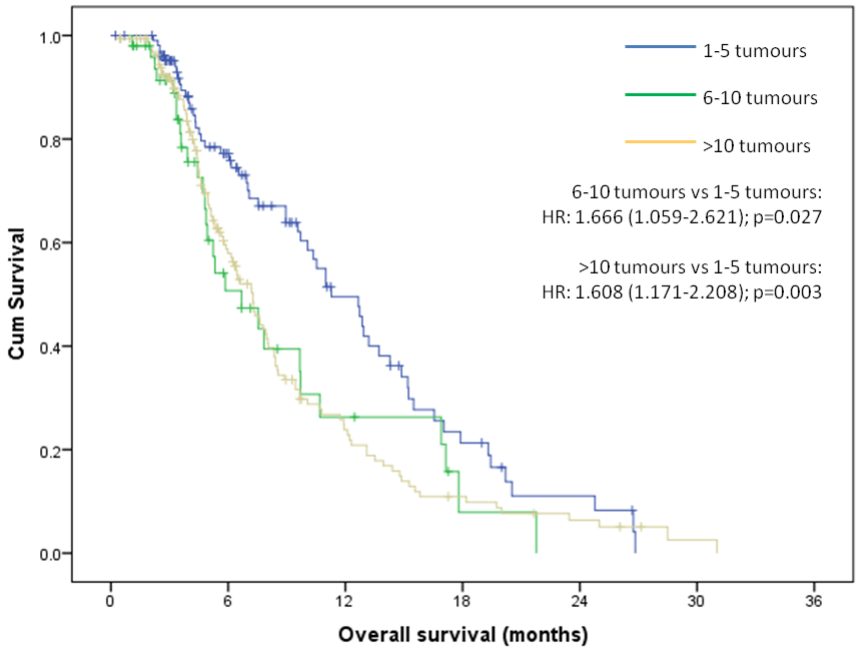


Figure 7.8. Kaplan-Meier curve of OS in patients following SIRT (CRC cohort); results from male and female patients shown separately; hazard ratio (95% CIs) shown with p-value.

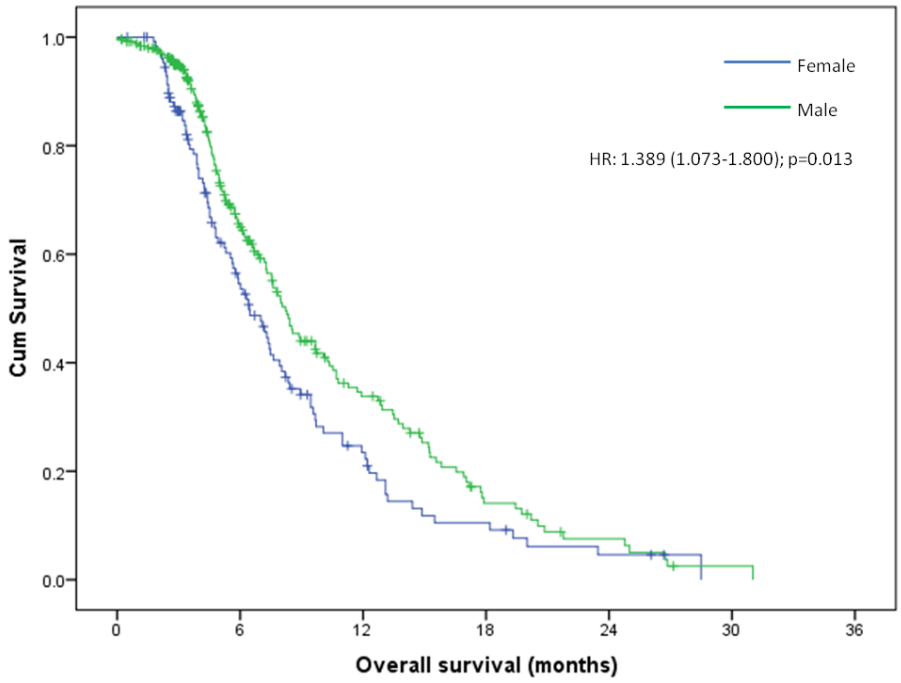


Figure 7.9. Kaplan-Meier curve of OS in patients following SIRT (CRC cohort); results patients with a tumour to liver volume percentage of ≤25%, 26-50%, and >50% shown separately; hazard ratio (95% CIs) shown with p-value.

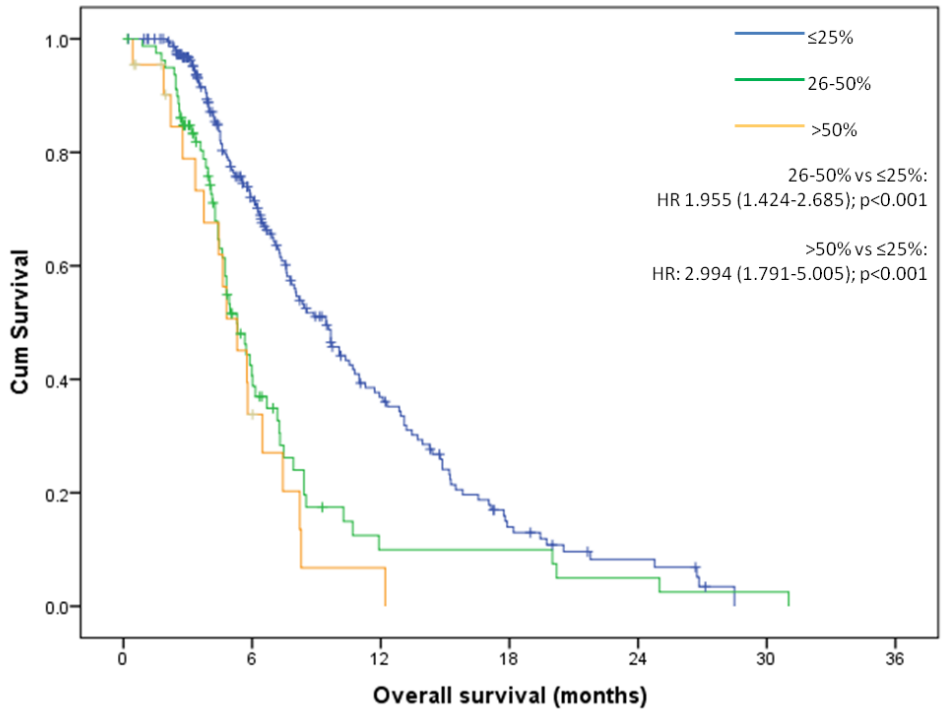


Figure 7.10. Mean EQ-5D-5L scores and EQ-VAS at baseline and four follow-up time points in the CRC cohort (SD error bars; non-paired samples)

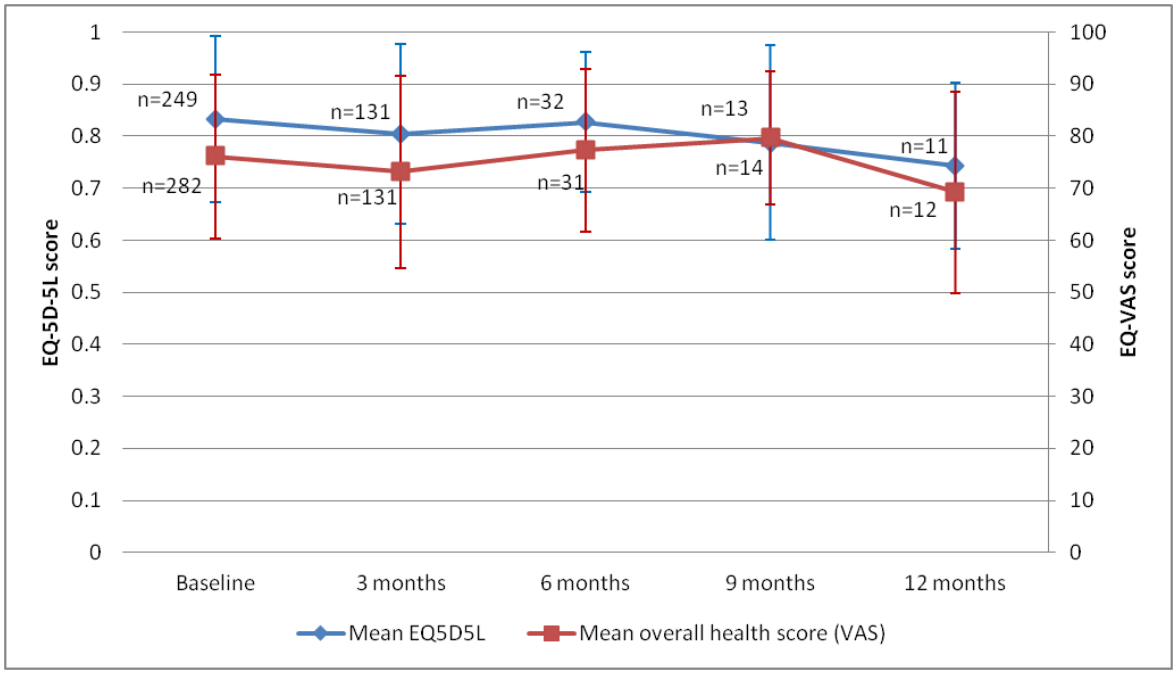


Figure 7.11. Mean EQ-5D-5L scores and EQ-VAS at baseline and four follow-up time points in the ICC cohort (SD error bars; non-paired samples)

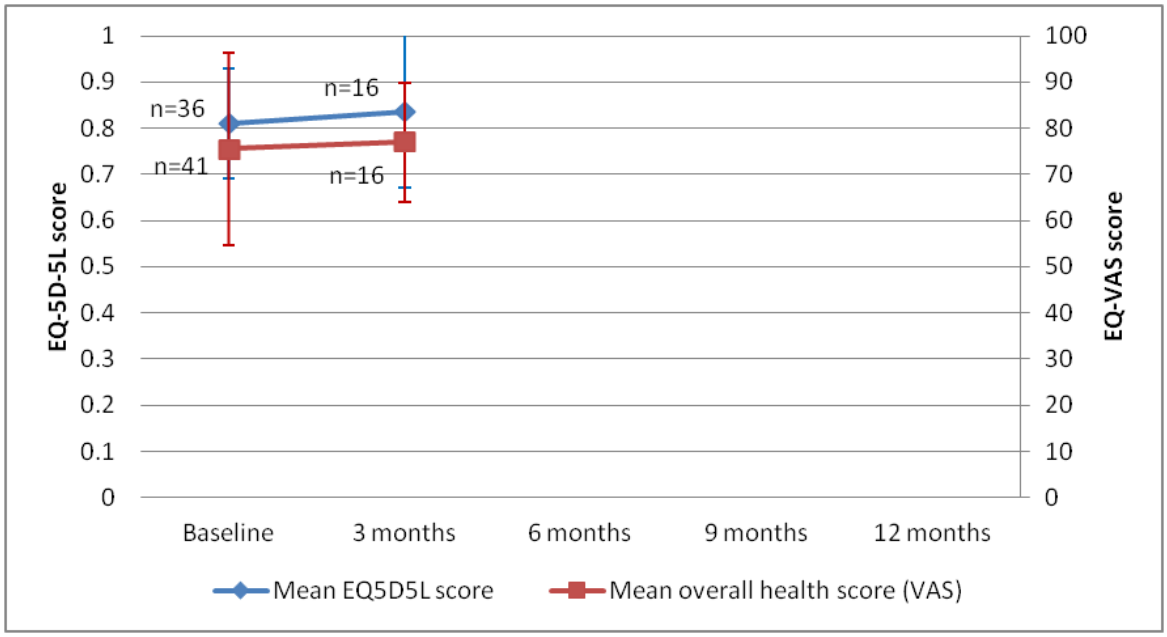


Table 7.9. Changes in EQ-5D-5L scores from baseline to four follow-up time points in the CRC cohort

Change in EQ-5D-5L score	n	Baseline score (mean (SD))	Post-SIRT score (mean (SD))	Mean difference (95% CIs); p-value
Baseline to 3 months	120	0.85 (0.14)	0.81 (0.17)	0.042 (0.012-0.072); p=0.006
Baseline to 6 months	32	0.86 (0.12)	0.83 (0.13)	0.029 (-0.026-0.084); p=0.290
Baseline to 12 months	8	0.83 (0.16)	0.80 (0.05)	0.032 (-0.050-0.113); p=0.389
Baseline to 24 months	0	-	-	-

Table 7.10. Changes in EQ-VAS from baseline to four follow-up time points in the CRC cohort

Change in EQ-VAS	n	Baseline score (mean (SD))	Post-SIRT score (mean (SD))	Mean difference (95% CIs) p-value
Baseline to 3 months	122	76.8 (15.6)	73.7 (17.3)	3.05 (0.22-5.88); p=0.035
Baseline to 6 months	31	82.0 (10.4)	77.3 (15.6)	4.74 (-1.21-10.70); p=0.114
Baseline to 12 months	9	86.1 (10.2)	73.3 (16.4)	12.78 (-3.43-28-98); p=0.107
Baseline to 24 months	0	-	-	-

Table 7.11. Changes in EQ-5D-5L scores from baseline to four follow-up time points in the ICC cohort

Change in EQ-5D-5L score	n	Baseline score (mean (SD))	Post-SIRT score (mean (SD))	Mean difference (95% CIs); p-value
Baseline to 3 months	15	0.84 (0.13)	0.86 (0.14)	-0.016 (-0.075-0.044); p=0.584
Baseline to 6 months	1	-	-	-
Baseline to 12 months	1	-	-	-
Baseline to 24 months	0	-	-	-

Table 7.12. Changes in EQ-VAS from baseline to four follow-up time points in the ICC cohort

Change in EQ-VAS	n	Baseline score (mean (SD))	Post-SIRT score (mean (SD))	Mean difference (95% CIs) p-value
Baseline to 3 months	16	71.75 (20.45)	77.0 (12.9)	-5.25 (-14.0-3.5); p=0.223
Baseline to 6 months	2	-	-	-
Baseline to 12 months	1	-	-	-
Baseline to 24 months	0	-	-	-

7.3.7 Safety

7.3.7.1 Day-of-treatment complications

Severe complications and incidents associated with the microsphere product were recorded at the time of the SIRT procedure[1]. A total of 11 patients (3%) experienced severe day-of-treatment complications in the CRC cohort, and 1 (2%) in the ICC cohort (Table 7.13). In one reported product-related incident the microspheres were spilled and the procedure had to be cancelled. Severe AEs within the first week after SIRT were rare; 3 patients experienced grade ≥3 fatigue in the 7 days after SIRT, and 1 patient experienced grade ≥3 abdominal pain in the first week after SIRT across (CRC and ICC cohorts combined).

7.3.7.2 Deaths related to complications

The SIRT registry included a field for the reason for death but this was poorly defined. Four patients (2 CRC, 2 ICC) had "complication" recorded as the cause of death. Details of these complications were as follows: i) one ICC patient had "tumour lysis syndrome" recorded and died 15 days following SIRT; ii) one ICC patient had "portal vein thrombosis and liver decompensation" recorded and died 45 days after SIRT; iii) one CRC patient had "mild RILD developed at week 10; responding initially but then had upper GI bleed from duodenal ulcer; decompensated and developed fulminant hepatorenal failure" recorded and died 117 days following SIRT; iv) a CRC patient had "jaundice and biliary dilatation; following MRCP [Magnetic resonance cholangiopancreatography] patient developed bleeding and did not recover" recorded and died 184 days following SIRT. Relatedness of complications to the SIRT procedure was not recorded.

7.3.7.3 Adverse events at follow-up

AEs were recorded at follow-up visits every 2 to 3 months until progression. Amongst CRC patients, 143 patients experienced an AE[2]. A total of 253 AEs were recorded of which 19 (8%) were grade 3 or above (Table 7.14). A total of 30 ICC patients experienced a total of 49 AEs, of which 4 (8%) were grade 3 or above (Table 7.14). Relatedness to the SIRT intervention was not recorded in the registry. The most common events were mild (grade 1-2) fatigue and abdominal pain in both cohorts. No severe cases of radiation induced liver disease (RILD), gastrointestinal ulceration, radiation pneumonitis, radiation cholecystitis, or radiation pancreatitis were recorded in either cohort.

Events categorised as "other" with a free-text description accounted for 53 (21%) of the total in the CRC population. Most common AEs of grade 1 and 2 categories were anorexia (8 events), diarrhoea (7 cases), abdominal pain (6), and mucositis (2 cases). Seven events of grade ≥3 were recorded in the "other" category in CRC patients which were as follows: acute kidney injury (grade 3; occurred 28 days after SIRT), bowel obstruction (grade 3; 21 days after SIRT); liver abscess (grade 3; 138 days after SIRT), skin rash (grade 3; 90 days after SIRT), delirium/dementia (grade 4; 79 days after SIRT), pulmonary emboli (grade 4; 47 days after SIRT); sepsis (grade 4; 18 days after SIRT). In the ICC group

[1] The registry did not record a grade for day-of-treatment complications, instead the question was worded as "were any severe day of treatment complications experienced?"
[2] Percentages are not given because patients with a short follow-up period should not be included in the denominator.

16 events were recorded under in the “other” category which were in most cases gastrointestinal-related such as diarrhoea, constipation, anorexia, and indigestion/reflux. One grade 3 event was recorded in the “other” category which was diarrhoea & abdominal cramping (date unknown).

A total of 430 events were recorded as abnormal laboratory values across the CRC and ICC cohorts (Table 7.15). The most common event categories were raised aspartarte aminotransferase (22%), raised alanine aminotransferase (20%), and hypoalbuminemia (18%). In the CRC cohort, 18 of the 353 events (5%) were grade ≥3 (mostly hyperbilirubinemia (8 cases), hypoalbuminemia (4 cases), and decreased neutrophil count (3 cases). In the ICC cohort, 3 of the 77 (4%) events were grade ≥3 (Table 7.15).

Table 7.13. Number of patients with severe day-of-treatment complications, product incidents recorded at time of procedure, and all causality adverse events in CRC and ICC populations (percentage of patients within each cohort shown)

Event type	Number of CRC patients (n=399)	Number of ICC patients (n=61)
Severe day-of-treatment complications		
Yes	11 (3%)[1]	1 (2%)[2]
No	375 (94%)	58 (95%)
Missing	13 (3%)	2 (3%)
Product incident		
Yes	1 (0.3%)[3]	0
No	300 (75%)	39 (64%)
Missing	98 (25%)	22 (36%)
All causality adverse events (at least 1 event)		
Yes	143 (36%)	30 (49%)
No	256 (64%)	31 (51%)

Table 7.14. Total number of all-cause adverse events and grade ≥3 events recorded across all follow-ups in CRC and ICC cohorts (does not include day of treatment complications recorded in procedural data; percentage of total number of AEs shown)

Category of event	CRC cohort		ICC cohort	
	All adverse events (percentage of all AEs)	Grade ≥3 adverse events	All adverse events (percentage of all AEs)	Grade ≥3 adverse events)
Fatigue	89 (35%)	8	16 (33%)	2
Abdominal pain	58 (23%)	3	11 (22%)	0
Nausea	22 (9%)	0	2 (4%)	0
Vomiting	14 (6%)	0	0	0
Fever	10 (4%)	1	2 (4%)	1
Gastritis	5 (2%)	0	0	0
Gastrointestinal ulcer	1 (0.4%)	0	0	0
RILD	1 (0.4%)	0	1 (2%)	0
Radiation pneumonitis	0	0	0	0
Radiation cholecystitis	0	0	1 (2%)	0
Radiation pancreatitis	0	0	0	0
Other	53 (21%)	7 (see below)	16 (33%)	1
Total	253 (100%)	19	49 (100%)	4

RILD: radiation-induced liver disease

[1] 5 cases of severe abdominal pain; 1 minor vascular; 1 missing; 5 severe "other" (hypertension, chest pain, allergy to visipaque, syncope, rigors, unwell).
[2] Severe abdominal pain.
[3] Procedure cancelled due to spillage.

Table 7.15. Total number of abnormal laboratory value events by CRC, ICC, and all patients and by grade ≥3.

Category of abnormal laboratory result event	CRC cohort		ICC cohort		All patients	
	All events	Grade ≥3	All events	Grade ≥3	All events	Grade ≥3
AST increased	79 (22%)	0	17 (22%)	1	96 (22%)	1
ALT increased	73 (21%)	1	14 (18%)	0	87 (20%)	1
Hypoalbuminemia	67 (19%)	4	12 (16%)	0	79 (18%)	4
Hyperbilirubinemia	44 (12%)	8	10 (13%)	2	54 (13%)	10
INR increased	1 (0.3%)	0	0	0	1 (0.2%)	0
Neutrophil count decreased	10 (3%)	3	1 (1%)	0	11 (3%)	3
Platelet count decreased	28 (8%)	0	12 (16%)	0	40 (9%)	0
Other	51 (14%)	2	11 (14%)	0	62 (14%)	2
TOTAL	**353 (100%)**	**18**	**77 (100%)**	**3**	**430 (100%)**	**21**

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

7.4 Discussion

This is the largest UK study to examine the survival of patients with unresectable, chemotherapy-refractory metastatic CRC and primary ICC treated with selective internal radiation therapy (SIRT).

7.4.1 Overall survival

The primary outcome of interest was OS. The estimate of 7.6 months OS for the CRC cohort fitted within the lower end of the range of previously published data. Subgroup analyses showed that male patients survived significantly longer than females. Also patients without extrahepatic disease had a significantly better overall survival than those with extrahepatic disease, as did patients with smaller numbers of tumours, and patients with a smaller tumour to liver volume percentage. Our systematic review (Section 4) reported that OS from 23 included studies ranged from 6.0 to 12.7 months (weighted mean 9.6 months). Interpretation of any survival benefit from SIRT is challenging in the absence of a control group treated with best supportive care.

The results from the CtE cohort are in accord with those from the SIRT arm of the retrospective comparative cohort from Seidenticker et al. (2012) whose study reported an OS of 8.3 months in the SIRT arm compared to 3.5 months in the best supportive care arm, which was a statistically significant improvement (HR 0.26; $p<0.001$). The CtE CRC cohort had similar baseline characteristics compared with patients in Seidensticker et al. (2012). The higher OS estimate from the SIRT arm in the Bester et al. (2012) study of 11.9 months may be explained by the high proportion of patients with an ECOG performance score of 0 (85%) compared to 50% in the CtE cohort; in addition the Bester et al. study may include a higher proportion of chemotherapy naive patients (in the combined CRC and non-CRC group this value was 14%).

Our review of survival estimates in a similar population of CRC patients treated in control arm of clinical trials and receiving BSC (Section 5) reported that median OS estimates ranged from 2.4 to 6.6 months across seven identified studies, with a pooled estimate of 5.3 months. Direct comparisons of SIRT data (from observational studies and CtE) with data from patients treated with BSC from higher quality RCTs are not appropriate and should be interpreted with extreme caution. Differences in study designs and patient selection between the identified RCTs (drugs versus BSC) and this observational cohort are very likely to influence outcomes across the study

NICE recently recommended trifluridine–tipiracil for chemotherapy-refractory CRC patients (i.e. those previously treated with other therapies such as fluoropyrimidine-, oxaliplatin- or irinotecan-based chemotherapies, and biological agents) (NICE 2016). The clinical evidence was based on two RCTs (Mayer et al. 2015; Yoshino et al. 2012); median overall survival was extended by 2.0 months 2.4 months, respectively. The NICE committee concluded that the survival benefit of trifluridine–tipiracil, although relatively small, was clinically meaningful.

In the ICC cohort, the median OS of 8.7 months was much lower than the pooled estimate of 15.3 months presented from our systematic review (Section 4). This is likely to be in part due to the inclusion of chemotherapy naive patients in several previous studies. Many of the identified studies were small and had wide confidence intervals around their OS estimates. No comparative studies of SIRT in the ICC population were identified, and neither were any studies that reported overall

survival in patients with chemotherapy-refractory ICC who received BSC. To provide some context, extrapolated results, likely to involve bias, indicate that patients receiving BSC following first-line progression survive approximately 4 months. ICC patients receiving second-line chemotherapy regimens survive for a median of 7.2 months (Lamarca et al. 2014a).

The results from the CtE study were at the lower end of the range from previous studies, which may be explained in part by pragmatic design of this service evaluation. The results reported may reflect more accurately the survival of patients subjected to standard care alongside SIRT. In an observational registry study, high levels of missing data can be problematic. This was exacerbated in this CtE because of the absence of a follow-up phase after the last patient received the SIRT procedure. As such patients treated shortly before the data was extracted for analysis would almost inevitably be censored or excluded from survival estimates; although sensitivity analysis using patients treated at least 1 year before the study end indicated that results were robust. In this study, with date of death not recorded, we used as a proxy the last date recorded in the registry of having interaction with the healthcare team. In fact, some of these patients may have lived longer but their date of death was not recorded. No external validation of the date of death recorded in the registry was possible further reducing the reliability of this outcome. The ECOG scores of mostly 0 and 1 do not suggest that the CtE patients' performance was considerably worse than in previous studies. In addition the presence of limited extrahepatic disease in around 40% of CRC patients and 36% of ICC patients is in line with the proportions observed in previous studies. Importantly, no sample size calculations were conducted for subgroup analysis therefore there is a greater risk of falsely accepting the null hypothesis in an underpowered comparison.

7.4.2 Progression free survival

The PFS in the CRC cohort of 3.0 months was at the lower end of the range from previous studies of 2.8 to 9.2 months (Section 4). No previous studies reported PFS in the ICC population. LPFS was 3.7 months in the CRC cohort in the CtE study which was comparable to the range of 2.0 to 9.0 months from previous studies that reported this outcome. PFS estimates from the CtE study (and other studies) should be interpreted with caution given the inherent risk of bias in this measure, which may be further compounded by the observational design of the CtE study.

PFS and TTP rely on objective tumour response assessments. Tumour response as defined by RECIST criteria (Eisenhauer et al. 2009) is useful as a consistent measure for what happens to a tumour during therapy (Booth and Eisenhauer 2012). PFS also offers a useful outcome when longer follow-up is impractical. PFS may, however, be unreliable if its associated pitfalls (described below) are not adequately accounted for (Korn and Crowley 2013; Sridhara et al. 2013). Firstly, PFS may not correspond to a measurable improvement in survival or HRQoL, which are arguably more meaningful outcomes to patients. Secondly, progression in the CtE study is recorded as interval-censored data, and the frequency of assessments impacts directly on the PFS estimate. SIRT CtE clinicians report that their assessment schedule is every 2-3 months, but the registry data suggests that missing data is a considerable issue. PFS relies not only on accurate recording of the date of progression but also the preceding non-progressed result. Assuming that progression occurred on the date when it was confirmed by clinical assessment results in an inflated PFS estimate. Use of midpoint intervals (i.e. the midpoint between the date of the assessment prior to progression and the date of the

assessment at which progression was observed) may reduce the PFS and LPFS estimates reported here. Also, PFS includes death as an event in the absence of a progression date. Missing progression data (unrecorded assessments) introduce further bias which may inflate PFS estimates further.

Finally, the assessment criteria not set out in advance in a protocol in the CtE study, which may lead to variation in assessments. In the CRC cohort, use of the RECIST criteria was recorded in 85% of imaging scans, although this did not include the version which changed from 1.0 to 1.1 in recent years. Even a set protocol (a tightly prescribed procedure) would entail subjective clinical judgment. This could be ameliorated by using an independent (blinded) assessor, and possibly some arrangements to resolve discrepancies. An approach not applied routinely in the CtE study.

The CtE study reports a 0.7 month improvement in liver-specific PFS compared to PFS, which may mirror results observed in the RCT by Hendlisz et al., although such small changes cannot be interpreted reliably and may not be clinically relevant. The authors report that use of RECIST is an insensitive assessment criteria for SIRT-treated tumours because of issues such as necrosis which renders volumetric analyses insensitive (Hendlisz, Van den Eynde, Peeters, Maleux, Lambert, Vannoote, De, Verslype, Defreyne, Van, Delatte, Delaunoit, Personeni, Paesmans, Van Laethem, & Flamen 2010). The authors recommend metabolic-based imaging such as FDG-PET.

7.4.3 Health related quality of life

Improved HRQoL is a potential benefit of SIRT. Average changes in EQ-5D-5L and EQ-VAS from baseline to follow-up in the CtE study were challenging to interpret and likely limited by the small sample size due to rapid drop-out of patients in these measures after receiving SIRT. Changes were very small and ranged over less than 5% of the EQ-5D-5L scale. The minimally important difference (MID) defined as the smallest change in a patient reported outcome measure (PROM) that is perceived by patients as beneficial or that would result in a change in treatment. The MID for EQ-5D-5L in cancer patients is between 0.10 and 0.12 (over a scale range of approximately 0 to 1) (Pickard et al. 2007); the statistically significant reduction in EQ-5D-5L from baseline to 3 months in the CRC group was small (0.042) and below the MID threshold. No EQ-VAS scores differences between baseline and follow-up reached statistical significance. The palliative nature of SIRT in this patient group whose HRQoL may be declining consistently over time makes interpretation of the results difficult and detection of any trend over time impossible. Importantly, without a control group we could not observe whether SIRT resulted in any improvement in HRQoL.

EQ-5D-5L is a validated generic HRQoL measurement tool which can produce useful utility measurements for the purposes of economic analysis. It was selected because NICE recommends its use in economic assessments. However, a generic tool may lack the sensitivity to detect changes in HRQoL which result from control of hepatic tumour burden. The non-blinded nature of this study may introduce bias because the measurement of HRQoL is subjective and may be influenced by patients' expectations about SIRT. Use of disease specific tools (such as the Functional Assessment of Cancer Therapy-colorectal (FACT-C) and hepatic (FACT-H)) may improve the likelihood of detecting clinically relevant changes in HRQoL.

No studies were identified in our systematic review that provide robust evidence on the impact of SIRT on patients' HRQoL (a single study in the CRCLM population assessed QoL but results were

poorly reported). This absence of evidence on QoL highlights the need to collect high quality data on this outcome using validated disease-specific tools.

7.4.4 Safety

Severe complications on the day of treatment were rare in the CRC and ICC groups; abdominal pain was the most common event. Adverse events in the follow-up period occurred in 36% of CRC patients and 49% of ICC patients treated with SIRT. However, unequal follow-up will impact on this rate. A total of 19 grade ≥3 AEs occurred in 399 CRC patients; in the ICC group 4 grade ≥3 AEs occurred in 61 patients. These were mostly abdominal pain and fatigue. Clinically important events such as RILD, radiation pneumonitis, radiation cholecystitis, and radiation pancreatitis were very rare or not reported at all. Two patients experienced mild (grade 1) RILD 84 days and 194 days following SIRT. These rates are much lower than the grade 3–4 toxicity rate of 26% reported in the systematic review by Zacharias et al. (2015). This difference may be explained by the very short follow-up period of patients recruited most recently to the CtE study, and the inclusion of several chemotherapy-related AEs by Zacharias et al. (2015). The rates were comparable in number and type to those reported in the review by Saxena et al. (2014). The registry did not record the relatedness of the event to the SIRT treatment. Because patients were not followed-up by the SIRT centres past progression it is unlikely that this study will capture events in the post-progression phase of the disease. The lack of defined grading criteria is a weakness which is likely to introduce variability across the 10 sites. Although it is likely that many of the sites used the Common Terminology Criteria for Adverse Events (CTCAE) this cannot be relied upon. Unusually the registry records only day-of-treatment complications when they are classified as “severe”; again the grading criteria are not defined, but non-severe events are not recorded.

7.4.5 Strengths & limitations

The study of more than 450 patients is the largest UK-based cohort and worldwide comes second only in size to the Kennedy et al. (2015) retrospective non-comparative cohort study conducted in the US. This is the first project within the CtE programme to report results and it shows that large scale prospective collection of observational data to a registry across several centres is feasible. The presented results are generalisable and have been obtained from patients treated under standard care arrangements in the NHS. The drawbacks associated with clinical trial effects are unlikely to be an issue. In addition, the conduct and analysis have been independent of the two device manufacturers; the analysis and reporting has been entirely independent of manufacturers, clinical teams, and NHS England. The authors of this evaluation report have no conflicts of interest.

Limitations of this study have been described above in relation to the individual outcome measures. A number of additional limitations and learning points have been identified. Importantly, research questions were not defined in advance of data collection activities; this was partly a consequence of classifying the project as service evaluation rather than research. As such, the practicalities of collecting the necessary data, and definitions of outcome measures were not adequately considered. External validation of each patient against the CtE eligibility criteria was not possible, and from the information gathered in the SIRT registry it was not possible to confirm that patients who received only 1 previous line of chemotherapy were in fact intolerant to standard chemotherapy.

Anonymisation of the registry was necessary to meet information governance rules; the result however was that external validation of date of death (and other outcomes) against routinely collected datasets could not be carried out. Ultimately the absence of a contemporaneous comparator group (preferably patients receiving best supportive care) hampers the interpretation of results from the CtE cohort. This in turn limits the usefulness of the study to clinical practice. A prospective comparative matched-pair cohort, such as Seidensticker et al. (2012,) would provide comparative evidence on the survival benefit of SIRT in salvage mCRC and ICC populations. As is noted in Fleming et al. 2009 “except in settings where huge treatment effects can be expected, ITT analyses of data from RCTs are required to distinguish the effects of treatment from the influence of prognostic factors”. The recent publication of high quality randomised controlled trials necessary to produce a positive recommendation for trifluridine–tipiracil indicates the feasibility of such an approach to evidence generation for SIRT in this patient population (NICE 2016), although the ethical challenges of such a design are well-recognised.

8 Cost-effectiveness of SIRT in unresectable, chemotherapy-refractory metastatic colorectal cancer

8.1 Summary

8.1.1 Published evidence on the cost-effectiveness of SIRT

A systematic review of economic literature on the cost-effectiveness of SIRT yielded 144 studies. One study was relevant to the decision problem and selected for inclusion in the review (Pennington et al. (2015)). This study describes a 3-state partitioned survival model comparing the cost-effectiveness of SIRT to BSC in patients with inoperable chemotherapy-refractory colorectal cancer liver metastases. The model calculated an increase in life years of 1.12 years in patients treated with SIRT (mean survival 2.09 years) compared to BSC (0.97 years). It also demonstrated a total cost of £35,487 for SIRT and £12,730 for BSC; the difference was driven primarily by the initial cost of the SIRT procedure and the monthly costs for monitoring and treatment during the additional survival time in SIRT patients. Quality adjusted life years (QALYs) were improved in the SIRT group by 0.81 in the model compared to BSC (1.50 vs 0.69), and the improved survival resulted in a cost per QALY gained (or incremental cost-effectiveness ratio [ICER]) of £28,216.

This manufacturer-funded model used an appropriate structure and included relevant costs with most assumptions well described. The model was limited by the paucity of high quality comparative evidence. The overall survival time used for SIRT patients was longer than the alternative studies, and this is likely to favour SIRT. Sensitivity analysis was carried out to test the robustness of the model's results to changes in key inputs, although the cost of SIRT (another key driver) was inadequately explored. The choice of inputs and ranges used for sensitivity analysis may underestimate the overall cost per QALY and ICER and the uncertainty reported in the model. Alternative approaches used in external assessment centre model highlight the impact of these choices.

8.1.2 *De novo* cost-effectiveness model of SIRT compared to best supportive care by the external assessment centre

Methods: A new model was created by the external assessment centre to estimate the cost-effectiveness of SIRT compared with BSC in patients with unresectable, chemotherapy-refractory CRC. Model inputs were derived, where available and reliable, from the SIRT CtE registry data. Published studies, NICE technology appraisals, and clinical opinion were also used as sources of model inputs.

The model used a 3-state partitioned survival analysis where the three health states were progression-free, progressed, and death. The time horizon was five years, the cycle length was one month, the perspective was from the NHS and personal social services, and a 3.5% discount rate was applied. Kaplan-Meier curves from the SIRT CtE registry data for OS and PFS were extrapolated using a Weibull distribution. In the base case, hazard ratios for OS and PFS were taken from available published comparative studies and used to create a survival curve corresponding to a BSC cohort. A

SIRT procedure cost (including work-up) of £21,870 was used to reflect the NHS England tariff used in the CtE project. A cost of chemotherapy was applied to both SIRT and BSC arms based on the assumption that a proportion of patients receive standard chemotherapy and a small proportion receive more expensive drug therapies such as biologics. In addition costs associated with monitoring and treating adverse events were applied. Utilities derived from HRQoL data from the SIRT CtE registry were not reliable and therefore published utilities were applied to the progression-free and progressed states. Key assumptions were described.

Results

The ICER for SIRT was £85,350 in the base case of the external assessment centre's model. Treatment with SIRT resulted in an increase in QALYs of 0.32 (0.58 vs 0.26). The model showed that SIRT was £27,406 more expensive than BSC (£31,028 vs £3,623 discounted costs). This was primarily due to high initial procedure costs in the SIRT arm.

The cost of the SIRT procedure and the increased length of survival were the main drivers in the model. There was uncertainty around certain inputs such as the cost of chemotherapy and the utilities used for in the progression-free and progressed states. The former had a very low impact on the ICER, the latter had a moderate impact. Probabilistic sensitivity analysis showed that all simulations resulted in additional benefits in QALYs from SIRT compared to BSC for additional costs. The cost-effectiveness plane showed that 0% of simulations fell under the WTP threshold of £20K, 0.7% fell under the £30K threshold, and 11.0% fell under the £50K threshold.

Discussion

The *de novo* cost-effectiveness model by the external assessment centre demonstrates that SIRT is unlikely to be considered cost effective in the UK (by the usual WTP threshold used by NICE) when the technology is used in patients with CRC which has failed standard available therapies. The ICER for SIRT compared to BSC may be lower when used in patients with a longer life expectancy where the initial procedure cost is spread over a longer period.

The model was limited by the absence of a control group in the SIRT CtE registry data and uncertainty around the length of survival in the BSC arm. The hazard ratio from a retrospective cohort study was used to create survival estimates for the BSC arm which risks inflating the survival benefit from SIRT

In the absence of high quality granular information, assumptions were made in relation to the cost of chemotherapy which may not accurately reflect clinical practice. The variability in the definition and application of BSC in practice, particularly following the recent introduction of trifluridine-tipiracil to the patient pathway, impacts the generalisability of the model outputs.

The higher base case ICER in the external assessment centre model of £85K compared to that of the published model by Pennington et al. of £28K can be primarily attributed to a higher cost for the SIRT procedure and a longer OS estimate in the model by Pennington et al. (2015). The Pennington et al. model used a study which appeared to be a population with higher performance status and possibly more chemotherapy-naive patients compared with the SIRT CtE registry population. The

higher cost of SIRT (absent from the BSC arm) used in the current model was spread over a shorter survival time producing a higher cost per QALY.

There is inadequate data to make a reliable conclusion about the generalisability of the model to the ICC population. Available data from the CtE registry indicate that several inputs are similar to those in the CRC population. The longer OS in the ICC cohort may slightly reduce the ICER in this group.

8.2 Objectives of section

The aim of this section of the SIRT CtE evaluation report is to provide evidence on the cost-effectiveness of SIRT for the treatment of unresectable and chemotherapy-refractory metastatic colorectal cancer (mCRC). There are three specific objectives:

1) To undertake a systematic literature review to identify published cost-effectiveness evaluations of SIRT in patients with unresectable and chemotherapy-refractory mCRC.

2) To conduct a targeted literature review (building upon those presented in sections 4 and 5) to identify evidence to inform the model inputs.

3) To develop an economic model to estimate the cost-effectiveness of SIRT compared to best supportive care in the treatment of patients with mCRC. Results will be presented as an incremental cost-effectiveness ratio (ICER) describing cost per quality adjusted life year (QALY) gained with a range of scenarios and appropriate sensitivity analyses exploring uncertainty.

In addition, this section will describe the costs associated with SIRT in the treatment of patients with unresectable, chemotherapy-refractory intrahepatic cholangiocarcinoma (ICC).

8.3 Systematic literature review on the cost-effectiveness of SIRT

8.3.1 Literature search methodology

A literature search was designed to capture evidence relating to the clinical effectiveness of SIRT (described in Section 4). This same search encompassed cost-effectiveness evidence. A total of 1170 studies were retrieved following deduplication. These studies were reviewed for relevance to clinical and cost-effectiveness. To identify economic studies, a simple search was run within Reference Manager ({cost} OR {economic} OR {model} using the “all non-indexed fields” search function). A total of 144 references were identified and sifted by one researcher using title and abstract (JW). Eight studies were identified as being potentially relevant (Beg et al. 2014; Bester et al. 2013a; Cosimelli et al. 2013; Loveman et al. 2014; Pennington et al. 2014; Pennington 2015; Sella and Rilling 2011; Wasan 2014). Following a full text review, one study was identified as relevant and retained for full quality appraisal (Pennington 2015). Quality appraisal was based on NICE’s cost-effectiveness model appraisal guidance (NICE 2014b). The quality appraisal and results are presented below. Two studies (Loveman et al. 2014; Wasan 2014) were identified as potential sources of costs but were either out of scope or did not contain primary research. Five studies were excluded as they were conference abstracts with limited information available to adequately assess study quality.

8.3.2 Description and critical appraisal of included study

8.3.2.1 Results from the Pennington et al. (2015) cost-effectiveness model

Pennington et al. (2015) describes a 3-state partitioned survival model comparing the cost-effectiveness of SIRT to BSC in patients with inoperable chemotherapy-refractory colorectal cancer liver metastases. The model uses one-day cycles over a lifetime horizon (an unusually short cycle

length) from an NHS perspective. The key outcomes were life years gained, QALYs gained, cost per life year and cost per QALY gained. As such, the study is directly applicable to the evaluation of the SIRT commissioning through evaluation programme.

Key results from Pennington et al. (2015) are presented below.

- An increase in life years of 1.12 years in patients treated with SIRT (mean survival 2.09 years) compared to BSC (0.97 years) resulted from fitting a parametric curve to OS Kaplan-Meier curve.
- SIRT increased QALYs by 0.81 (1.50 vs 0.69).
- The total cost was £35,487 for SIRT and £12,730 for BSC, a difference of £22,757. This was driven by the high cost of initial SIRT treatment vs no initial costs for BSC and the monthly costs for monitoring and chemotherapy accumulated by SIRT patients during their additional survival time.
- The improved survival in the SIRT arm resulted in a cost per QALY gained of £28,216, and cost per life year gained of £20,323.
- Scenario analysis showed the model was robust to changes in key parameters with ICERs between £25,015 and £28,817.
- There was a 57% probability of SIRT being cost-effective at a willingness to pay (WTP) threshold of £30K/QALY, and a 0% at a WTP threshold of £20K/QALY (read from graph).
- A tornado diagram demonstrated that parameters relating to the OS curve had the largest impact on the ICER. The authors applied a scale parameter to the survival curve for SIRT and varied this in sensitivity analysis. It is difficult to visualise how the scale parameter affects the survival curve, but the impact on the results of the model was a variation in the ICER between approximately £20,000 and £68,000.

8.3.2.2 Appraisal of Pennington et al. (2015) cost-effectiveness model

Pennington et al. (2015) used an appropriate model structure for the decision problem in question, and the study is relevant to the SIRT CtE evaluation. The 3-state partitioned survival model, defined health states as progression free, progressed disease, and death. This type of model does not look at the probability of moving from one state to another. Instead it directly uses the number of patients in each state during a cycle applying data from a survival curve. It does not consider the route by which patients arrive at each state.

The model was produced by BresMed (Sheffield, UK) and funded by Sirtex Medical Ltd (the manufacturer of SIR-spheres). One author was employed by Sirtex Ltd, and others were advisors for the company. The study's first author (RP) has not contributed to this critical appraisal. A read-only Excel model was supplied to Cedar by Sirtex Medical Ltd.

Utility values were assigned to the progression free, progressed, and death states; these were not specific to the treatment type. There is no published evidence on the impact of SIRT on HRQoL in this population and therefore utility values were appropriately taken from a NICE HTA systematic review and cost-effectiveness model of biologic drugs used after first line therapy (Hoyle et al. 2013a; Hoyle et al. 2013b).

The authors chose the retrospective matched-pair study by Bester et al. (2012) as the source of survival data (described in Section 4.4.4). The reasons given were the more generalisable definition of BSC than the chemotherapy regimen in control group of the RCT by Hendlisz et al. (2010), the risk of confounding from the RCT's cross-over design, and underpowering of the RCT to detect a survival benefit. Whilst this justification is valid, the limitation associated with the retrospective, observational study design of Bester et al. (2012) makes the survival benefit attributed to SIRT less reliable. The authors do not provide a reason why Bester et al. (2012) was selected over Seidensticker et al. (2012). The longer survival times in the former study tend to favour SIRT in the model by reducing the ICER as the initial cost of SIRT is spread over a longer time period.

The authors fitted a log-normal curve to the Kaplan-Meier survival data from a retrospective matched pair study by Bester et al. (2012) to account for patients alive at the end of the study. The small number of patients in the standard care arm (n=29) produced high uncertainty in the tail of the survival curve which may have a large impact on the model results.

The authors assumed that there were equal patient numbers in progression free and progressed states at any point in time which may not be appropriate. As costs were assumed to be the same in each state, the total cost is unaltered, as shown by the sensitivity analysis. Additionally, the authors use the same utility values for both arms to represent progression-free, progressed disease and death. SIRT may offer local liver control following extra-hepatic progression which may produce different QOL utilities across the arms. However, there is no published data on the effect of SIRT on QoL or symptom control in the salvage setting.

The cost of work-up procedures for patients who do not go on to have SIRT was not included in the model. However, the model includes patients who require multiple SIRT treatments (based on 2.2% at Christie Hospital), and patients who require more than one work-up procedure.

The model included costs for the SIRT work up and procedure (£14,248), BSC, monitoring, further treatment, adverse events, and death. SIRT costs were derived from NHS reference costs and equipment costs from the Christie NHS Hospital. Adverse event rates (grade 3 and 4) were taken from a Phase III randomised controlled trial (Hendlisz et al. 2010). An end of life cost of £5,800 was applied to reflect the cost of palliative care. Ongoing care costs including monitoring and chemotherapy were assumed to continue at a constant value for the patient's entire lifetime. The costs for SIRT and work up used by Pennington et al. were derived using a micro-costing approach. This is a reasonable method, however the full details of this are not available and uncertainty was not explored in sensitivity analysis.

One-way sensitivity analysis and probabilistic sensitivity analysis were used to investigate the robustness of the ICER when parameter uncertainty was considered. In one-way sensitivity analysis the authors varied the cost of SIRT by just ±£2, therefore uncertainty in the cost of SIRT was not fully explored, nor was cost of SIRT identified as a key driver of the model. Varying the key driver of SIRT overall survival resulted in ICER values between approximately £20,000 and £68,000. Given the selection of the most optimistic inputs for SIRT it is likely that the cost per QALY gained of £28,216 is overly optimistic.

Summary of strengths

- An appropriate model structure was chosen.
- The patient population was relevant to the current decision problem.
- Most relevant costs were included.
- Most assumptions were well described.
- Most parameters were explored appropriately in sensitivity analysis.

Summary of limitations

- High quality clinical evidence was unavailable. The lack of comparative evidence on survival, and the impact of SIRT on quality of life reduces the reliability of cost-effectiveness estimates.
- The assumption used for time spent in progression-free and progressed (i.e. 50% of patients in either state at any time) is unlikely to reflect real life.
- The following limitations in the model are likely to favour SIRT:
    - The study from which OS was taken has a longer survival time than Seidensticker et al., which was an alternative source. A longer OS will reduce the ICER, as the cost of treatment is spread over a longer time.
    - The cost of SIRT was inadequately explored in the sensitivity analysis.
    - The cost of providing work-up for patients who do not receive SIRT was not included.

8.4 Directed search for model inputs

In addition to the systematic search for cost-effectiveness literature on SIRT described above, a pragmatic, directed information search was used to identify model inputs. Key sources of information are described below, including the new primary data collected from the SIRT CtE registry study, and systematic searches for effectiveness data on both SIRT and BSC, described in detail in earlier chapters.

8.4.1 *De novo* data collected from the SIRT CtE registry study (see section 7)

Data gathered in the SIRT CtE registry study was considered highly relevant to the cost-effectiveness question. Data was prospectively collected from 399 patients with unresectable, chemotherapy-refractory colorectal cancer treated with SIRT at 10 NHS centres in England onto a registry (full methods and results are described in section 7). Outcomes which were of relevance to the model were OS, PFS, complications, adverse event rates and types, and utility data derived from EQ-5D-5L questionnaires. In addition, details about the SIRT procedure, length of hospitalisation, concomitant chemotherapy, post-SIRT chemotherapy, frequency of imaging scans and follow-up appointments were recorded. No comparator data were collected in this study.

8.4.2 Systematic review of the efficacy of SIRT in CRC patients (see section 4)

A systematic review was carried out to summarise the clinical evidence on the efficacy of SIRT in patients with unresectable, chemotherapy-refractory mCRC (section 4). Three comparative studies were identified (1 RCT and 2 retrospective cohorts) and 21 non-comparative studies. All studies underwent critical appraisal. Results from the three comparative studies identified during this

review (Bester et al. 2012; Hendlisz et al. 2010; Seidensticker et al. 2012) were used to inform model parameters for SIRT and BSC including OS, PFS, adverse event rates, and ongoing treatment frequency and type.

8.4.3 Rapid review of the efficacy of best supportive care in CRC patients (see section 5)

A literature review was conducted to identify studies which report the survival of patients with unresectable, chemotherapy-refractory mCRC who have received BSC (section 5). This strategy was designed to identify high quality comparative studies in which BSC was the control arm, and which presented OS or PFS. Individual studies underwent critical appraisal and were used to inform survival estimates in the best supportive care arm of the model.

8.4.4 Identification of relevant NICE guidance

The NICE website was searched for guidance relevant to the decision problem. The following technology appraisals (TAs) were considered relevant and likely to include evidence to inform the model:

- **Technology appraisal guidance [TA405] Trifluridine–tipiracil for previously treated metastatic colorectal cancer (August 2016) (NICE 2016).** This technology appraisal evaluated the clinical and cost evidence on Trifluridine–tipiracil compared to BSC in patients with CRC which has progressed following treatment with standard chemotherapy. Whilst the intervention does not match the decision problem on SIRT the population is similar.

- **Technology appraisal guidance [TA242] Cetuximab, bevacizumab and panitumumab for the treatment of metastatic colorectal cancer after first-line chemotherapy: Cetuximab (monotherapy or combination chemotherapy), bevacizumab (in combination with non-oxaliplatin chemotherapy) and panitumumab (monotherapy) for the treatment of metastatic colorectal cancer after first-line chemotherapy (January 2012) (NICE 2012).** This technology appraisal evaluated the use of a range of biologic therapies compared to BSC for the treatment of patients who have failed at least one previous line of chemotherapy. The evidence includes an independent systematic review and economic model conducted by Peninsula Technology Assessment Group (PenTAG) and commissioned by the NIHR HTA programme (Hoyle et al. 2013a). Key results from a sub population of patients who have progressed following three or more previous lines of chemotherapy were also published in a peer reviewed journal (Hoyle et al. 2013b). The authors kindly provided a copy of the executable Microsoft Excel model to Cedar.

8.4.5 Clinician questionnaire

A questionnaire was designed by Cedar to obtain clinical feedback about usual practice in the UK regarding the treatment pathway for patients treated with SIRT and best supportive care (Appendix 6). Responses were collated and used to inform the model.

8.5 *De novo* cost-effectiveness model by the external assessment centre

A full cost-effectiveness model comparing SIRT to BSC in patients with colorectal cancer was undertaken by an independent external assessment centre (Cedar, Cardiff & Vale University Health Board).

8.6 Methods

8.6.1 Population

The population modelled matched that of patients with unresectable, chemotherapy-refractory CRC recruited into the SIRT CtE registry study. This comprised patients with metastatic colorectal cancer which progressed following treatment with at least two lines of standard chemotherapy. All patients entered the model at the point at which they received SIRT treatment or continued with BSC, and are followed to progression based on the actual data from the SIRT CtE study and comparator data from the literature.

8.6.2 Intervention and comparator

The intervention was SIRT treatment, as described in previous sections. The comparator was best supportive care (BSC); however this is not clearly defined in practice. Published literature and clinical advice indicate that wide variations exist based on patient and clinician preference, regional and temporal variations.

8.6.3 Patient pathway

The patient pathway was based on SIRT CtE registry data, questionnaires to clinicians and published information, with the intention of reflecting current practice within the NHS.

For the SIRT arm, patients receive a work-up procedure followed by treatment in the first one-month cycle of the model. Approximately 5% of patients receive a work-up procedure without progressing to SIRT (to reflect patients who are found to be ineligible for SIRT following their work-up procedure, based on the clinician questionnaire); 8% require more than one work up, usually for additional embolisation (source: CtE registry data); 3% require two complete SIRT procedures (source: CtE registry data).

Following SIRT treatment, patients will have regular follow-up appointments and scans, and a proportion will also have chemotherapy treatment (source: CtE registry data and clinician questionnaire).

The comparative arm is BSC. Due to the variation in practice, assumptions have been made for the model based on clinician questionnaires and published literature (Table 8.1). It has been assumed that the BSC arm has the same level of monitoring and chemotherapy as SIRT. This is investigated further in alternative scenarios.

8.6.4 Model structure

A three state model was created in Microsoft Excel, applying partitioned survival state analysis commonly used for cost-effectiveness models in oncology populations. The three states, and patient movement between them are shown in Figure 8.1.

- **Progression free:** This was the entry state for all patients, and is defined as no progression since entry into the model. SIRT treatment occurs at entry to the model for the SIRT arm.
- **Progressed:** At disease progression (hepatic or extrahepatic) identified by a clinician.
- **Death:** Patient has died

The time horizon was five years, which reflects a lifetime horizon for this patient population. The cycle length for the model was one month, which was sufficiently short to see differences between the two treatment arms. An NHS and personal social services perspective was used, together with a 3.5% discount rate as is standard for the NICE reference case.

The partitioned survival analysis considers the actual number of patients in each state at each month, and does not calculate the transition probabilities between each state. This can give simpler calculations and reflects the availability of survival data from clinical trials. In the case of SIRT CtE, survival data was available for PFS, and for OS. Survival data for BSC was available from published papers.

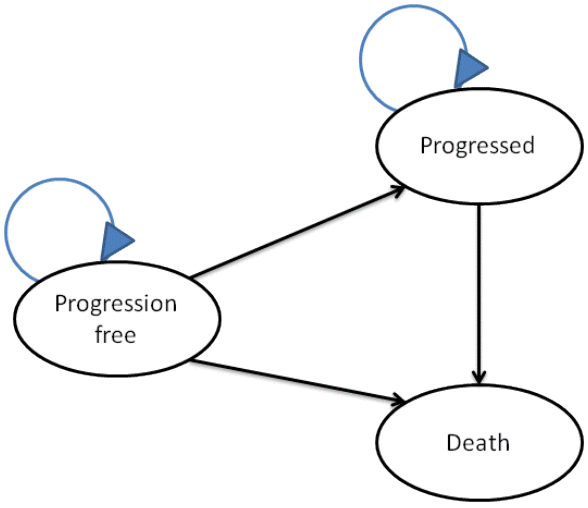


Figure 8.1. Three state model for cancer progression

8.6.5 Key assumptions

- Quality of life decreases when the patient moves from progression free to progressed state.
- There is a proportionate hazard assumption between SIRT CtE survival and BSC survival.
- Costs of progression-free treatment are comprised of monitoring costs and chemotherapy costs.

- Monitoring and chemotherapy costs are the same in BSC and SIRT during the progression-free state.
- A proportion of patients will have a limited number of chemotherapy cycles (up to 4 cycles, if they continue in the progression-free state).
- Patients who live longer than 4 months in the progression-free state will not have further chemotherapy. There is no chemotherapy in the progressed state.
- Costs (including nursing time, hospitalisation, and interventions) in progressed state are the same for SIRT and BSC patients.

8.6.6 Model inputs (base case)

Model inputs are described in detail below. Table 8.1 summarises the inputs that were used in the model; full details on the information sources that were considered, together with considerations on their appropriateness for use in this model are presented in Appendix 7.

Table 8.1. Summary of model and inputs.

Input	Base Case value	Source
Time horizon	5 years	Based on observed survival times
Discount rate	3.5%	NICE reference case
Perspective	NHS and personal social services	NICE reference case
Survival (mean, months)		
SIRT overall survival	9.8	SIRT CtE data, Weibull distribution fitted
BSC overall survival	4.2	0.27 hazard ratio (Seidensticker et al. 2012)
SIRT progression free survival	4.3	SIRT CtE data, Weibull distribution fitted
BSC progression free survival	2.7	0.51 hazard ratio (Hendlisz et al. 2010)
Procedure costs (per patient)		
SIRT procedure, including work-up	£21,870.00	CtE Tariff, using 2016-17 NHS tariff (source: NHSE England pricing)
Patients receiving work-up and not proceeding to SIRT	£298.79	Weighted cost per patient: 5% of total patients routed to SIRT (source: clinician questionnaire)
SIRT patients receiving 2 work-up procedures, 1 SIRT	£454.16	Weighted cost per patient: 8% of patients receiving SIRT (source: SIRT CtE registry data)
SIRT patients receiving 2 complete SIRT treatments	£656.1	Weighted cost per patient: 3% of patients receiving SIRT (source: SIRT CtE registry data)
Total SIRT Procedure	**£23,279.05**	Total cost used in model, per patient, including all weighted costs above.
Chemotherapy costs (per patient; each cost is a cost per chemotherapy cycle applied once per month), see section 8.6.9 for details		
Cost of standard chemotherapy regimen (e.g. FOLFOX)	£978.00	Based on NHS Reference Costs 2015-16 (Department of Health 2016)

Cost of biologic drug cycle, or similarly priced regimen	£2,770.00	Based on NHS Reference Costs 2015-16 (Department of Health 2016)
Cost of first cycle of chemotherapy	£396.06	Assumption: 32% receive standard chemotherapy (e.g. FOLFOX); 3% receive biologic drug, or similarly priced regimen
Cost per cycle, for subsequent 3 chemotherapy cycles	£286.84	Assumption: 18% receive standard chemotherapy (e.g. FOLFOX); 4% receive biologic drug, or similarly priced regimen
Cost of chemotherapy after 4 months	£0.00	This assumption was made due to lack of high quality data for both SIRT and BSC arms. Other models assumed either no chemotherapy, or chemotherapy for patient lifetime. SIRT CtE data did not support fully either assumption. The impact on the ICER is very low due to short survival times, and is tested in sensitivity analysis
Monitoring Costs (per patient, per month)		
SIRT monitoring	£161.00	CtE questionnaire plus NHS Reference Costs 2015-16 (Department of Health 2016). Assume until progression.
BSC monitoring	£161.00	Assume same as SIRT
Costs per patient in each state		
Progression free	Not fixed	Monitoring costs plus chemotherapy costs
Progressed	£952.05	Taken from Remak and Brazil (2004), supportive care costs. Assumption of same costs for BSC and SIRT arms. Inflated to 2016
Transition to death	£875.31	Taken from Remak & Brazil (2004), using stated monthly cost for end of life, and stated length of end of life stage. Inflated to 2016
Death	£0.00	Any costs are in the transition element.
Adverse Events		
SIRT adverse events	£21.20	AEs from CtE data, costed using NHS Reference costs (Department of Health 2016) and costs from Mickisch et al. (2010), inflated to 2016. Relatedness of AEs to SIRT not captured in registry.
BSC adverse events	£21.20	Assumed to be the same (cost of SIRT-specific AEs not known). See section 8.5.13 for further details. The impact of this assumption on the ICER is likely to be very low, and is tested in sensitivity analysis.
Quality of Life		
Progression free	0.75	From Hoyle, 2013b
Progressed	0.69	From Hoyle, 2013b
Transition to death	0.10	From Pennington et al. applied for 1 month, on transition to death

AE, adverse event; BSC, best supportive care; CtE, commissioning through evaluation; ICER, incremental cost-effectiveness ratio.

8.6.7 Survival

8.6.7.1 Extrapolation of OS and PFS data from the SIRT CtE registry

Kaplan-Meier survival analysis was used to analyse data from the SIRT CtE registry study for OS and PFS from patients treated with SIRT. The SIRT CtE registry data was considered the best source of OS and PFS data for the SIRT arm of the model. It was a large dataset collected recently in the NHS setting and from a population relevant to the economic evaluation.

A Weibull curve was fitted to the SIRT CtE data for OS and PFS. For OS, a Weibull distribution was both graphically and using the Akaike information criterion (AIC) a reasonable option, however for PFS the fit was less close (Figure 8.2; Table 8.2). The requirement to meet the assumption of proportional hazards to use published hazard ratios restricted the choice of methods for curve fitting. The limitations of this approach were recognised but no other data was available. The mean values used for OS and PFS in the sensitivity analysis include the range that would have been seen using an alternative distribution.

8.6.7.2 Survival data for the BSC arm of the model

No comparator data were collected during the SIRT CtE registry study, therefore previously published work was used. The best option for obtaining OS and PFS data for the BSC arm of the model was to use hazard ratios from published evidence applied to the SIRT CtE registry data. The options considered to obtain survival data for BSC were two observational studies (Bester et al. 2012; Seidensticker et al. 2012) and one RCT (Hendlisz et al. 2010; Table 8.3). A number of considerations were taken into account and described below.

- The Hendlisz et al. (2010) RCT was excluded as a source of OS data for the BSC arm because a cross-over design was used whereby patients from the control group were permitted to receive SIRT following progression which would confound estimates of OS. In addition, the RCT only reported a median value for OS with no Kaplan-Meier curve.

- Bester et al. (2012) was excluded because patients with CRC recruited to the SIRT group of the Bester et al. study were likely to have better health at baseline compared to those in the SIRT CtE cohort (85% of the SIRT group in Bester et al. were ECOG 0 compared to 50% in the SIRT CtE cohort, and the performance status for BSC group was not reported). The OS curve for SIRT patients in Bester et al. showed longer survival than the SIRT CtE registry data suggesting that the BSC population may not be comparable to the SIRT CtE registry data (Figure 8.3)

- The Kaplan-Meier OS curve for the SIRT CtE registry data was more similar to that of the Seidensticker et al. (2012) OS data than the extrapolated curve for OS fitted to patient data from the Bester et al. study (extrapolated data was taken from the Pennington et al. 2015 model with permission; Figure 8.3). As a result, Seidensticker et al. was chosen as the source for the hazard ratio to apply to OS data from the SIRT CtE registry data to create a survival curve for the BSC arm of the model.

Access was requested to patient level data for all three papers, but was not granted. Therefore Seidensticker et al. data was taken electronically from the published graph and data points reproduced using DataThief (Tummers 2006).

Neither Bester et al. (2012) nor Seidensticker et al. (2012) reported survival curves or hazard ratios for PFS therefore the hazard ratio from Hendlisz et al. (2010) was used. The hazard ratio from Hendlisz et al. was applied to the SIRT CtE registry data to create a PFS curve for the BSC arm of the model. The PFS curve is not affected by the cross-over design because cross-over occurred after progression. The SIRT PFS curve for Hendlisz et al. (2010) was similar to SIRT CtE data. A limitation of using Hendlisz et al. as a source is the fact that the control arm received a fluorouracil chemotherapy regimen rather than BSC.

A hazard ratio of 0.27 from Seidensticker et al. (2012) was applied to the extrapolated overall survival curve from the CtE registry data in order to create a corresponding curve for the BSC arm of the model (Tables 8.1 and 8.3; Figure 8.4). Similarly, a hazard ratio of 0.51 from Hendlisz was applied to the PFS data from the CtE registry (Figure 8.4). It was not possible to directly fit curves to the Seidensticker et al. (2012) and Hendlisz et al. (2010) data because patient-level data was not available, and because the original data would have led to some points in time having progression free survival greater than OS. The final extrapolated SIRT CtE for OS and PFS curves and corresponding BSC curves created using hazard ratios used in the base case model are shown in Figure 8.4

Table 8.2. Mean survival and AIC value using alternative distributions fitted to CtE data

	OS, SIRT CtE		PFS, SIRT CtE	
	AIC	**Mean (months)**	**AIC**	**Mean (months)**
Exponential	751.8229	11.22597	830.9573	4.29868
Weibull	673.6352	9.823486	742.4854	4.251284
Loglogistic	648.0379	10.41232	629.95	3.961386
Lognormal	644.3761	10.10061	657.05	4.153542

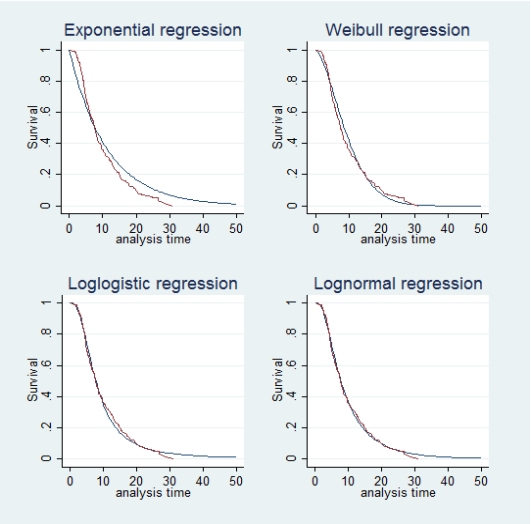
AIC, Akaike information criterion (lower values indicate better fit); OS, overall survival; PFS, progression free survival

Table 8.3. Summary of survival data available from different sources

Study	Overall survival (months)				Progression free survival (months)			
	SIRT		Comparator		SIRT		Comparator	
	Median	**Mean**	**Median**	**Mean**	**Median**	**Mean**	**Median**	**Mean**
SIRT CtE registry	7.6	9.8	-	-	3.0	4.188	-	-
Bester et al. (2012)	11.9	NR	6.6	NR	NR	NR	NR	NR
Seidensticker et al. (2012)	8.3	NR	3.5	NR	5.5	NR	2.1	NR
Hendlisz et al. (2010)	10 *	NR	7.3	NR	4.5	NR	2.1	NR

*Cross over design permitted patients randomised to control group to receive SIRT following progression. NR, not reported.

Overall Survival



Progression Free Survival

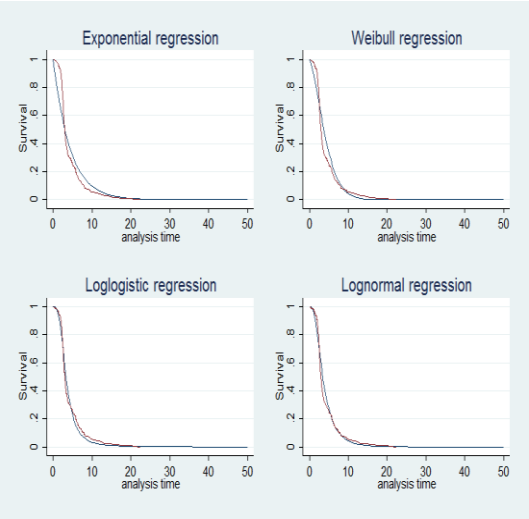


Figure 8.2. Extrapolated curves fitted to SIRT CtE survival data using various distributions

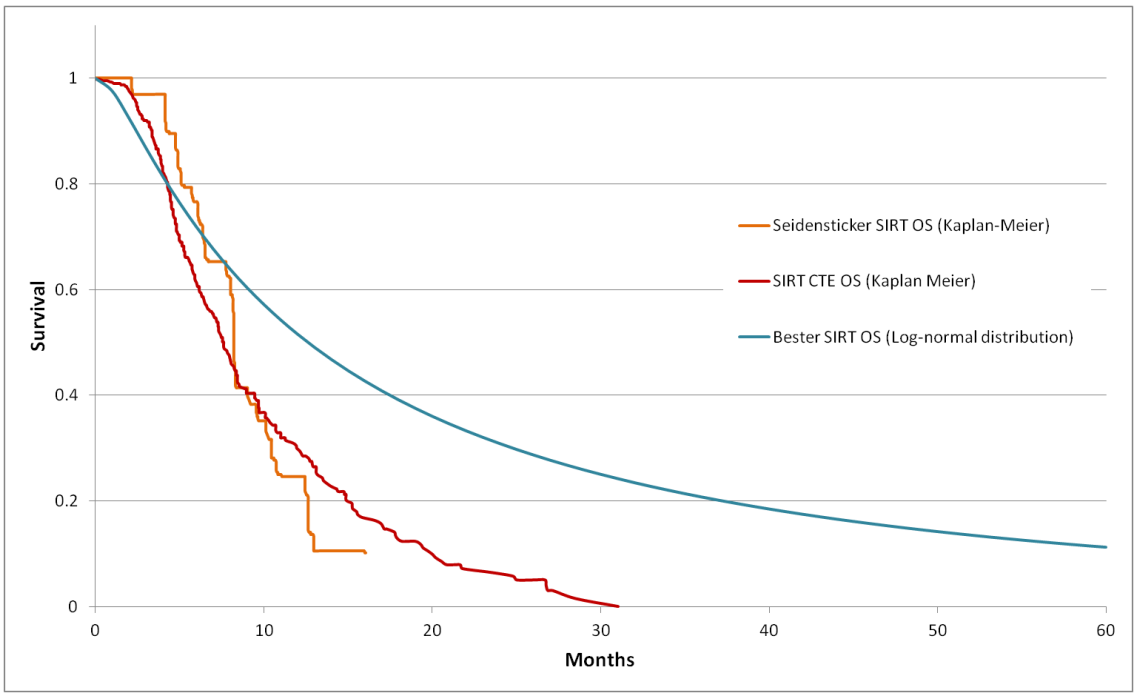


Figure 8.3. Overall survival for SIRT patients from different data sources

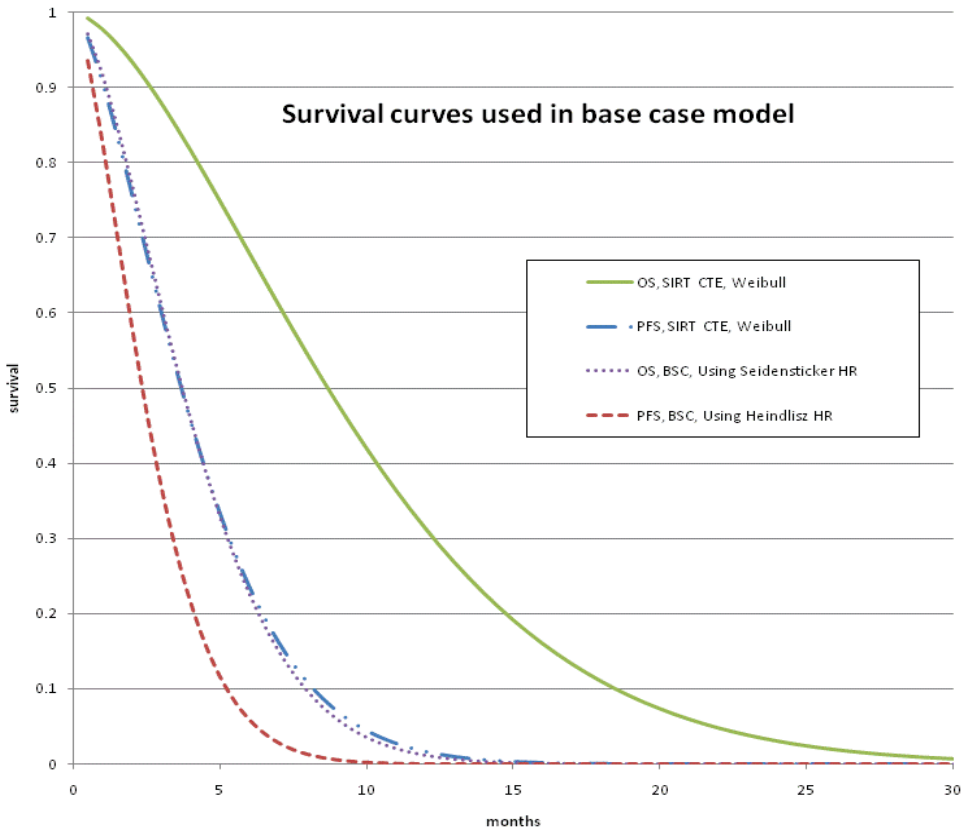


Figure 8.4. OS and PFS curves for SIRT and BSC arms used for base case model

8.6.8 SIRT procedure costs

The cost of the SIRT procedure was based on the current NHSE England tariff of £21,870, calculated using NHS Reference Costs 2015-16 (Department of Health 2016). This was then weighted to reflect scenarios in which patients' treatment deviates from the usual format of one work-up followed by one SIRT procedure. The following alternative scenarios were costed.

- 5% of total patients routed to SIRT receive a work-up, but do not proceed to receive SIRT. This was due to findings at work-up showing ineligibility for SIRT or progression of disease between an initial assessment and work-up (source: clinician questionnaire).
- 8% of patients receiving SIRT received two work-ups. A second work-up may be required to carry out additional embolisation (source: SIRT CtE registry data).
- 3% of patients receiving SIRT had two complete SIRT procedures; it is assumed that this involved an additional work up as well as the procedure. Sequential SIRT procedures are required in certain circumstances (source: SIRT CtE registry data).

As a result of weighting the additional scenarios, the total cost per person for SIRT and work-up used in the model was £23,279.05 (Table 8.1).

Data collected from the CtE registry was not detailed enough to enable a micro-costing approach for the SIRT procedure.

8.6.9 Chemotherapy costs

The SIRT CtE registry captured data on the use of chemotherapy and biologic drugs either concurrently with SIRT, or after SIRT treatment. There was considerable variation in descriptions of drug regimens, and some missing data. Furthermore, the level of detail required to cost each patient's individual treatment was unavailable for the entire patient group. For this reason, the CtE registry data was used only as a basis for an assumption on the cost of drug treatment.

The results of the SIRT CtE data for chemotherapy are described in Section 7, Table 7.4. These show that 35% of patients received chemotherapy (including biologics) concurrently with SIRT, with only 4% missing data. Following SIRT, 22% patients were recorded as receiving chemotherapy (including biologics). However, 24% had missing data. Most of these patients received a standard chemotherapy regimen such as FOLFOX, or other similarly priced fluoropyrimidine-, oxaliplatin- or irinotecan-based regimens. A small number were receiving more expensive regimens including biologics such as cetuximab + irinotecan, or regimens such as trifluridine–tipiracil.

It was assumed that in the first month following SIRT, 32% of patients had one cycle of FOLFOX (£978) or similarly priced regimen and 3% had one cycle of a regimen priced to include a biologic (£2,770; Table 8.4); this is based on the figure of 35% patients who received concomitant chemotherapy in the SIRT CtE cohort. The costs were calculated using NHS Reference costs 2015-16 (Department of Health 2016; Table 8.4) and calculated by combining the cost code for procuring the drug, with the cost of delivery, according to the type of regimen (full details are available from HSCIC [201]). Based on these weighted values, a cost of £396.06 per patient for the first cycle of chemotherapy was applied in the model (Table 8.1).

In the next 3 months following SIRT, of those patients who were still in the progression-free state, 18% had one cycle of FOLFOX or similarly priced regimen (£978) and 4% had 1 cycle of a regimen priced to include a biologic (£2,770). This gave a weighted value for subsequent chemotherapy cycles of £286.84 per patient which was used in the model (Table 8.1).

Once patients progressed, it was assumed that they were no longer receiving chemotherapy.

We are aware that these assumptions do not accurately reflect routine clinical practice as chemotherapy cycles are not necessarily monthly, and the treatment options available are more varied and complex. However, in the absence of more detailed and reliable data, this method was chosen as a necessary compromise which avoids front-loading the cost of drugs at the start of the model, which would overestimate costs for patients who die before receiving chemotherapy, and avoids distributing chemotherapy over the patients' entire life span which would overestimate costs in patients who live longer.

It is assumed for the base case that the same costs for chemotherapy apply to SIRT and BSC. This assumption will result in a slightly higher cost for SIRT chemotherapy than for BSC chemotherapy, because fewer BSC patients remain in the progression-free state for 3 months or longer.

Table 8.4. Cost of relevant drug regimens from NHS Reference costs 2015-16

Drug regimen	Procuring drugs		1st drug delivery		2nd drug delivery	Per cycle cost
	NHS Code	Cost	NHS Code	Cost	Cost	
FOLFOX	SB06Z	£462	SB14Z	£304	£212	£978
Cetuximab + irinotecan + capecitabine	SB10Z	£2,466	SB14Z	£304	n/a	£2,770

8.6.10 Monitoring costs (progression-free state only)

Monitoring costs have been based on responses to the clinician questionnaire (Appendix 6) and SIRT CtE registry data on the number of MRI and PET scans carried out. As standard, patients were followed-up every 2 to 3 months with a CT scan. SIRT CtE registry data from the first and second follow-up appointments indicated that in addition to CT scans, 2.1% of patients received a MRI scan and 12.0% received a PET scan at each follow-up. Costs are taken from NHS Reference costs 2015-16 (Department of Health 2016) (Table 8.5). The following assumptions were used in the model.

All patients would receive a follow-up examination every 2.5 months including:

- an appointment with a consultant
- a CT scan
- 2% would have an MRI scan
- 12% would have a PET scan

For the base case a cost of £161 per patient, per month was used for monitoring (Table 8.1). It was assumed that the same monitoring costs apply to the SIRT and BSC arms of the model. Alternative costs have been used during sensitivity analysis. These include outpatient visits every 2 weeks for the BSC patients (source: SIRT data working group).

Table 8.5. Costs of monitoring used in the model

Item	Frequency for SIRT patients , every 2-3 months	Cost per item	Monthly cost	NHS Ref Code
CT scan of chest, abdomen, pelvis	1	£121	£48	RD26Z
MRI scan	1 for 2% of patients – CtE data	£213	£2	RD05Z
PET scan	1 for 12% of patients –CtE data	£944	£45	RN031
Outpatient consultant visits	1	163	£65	WF10A

Laboratory tests	1	2.08	£1	Weighted cost of DAPS01-09
Total (per patient)			**£161**	

8.6.11 Costs of supportive care in the progressed state

Costs of supportive care during the progressed state are taken from a study on breast cancer patient care (Remak & Brazil 2004), inflated to 2016 prices (Table 8.6). This source was also used in a previous HTA (Hoyle et al. 2013) in a similar patient population as this SIRT CtE study. The original data came from a questionnaire to clinicians on the proportion of different interventions at different stages in progression of disease. The total of £672.73 was inflated from 2000 to 2016 to give a monthly cost of £952.05 which was used in the base case (Table 8.1).

Table 8.6 Costs per patient during progressed state, taken from Remak & Brazil (2004).

Item	Cost
Radiotherapy	£17.80
Medication	£62.90
Special interventions	£101.66
Scans and laboratory tests	£77.77
Hospitalisations 42%	£157.40
Outpatient visits Specialist (90%)	£255.20
MacMillan nurse (65%)	
District nurse (50%)	
TOTAL	**£672.73**

8.6.12 Costs at end of life

The study by Remak and Brazil (2004) calculated a cost of end of life, which inflated to 2016, was £875.31 and used in the base case (Table 8.1). It was assumed that supportive care for breast cancer is similar to mCRC, and that procedures are still similar to those recorded in 2000. The study was used in previous models for mCRC, and is in line with other costs reported. For example, using Round et al. (2015) a study used in the NICE technology appraisal of trifluridine-tipiracil (TA405 (NICE 2016)) the costs during palliative care [1] would equate to £927.5 per month (having removed the end of life cost of £875.31). Thus, although neither Remak and Brazil (2004) nor Round et al. et al. (2015) were ideal sources of costs for patients in the progressed stage, the similarity of monthly costs between these sources provided confidence that the figure was a reasonable estimation of the real cost. Sensitivity analysis encompassed the variation between the two studies.

It was assumed that the same costs apply to the SIRT and BSC arms of the model.

[1] Defined as the period from the point when the patient starts to take strong opioids, expected to be 6.6 months for mCRC with a total cost for health and social care of £6910.

8.6.13 Adverse events

The only information source with adverse events data on SIRT compared with BSC was Hendlisz et al. (2010). There were a number of limitations with using AE data from Hendlisz et al. (2010) such as the small sample size, differences between the control arm (active chemotherapy) and the definition of BSC used in this model. As a result, we decided not to use these data in the model.

Since AE data were collected as part of the SIRT CtE registry study, this was used to calculate costs for those events at Grade 3 or over, using NHS reference costs (Department of Health 2016), or where these were not available, costs from (Mickisch et al. 2010) (Table 8.7). In the absence of further information, an assumption was made for the costs of "other adverse events" as twice the cost of fatigue (the highest cost of any of the included events). A one-off cost per patient of £21.20 was used for adverse events in the base case (Table 8.1).

There were no grade ≥3 occurrences of radiation induced liver disease (RILD) seen in the SIRT CtE study. No RILD events were reported in 21 patients in Hendlisz et al. (2010), 3 cases were reported in 29 patients in Seidensticker et al. (2012), and 1 case was reported in 339 patients in Bester et al. (2012). Advice from clinicians was that treating severe RILD would be costly if it were to occur. An investigation of the impact of a rare high cost event was therefore carried out and results indicated that it would have a minimal impact on the results of the model overall. For example, if the treatment cost was assumed to be £8,000, with an event probability of 1%, this would add an additional £80 on to the cost per patient. Although this increases the AE cost by several times, it is only applied once at the model start, and has very little impact on the total procedural cost.

The relatedness of adverse events to SIRT was not captured in the SIRT CtE registry. No data were available on BSC patients in the SIRT CtE registry. The variance in approaches reported in other economic evaluations is detailed in Appendix 7, with adverse event-related costs ranging from £42.55 to £2,760. This may be more, less or the same as the AE cost used for the intervention, in different models. Due to uncertainty in the direction of change of AE costs between SIRT and BSC, an assumption was made in the model that the costs of AEs were the same (and using cost calculated from the SIRT CtE registry data [Table 8.7]). One way sensitivity analysis uses a large range to investigate the implications of this choice.

Table 8.7 Costs of adverse events used in the model (data from SIRT CtE cohort).

Adverse event type	Number of grade ≥3 AEs	% of patients	Cost per event	Cost inflated to 2017 and converted to £*	Cost of AE per patient (grade ≥3)
Abdominal pain	3	0.8%	£139.52	£141.81	£1.07
Fatigue	8	2.0%	€372[1]	£332.92	£6.68
Fever	1	0.3%	£158.43	£161.03	£0.40
Other	7	1.8%	£744.00	£665.84	£13.05
TOTAL	19	4.8%			**£21.20**

*EPPI Cost converter: http://eppi.ioe.ac.uk/costconversion/default.aspx

[1] Original source uses euros

8.6.14 Quality of life

Quality of life data were collected during the SIRT CtE registry study. However, there were concerns about missing data and the appropriateness of the study design for this outcome. In the CRC cohort, only 32% of patients had an EQ-5D-5L measurement at 3 months which dropped further to 3% at 12 months (see Section 7.3.6). The mean pre- and post-progression utility scores in the CRC cohort were 0.82 (SD 0.17; n=68) and 0.77 (SD 0.16; n=105), respectively. The SIRT CtE registry study was not designed to collect post-progression data and therefore there is a high risk of bias in this measure. Furthermore, the SIRT CtE data does not provide information for patients treated with BSC.

Utilities data used in previous models (Hoyle et al. 2013a; Pennington 2015) were therefore used in the current model. The progression free utility value used was 0.75, and the progressed disease utility value was 0.69 (Table 8.1). Values were taken from the BSC arm of a study of mCRC, comparing cetuximab to BSC (Karapetis et al. 2008). In the absence of reliable utility values from patients treated with SIRT an assumption was made that the same utility values for progression-free and progressed disease were applied to both the SIRT and BSC arms of the model, as described by Pennington et al. (2015). The potential impact of SIRT on quality of life would be reflected in the model from the longer time spent in the progression-free state. Other sources of utility values are described in Appendix 7. For example, NICE's technology appraisal TA405 {NICE, 2016 10 /id} used a value of 0.75 for the progression-free state and 0.59 for the progressed state, taken from the CORRECT study of regorafenib monotherapy for previously treated metastatic colorectal cancer {Grothey, 2013 316 /id} demonstrating comparable values with those used in our *de novo* model.

A pre-death transition utility value of 0.10 was applied for 1 month on transition to death as described in Pennington et al. (2015). This was applied to both arms and because all patients die within the time horizon it does not impact on the incremental results.

8.7 Sensitivity analysis methods

8.7.1 Deterministic one-way sensitivity analysis

Deterministic one-way sensitivity analysis varies one input at a time, with all other inputs staying at the same value. This was used to examine the variables with the most influence on the model results given the uncertainty surrounding the input parameters. Low and high values which vary around a base case value were tested (Table 8.8).

Survival curves were also investigated using one-way sensitivity analysis. For SIRT, a hazard ratio of 0.8 and 1.2 were applied to the base case curve (Table 8.8). For BSC, the hazard ratios used to create a BSC curve were altered by ±20%. It should be noted that both PFS and OS are varied at the same time, by the same HR, while SIRT and BSC are varied separately. The variations in the HR applied to the survival curves resulted in the mean survival times that are shown in table 8.9.

Table 8.8. Cost and utility values used in one way sensitivity analysis

Model input	Base case	Low	High	Notes
Costs				
Initial cost of SIRT procedure	£23,279	£14,747	£26,000	Low value reported in Pennington (2015), inflated to 2016; high value was estimated.
Cost of first cycle of chemotherapy	£396.06	£0	£600	Lowest value chosen as no chemotherapy; high value assumed based on monthly values in Pennington (2015)
Cost per cycle, for subsequent 3 chemotherapy cycles	£286.84	£0	£600	Lowest value chosen as no chemotherapy; high value assumed based on monthly values in Pennington (2015)
Monitoring	£161	£73	£500	Low value based on quarterly visits and no PET scans; high value based on clinical advice on additional monitoring visits
Adverse events in SIRT arm	£21.20	£0	£2,760	Lowest value chosen; high value from Hoyle (2013)
Adverse events in BSC arm	£21.20	£0	£2,760	Lowest value chosen; high value from Hoyle (2013)
Costs per patient in progressed state	£952.05	£200	£1,039	Low value estimate informed by TA405 monthly cost (but does not include lump sum); high value from Hoyle (2013)
Transition to death	£875.31	£0	£7,000	Lowest value chosen; high value from NICE (2016)
Utilities				
Progression free state	0.75	0.6	0.9	±20%
Progressed state	0.69	0.552	0.828	±20%
Hazard ratios				
SIRT HR applied to base case	1*	0.8	1.2	±20%
Overall survival for BSC	0.26	0.208	0.312	±20%
Progression free survival for BSC	0.51	0.408	0.612	±20%

*patient-level data was used to estimate survival for SIRT cases therefore there was no HR used in the base case; 1 is the reference value which was varied in the one-way sensitivity analysis.

Table 8.9. Mean overall survival from variation in hazard ratios used in sensitivity analysis

	Base case	Low SIRT	High SIRT	Low BSC	High BSC
SIRT OS	9.82	8.54	11.02	no change	no change
SIRT PFS	4.25	3.67	4.80	no change	no change
BSC OS	4.21	no change	no change	3.66	4.72

BSC PFS	2.72	no change	no change	2.35	3.07

BSC, best supportive care; OS, overall survival; PFS, progression-free survival.

8.7.2 Scenario analyses

Eight scenarios were used to examine the effect of different assumptions on the results produced by the model. The following scenarios were explored:

1. Higher monitoring costs for BSC, reflecting clinical advice that patients have outpatient appointments every two weeks.
2. Chemotherapy continuing at a constant cost (£286.64) throughout progression-free state for both SIRT and BSC arms.
3. No chemotherapy for the entire model duration (£0) for both SIRT and BSC arms.
4. Higher BSC costs, reflecting clinical opinion that a greater proportion of BSC patients would have chemotherapy, and that this would result in additional monitoring requirements, and additional adverse events. Costs included were an additional outpatient visit each month, cost of adverse events doubled compared to SIRT at £42.40 and cost of chemotherapy doubled at £573.68.
5. Use of alternative lower initial cost of SIRT treatment of £14,747, as used by Pennington et al. (2015) inflated to 2016
6. Use of longer survival data taken from Bester et al. (2012).
7. Use of longer survival data from Bester et al. 2012 **AND** a lower initial cost of SIRT treatment, as used by Pennington et al. (2015).
8. Use of longer survival data from Bester et al. 2012 **AND** a lower initial cost of SIRT treatment, as used by Pennington et al. (2015) with a 10 year time horizon. The extended time horizon was required to fully explore the impact of longer overall survival estimates on the model outcomes.

8.7.3 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) uses a distribution curve for each input to be varied. Every time that the model is run, a different value for every input is randomly generated based on these distributions. The model is run many times, and allows for investigation of the effect of all inputs varying at the same time, independently. All inputs to the SIRT cost-effectiveness model were varied in the PSA (Table 8.10) over 3,000 simulations. The time horizon was extended to 10 years to fully account for longer survival times during some simulations. In approximately 10% of simulations there was some cross-over of the survival curves, where PFS became greater than OS. This is not a clinically possible scenario and these simulations were excluded from the final results.

8.8 Base case results

The model base case results demonstrated a total treatment cost for SIRT of £31,028 compared to £3,623 for BSC over a patient's lifetime. The incremental cost was £27,406 for SIRT. Extrapolated

survival data showed an improvement in mean OS of 5.6 months in the SIRT arm (SIRT 9.8 months; BSC 4.2 months).
The model estimated an improvement in quality adjusted life years (QALYs) of 0.321 for SIRT patients compared to BSC patients (0.58 vs 0.26). The incremental cost-effectiveness ratio (ICER) was calculated to be £85,350 (Table 8.11).

The state curves, or time spent in each stage of the model are displayed in Figure 8.5. All patients begin in the progression-free state and move into the progressed state. Simultaneously, patients can move into the death state until all patients have died. BSC patients were found to spend less time in the progressed state compared with SIRT patients as overall mortality is higher.

Table 8.10. Probabilistic sensitivity analysis inputs

Survival	**Mean**	**Standard Error**	**Distribution type**
Survival curve for SIRT OS (gamma coefficient)	**1.5059**	0.188	lognormal
Survival curve for SIRT PFS (gamma coefficient)	**1.5899**	0.199	lognormal
Survival curve for BSC OS (HR OS)	**0.26**	0.033	lognormal
Survival curve for BSC PFSS (HR PFS)	**0.51**	0.064	lognormal
Costs			
Initial SIRT cost	**£23,279.05**	29,09.88	gamma
Initial chemotherapy cost (1st cycle only) for BSC and SIRT	**£396.06**	49.51	gamma
Chemotherapy cost for subsequent 3 cycles for BSC and SIRT	**£286.84**	35.86	gamma
Monitoring cost for BSC and SIRT	**£161**	20.13	gamma
Progression cost for BSC and SIRT	**£952.05**	119.01	gamma
Utilities			
Utility, progression free state, for BSC and SIRT	**0.75**	0.1	beta
Utility, progressed state, for BSC and SIRT	**0.69**	0.1	beta

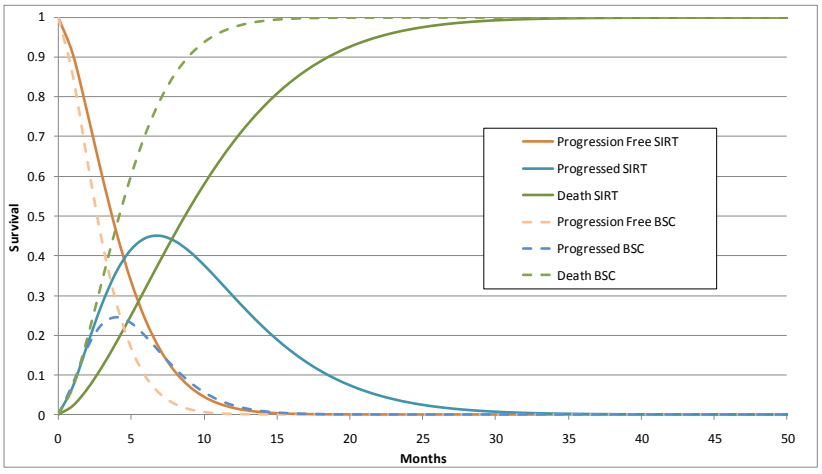


Figure 8.5. State curves of progression free, progressed, and death for base case for SIRT and BSC arms

Table 8.11. Base case results from cost-effectiveness model per patient over lifetime horizon (5 years)

	Total cost			Quality adjusted life years (QALYs)			Incremental cost-effectiveness ratio (ICER)
	SIRT	BSC	Incremental cost	SIRT	BSC	Incremental QALYs	
Base Case	£31,028	£3,623	£27,406	0.583	0.262	0.321	£85,350

8.9 Sensitivity analysis results

8.9.1 Deterministic one-way sensitivity analysis

Inputs were varied in one-way sensitivity analysis as described previously (Table 8.8). The impact on the model is shown in a tornado diagram (Figure 8.6). The SIRT initial treatment cost and the length of survival are the main drivers in the model. This is expected since the SIRT initial treatment cost is high relative to subsequent costs, and the shorter the survival time, the higher proportion of the total cost is derived from the initial treatment. With a shorter survival time, there is a lower accumulation of cost in the BSC arm, since this has no large initial cost. Therefore at shorter survival times the cost difference between the two arms will be greater. The impact of monitoring costs, transition to death, and cost of chemotherapy were very small.

8.9.2 Scenario analyses results

Eight scenarios described in section 8.6.2 were examined (results in Table 8.12). Applying higher monitoring costs to the BSC arm (reflecting comments from clinicians that some patients receiving chemotherapy may have more appointments) had limited impact on the model results (scenario 1; ICER £82,531). Changing the model to apply the cost chemotherapy throughout the progression-free state had little impact on the overall results (scenario 2; ICER: £86,263), due to the short amount of time that most patients spend in this state (Table 8.12). For the same reason, the increase in chemotherapy costs, monitoring costs, and adverse events for BSC patients also has little impact on the result (scenario 4; ICER £79,259). Removing the cost of chemotherapy entirely from the SIRT and BSC arms of the model had a very small impact (scenario 3; ICER £84,916).

As was shown by the deterministic sensitivity analysis, the strongest drivers on the model are the cost of the initial SIRT treatment, and the length of survival. The ICER calculated in the base case is much higher than that reported in a previous model by Pennington et al. (£85,254 current model vs £28,216 in Pennington). The previous model used survival data from Bester et al. (2012), which gave a longer mean survival time than the SIRT CtE data, possibly due to the inclusion of healthier patients. The impact of lowering the initial cost of the SIRT procedure of £14,747 (scenario 5; ICER £58,779) and using survival data from Bester et al. (scenario 6; ICER £53,709) individually had a moderately high impact on the model. When the survival data from Bester et al. was used together with the lower SIRT initial treatment cost (scenario 7) the resulting ICER was reduced considerably to £37,121. In scenario 8, the time horizon was extended from 5 years to 10 years to fully account for

the impact of longer survival. This reduced the ICER to £31,888 which is close to that reported in the Pennington et al. base case. With longer survival time, the impact of the initial treatment cost over the whole lifetime is reduced, while more QALYs are accumulated resulting in a reduced ICER.

8.9.3 Probabilistic sensitivity analysis

Mean values from 3,000 simulations were calculated during the probabilistic sensitivity analysis (Table 8.13). The mean ICER from the PSA was £83,506. The individual results of the 3,000 simulations are shown in the cost-effectiveness plane which also depicts results in relation to willingness to pay (WTP) thresholds of £20K, £30K, £40K, and £50K per QALY gained (Figure 8.7). The cost-effectiveness plane demonstrates that all simulations resulted in ICERs located in the North-East quadrant, i.e. additional QALY benefits for SIRT compared to BSC at an additional cost.

The PSA showed that the probability of SIRT being cost-effective compared to BSC is 0% at a WTP threshold of £20K, 0.7% at a WTP threshold of £30K and 11% at a WTP threshold of £50K (Figure 8.7).

In the depicted cost-effectiveness plane, results where SIRT is considered cost-effective at a certain WTP threshold would be situated underneath the WTP line. Furthermore, the cost-effectiveness acceptability curve (CEAC) shows the probability of either SIRT or BSC being cost-effective at WTP thresholds of £0 to £200,000 per QALY gained (Figure 8.8). While the probability of BSC being cost-effective decreases as the WTP for a QALY increases, SIRT becomes more cost-effective.

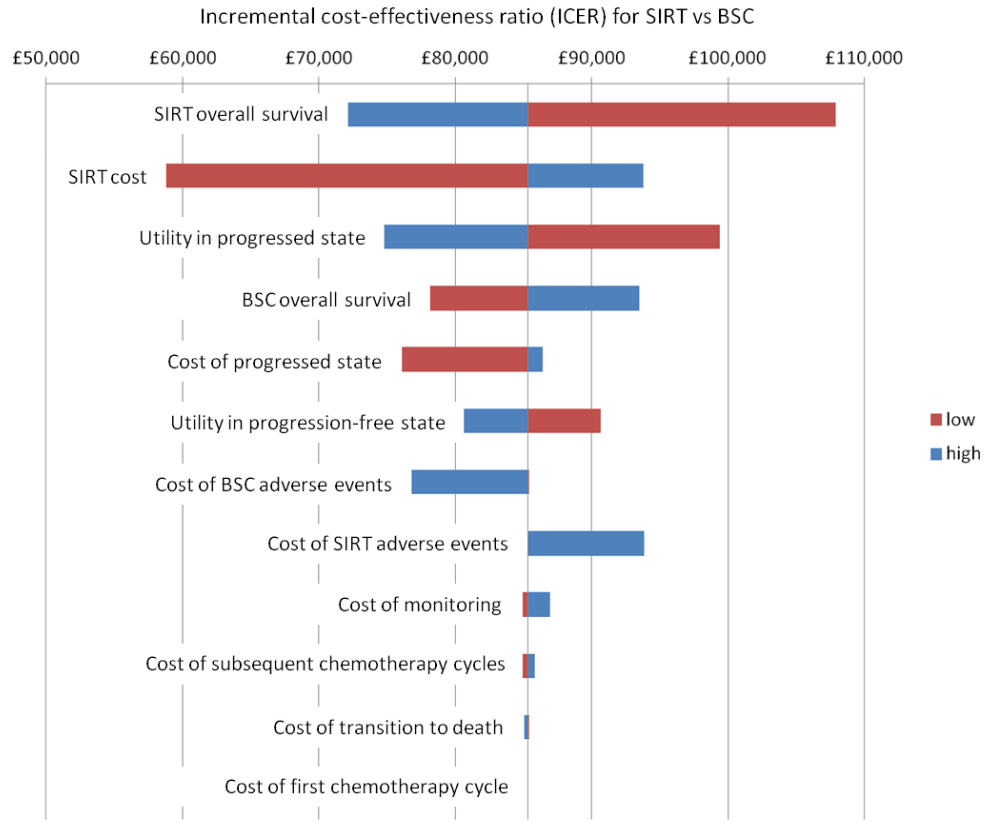


Figure 8.6. Tornado diagram from one way sensitivity analysis.

Table 8.12. Results of scenarios analyses modelled

Scenario	Total cost			Quality adjusted life years (QALYs)			Incremental cost-effectiveness ratio (ICER)
	SIRT	BSC	Increment	SIRT	BSC	Increment	
Base Case	£31,028	£3,623	£27,406	0.583	0.262	0.321	£85,350
1. Higher BSC monitoring costs	£31,028	£4,528	£26,500	0.583	0.262	0.321	£82,531
2. Chemotherapy continues throughout progression free state	£31,447	£3,748	£27,99	0.583	0.262	0.321	£86,263
3. No chemotherapy for the entire model duration (£0)	£29,985	£2719	£27,266	0.583	0.262	0.321	£84,916
4. BSC costs increased for chemotherapy, monitoring and AEs	£31,028	£5,579	£25,450	0.583	0.262	0.321	£79,259
5. SIRT initial treatment of £14,747	£22,496	£3,623	£18,873	0.583	0.262	0.321	£58,779
6. Bester OS data used for SIRT and BSC	£35,838	£6,893	£28,944	1.182	0.643	0.539	£53,709
7. Bester OS plus initial cost of SIRT of £14,747	£27,306	£6,893	£20,412	1.182	0.643	0.539	£37,877
8. Bester OS plus initial cost of SIRT of £14,747 (10 year time horizon)	£29,117.	£7,336	£21,780	1.373	0.689	0.683	£31,888

AEs, adverse events; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; OS, overall survival; QALYs, quality adjusted life years.

Table 8.13. Mean values from probabilistic sensitivity analysis (3,000 simulations)

	Total cost			Quality adjusted life years (QALYs)			Incremental cost-effectiveness ratio (ICER)
	SIRT	BSC	Increment	SIRT	BSC	Increment	
Mean values from PSA, 3,000 simulations	£32,457	£3,905	£28552	0.656	0.27	0.390	£83,506

BSC, best supportive care; ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALYs, quality adjusted life years.

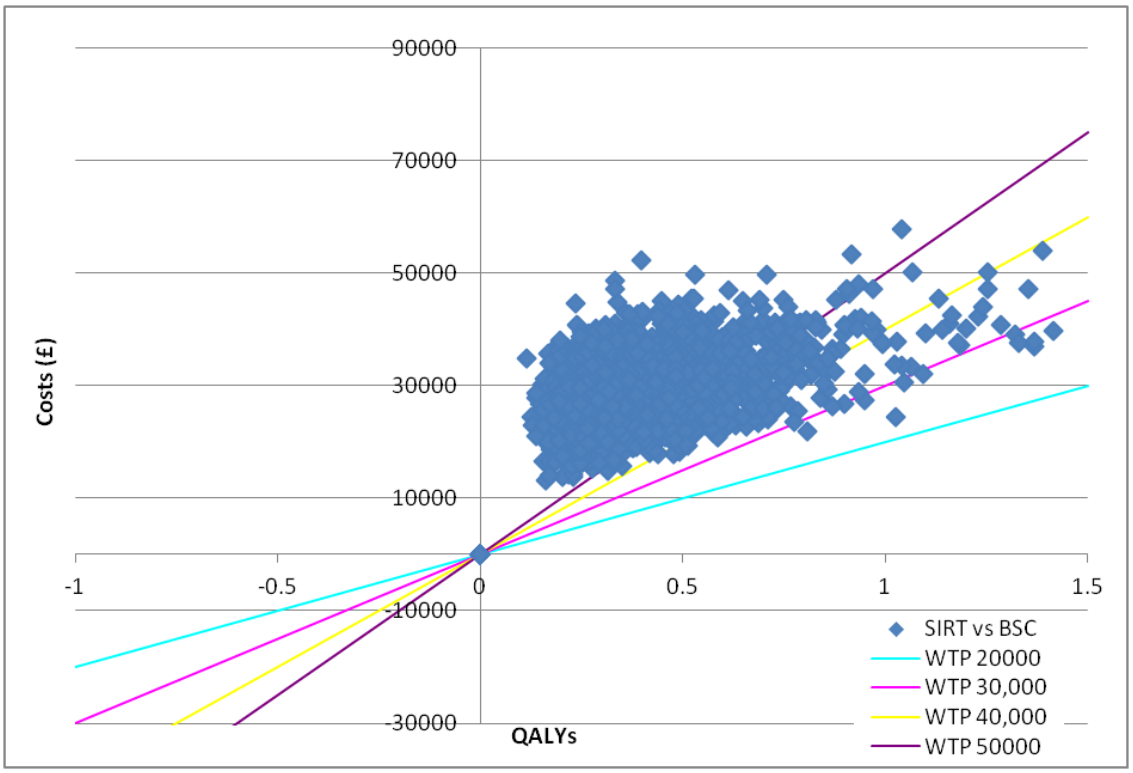


Figure 8.7. Cost-effectiveness plane, showing incremental cost-effectiveness of SIRT compared to BSC with a range of willingness-to-pay thresholds (WTP) displayed. Points displayed at 0 are excluded scenarios

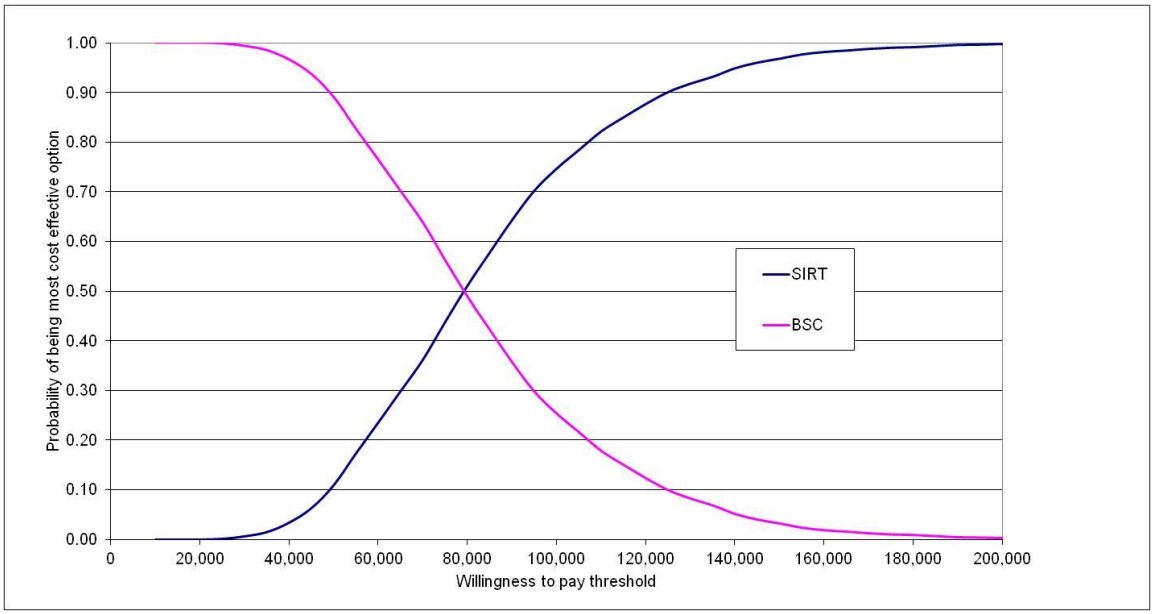


Figure 8.8. Cost-effectiveness acceptability curve for SIRT and BSC

8.10 Discussion

This independent *de novo* economic model was created for the SIRT CtE project, and is the second cost-effectiveness model on this decision problem. In this analysis, SIRT was likely to be clinically effective (increased QALYs) for an additional cost. ICER values were high when compared to BSC for patients who have unresectable CRC liver metastases which has progressed following at least two lines of standard chemotherapy, and is unlikely to fall below a willingness to pay threshold of £50K. Key drivers of the model were the cost of the SIRT procedure, and the length of overall survival; the application of SIRT in patients with longer life expectancy may decrease the cost per QALY gained as initial SIRT costs are spread over a longer period of time.

If a subgroup of patients was shown to have a longer survival time (such as those with limited tumour burder), the cost-effectiveness is likely to be improved for this group. This is shown in the sensitivity and scenario analysis.

In the cost-effectiveness plane, results occupy the North-East quadrant indicating QALY benefit at an additional cost. This result is dependent on the assumption of improved OS reported in the two retrospective comparative cohort studies. These studies are prone to bias which may make their OS and PFS findings unreliable; this in turn introduces uncertainty into the cost-effectiveness model. There is no high quality RCT evidence demonstrating a survival benefit; one small RCT (Hendlisz et al. 2010) showed a significant improvement in PFS.

NICE recently recommended trifluridine-tipiracil in patients with mCRC which has progressed following standard chemotherapy, and reported an ICER of £49,392 per QALY (NICE 2016). This recommendation is based on a discount agreed in the patient access scheme. The introduction of this new drug to the patient pathway adds uncertainty to the model outputs. If trifluridine-tipiracil becomes standard practice in the NHS, it would be a relevant comparator to SIRT. This scenario was not modelled because of the absence of any data comparing SIRT to trifluridine-tipiracil and uncertainty around the comparability of populations.

8.10.1 Strengths of the analysis

The strengths of this economic evaluation include that key inputs of efficacy, chemotherapy costs, and AE costs for the SIRT arm were based on patient-level data from a large UK cohort; this resolves issues of generalisability/relevance when efficacy data is taken from RCTs with restrictive eligibility criteria. Efficacy and cost inputs for BSC and the cost of SIRT were based on assumptions and summary data. Most other inputs were based on evidence identified from systematic reviews. The model was created by an independent research group with comprehensive quality assurance from external researchers of the model structure and inputs. All assumptions were described, and where possible checked with clinical advisors to ensure that they reflected clinical practice. Extensive sensitivity analyses were carried out to test the robustness of model outcomes, varying model inputs across a plausible range as well as structural elements. The model was compared to a published model and differences in outcomes were identified and justified. Scenario analysis using key inputs from the published model replicated the base case results fairly closely which further validates the *de novo* model.

8.10.2 Limitations of the analysis

The key limitation of the model was the unavailability of comparative survival data in the SIRT CtE registry or from high quality RCTs (the available RCT was confounded by cross-over). Coupled with the lack of patient-level data from Bester et al. (2012) and Seidensticker et al. (2012) meant that hazard ratios for OS and PFS from Seidensticker et al. (2012) and Hendlisz et al. (2010) were applied to SIRT CtE data to create BSC survival estimates. Hazard ratios based on matched-pair cohorts can be prone to bias and risk inflating the survival benefit.

Data on resource use were inadequately collected during the SIRT CtE registry study. Data on chemotherapy, adverse events data, monitoring, and treatment during the progressed state were not captured accurately enough to inform the model and had to be supplemented using published evidence, clinical advice, and assumptions.

Utilities were captured using the EQ-5D-5L tool in the SIRT CtE registry cohort. However, the general, non-disease specific nature of this outcome measure, poor compliance, and high levels of missing data made this an unreliable source. As a result, utilities values were taken from published sources and assumed to be equal for both treatment arms which might not reflect any potential improvement or disutility in HRQoL as a result of SIRT. However, utility inputs only moderately impacted on the ICER values in the one-way sensitivity analysis.

There is no single, well defined, pathway for patients receiving BSC. Advice from clinical advisors was that treatment type and duration varied depending on patients' preference and characteristics as well as clinician preference. As a result the patient pathway for BSC was challenging to model and may lack generalisability to clinical practice.

There is a high degree of uncertainty in the overall cost of chemotherapy in both SIRT and BSC arms, but impact on the results is minimal due to the short progression free survival time for the population modelled.

Probabilistic sensitivity analysis does not change the assumption that costs of chemotherapy, monitoring, adverse events and care during the progressed state are equal, although this is investigated in the scenario analysis. Probabilistic sensitivity analysis occasionally resulted in simulations where the PFS artificially exceeded the OS. These simulations were excluded from the final results. In addition, a five year time horizon was chosen as being greater than life time for the base case model, however, sensitivity analysis scenarios using Bester survival data require a longer time horizon than 5 years. An extended time horizon of 10 years was used in a scenario analysis, and in the probabilistic sensitivity analysis.

8.10.3 Key differences between the *de novo* model and published study

The higher base case ICER in the current *de novo* model (£85K) compared to Pennington et al. (£28K) was mainly due to the following.

- A shorter OS estimate was used in the *de novo* model based on SIRT CtE registry data (extrapolated mean OS 9.8 months) whereas Pennington et al. used OS data from Bester et al. (mean OS 25.1 months) which appeared to be a less severely unwell population with

higher performance status and more chemotherapy-naive patients compared to the SIRT CtE registry population. This meant the cost of SIRT is spread over a shorter period in the *de novo* model, thus increasing the cost per QALY gained.

- A higher procedure cost of £21,870 was used in the *de novo* model compared to £14,248 used in the Pennington et al. model. The higher cost was derived from the NHS England tariff used in the CtE study, whereas Pennington et al. used NHS reference costs combined with bottom-up costings provided by The Christie NHS hospital.

Scenario analyses explored the impact of using longer survival time and lower cost of SIRT in the *de novo* model (to reflect those used in Pennington et al.). The ICER was reduced to approximately £37,877 in this scenario, and further reduced to £31,888 when the time horizon was extended to 10 years (a more appropriate value for a patient group with longer expected survival time). The remaining difference was due to slightly different assumptions in the calculation of chemotherapy and monitoring costs.

8.11 Generalisability of the model to an intrahepatic cholangiocarcinoma population

In light of the absence of any published comparative data in the ICC population and the much smaller cohort of ICC patients in the SIRT CtE registry (n=61), it was decided not to conduct *de novo* modelling in this group. The median OS results from the SIRT CtE registry are slightly higher for the ICC group but with wider confidence intervals, 8.7 months (95% CIs 5.3-12.1) and based on only 33 events. All other inputs being equal to the CRC population (including hazard ratios used to demonstrate a survival benefit), this longer survival would be expected to marginally reduce the ICER for the ICC population, but would depend on the impact of extrapolating a survival curve to the Kaplan-Meier data.

The SIRT CtE data indicates that more ICC patients require 2 SIRT session (8% ICC vs 3% CRC) which indicated that the cost of SIRT may be higher in the ICC group. The time spent in hospital was similar to the CRC cohort, as were the proportions of complications and adverse events. Fewer patients in the ICC group required chemotherapy concomitantly with SIRT or after SIRT but within the structure of the current model this is unlikely to significantly affect the results. These findings should be interpreted cautiously due to the small sample size.

There is insufficient information available to adequately address whether the costs associated with BSC in the ICC population mirror those in the CRC group.

There is no data available to indicate whether SIRT provides a survival benefit compared with BSC in the ICC group. As a result, the assumption of clinical effectiveness required to justify cost modelling for an intervention likely to be more expensive than BSC cannot be reliably made.

9 Provider feedback and implementation considerations

Clinical teams at the ten CtE provider centres were given the opportunity to feed back about their experiences of implementing SIRT in the NHS.

9.1 Questions

The following questions were provided as prompts:

- Selection criteria; were they clear and appropriate or do they need further clarification?
- Is the protocol for work up of patients appropriate or does it need further clarification?
- Were appropriate patients referred to the specialist centres or is more work needed to improve the quality and nature of referrals for SIRT?
- Do the hospitals have data on referrals received per month in order to inform NHSE planning if SIRT is accepted for regular commissioning?

9.2 Feedback

The following feedback was received and collated.

A representative from Nottingham University Hospitals NHS Trust provided the following feedback:

- The selection criteria were considered to be clear and appropriate, and consistent with the inclusion/exclusion criteria expected from randomised clinical trials.
- A standardised work-up framework was considered to be a good idea to ensure consistency across sites and to specify the minimal work up requirements needed.
- Their experience was that referrals from external centres needed more work after commencement of the commissioning programme to both foster investment in the scheme and ensure the appropriateness of referrals. External site training was felt to be important to facilitate appropriate referrals, both of appropriate patients and in the provision of appropriate levels of information to be able to discern if the patient is eligible.
- The respondent confirmed that referrals for the procedure and the reasons the patients were not eligible or were unable to proceed are recorded locally.

A respondent from Leeds Teaching Hospitals NHS Trust provided the following information:

- Many more patients were referred to the site than were treated. A record has been kept locally of reasons for non-treatment and outcomes for those who were treated or who had surgery compared to others.

A respondent from Royal Free London NHS Foundation Trust provided the following information:

- A total of 63 patients were treated during the CtE project from a total of 133 referrals. Seventy patients were ineligible due to clinical progression or not fitting the referral guidelines (30% were patients who had not received both lines of chemotherapy; 10% progressed within the timeframe of assessment to therapy such that they became ineligible; 60% had disease which was clinically unsuitable for therapy (usually the volume was too large or there was ascites / bone mets) but which warranted discussion to exclude SIRT as a useful modality).

References

Al-Adra, D.P. (2015) Treatment of unresectable intrahepatic cholangiocarcinoma with yttrium-90 radioembolization: a systematic review and pooled analysis. *European Journal of Surgical Oncology*, 41, (1) 120-127.

Beg, M.S., Adhami, F., Xuan, L., Hodges, J., Meyer, J., Halm, E., & Pruitt, S. (2014) Liver-directed therapies for colorectal cancer liver metastasis (CLRM): A Surveillance, Epidemiology, and End Results (SEER)-Medicare analysis. *Journal of Clinical Oncology*, Conference.

Benson, A.B. (2013) Radioembolisation for liver metastases: results from a prospective 151 patient multi-institutional phase II study. *European Journal of Cancer*, 49, (15) 3122-3130.

Bester, L., Meteling, B., Pocock, N., Pavlakis, N., & Chua, T. (2012) Radioembolization versus standard care of hepatic metastases: comparative retrospective cohort study of survival outcomes and adverse events in salvage patients. *Journal of Vascular & Interventional Radiology*, 23, (1) 96-105.

Bester, L., Wasan, H., Sangro, B., Kennedy, A., Pennington, B., & Sennfalt, K. (2013a) Selective internal radiotherapy (SIRT) using resin yttrium-90 microspheres for chemotherapy-refractory metastatic colorectal cancer: A UK cost-effectiveness analysis. *Value in Health*, Conference, A413.

Bester, L., Meteling, B., Pocock, N., Saxena, A., & Chua, T. (2013b) Radioembolisation with Yttrium-90 microspheres: an effective treatment modality for unresectable liver metastases. *Journal of Medical Imaging & Radiation Oncology*, 57, (1) 72-80.

Beuzit, L., Edeline, J., Brun, V., Ronot, M., Guillygomarc'h, A., Boudjema, K., Gandon, Y., Garin, E., & Rolland, Y. (2016) Comparison of Choi criteria and Response Evaluation Criteria in Solid Tumors (RECIST) for intrahepatic cholangiocarcinoma treated with glass-microspheres Yttrium-90 selective internal radiation therapy (SIRT). *European Journal of Radiology*, 85, (8) 1445-1452.

Boehm, L.M. (2015) Comparative effectiveness of hepatic artery based therapies for unresectable intrahepatic cholangiocarcinoma. *Journal of Surgical Oncology*, 111, (2) 213-220.

Booth, C.M. & Eisenhauer, E.A. (2012) Progression-free survival: meaningful or simply measurable? *Journal of Clinical Oncology*, 30, (10) 1030-1033.

Bridgewater, J., Galle, P.R., Khan, S.A., Llovet, J.M., Park, J.W., Patel, T., Pawlik, T.M., & Gores, G.J. (2014) Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma. *Journal of Hepatology*, 60, (6) 1268-1289.

Caballero-Baños, M., Benitez-Ribas, D., Tabera, J., Varea, S., Vilana, R., Bianchi, L., Ayuso, J.R., Pagés, M., Carrera, G., Cuatrecasas, M. and Martin-Richard, M. (2016) Phase II randomised trial of autologous tumour lysate dendritic cell plus best supportive care compared with best supportive care in pre-treated advanced colorectal cancer patients. *European Journal of Cancer*, 64, 167-174.

Camacho, J.C. (2014) Modified response evaluation criteria in solid tumors and European Association for The Study of the Liver criteria using delayed-phase imaging at an early time point predict survival in patients with unresectable intrahepatic cholangiocarcinoma following yttrium-90 radioembolization. *Journal of Vascular & Interventional Radiology*, 25, (2) 256-265.

Cancer Research UK. (2015) *Survival statistics for bile duct cancer*. Available from: http://www.cancerresearchuk.org/about-cancer/type/bile-duct-cancer/bile-duct-cancer-treatment/statistics-outlook-bile-duct-cancer [Accessed May 2017].

Cancer Research UK. (2015) *Bowel cancer statistics*. Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bowel-cancer [Accessed May 2017].

Chan, K. & Bhandari, M. (2011) Three-minute critical appraisal of a case series article. *Indian Journal of Orthopaedics*, 45, (2) 103.

Chua, T.C. (2011) Radioembolization and systemic chemotherapy improves response and survival for unresectable colorectal liver metastases. *Journal of Cancer Research & Clinical Oncology*, 137, (5) 865-873.

Cianni, R., Urigo, C., Notarianni, E., Saltarelli, A., Salvatori, R., Pasqualini, V., Dornbusch, T., & Cortesi, E. (2009) Selective Internal Radiation Therapy with SIR-Spheres for the Treatment of Unresectable Colorectal Hepatic Metastases. *CardioVascular and Interventional Radiology*, 32, (6) 1179-1186.

Cosimelli, M., Golfieri, R., Cagol, P.P., Carpanese, L., Sciuto, R., Maini, C.L., Mancini, R., Sperduti, I., Pizzi, G., Diodoro, M.G., Perrone, M., Giampalma, E., Angelelli, B., Fiore, F., Lastoria, S., Bacchetti, S., Gasperini, D., Geatti, O., & Izzo, F. (2010) Multi-centre phase II clinical trial of yttrium-90 resin microspheres alone in unresectable, chemotherapy refractory colorectal liver metastases. *British Journal of Cancer*, 103, (3) 324-331.

Cosimelli, M., Golfieri, R., Pennington, B., & Sennfalt, K. (2013) Selective internal radiotherapy (SIRT) using resin yttrium-90 microspheres for chemotherapy-refractory metastatic colorectal cancer: An Italian cost-effectiveness analysis. *Value in Health*, Conference, A409.

Damm, R., Seidensticker, R., Ulrich, G., Breier, L., & Steffen, I. (2016) Y90 Radioembolization in chemo-refractory metastastic, liver dominant colorectal cancer patients: outcome assessment applying a predictive scoring system. *BMC Cancer*, 16, 509.

Department of Health. (2016) *NHS reference costs 2015 to 2016.* Available from: https://www.gov.uk/government/publications/nhs-reference-costs-2015-to-2016 [Accessed May 2017].

Dutton, S.J., Kenealy, N., Love, S.B., Wasan, H.S., & Sharma, R.A. (2014) FOXFIRE protocol: An open-label, randomised, phase III trial of 5-fluorouracil, oxaliplatin and folinic acid (OxMdG) with or without interventional Selective Internal Radiation Therapy (SIRT) as first-line treatment for patients with unresectable liver-only or liver-dominant metastatic colorectal cancer. *BMC Cancer*, 14, (1) 497.

Eisenhauer, E.A., Therasse, P., Bogaerts, J., Schwartz, L.H., Sargent, D., Ford, R., Dancey, J., Arbuck, S., Gwyther, S., & Mooney, M. (2009) New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *European Journal of Cancer*, 45, (2) 228-247.

Fendler, W.P., Philippe Tiega, D.B., Ilhan, H., & Paprottka, P. (2013) Validation of several SUV-based parameters derived from 18F-FDG PET for prediction of survival after SIRT of hepatic metastases from colorectal cancer. *Journal of Nuclear Medicine*, 54, (8) 1202-1208.

Filippi, L., Pelle, G., Cianni, R., Scopinaro, F., & Bagni, O. (2015) Change in total lesion glycolysis and clinical outcome after (90)Y radioembolization in intrahepatic cholangiocarcinoma. *Nuclear Medicine & Biology*, 42, (1) 59-64.

Fleming, T.R., Rothmann, M.D., & Lu, H.L. (2009) Issues in using progression-free survival when evaluating oncology products. *Journal of Clinical Oncology*, 27, (17) 2874-2880.

Giammarile, F., Bodei, L., Chiesa, C., Flux, G., Forrer, F., Kraeber-Bodere, F., Brans, B., Lambert, B., Konijnenberg, M., & Borson-Chazot, F. (2011) EANM procedure guideline for the treatment of liver cancer and liver metastases with intra-arterial radioactive compounds. *European journal of nuclear medicine and molecular imaging*, 38, (7) 1393.

Gibbs, P., Gebski, V., Van Buskirk, M., Thurston, K., & Cade, D. (2014) Selective Internal Radiation Therapy (SIRT) with yttrium-90 resin microspheres plus standard systemic chemotherapy regimen of FOLFOX versus FOLFOX alone as first-line treatment of non-resectable liver metastases from colorectal cancer: the SIRFLOX study. *BMC Cancer*, 14, 897.

Golfieri, R., Mosconi, C., Giampalma, E., Cappelli, A., Galaverni, M.C., Pettinato, C., Renzulli, M., Monari, F., Mazzarotto, R., Pinto, C., & Angelelli, B. (2015) Selective transarterial radioembolisation of unresectable liver-dominant colorectal cancer refractory to chemotherapy. *Radiologia Medica*, 120, (8) 767-776.

Grothey, A., van Cutsem, E., Sobrero, A., Siena, S., Falcone, A., Ychou, M., Humblet, Y., Bouche, O., Mineur, L., Barone, C., Adenis, A., Tabernero, J., Yoshino, T., Lenz, H.J., Goldberg, R.M., Sargent, D.J., Cihon, F., Cupit, L., Wagner, A., & Laurent, D. (2013) Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): An international, multicentre, randomised, placebo-controlled, phase 3 trial. *The Lancet*, 381, (9863) 303-312.

Haug, A.R. (2011) 18F-FDG PET independently predicts survival in patients with cholangiocellular carcinoma treated with 90Y microspheres. *European Journal of Nuclear Medicine & Molecular Imaging*, 38, (6) 1037-1045.

Hendlisz, A., Eynde, M.V.D., Peeters, M., Maleux, G., Lambert, B., Vannoote, J., Keukeleire, K.D., Verslype, C., Defreyne, L., Cutsem, E.V. and Delatte, P. (2010) Phase III trial comparing protracted intravenous fluorouracil infusion alone or with yttrium-90 resin microspheres radioembolization for liver-limited metastatic colorectal cancer refractory to standard chemotherapy. *Journal of clinical oncology*, 28, (23) 3687-3694.

Herdman, M., Gudex, C., Lloyd, A., Janssen, M.F., Kind, P., Parkin, D., Bonsel, G., & Badia, X. (2011) Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Quality of life research*, 20, (10) 1727-1736.

Hickey, R., Lewandowski, R.J., Prudhomme, T., Ehrenwald, E., Baigorri, B., Critchfield, J., Kallini, J., Gabr, A., Gorodetski, B., Geschwind, J.F. and Abbott, A. (2016) 90Y Radioembolization of Colorectal Hepatic Metastases Using Glass Microspheres: Safety and Survival Outcomes from a 531-Patient Multicenter Study. *Journal of Nuclear Medicine*, 57(5), 665-671.

Hickish, T., Andre, T., Wyrwicz, L., Saunders, M., Sarosiek, T., Kocsis, J., Nemecek, R., Rogowski, W., Lesniewski-Kmak, K., & Petruzelka, L. (2017) MABp1 as a novel antibody treatment for advanced colorectal cancer: a randomised, double-blind, placebo-controlled, phase 3 study. *The Lancet Oncology*, 18, (2) 192-201.

Hoffmann, R.T. (2012) Transarterial hepatic yttrium-90 radioembolization in patients with unresectable intrahepatic cholangiocarcinoma: factors associated with prolonged survival. *Cardiovascular & Interventional Radiology*, 35, (1) 105-116.

Hoyle, M., Crathorne, L., Peters, J., Jones-Hughes, T., Cooper, C., Napier, M., Tappenden, P. and Hyde, C. (2013a) The clinical effectiveness and cost-effectiveness of cetuximab (mono-or combination chemotherapy), bevacizumab (combination with non-oxaliplatin chemotherapy) and panitumumab (monotherapy) for the treatment of metastatic colorectal cancer after first-line chemotherapy (review of technology appraisal No. 150 and part review of technology appraisal No. 118): a systematic review and economic model. Available at: https://www.nice.org.uk/guidance/ta242/resources/colorectal-cancer-metastatic-2nd-line-cetuximab-bevacizumab-and-panitumumab-review-assessment-report3

Hoyle, M., Peters, J., Crathorne, L., Jones-Hughes, T., Cooper, C., Napier, M., & Hyde, C. (2013b) Cost-effectiveness of cetuximab, cetuximab plus irinotecan, and panitumumab for third and further lines of treatment for KRAS wild-type patients with metastatic colorectal cancer. *Value in Health*, 16, (2) 288-296.

HSCIC (2014) *Chemotherapy Regimnes Clinical Coding Standards and Guidance OPCS-4*. Available at: http://www.nwisinformationstandards.wales.nhs.uk/sitesplus/documents/299/ChemoRegClinCodStanGuidOPCS-4v1.0.pdf [Accessed May 2017].

Hyder, O. (2013) Intra-arterial therapy for advanced intrahepatic cholangiocarcinoma: a multi-institutional analysis. *Annals of Surgical Oncology*, 20, (12) 3779-3786.

Ibrahim, S.M., Mulcahy, M.F., Lewandowski, R.J., Sato, K.T., Ryu, R.K., Masterson, E.J., Newman, S.B., Benson, A., III, Omary, R.A., & Salem, R. (2008) Treatment of unresectable cholangiocarcinoma using yttrium-90 microspheres: results from a pilot study. *Cancer*, 113, (8) 2119-2128.

Jakobs, T.F. (2017) Robust evidence for long-term survival with 90Y radioembolization in chemorefractory liver-predominant metastatic colorectal cancer. *European Radiology*, 27, (1) 113-119.

Jakobs, T.F., Hoffmann, R.T., Dehm, K., Trumm, C., Stemmler, H.J., Tatsch, K., La Fougere, C., Murthy, R., Helmberger, T.K., & Reiser, M.F. (2008) Hepatic yttrium-90 radioembolization of chemotherapy-refractory colorectal cancer liver metastases. *Journal of Vascular and Interventional Radiology*, 19, (8) 1187-1195.

Janowski, E., Timofeeva, O., Chasovskikh, S., Goldberg, M., Kim, A., Banovac, F., Pang, D., Dritschilo, A., & Unger, K. (2017) Yttrium-90 radioembolization for colorectal cancer liver metastases in KRAS wild-type and mutant patients: Clinical and ccfDNA studies. *Oncology Reports*, 37, (1) 57-65.

Jia, R., Wang, Y., Mao, X.-Y., Li, S.-S., Xu, N., Xiong, J.-P., Shen, L., Bai, L., Liu, W., Liu, L.-J., Ge, F.-J., Chen, Y.-L., Lin, L., & Xu, J.-M. (2015) Phase II Study of Recombinant Antitumor and Antivirus Protein Injection Compared With Placebo in Metastatic Colorectal Cancer After Failure of Standard Treatment. *Oncologist*, 20, (6) 619-620.

Jia, Z. (2016) Resin-based Yttrium-90 microspheres for unresectable and failed first-line chemotherapy intrahepatic cholangiocarcinoma: preliminary results. *Journal of Cancer Research and Clinical Oncology,* 1-9.

Jonker, D.J., O'Callaghan, C.J., Karapetis, C.S., Zalcberg, J.R., Tu, D., Au, H.J., Berry, S.R., Krahn, M., Price, T., Simes, R.J., Tebbutt, N.C., van, H.G., Wierzbicki, R., Langer, C., & Moore, M.J. (2007) Cetuximab for the treatment of colorectal cancer. *New England Journal of Medicine*, 357, (20) 2040-2048.

Kalva, S.P., Rana, R.S., Liu, R., Rachamreddy, N., Dave, B., Sharma, A., Ganguli, S., Rabito, C., Kwak, E., & Blaszkowsky, L.S. (2014). Yttrium-90 Radioembolization as Salvage Therapy for Liver Metastases From Colorectal Cancer. *American journal of clinical oncology.*

Kaplan, E.L. & Meier, P. (1958) Nonparametric Estimation from Incomplete Observations., 53, (282) 457-481.

Karapetis, C.S., Khambata-Ford, S., Jonker, D.J., O'callaghan, C.J., Tu, D., Tebbutt, N.C., Simes, R.J., Chalchal, H., Shapiro, J.D., & Robitaille, S. (2008) K-ras mutations and benefit from cetuximab in advanced colorectal cancer. *New England Journal of Medicine*, 359, (17) 1757-1765.

Karpf, M.A. (2015) Phase 3 clinical Trial Evaluating 90y glass microspheres in patients with metastatic colorectal carcinoma of the liver who have failed first-line chemotherapy. *Journal of clinical oncology*, 33.

Kennedy, A.S., Coldwell, D., Nutting, C., Murthy, R., Wertman, D.E., Loehr, S.P., Overton, C., Meranze, S., Niedzwiecki, J. and Sailer, S., (2006) Resin 90 Y-microsphere brachytherapy for unresectable colorectal liver metastases: modern USA experience*. International Journal of Radiation Oncology* Biology* Physics,* 65(2), pp.412-425.

Kennedy, A.S., Ball, D., & Cohen, S. (2015) Multicenter evaluation of the safety and efficacy of radioembolization in patients with unresectable colorectal liver metastases selected as candidates for (90)Y resin microspheres. *Journal of Gastrointestinal Oncology*, 6, (2) 134-142.

Kloeckner, R., Ruckes, C., Kronfeld, K., Worns, M.A., Weinmann, A., Galle, P.R., Lang, H., Otto, G., Eichhorn, W., Schreckenberger, M., Dueber, C., & Pitton, M.B. (2014) Selective internal radiotherapy (SIRT) versus transarterial chemoembolization (TACE) for the treatment of intrahepatic cholangiocellular carcinoma (CCC): study protocol for a randomized controlled trial. *Trials*, 15, 311.

Korn, R. L. & Crowley, J. J. (2013) Overview: progression-free survival as an endpoint in clinical trials with solid tumors. 2607-2612.

Lahti, S.J. (2015) KRAS Status as an Independent Prognostic Factor for Survival after Yttrium-90 Radioembolization Therapy for Unresectable Colorectal Cancer Liver Metastases. *Journal of Vascular & Interventional Radiology*, 26, (8) 1102-1111.

Lam, M.G.E.H., Louie, J.D., Abdelmaksoud, M.H.K., Fisher, G.A., Cho-Phan, C.D., & Sze, D.Y. (2014) Limitations of body surface area-based activity calculation for radioembolization of hepatic metastases in colorectal cancer. *Journal of Vascular and Interventional Radiology*, 25, (7) 1085-1093

Lamarca, A., Hubner, R.A., David, R.W., & Valle, J.W. (2014a) Second-line chemotherapy in advanced biliary cancer: a systematic review. *Ann.Oncol.*, 25, (12) 2328-2338.

Lamarca, A., Palmer, D., Wasan, H., Ryder, W.D., Davies, L., Flight, H., Rogan, J., Hubner, R., Bridgewater, J.A., & Valle, J.W. (2014b) 748TiPABC-06: a randomised phase iii, multi-centre, open-label study of active symptom control (ASC) alone or ASC with oxaliplatin/5-FU chemotherapy for

patients with locally advanced/metastatic biliary tract cancers (ABC) previously treated with cisplatin/gemcitabine chemotherapy. *Annals of Oncology*, 25, (suppl 4) iv252.

Lee, S., Oh, S.Y., Kim, B.G., Kwon, H.C., Kim, S.H., Rho, M.H., Kim, Y.H., Rho, M.S., Jeong, J.s., & Kim, H.J. (2009) Second-line treatment with a combination of continuous 5-fluorouracil, doxorubicin, and mitomycin-C (conti-FAM) in gemcitabine-pretreated pancreatic and biliary tract cancer. *American Journal of Clinical Oncology*, 32, (4) 348-352.

Lewandowski, R.J. (2014). Twelve-year experience of radioembolization for colorectal hepatic metastases in 214 patients: survival by era and chemotherapy. *European Journal of Nuclear Medicine & Molecular Imaging*, 41, (10) 1861-1869.

Li, J., Qin, S., Xu, R., & Yau, T. (2015). Regorafenib plus best supportive care versus placebo plus best supportive care in Asian patients with previously treated metastatic colorectal cancer (CONCUR): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncology*, 16, (6) 619-629.

Loveman, E., Jones, J., & Clegg, A. (2014). The clinical effectiveness and cost-effectiveness of ablative therapies in the management of liver metastases: systematic review and economic evaluation. *Health Technology Assessment (Winchester, England)*, 18, (7) vii-viii.

Maleux, G., Deroose, C., Laenen, A., Verslype, C., Heye, S., Haustermans, K., De, H.G., Sagaert, X., Topal, B., Aerts, R., Prenen, H., Vanbeckevoort, D., Vandecaveye, V., & Van, C.E. (2015) Yttrium-90 radioembolization for the treatment of chemorefractory colorectal liver metastases: Technical results, clinical outcome and factors potentially influencing survival. *Acta Oncol.* 1-10

Mayer, R.J., Van Cutsem, E., Falcone, A., Yoshino, T., Garcia-Carbonero, R., Mizunuma, N., Yamazaki, K., Shimada, Y., Tabernero, J., Komatsu, Y., Sobrero, A., Boucher, E., Peeters, M., Tran, B., Lenz, H.J., Zaniboni, A., Hochster, H., Cleary, J.M., Prenen, H., Benedetti, F., Mizuguchi, H., Makris, L., Ito, M., & Ohtsu, A. (2015) Randomized Trial of TAS-102 for Refractory Metastatic Colorectal Cancer. *New England Journal of Medicine*, 372, (20) 1909-1919.

Mickisch, G., Gore, M., Escudier, B., Procopio, G., Walzer, S., & Nuijten, M. (2010) Costs of managing adverse events in the treatment of first-line metastatic renal cell carcinoma: bevacizumab in combination with interferon-α2a compared with sunitinib. *British journal of cancer*, 102, (1) 80-86.

Mosconi, C., Gramenzi, A., Ascanio, S., Cappelli, A., Renzulli, M., Pettinato, C., Brandi, G., Monari, F., Cucchetti, A., Trevisani, F., & Golfieri, R. (2016) Yttrium-90 radioembolization for unresectable/recurrent intrahepatic cholangiocarcinoma: a survival, efficacy and safety study. *British journal of cancer*, 115, (3) 297-302.

Mouli, S., Memon, K., Baker, T., Benson III, A.B., Mulcahy, M.F., Gupta, R., Ryu, R.K., Salem, R., & Lewandowski, R.J. (2013) Yttrium-90 radioembolization for intrahepatic cholangiocarcinoma: Safety, response, and survival analysis. *Journal of Vascular and Interventional Radiology*, 24, (8) 1227-1234.

Mulcahy, M.F., Lewandowski, R.J., Ibrahim, S.M., Sato, K.T., Ryu, R.K., Atassi, B., Newman, S., Talamonti, M., Omary, R.A., Benson, A., & Salem, R. (2009) Radioembolization of colorectal hepatic metastases using yttrium-90 microspheres. *Cancer*, 115, (9) 1849-1858.

NHS Choices (2016a) *Bile duct cancer (cholangiocarcinoma).* Available at: http://www.nhs.uk/Conditions/Cancer-of-the-bile-duct/Pages/Introduction.aspx [Accessed May 2017].

NHS Choices. (2016b) *Bowel cancer*. Available at: http://www.nhs.uk/conditions/Cancer-of-the-colon-rectum-or-bowel/Pages/Introduction.aspx [Accessed May 2017].

NHS England (2013) *Interim Clinical Commissioning Policy Statement: Selective Internal Radiotherapy (SIRT).* Available at: https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2013/07/b01-psa-sirt.pdf.

NICE (2005) *Interventional procedures guidance [IPG134] Photodynamic therapy for bile duct cancer*. Available at: https://www.nice.org.uk/guidance/IPG134.

NICE (2012) *Technology appraisal guidance [TA242] Cetuximab, bevacizumab and panitumumab for the treatment of metastatic colorectal cancer after first-line chemotherapy: Cetuximab (monotherapy or combination chemotherapy), bevacizumab (in combination with non-oxaliplatin chemotherapy) and panitumumab (monotherapy) for the treatment of metastatic colorectal cancer after first-line chemotherapy*. Available at: https://www.nice.org.uk/guidance/ta242

NICE (2013a) *Interventional procedures guidance [IPG 401] Selective internal radiation therapy for non-resectable colorectal metastases in the liver*. https://www.nice.org.uk/guidance/IPG401.

NICE (2013b) *Interventional procedures guidance [IPG459] Selective internal radiation therapy for primary intrahepatic cholangiocarcinoma*. Available at: https://www.nice.org.uk/guidance/IPG459.

NICE (2013c), *Interventional procedures guidance [IPG464] Endoscopic bipolar radiofrequency ablation for treating biliary obstruction caused by cholangiocarcinoma or pancreatic adenocarcinoma*. https://www.nice.org.uk/guidance/IPG464.

NICE (2014a) *Clinical guideline [CG131] Colorectal cancer: diagnosis and management*. Available at: https://www.nice.org.uk/guidance/cg131.

NICE (2014b) Developing NICE guidelines: the manual. Available at: https://www.nice.org.uk/process/pmg20/chapter/introduction-and-overview.

NICE (2015) *Technology appraisal guidance [TA334] Regorafenib for metastatic colorectal cancer after treatment for metastatic disease (terminated appraisal)*. Available at: https://www.nice.org.uk/guidance/ta334.

NICE (2016) *Technology appraisal guidance [TA405] Trifluridine–tipiracil for previously treated metastatic colorectal cancer*. Available at: https://www.nice.org.uk/guidance/ta405.

Nielsen, D.L., Palshof, J.A., Larsen, F.O., Jensen, B.V., & Pfeiffer, P. (2014) A systematic review of salvage therapy to patients with metastatic colorectal cancer previously treated with fluorouracil, oxaliplatin and irinotecan +/- targeted therapy. *Cancer Treatment Reviews*, 40, (6) 701-715.

Oh, S.Y., Jeong, C.Y., Hong, S.C., Kim, T.H., Ha, C.Y., Kim, H.J., Lee, G.W., Hwang, I.G., Jang, J.S., & Kwon, H.C. (2011) Phase II study of second line gemcitabine single chemotherapy for biliary tract cancer patients with 5-fluorouracil refractoriness. *Investigational new drugs*, 29, (5) 1066-1072.

Pennington, B. (2015) Cost-effectiveness of selective internal radiation therapy using yttrium-90 resin microspheres in treating patients with inoperable colorectal liver metastases in the UK. *Journal of Medical Economics*, 18, (10) 797-804.

Pennington, B., Sennfalt, K., Cosimelli, M., & Golfieri, R. (2014). Selective internal radiotherapy (SIRT) using resin yttrium-90 microspheres for chemotherapy-refractory metastatic colorectal cancer: An Italian cost-effectiveness analysis. *CardioVascular and Interventional Radiology*, Conference, S319.

Pickard, A.S., Neary, M.P., & Cella, D. (2007) Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. *Health and quality of life outcomes*, 5, (1) 70.

Rafi, S., Piduru, S.M., El-Rayes, B., Kauh, J.S., Kooby, D.A., Sarmiento, J.M., & Kim, H.S. (2013). Yttrium-90 radioembolization for unresectable standard-chemorefractory intrahepatic cholangiocarcinoma: survival, efficacy, and safety study. *Cardiovasc.Intervent.Radiol.*, 36, (2) 440-448.

Rayar, M. (2015) Intra-arterial yttrium-90 radioembolization combined with systemic chemotherapy is a promising method for downstaging unresectable huge intrahepatic cholangiocarcinoma to surgical treatment. *Annals of Surgical Oncology*, 22, (9) 3102-3108.

Remak, E. & Brazil, L. (2004). Cost of managing women presenting with stage IV breast cancer in the United Kingdom. *British journal of cancer*, 91, (1) 77-83.

Rosenbaum, C.E.N.M., van den Hoven, A.F., Braat, M.N.G.J., Koopman, M., Lam, M.G.E.H., Zonnenberg, B.A., Verkooijen, H.M., & van den Bosch, M.A.A.J. (2016) Yttrium-90 radioembolization for colorectal cancer liver metastases: a prospective cohort study on circulating angiogenic factors and treatment response. *EJNMMI research*, 6, (1) 92.

Rosenbaum, C.E.N.M. (2013) Radioembolization for treatment of salvage patients with colorectal cancer liver metastases: a systematic review. *Journal of Nuclear Medicine*, 54, (11) 1890-1895.

Round, J., Jones, L., & Morris, S. (2015). Estimating the cost of caring for people with cancer at the end of life: A modelling study. *Palliative medicine*, 29, (10) 899-907.

Sabet, A., Meyer, C., Aouf, A., Sabet, A., Ghamari, S., & Pieper, C. (2015) Early post-treatment FDG PET predicts survival after 90Y microsphere radioembolization in liver-dominant metastatic colorectal cancer. *European Journal of Nuclear Medicine & Molecular Imaging*, 42, (3) 370-376.

Sato, K.T., Lewandowski, R.J., Mulcahy, M.F., Atassi, B., Ryu, R.K., Gates, V.L., Nemcek, A.A., Jr., Barakat, O., Benson, A., III, Mandal, R., Talamonti, M., Wong, C.Y., Miller, F.H., Newman, S.B., Shaw, J.M., Thurston, K.G., Omary, R.A., & Salem, R. (2008) Unresectable chemorefractory liver metastases: radioembolization with 90Y microspheres--safety, efficacy, and survival. *Radiology*, 247, (2) 507-515.

Saxena, A., Meteling, B., Kapoor, J., Golani, S., Morris, D.L., & Bester, L. (2015) Is yttrium-90 radioembolization a viable treatment option for unresectable, chemorefractory colorectal cancer liver metastases? A large single-center experience of 302 patients. *Annals of Surgical Oncology*, 22, (3) 794-802.

Saxena, A., Bester, L., Chua, T.C., Chu, F.C., & Morris, D.L. (2010) Yttrium-90 radiotherapy for unresectable intrahepatic cholangiocarcinoma: a preliminary assessment of this novel treatment option. *Annals of Surgical Oncology*, 17, (2) 484-491.

Saxena, A., Bester, L., Shan, L., Perera, M., Gibbs, P., Meteling, B., & Morris, D. (2014) A systematic review on the safety and efficacy of yttrium-90 radioembolization for unresectable, chemorefractory colorectal cancer liver metastases. *Journal of Cancer Research & Clinical Oncology*, 140, (4) 537-547.

Schemper, M. & Smith, T.L. (1996) A note on quantifying follow-up in studies of failure time. *Controlled clinical trials*, 17, (4) 343-346.

Schmeel, F.C. (2016) Diffusion-weighted magnetic resonance imaging predicts survival in patients with liver-predominant metastatic colorectal cancer shortly after selective internal radiation therapy. *European Radiology*, 1-10.

Schonewolf, C.A. (2014) Patterns of failure in colorectal patients with liver metastases after yttrium-90 radioembolization. *American Journal of Clinical Oncology*, 37, (3) 234-240.

Seidensticker, R., Denecke, T., Kraus, P., Seidensticker, M., Mohnike, K., Fahlke, J., Kettner, E., Hildebrandt, B., Dudeck, O., Pech, M., Amthauer, H., & Ricke, J. (2012). Matched-pair comparison of radioembolization plus best supportive care versus best supportive care alone for chemotherapy refractory liver-dominant colorectal metastases. *Cardiovascular & Interventional Radiology*, 35, (5) 1066-1073.

Sella, D. & Rilling, W.S. (2011) Cost considerations in interventional oncology: Are IO treatments expensive relative to the alternatives? *Journal of Vascular and Interventional Radiology*, Conference, S108-S109.

Shady, W., Kishore, S., Gavane, S., & Do, R. (2016a) Metabolic tumor volume and total lesion glycolysis on FDG-PET/CT can predict overall survival after (90)Y radioembolization of colorectal liver metastases: A comparison with SUVmax, SUVpeak, and RECIST 1.0. *European Journal of Radiology*, 85, (6) 1224-1231.

Shady, W., Sotirchos, V.S., & Do, R. (2016b). Surrogate Imaging Biomarkers of Response of Colorectal Liver Metastases After Salvage Radioembolization Using 90Y-Loaded Resin Microspheres. *American Journal of Roentgenology*. 207, (3) 661-670.

Sharma, R. A., Harpreet, S. W., Van Hazel, G., Heinemann, V., Sharma, N. K., Taieb, J., Ricke, J., Mills, J., Tait, N. P., Boardman, P., Peeters, M., Findlay, M. P. N., Virdee, P. S., Moschandreas, J., Gebski, V., Love, S. B., Gray, A., & Gibbs, P. (2017) Overall survival analysis of the FOXFIRE prospective randomized studies of first-line selective internal ratiotherpay (SIRT) in patients with liver metastases from colorectal cancer. *Journal of Clinical Oncology* 35 (suppl;abstract 3507).

Smits, M.L.J. (2013) Clinical and laboratory toxicity after intra-arterial radioembolization with (90)y-microspheres for unresectable liver metastases. *PLoS ONE*, 8, (7),

Sofocleous, C.T. (2015). Radioembolization as a Salvage Therapy for Heavily Pretreated Patients With Colorectal Cancer Liver Metastases: Factors That Affect Outcomes. *Clinical Colorectal Cancer*, 14, (4) 296-305.

Soydal, C., Kucuk, O.N., Bilgic, S., & Ibis, E. (2016). Radioembolization with ⁹⁰Y resin microspheres for intrahepatic cholangiocellular carcinoma: prognostic factors. *Annals of Nuclear Medicine*, 30, (1) 29-34.

Sridhara, R., Mandrekar, S. J., & Dodd, L. E. (2013) Missing data and measurement variability in assessing progression-free survival endpoint in randomized clinical trials. *Clinical cancer research*, 19, (10) 2613-2620.

Tummers, B. (2006) DataThief III. Available at: http://datathief.org/.

University of Oxford website (2017) FOXFIRE Combined Analysis indicates no benefit in overall survival from adding selective internal radiotherapy [SIRT] to first-line oxaliplatin-based chemotherapy for metastatic colorectal cancer. Available at: https://www.radiationoncology.ox.ac.uk/article/foxfire-combined-analysis-indicates-no-benefit-overall-survival-adding-selective-internal [Accessed 19 May 2017].

Valle, J., Wasan, H., Palmer, D.H., Cunningham, D., Anthoney, A., Maraveyas, A., Madhusudan, S., Iveson, T., Hughes, S., Pereira, S.P., Roughton, M., & Bridgewater, J. (2010) Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. *New England Journal of Medicine*, 362, (14) 1273-1281.

Valle, J.W., Borbath, I., Khan, S.A., Huguet, F., Gruenberger, T., & Arnold, D. (2016) Biliary cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*, 27, (suppl 5) v28-v37.

van Cutsem, E., Peeters, M., Siena, S., Humblet, Y., Hendlisz, A., Neyns, B., Canon, J.L., Van Laethem, J.L., Maurel, J., Richardson, G., Wolf, M., & Amado, R.G. (2007) Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy- refractory metastatic colorectal cancer. *Journal of Clinical Oncology*, 25, (13) 1658-1664.

van Hazel, G., Blackwell, A., Anderson, J., Price, D., Moroz, P., Bower, G., Cardaci, G., & Gray, B. (2004) Randomised phase 2 trial of SIR-spheres plus fluorouracil/leucovorin chemotherapy versus fluorouracil/leucovorin chemotherapy alone in advanced colorectal cancer. *Journal of Surgical Oncology*, 88, (2) 78-85.

Wasan, H.S. (2014) Cost of selective internal radiation therapy versus other modalities. *Future Oncology*, 10, 101-104.

Xing, M., Lahti, S., Kokabi, N., & Schuster, D. (2016) 90Y Radioembolization Lung Shunt Fraction in Primary and Metastatic Liver Cancer as a Biomarker for Survival. *Clinical Nuclear Medicine*, 41, (1) 21-27.

Yoshino, T., Mizunuma, N., Yamazaki, K., Nishina, T., Komatsu, Y., Baba, H., Tsuji, A., Yamaguchi, K., Muro, K., Sugimoto, N., Tsuji, Y., Moriwaki, T., Esaki, T., & Hamada, C. (2012) TAS-102 monotherapy for pretreated metastatic colorectal cancer: a double-blind, randomised, placebo-controlled phase 2 trial. *Lancet Oncology*, 13, (10) 993-1001.

Zacharias, A.J. (2015) Comparative Effectiveness of Hepatic Artery Based Therapies for Unresectable Colorectal Liver Metastases: A Meta-Analysis. *PLoS ONE*, 10, (10) e0139940.

Zafar, S.Y., Currow, D., & Abernethy, A.P. (2008) Defining best supportive care. *Journal of Clinical Oncology*, 26, (31) 5139-5140.

Zampino, M.G., Magni, E., Ravenda, P.S., Cella, C.A., Bonomo, G., Della Vigna, P., Galdy, S., Spada, F., Varano, G.M., & Mauri, G. (2016). Treatments for colorectal liver metastases: A new focus on a familiar concept. *Critical Reviews in Oncology/Hematology*, 108, 154-163.

Appendix 1: Data Working Group membership

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Dr Greg Wilson, The Christie Hospital
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Appendix 2: Literature search strategy for systemic review on SIRT

Database: Ovid MEDLINE(R) <1946 to January Week 3 2016>

1 Yttrium/ (2393)
2 exp Yttrium Radioisotopes/ (2426)
3 yttrium*.tw. (3255)
4 (90Y or Y-90).tw. (1684)
5 SIR-Sphere*.tw. (67)
6 TheraSphere*.tw. (46)
7 (sirtex or nordion).tw. (40)
8 SIRT.tw. (493)
9 (selective* adj3 internal* adj3 radiotherap*).tw. (49)
10 (selective* adj3 internal* adj3 radiation* adj3 therap*).tw. (174)
11 (internal* adj3 radiation* adj3 therap*).tw. (266)
12 radioemboli*.tw. (626)
13 or/1-12 (7547)
14 (liver adj2 metasta*).tw. (19428)
15 mCRC.tw. (1136)
16 ((unresectable or non-rectable) adj (liver or heaptic) adj (tumo?*s or malignanc*)).tw. (150)
17 (inoperable adj (hepatic or liver) adj tumo?r*).tw. (26)
18 (bile duct adj (cancer or neoplasm)).tw. (886)
19 Liver Neoplasms/sc (25346)
20 Bile Duct Neoplasms/ (11474)
21 Cholangiocarcinoma/ (6043)
22 Cholangiocarcinoma*.tw. (7164)
23 or/14-22 (47672)
24 13 and 23 (505)
25 limit 24 to yr="2011-Current" (253)
26 Economics/ (26624)
27 exp "costs and cost analysis"/ (193223)
28 Economics, Dental/ (1874)
29 exp economics, hospital/ (21007)
30 Economics, Medical/ (8842)
31 Economics, Nursing/ (3931)
32 Economics, Pharmaceutical/ (2599)
33 (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (463242)
34 (expenditure$ not energy).ti,ab. (18698)
35 value for money.ti,ab. (966)
36 budget$.ti,ab. (18471)
37 or/26-36 (592821)
38 ((energy or oxygen) adj cost).ti,ab. (2790)
39 (metabolic adj cost).ti,ab. (858)

40 ((energy or oxygen) adj expenditure).ti,ab. (17142)
41 or/38-40 (20048)
42 37 not 41 (588352)
43 letter.pt. (868989)
44 editorial.pt. (368875)
45 historical article.pt. (325566)
46 or/43-45 (1547448)
47 42 not 46 (558537)
48 exp animals/ not humans/ (4175116)
49 47 not 48 (520990)
50 bmj.jn. (63068)
51 "cochrane database of systematic reviews".jn. (10964)
52 health technology assessment winchester england.jn. (889)
53 or/50-52 (74921)
54 49 not 53 (516307)
55 24 and 54 (4)
56 25 or 55 (254)

Appendix 3: Literature search strategy for best supportive care evidence

Search strategy for review of best supportive care in the metastatic colorectal cancer population

Search strategy

Ovid MEDLINE(R) <1946 to August Week 4 2016>

1 (liver adj2 metasta*).tw. (20550)

2 (inoperable adj (hepatic or liver) adj (tumo?r* or malignanc* or cancer* or carcinoma* or neoplasm*)).tw. (52)

3 ((unresectable or non-resectable) adj (liver or hepatic) adj (tumo?r* or malignanc* or cancer* or carcinoma* or neoplasm*)).tw. (395)

4 (or/1-3) and (colorectal or rectal or rectum or colon).tw. (9169)

5 (("metastatic colorectal cancer" or mCRC) and (hepatic or liver)).tw. (1076)

6 Liver Neoplasms/sc and (colorectal or rectal or rectum or colon).tw. (10378)

7 or/4-6 (12855)

8 Palliative Care/ (45330)

9 Supportive care.tw. (9662)

10 8 or 9 (54116)

11 7 and 10 (320)

12 limit 11 to (english language and yr="2006 -Current") (96)

Search results

Date	Database Name	Database Host	Searcher	Total Number of records retrieved	Total number of records from database after de-duplication
07/09/16	Medline	Ovid	HM	96	93
07/09/16	Medline In Process	Ovid	HM	5	5
07/09/16	Embase	Ovid	HM	174	159
07/09/16	Cochrane Library: CDSR OTHER REVIEWS CENTRAL NHE EED	Wiley	HM	14	10
07/09/16	EconLit	EBSCOHost	HM	1	1
07/09/16	Scopus	Elsevier	HM	152	138
07/09/16	Pubmed ('epub ahead of print' only)		HM	7	7
					Total = 362
Six additional studies were identified from supplementary searching and based on advice from clinical experts.					

Search strategy for review of best supportive care in the intrahepatic cholangiocarcinoma population

Search strategy

Ovid MEDLINE(R) <1946 to January Week 3 2017>

1 (bile duct adj (cancer* or neoplasm*)).tw. (938)
2 Bile Duct Neoplasms/ (12222)
3 Cholangiocarcinoma/ (6672)
4 Cholangiocarcinoma*.tw. (7931)
5 or/1-4 (15869)
6 Palliative Care/ (46116)
7 Supportive care.tw. (9926)
8 6 or 7 (55127)
9 5 and 8 (850)
10 limit 9 to (english language and yr="2006 -Current") (240)

Search results

Date	Database Name	Database Host	Searcher	Total Number of records retrieved	Total number of records from database after de-duplication
01/02/17	Medline	Ovid	HM	240	234
01/02/17	Medline In Process	Ovid	HM	5	5
01/02/17	Embase	Ovid	HM	572	543
01/02/17	Cochrane Library: CDSR OTHER REVIEWS CENTRAL NHE EED	Wiley	HM	41	33
01/02/17	EconLit	EBSCOHost	HM	0	0
01/02/17	Scopus	Elsevier	HM	223	128
01/02/17	Pubmed ('epub ahead of print' only)		HM	3	3
					Total = 753

Appendix 4: Less relevant ongoing clinical trials on SIRT

Identifier	Title	Status	Enrolment	Study type	Design	Start date	Estimated completion date	Primary Completion Date	Outcome measures	Population	Relevance	Location
NCT02512692	90Y Transarterial Radioembolization (TARE) Plus Gemcitabine and Cisplatin in Unresectable Intrahepatic Cholangiocarcinoma	Recruiting	20	Interventional	Single arm	2015	Not reported	2018	Toxicity	ICC	Non comparative	USA
NCT02195011	Safety Study of Regorafenib and SIR-Sphere Microspheres Radioembolization in Patients With Refractory Metastatic Colorectal Cancer With Liver Metastases	Recruiting	50	Interventional	Comparison between drug regimes	2014	2017	2017	Safety, response rate, PFS, OS	CRC	Non comparative	USA
NCT01912053	Efficacy Study of Intra-hepatic Administration of Therasphere in Association With Intravenous Chemotherapy to Treat Cholangiocarcinoma	Not recruiting	41	Interventional	Single arm	2013	2018	2017	Response rate, toxicity/safety	ICC	Non comparative	France
NCT01177007	Intra-arterial Y-90 TheraSpheres for Hepatic Metastases From Solid Tumors	Not recruiting	50	Interventional	Single arm	2010	2014	2014	TTP, safety, OS	Mixed	Non comparative	USA
NCT01098422	A Study of Yttrium-90 Radioactive Resin Microspheres to Treat Colorectal Adenocarcinoma Metastatic to the Liver	Status unknown	10	Interventional	Single arm	2010	2015	2015	PFS, OS, tumour response, safety, mortality	CRC	Non comparative	USA
NCT00972036	Selective Internal Radiation Therapy (SIRT) in Patients With Unresectable Colorectal Cancer Liver Metastases Who Failed Prior Intraarterial Pump Chemotherapy	Status unknown	32	Interventional	Single arm	2009	2014	2014	Safety, toxicity, tolerated dose	CRC	Non comparative	USA
NCT00858429	Yttrium Y 90 Glass Microspheres and Capecitabine in Treating Patients With Liver Cholangiocarcinoma or Liver Metastases	Not recruiting	30	Interventional	Single arm	2009	2018	2017	Safety, toxicity, tolerated dose	ICC	Non comparative	USA
NCT00766220	Yttrium Microspheres With Cetuximab Plus Irinotecan for Patients With Advanced Colorectal Cancer Mets to Liver	Withdrawn prior to enrollment	0	Interventional	Single arm	2009	2012	2012	PFS	CRC	Withdrawn prior to enrolment	USA
NCT00735241	FOLFOX6 Plus Sir-Spheres Microspheres Plus Avastin in Patients With Nonresectable Liver Metastases From Colorectal Carcinoma	Withdrawn prior to enrollment	0	Interventional	Single arm	2008	2009	2009	Toxicity and safety	CRC	Withdrawn prior to enrolment	USA
NCT00408551	Chemotherapy and Internal Radiation in Treating Patients With Colorectal Cancer That Has Spread to the Liver	Recruiting	20	Interventional	Comparison between drug regimes	2005		2009	Response rate, toxicity, PFS, downstaging	CRC	Non comparative (SIRT)	USA

Identifier	Title	Status	Enrolment	Study type	Design	Start date	Estimated completion date	Primary Completion Date	Outcome measures	Population	Relevance	Location
NCT00532740	Radiolabeled Glass Beads in Treating Patients With Metastatic Liver Cancer That Cannot Be Removed by Surgery	Recruiting (early results published)	500	Observational	Prospective observational	2004	2019	2018	Patient experience and toxicity	CRC	Non comparative	USA

Acronyms: CRC, colorectal cancer; ICC, intrahepatic cholangiocarcinoma; mCRC, metastatic colorectal cancer; OS, overall survival; PFS, progression free survival; QoL, quality of life; RCT, randomised controlled trial; TTP, time to progression.

Appendix 5: SIRT registry data dictionary

Question	Type	Selection
PATIENT SECTION		
Patient's general practitioner's postcode	Text	
Is the patient receiving SIRT within a clinical trial?	Radio Buttons	Yes,No,Unknown
Name of clinical trial	Text	
Deceased date	Date	
Reason for death	Checkbox	Extra-Hepatic Disease Progression,Intra-Hepatic Disease Progression,Complication,Unrelated,Other
Complication details	Comment	
Unrelated details	Comment	
Other details	Comment	
Lost to follow-up date	Date	
Patient notes	Comment	
What type of Liver Cancer?	Radio Buttons	Primary,Secondary/Metastatic
Pre-SIRT Diagnosis Primary	SelectList	Cholangiocarcinoma,Hepatocellular Carcinoma,Primary Other
Pre-SIRT Diagnosis Primary Other	Text	
Pre-SIRT Diagnosis Secondary/Metastatic	SelectList	Breast Cancer,Cancer of Unknown Primary,Colorectal Cancer,Gastric Cancer,Head & Neck Cancer,Lung Cancer,Melanoma,Neuroendocrine Tumor,Oesophageal Cancer,Pancreatic Cancer,Renal Cell Carcinoma,Sarcoma,Secondary/Metastatic Other
Pre-SIRT Diagnosis Secondary/Metastatic Other	Text	
Histological types	Text	
Date of Primary Diagnosis	Date	
Date of Metastatic Diagnosis	Date	
Was the Primary Tumor reseCtEd?	Radio Buttons	Yes,No
Prior Hepatic Procedures?	Radio Buttons	Yes,No
Prior Treatment Hepatic Surgery Date	Date	
Type of surgery	Radio Buttons	Open,Laparoscopy
Was it major surgery (>3 segments)?	Radio Buttons	Yes,No
Was it RO resection?	Radio Buttons	Yes,No,Unknown
Liver Transplant Date	Date	
Surgical Other	Text	
Surgical Other Date	Date	
Surgical Notes	Comment	
Radiofrequency Ablation Date	Date	
Radiofrequency Ablation	Checkbox	Radiofrequency Ablation
Microwave Ablation	Checkbox	Microwave Ablation
Microwave Ablation Date	Date	
Percutaneous Ethanol Injection	Checkbox	Percutaneous Ethanol Injection
Percutaneous Ethanol Injection Date	Date	
Irreversible Electroporation	Checkbox	Irreversible Electroporation
Irreversible Electroporation Date	Date	
Cryoablation	Checkbox	Cryoablation
Cryoablation Date	Date	
Ablative Other	Text	
Ablative Other Date	Date	
Chemoembolization (TACE)	SelectList	Select...,Conventional TACE,Drug-Eluting TACE,Other
Other	Text	
TACE Date	Date	
TACE Type	SelectList	Select...,Cisplatin,Doxorubicin,Doxorubicin + cisplatin + FUDR or 5FU,Doxorubicin + cisplatin + mitomycin C,Epirubicin,Mitomycin C,Other
TACE Type Other	Text	
Hepatic-Arterial Chemotherapy	SelectList	Select...,FUDR or 5FU,Irinotecan,Oxaliplatin,Other
Hepatic-Arterial Chemotherapy Date	Date	
Other Hepatic-Arterial Chemotherapy	Text	

Portal Vein Embolization	Checkbox	Portal Vein Embolization
Portal Vein Embolization Date	Date	
Bland Embolization	Checkbox	Bland Embolization
Bland Embolization Date	Date	
Vascular Other	Text	
Vascular Other Date	Date	
Selective Internal Radiation Therapy (SIRT)	SelectList	Select...,SIR-Spheres,TheraSphere,Other
SIRT Date	Date	
SIRT Other	Text	
EBRT Date	Date	
External Beam Radiation Therapy (EBRT/SBRT)	Checkbox	External Beam Radiation Therapy (EBRT/SBRT)
Radiation Therapy Other	Text	
Radiation Therapy Other Date	Date	
Prior Systemic Chemotherapy?	Radio Buttons	Yes,No
How many lines?	SelectList	1,2,3,4,5,6,>6
Line 1	Comment	
Start Date	Date	
End Date...[continued for 6 lines]	Date	
Additional lines	Comment	
End Date	Date	
Start Date	Date	
Prior Adjuvant Therapy?	Radio Buttons	Yes,No
How many lines?	SelectList	1,2,3
Line 1	Comment	
Start Date	Date	
End Date...[continued for 3 lines]	Date	
TREATMENT SECTION		
Date EQ-5D-5L questionnaire was filled out	Date	
Mobility	SelectList	I have no problems in walking about,I have slight problems in walking about,I have moderate problems in walking about,I have severe problems in walking about,I am unable to walk about
Self-Care	SelectList	I have no problems washing or dressing myself,I have slight problems washing or dressing myself,I have moderate problems washing or dressing myself,I have severe problems washing or dressing myself,I am unable to wash or dress myself
Usual Activities (e.g. work, study, housework,	SelectList	I have no problems doing my usual activities,I have slight problems doing my usual activities,I have moderate problems doing my usual activities,I have severe problems going my usual activities,I am unable to do my usual activities
Pain / Discomfort	SelectList	I have no pain or discomfort,I have slight pain or discomfort,I have moderate pain or discomfort,I have severe pain or discomfort,I have extreme pain or discomfort
Anxiety / Depression	SelectList	I am not anxious or depressed, I am slightly anxious or depressed, I am moderately anxious or depressed,I am severely anxious or depressed,I am extremely anxious or depressed
Scale	SelectList	1-100
First Name (Treating IR)	Text	
Last Name	Text	
BSA m^2 (Body Surface Area)	Numeric	
Lung Shunt Study %	Numeric	
Lung Shunt Study Date	Date	
ECOG Performance Status	SelectList	0-4
Portal Vein	SelectList	Patent,Segmental Thrombosis,Lobar Thrombosis,Main Thrombosis
Liver Tumor Location	Radio Buttons	Left,Right,Bilobar
How many Liver Tumors?	SelectList	1,2,3,4,5,6,7,8,9,10,>10,Other,Uncountable
Number of Liver Tumors	Numeric	
Does the patient have active extra-hepatic disease now?	Radio Buttons	Yes,No
Location	Checkbox	Bone,Brain,Lung,Lymph Nodes,Other

Other Location	Comment	
Does the patient have cirrhosis?	Radio Buttons	Yes,No
Cause of cirrhosis	SelectList	Hepatitis-B,Hepatitis-C,Alcohol,NASH,Other
Other	Comment	
Is the Liver grossly abnormal?	Radio Buttons	Yes,No
Does the patient have ascites?	Radio Buttons	Yes,No
Ascites Type	SelectList	Mild,Moderate,Severe,Other
Other	Comment	
Has the patient had any arteries embolized before SIRT therapy?	Radio Buttons	Yes,No
Arteries embolized before SIRT therapy	Radio Buttons	Yes,No
What was the intent of SIRT?	SelectList	Bridge to liver surgery,Bridge to liver transplant,Down-sizing/down-staging, Ablation,Palliative
Concomitant Chemotherapy?	Radio Buttons	Yes,No
Chemo	Comment	
Start Date	Date	
End Date	Date	
This SIRT treatment is targeted to	Radio Buttons	Whole Liver (single catheter),Whole Liver (split administration/single session),Whole Liver (sequential lobar/ two sessions),Right Lobe,Left Lobe,Segmental
Date of SIRT administration	Date	
Date of second SIRT administration	Date	
Brand of SIRT used	SelectList	SIR-Spheres microspheres - Y-90 resin microspheres,TheraSphere - Y-90 glass microspheres,Other
Methodology for determining the dose	SelectList	BSA,Modified BSA,Empiric,Partition Model,Other
Methodology for determining the dose	SelectList	Manufacturers Recommendation,Other
Other method for determining dose	Text	
SIRT batch number	Text	
Did you measure the whole liver or the right and left lobe separately?	Radio Buttons	Whole,Right and Left
Whole Liver %	Numeric	
Right Lobe %	Numeric	
Left Lobe %	Numeric	
Whole Liver %	Numeric	
Right Lobe %	Numeric	
Left Lobe %	Numeric	
Were all Liver Tumors targeted?	Radio Buttons	Yes,No,Unknown
Liver segments not treated by SIRT	Checkbox	I,II,III,IVa,IVb,V,VI,VII,VIII
Did you prescribe the whole liver or the right and left lobe separately?	Radio Buttons	Whole,Right and Left
Whole Liver	Numeric	
Right Lobe	Numeric	
Left Lobe	Numeric	
Unit of Measure	Radio Buttons	GBq,mci
Was the delivered activity within 90% of the prescribed activity?	Radio Buttons	Yes,No
Whole Liver	Numeric	
Right Lobe	Numeric	
Left Lobe	Numeric	
Unit of Measure	Radio Buttons	GBq,mci
Reason for non-delivery	Checkbox	Dissection,Slow flow/Stasis,Spasm,Other
Other Reason	Comment	
How many administrations were delivered to the patient?	SelectList	1,2,3
Serum BilirubinUnit of Measure?	Radio Buttons	mg/dL,µmol/L
Total Bilirubin (mg/dL)	Numeric	
Total Bilirubin (µmol/L)	Numeric	
Date	Date	
Albumin (g/dL)	Numeric	
Date	Date	

ALT (SGPT) (U/L)	Numeric	
Date	Date	
AST (SGOT) (U/L)	Numeric	
Date	Date	
Creatinine (mg/dl)	Numeric	
Date	Date	
Creatinine (mg/dl)	Numeric	
Date	Date	
Platelets (x10⁹/L)	Numeric	
Date	Date	
Leukocytes (x10⁹/L)	Numeric	
Date	Date	
Neutrophils (x10⁹/L)	Numeric	
Date	Date	
Date	Date	
Tumor Marker Other	Text	
Date	Date	
Length of Hospital Stay for SIRT Treatment	SelectList	Outpatient,1 night,2 nights,3 nights,4 nights,>4 nights
Were any severe day of treatment complications experienced?	Radio Buttons	Yes,No
Please select all treatment complications that occurred.	Checkbox	Vascular,Severe Abdominal Pain,Severe Vomiting,Severe Other
Severity	SelectList	Minor@A - No therapy no consequence B - Nominal therapy no consequence; includes overnight admission for observation only ,Major@C - Require therapy; minor hospitalization {<48 hours} D - Require major therapy; unplanned increase in level of care; prolonged hospitalization {>48 hours} E - Permanent adverse sequelae F - Death
Grade	SelectList	Grade 3,Grade 4
Was there a product incident or complaint associated with the treatment?	Radio Buttons	Yes,No
	Checkbox	SIR-Spheres
Sign-Off Date	Date	
Date EQ-5D-5L questionnaire was filled out	Date	
FOLLOW-UP SECTION		
Mobility	SelectList	As previous
Self-Care	SelectList	As previous
Usual Activities (e.g. work, study, housework,	SelectList	As previous
Pain / Discomfort	SelectList	As previous
Anxiety / Depression	SelectList	As previous
Scale	SelectList	1-100
Follow-Up Date	Date	
ECOG Performance Status	SelectList	0-4
Follow-Up Notes	Comment	
Were any clinical adverse events experienced?	Radio Buttons	Yes,No
Please select all adverse events that occurred.	Checkbox	Abdominal Pain,Fatigue,Fever,Nausea,Vomiting,Gastritis,GI Ulceration,Radioembolisation-Induced Liver Disease,Radiation Pneumonitis,Radiation Cholecystitis,Radiation Pancreatitis,Other
Onset Date	Date	
Grade	SelectList	Grade 1-5
Were any laboratory values abnormal?	Radio Buttons	Yes,No
Please select all laboratory values that were abnormal.	Checkbox	Hypoalbuminemia,Hyperbilirubinemia,ALT increased,AST increased,INR increased,Neutrophil count decreased,Platelet count decreased,Other
Onset Date	Date	
Grade	SelectList	Grade 1-5
Are imaging data available?	Radio Buttons	Yes,No
Extra-Hepatic tumor response	SelectList	Select..., Complete Response (CR)@: Disappearance of all target lesions.,Partial Response (PR), Stable Disease (SD),Progressive Disease (PD),Unevaluable

Hepatic tumor response	SelectList	Select..., Complete Response (CR)@: Disappearance of all target lesions.,Partial Response (PR), Stable Disease (SD),Progressive Disease (PD),Unevaluable
Imaging criteria used	SelectList	Select...,RECIST,mRECIST,EASL,Choi,Other
Imaging Date	Date	
Imaging method	SelectList	Select...,CT Scan,MRI,PET
Other imaging criteria	Text	
Post SIRT Hepatic Procedures?	Radio Buttons	Yes,No
Post Treatment Hepatic Surgery Date	Date	
Type of surgery	Radio Buttons	Open,Laparoscopy
Was it major surgery (>3 segments)?	Radio Buttons	Yes,No
Was it RO resection?	Radio Buttons	Yes,No,Unknown
Liver Transplant Date	Date	
Surgical Other	Text	
Surgical Other Date	Date	
Surgical Notes	Comment	
Radiofrequency Ablation	Checkbox	Radiofrequency Ablation
Radiofrequency Ablation Date	Date	
Microwave Ablation	Checkbox	Microwave Ablation
Microwave Ablation Date	Date	
Percutaneous Ethanol Injection	Checkbox	Percutaneous Ethanol Injection
Percutaneous Ethanol Injection Date	Date	
Irreversible Electroporation	Checkbox	Irreversible Electroporation
Irreversible Electroporation Date	Date	
Cryoablation	Checkbox	Cryoablation
Cryoablation Date	Date	
Ablative Other	Text	
Ablative Other Date	Date	
Chemoembolization (TACE)	SelectList	Select...,Conventional TACE,Drug-Eluting TACE,Other
Other	Text	
TACE Date	Date	
TACE Type	SelectList	Select...,Cisplatin,Doxorubicin,Doxorubicin + cisplatin + FUDR or 5FU,Doxorubicin + cisplatin + mitomycin C,Epirubicin,Mitomycin C,Other
TACE Type Other	Text	
Hepatic-Arterial Chemotherapy	SelectList	Select...,FUDR or 5FU,Irinotecan,Oxaliplatin,Other
Hepatic-Arterial Chemotherapy Date	Date	
Other Hepatic-Arterial Chemotherapy	Text	
Portal Vein Embolization	Checkbox	Portal Vein Embolization
Portal Vein Embolization Date	Date	
Bland Embolization	Checkbox	Bland Embolization
Bland Embolization Date	Date	
Vascular Other	Text	
Vascular Other Date	Date	
Selective Internal Radiation Therapy (SIRT)	SelectList	Select...,SIR-Spheres,TheraSphere,Other
SIRT Date	Date	
SIRT Other	Text	
EBRT Date	Date	
External Beam Radiation Therapy (EBRT/SBRT)	Checkbox	External Beam Radiation Therapy (EBRT/SBRT)
Radiation Therapy Other	Text	
Radiation Therapy Other Date	Date	
Post Systemic Chemotherapy?	Radio Buttons	Yes,No
How many lines?	SelectList	1,2,3,4,5,6,>6
Line 1	Comment	
Start Date...continues for 6 lines	Date	
End Date	Date	
Serum BilirubinUnit of Measure?	Radio Buttons	mg/dL,µmol/L
Total Bilirubin (mg/dL)	Numeric	
Total Bilirubin (µmol/L)	Numeric	

Date	Date	
Albumin (mg/L)	Numeric	
Date	Date	
ALT (SGPT) (U/L)	Numeric	
Date	Date	
AST (SGOT) (U/L)	Numeric	
Date	Date	
Creatinine (mg/dl)	Numeric	
Date	Date	
Platelets (x10⁹/L)	Numeric	
Date	Date	
Leukocytes (x10⁹/L)	Numeric	
Date	Date	
Neutrophils (x10⁹/L)	Numeric	
Date	Date	
Tumor Marker Other	Text	

Appendix 6: Resource use questionnaire sent to clinicians

Questionnaire to SIRT CtE clinicians – Resource use

This questionnaire related to the treatment of patients with unresectable metastatic colorectal cancer which has progressed on at least two lines of standard chemotherapy.

Please provide responses based on your experience in the NHS.

PRE-SIRT WORK UP

1. During the pre-SIRT work-up procedure, which of the following elements would typically be included?

Elements of work up procedure (NHS Ref costs suggested)	**Y/N**	**Comments** ***Please provide any further information or costs***
Angiography, including embolization where required *(RD32Z Contrast Fluoroscopy Procedures with duration of more than 40 minutes)*		
Injection of 99mTc MAA *(SC53Z Preparation for Intraluminal Brachytherapy, inpatient)*		
Cost of 99mTcMAA		
SPECT Scan *(RN04A SPECT-CT of one area, 19 years and over)*		
CT Scan *(RD20A Computerised Tomography Scan of one area, without contrast, 19 years and over)*		
Liver ultrasound		
PET-CT		
Outpatient attendance		
CEA test		
Liver function tests		
Please add more rows if required		

2. Is a typical work-up procedure done as an outpatient, day-case or inpatient procedure? What is would be the typical length of stay?

3. What consumables are used in a typical work-up procedure, which you would **not** expect to be included in NHS Reference Costs? Please estimate a cost if possible.

4. From your experience, what proportion of patients receives a work-up procedure and do not receive a SIRT procedure?

5. From your experience, what proportion of patients requires more than 1 work-up procedure?

6. In cases where more than one work up procedure is required, are all of the elements in Q1 repeated?

SIRT PROCEDURE

7. During the SIRT procedure, which of the following elements would typically be included?

Elements of SIRT procedure (NHS Ref costs suggested)	**Y/N**	**Comments** ***Please provide any further information or costs***
Angiography, including embolization where required *(RD32Z Contrast Fluoroscopy Procedures with duration of more than 40 minutes)*		
Injection of Y-90 microspheres *(SC53Z Preparation for Intraluminal Brachytherapy, inpatient)*		
Cost Y-90 microspheres (including administration set)		
SPECT Scan *(RN04A SPECT-CT of one area, 19 years and over)*		
CT Scan *(RD20A Computerised Tomography Scan of one area, without contrast, 19 years and over)*		
PET scan		
Disposal of radioactive waste		
Overnight stay		
Outpatient attendance		
Please insert rows as required		

8. Is a typical SIRT procedure done as an outpatient, day-case or inpatient procedure? What is would be the typical length of stay?

9. What consumables are used in a typical SIRT procedure, which you would **not** expect to be included in NHS Reference Costs? Please provide any details available.

10. Please describe procedures used to treat the following adverse events that may occur soon after SIRT.

Adverse events from SIRT	**Resources used to treat**

Fatigue	
Nausea	
Abdominal pain	
Radiation pneumonitis	
Gall bladder inflammation	
RILD	
GI ulceration	
Pancreatitis	
Fever	
Anaemia	
Diarrhoea	
Anorexia	
Please insert rows as required	

11. Do patients typically receive concomitant chemotherapy with SIRT?

FOLLOW-UP AFTER SIRT

12. Following SIRT, what procedures are typically used prior to disease progression?

Resources used during follow-up after SIRT	**Y/N**	**Comments** ***Please provide any further information or costs***
Chest, abdo, pelvis CT scan *(please describe frequency)*		
MRI scan *(please describe frequency)*		
PET scan *(please describe frequency)*		
Chemotherapy *(please describe regimen)*		
Outpatient consultant visits		
Laboratory tests		
Please insert rows as required		

13. Do patients typically receive chemotherapy following SIRT? *Please describe typical regimens.*

BEST SUPPORTIVE CARE

14. What is the most appropriate comparator to SIRT before disease progression? *i.e. in the absence of SIRT how would you manage these salvage/3rd line patients? Please describe chemotherapy regimens if appropriate.*

15. Please describe the resources/procedures used to provide best supportive care prior to disease progression.

16. Please describe typical adverse events associated with best supportive care (or an alternative comparator to SIRT) and the procedures used to treat them.

Adverse events from BSC	**Resources used to treat**
Fatigue	
Nausea/vomiting	
Abdominal pain	
Fever	
Anaemia	
Diarrhoea	
Anorexia	
Please insert rows as required	

MANAGEMENT AFTER DISEASE PROGRESSION

17. How are patients managed following disease progression? Would you describe this as best supportive care (BSC)?

Please describe resources associated with provision of best supportive care following disease progression

18. Following disease progression, would patients previously treated with SIRT be managed in the same way as patients previously treated with best supportive care? Please describe patient management.

Appendix 7: Sources for model inputs, and summary of available information

Input	Value	Source	Appraisal
Overall survival (OS)	**SIRT** Median OS: 7.6 months (95% CIs 6.9 – 8.3)	**Primary CtE registry data**	**Benefits** Patient-level data. In line with scope of decision problem. Contemporary data from NHS setting. De novo extrapolation of survival data possible. **Limitations** No comparator data. Unpublished data and no independent peer review.
	SIRT Median OS: 11.9 months (95% CIs 10.1-14.9) Mean OS: 25.2 months **BSC** Median OS: 6.6 months (95% CIs not reported) Mean OS: 11.6 months HR:0.57 (95% CIs 0.41-0.82)	**Bester et al. (2012)** retrospective matched-pair cohort. Survival curve from Bester et al. (2014) was extrapolated and presented in Pennington et al. (2015).	**Benefits** This peer reviewed study includes comparator data. Access to previously extrapolated data in Pennington et al. (2015) model has been kindly provided. Study cohort similar to CtE cohort. **Limitations** Observational design which is at increased risk of bias. Very small (n=29) control arm. Small numbers at end of curve gives rise to high uncertainty. Retrospective matched-pairs. Relies on assumption that extrapolation carried out by authors of Pennington et al. (2015) was correct. Cedar did not have access to patient-level data. BSC poorly defined. Date of SIRT doesn't have an equivalent in the BSC arm. Unclear how well the patients match to CtE patients. 85% of patients had ECOG 0 suggesting this population is healthier than that in the CtE study (50% of CtE patients were ECOG 0). All pts failed multiple lines but the authors do not report how many lines (14% chemo naive in the combined non-CRC and CRC group; proportion of chemo-naive patients in CRC-only group is not reported). ECOG scores of BSC patients were not reported. Patient characteristics are not directly compared for CRC subgroup.
	SIRT Median OS: 8.3 months (95% CIs 6.6-10.2) **BSC** Median OS: 3.5 months (95% CIs 1.9-5.7) HR: 0.26 (95% CIs 0.15-0.48)	**Seidensticker et al. (2012)** retrospective matched-pair cohort.	**Benefits** Includes comparator data. Cohort similar to CtE cohort. Performance status equivalent to ECOG 0-2. At least 2 failed lines of chemo (median 3). **Limitations** Observational design which is at increased risk of bias. Very small (n=29) control arm. Small numbers at end of curve make results unreliable. Risk of selection bias. Cedar did not have access to patient-level data, therefore extrapolation would need to come from tracing of curve in paper. Retrospective matched-pairs. BSC poorly defined. 31% received chemotherapy after SIRT. Possible error in the description of OS (authors state: "The primary endpoint was overall survival (OS) from the date of progression of the liver before radioembolization or prior commencement of BSC assessed radiologically until further progression

			(after radioembolization or BSC), evaluated by radiological imaging or clinically.")
	SIRT & FU Median OS: 10 months (95% CIs not reported) **FU alone** Median OS: 7.3 months (95% CIs not reported) HR: 0.92 (0.47-1.78) p=0.80	**Hendlisz et al. (2010)** randomised controlled trial	**Benefits** Includes comparator data. Randomised study therefore reduced risk of selection bias and effect of confounders. Patients resistant or intolerant to standard chemotherapy (FU, OXA, IRI) therefore similar cohort to SIRT CtE study. **Limitations** Small study (SIRT n=21 vs chemo n=23). No access to patient level data and no overall survival curve presented. FU chemotherapy rather than BSC in control arm (FU alone may not represent standard practice in UK). Control patients permitted to cross over to SIRT arm following progression which is likely to significantly affect OS estimates. Majority of patients were ECOG 0. Total number of previous chemo lines not reported. Patients with extrahepatic metastases were excluded (in CtE group these pts were included if metastases were liver dominant). Patients in both arms received further treatment.
	SIRT Pooled median OS: 9.6 (range 6.0-12.7).	Cedar systematic review	**Benefits** Pooled analysis across 23 studies (n=2517). Large cohort of patients well matched to CtE cohort. **Limitations** No access to patient-level data. No comparator. Data was based on retrospective and prospective single-arm observational studies.
	BSC Pooled median OS: 5.3 (range 2.4-6.6).	Cedar systematic review	**Benefits** Pooled analysis across 7 studies to produce large cohort (n=1156) **Limitations** Data from control arm of RCTs (non-SIRT intervention). BSC may not represent care in real-life setting. No access to patient-level data. Population may differ from SIRT CtE cohort. Likely to effect from RCT design ("trial effect").
	BSC Mean OS: 6.2 months	**Hoyle et al. (2013)** model for NICE TA	**Benefits** Extrapolated curves from Hoyle et al. (2013) model available. Model is based on NHS setting. **Limitations** Data from the control arm of one RCT (non-SIRT intervention). May not be comparable to SIRT.
Progression free survival (PFS)	**SIRT** Median PFS: 5.5 months (95% CIs not reported)	**Seidensticker et al. (2012)** retrospective matched-pair cohort.	**Benefits** Comparator data available. RECIST criteria used (although later it says where progression was defined as a clinically significant change in symptoms or CEA levels, or confirmed by radiological imaging, and this may apply to BSC arm only).

	BSC Median PFS: 2.1 months (95% CIs not reported) (no statistical comparison)		**Limitations** See above for further points. 31% received chemotherapy after SIRT (the authors do not report that this was after progression so may affect PFS). PFS measured from "progression" to "further progression" which is not how other studies record it. No Kaplan-Meier curve for PFS.
	SIRT & FU Median PFS: 4.5 months (95% CIs not reported) **FU alone** Median PFS: 2.1 months (95% CIs not reported) HR 0.51 (95% CIs 0.28-0.94) p=0.03	**Hendlisz et al. (2010)** randomised controlled trial	**Benefits** PFS measured using RECIST criteria. Cross over was only permitted after progression was documented, therefore limited impact PFS results. **Limitations** See above for further notes. PFS data reported in Kaplan-Meier curve. Time to liver progression (TTLP) was primary outcome for trial. TTP and TTLP calculated from randomisation to "first documented progression in the liver or first documented progression at any site, death, or date of last observation (in patients lost to follow-up)"[1].
	Not reported	**Bester et al. (2012)**	Outcome not reported
	SIRT Pooled median 4.0 months (range 2.8 to 9.2 months)	Cedar systematic review	**Benefits** Pooled analysis from 9 studies (437 patients). Large cohort of patients well matched to CtE cohort. **Limitations** No access to patient-level data or survival curve. No comparator data. Based retrospective and prospective single-arm observational studies. Large range of PFS values from studies.
	BSC Pooled median 3.2 months (range 1-7.3 months)	Cedar systematic review	**Benefits** Pooled analysis across 5 studies to produce large cohort. **Limitations** Data from control arm of RCTs (non-SIRT intervention). BSC may not represent care in real-life setting. No access to raw data or survival curve. No comparator. Population may differ from SIRT CtE cohort.

[1] TTP is defined slightly differently to PFS. However in this case, TTP has the same definition as PFS (i.e. time to progression or death).

	BSC Mean PFS: 2.7 months	**Hoyle et al. (2013)** model for NICE TA	**Benefits** Extrapolated curves from Hoyle et al. (2013) model available. Model is based on NHS setting. **Limitations** Data from the control arm of one RCT (non-SIRT intervention). May not be comparable to SIRT.
Adverse events	**SIRT** List of AE types with grade and proximity to SIRT	Primary CtE registry data.	**Benefits** As described above. **Limitations** CTCAE grading criteria not explicitly defined across study but assumed to have been used. Registry design means no validation of data as in a trial, therefore there is a risk of missing data. Relatedness to SIRT not captured.
	SIRT List of AEs with grade[1] (separated to SIRT-related and delayed complications)	**Bester et al. (2012)** retrospective matched-pair cohort.	**Benefits** As described above. CTCAE criteria used. **Limitations** As described above. No AEs reported for comparator arm. No treatment described. No better than using CtE data. May be useful to compare to SIRT for reliability.
	SIRT List of AEs with grade. Likelihood of being related to SIRT is described.	**Seidensticker et al. (2012)** retrospective matched-pair cohort.	**Benefits** CTCAE criteria used. **Limitations** No AEs reported for comparator arm. No treatment described. Useful to compare to SIRT for validation purposes.
	SIRT & FU List of AEs with grade.	**Hendlisz et al. (2010)** randomised controlled trial	**Benefits** CTCAE criteria used. **Limitations** See above for further notes. Authors do not report whether AEs are related to the SIRT/FU or disease

[1] AEs in most studies are graded according to the CTCAE criteria. We could consider only costing AEs which are grade >2.

			progression.
	BSC Cost of AE: £2760	**Hoyle et al. (2013)** model for NICE TA	Hoyle et al. uses a cost for AEs in the BSC arm but it's not clear how this is calculated.
	BSC List of AEs of grade ≥3.	**Jonker et al. (2007)** RCT of BSC vs cetuximab.	**Benefits** Largest of BSC trials. **Limitations** Intervention is not SIRT. Trial setting may not be comparable to SIRT CtE cohort. Only reports Grade 3 and above. Does not report treatment. Patients in BSC did not received chemotherapy with which there may be associated AEs. In real life setting BSC will comprise chemotherapy in some patients.
Cost of initial SIRT treatment	£21,870	SIRT CtE current payments	**Benefits** Prices quoted for 2014-15. Current actually paid to SIRT CtE providers. **Limitations** Prices quoted for 2014-15. This is a tariff not a cost and therefore is may not reflect true cost, or potential future payments
	£14,248 (2013-14)	**Pennington et al. (2015)** taken from reference costs from NHS reference costs and The Christie NHS Foundation Trust	Includes work-up, treatment, hospital care (overnight for work up, 1.5 day stay for treatment) and additional equipment. Based on NHS reference cost and detailed NHS data. Appears to include 6.7% of patients with more than 1 workup, and 2.2% with more than 1 treatment. Needs to be inflated to current prices.
	SIRT Daily (2013-14) **BSC** Daily (2013-14)	Costs from **Pennington et al. (2015)** model based on daily costs from **Seidensticker et al. (2012).**	• Daily costs applied throughout patient lifetime • Chemotherapy regimen taken from another study (Seidensticker, 2012) whilst survival data are from Bester et al. (2015) • Chemo detail not in published paper (Seidensticker, 2012) • Not clear in model how data is being used • No mention of BSC chemo in published paper (Seidensticker, 2012) • The chemo regimens are included in the model, together with the total time spent on regimen by patients. This is used to give a total cost (with microcosting drug costs and NHS ref prices for administration). • The cost of each regimen is multiplied by the months/patient for which it was delivered to give a total cost of chemo per patient. This calculation appears to have missed out the cost of all 5-FU/FA therapy. Total cost including deliver is £4,712 per patient • This is then adjusted to give a price per patient per day (using total months survived for whole

			cohort). This daily cost is applied to the model. • Because Bester et al. (2012) has much longer survival times than Seidensticker et al. (2012), the total chemotherapy cost in the model is greater - £13,400.
Chemotherapy	**BSC** No chemotherapy costs	**Hoyle et al. (2013)**	• No Chemotherapy in BSC arm, other arms are drug treatments with high costs (£20-50,000 per patient), 3rd line treatments. • Assumes cost of any chemotherapy to be very small, and equal and not included.
	BSC No chemotherapy costs	**TA405** (NICE 2016)	• No chemotherapy costs were included for BSC
	SIRT & BSC	Primary CtE registry data.	• 2-3 months imaging and consultant appt until progression • Following progression hands over to normal clinical team, info not known
Monitoring costs	**£125 per month (2013)**	**Pennington et al. (2015)**	• Monthly oncology appt for each arm for entire patient lifetime • Based on NHS Reference costs • No imaging or testing costs included
	BSC £0	**Hoyle et al. (2013)**	• No costs included for BSC until progression
	BSC £182 monthly	**TA405** (NICE 2016)	• Based on estimated resource use of 1 oncology visit per month and 1 health visitor visit per 4 months. • Use of estimated resources criticised by ERG.
	SIRT £625.1 per month (2013-14) **BSC** £599.3 per month (2013-14)	**Pennington et al. (2015)** based on monthly oncology appointment for all and chemotherapy for some from Seidensticker et al. 2012.	• Costs applied for entire patient lifetime in Pennington model • Chemotherapy costs are included in this monthly cost
Total Cost of ongoing SIRT cohort in non-progressed state	**BSC** £0 It is only costed after progression	**Hoyle et al. (2013)**	
	BSC £182 monthly	**TA405** (NICE 2016)	• Based on estimated resource use of 1 oncology visit per month and 1 health visitor visit per 4 months. • Use of estimated resources criticised by ERG.
	SIRT £625.1 per month (2013-	**Pennington et al. (2015)** based on	• Costs applied for entire patient lifetime in Pennington model • See previous reservations on chemotherapy costs

	14) **BSC** £599.3 per month (2013-14)	monthly oncology appointment for all and chemotherapy for some from Seidensticker et al. 2012.	• Hendlisz withdraws chemotherapy after disease progression • Need to check with clinicians if it is likely to continue • Needs to be inflated to current prices
Cost of progressed state	**BSC** £1039 per month (2011)	**Hoyle et al. (2013)**	• This includes medication, hospitalizations, hospice stays, outpatient visits, scans, and laboratory test • Was included for both arms • Based on study on breast cancer (Remak & Brazil 2004) • Costs were inflated to 2010 prices. • Intervention arm included £295/month for consultant visits and £37 a month for CT scan. • And assumes cost of any chemotherapy to be very small, and equal and not included. • Cost from (Remak & Brazil 2004), inflated to 2011.
	BSC £193 per month, plus £1528 on progression.	**TA405** (NICE 2016)	• Some treatment assumed, given the initial lump sum applied.
Cost of death	**All** £5,800	**Pennington et al. (2015)**	• Applied on death
	No additional cost	**Hoyle et al. (2013)**	• The progressed state is costed at £1039 and described as palliative care. There is no additional cost upon death.
	All £6910	**TA405** (NICE 2016)	• Applied on death • Includes health care, social care and charity care. • Criticised by ERG for including charity care.
	SIRT Events listed, but no costs	Primary CtE registry data.	• Will collect data on actual adverse events, but will not have costs attached. • Can use reference costs to find cost.
Cost of AEs for SIRT and BSC	**SIRT** £7.43 (2013-14) **BSC** £42.55 (2013-14)	**Pennington et al. (2015)** total per patient costs for AE, based on Hendlisz data	• Applied once at start of model • Based on Grade 3 and 4 AE only. • Note that cost in model is different from that in paper. • There were very few AE of grades 3 or 4 in Hendlisz
	Other Intervention £3671	**Hoyle et al. (2013)** total per patient costs for AE	• Different interventions, not directly applicable • BSC based on data gathered in Karapetis RCT, calculated by Merck Sorono in their submission to NICE, reported by Hoyle, and used by PENTAG model.

	BSC £2760		• AE data not presented in Karapetis, but is presented in Jonkers (same trial), as numbers of patients experiencing AE, Hoyle uses number of AE, so hard to compare. • For PSA used gamma distribution and se of 20% of mean. • Includes grades 3 and 4. Grade 1 and 2 are assumed to be minor and require no intervention. • Included AE split to: non-serious (requiring outpatient treatment only), serious but not leading to hospitalisation, and serious leading to, or prolonging, hospitalisation. • Hoyle uses Merck Serano pricing, based on HRG groups. For AE not requiring hospitalisation, the corresponding body type/system is matched to appropriate HRG code and a mean assigned to the body type/system AE. The average cost per body type/system ranges from £106 for ocular AEs to £259 for infection and influenza-like symptom AEs. A similar method was used for serious AEs requiring hospitalisation, but in-patient procedure costs based on the HRG codes were allocated.
	BSC £426	**TA405** (NICE 2016), total per patient costs for AE	• Applied once for each patient on first cycle • Rates from RECOURSE trial
QALYs for SIRT and BSC arms	QALY for SIRT arm	Primary CtE registry data.	• EQ -5D-5L data collected but methodology limits its usefulness. Likely to be unreliable. Espectially for comparison of pre and post progression. No QALYs for pre-death state. Unlikely to capture deterioration in treatment as they are not followed up with EQ-5D-5L questionnaire after progression. High levels of missing data.
	QALY pre-progression 0.75 QALY post progression 0.69 QALY for 28 days pre death 0.1	**Pennington et al. (2015)** used **Hoyle et al. (2013)** information, to make an estimate	• Same data for used both arms
	QALY pre-progression0.75 SE 0.08 QALY post progression 0.69 se (0.07)	**Hoyle et al. (2013)**	• Took info from manufacturer and RCT (Karapetis et al. 2008), a study for advanced colorectal cancer, but with different treatments • Used a range of values that varied over time • We can only use BSC values, other values are for a drug regime. Assumed utilities to reflect both health gain from treatment and disutility due to adverse events • For PSA set se as 10% of mean, to reflect wider uncertainty than the data from the RCT (Karapetis, Khambata-Ford, Jonker, O'callaghan, Tu, Tebbutt, Simes, Chalchal, Shapiro, & Robitaille 2008)
	QALY pre-progression 0.74 **QALY post progression 0.59**	**TA405** (NICE 2016)	• From CORRECT study (Grothey et al. 2013) for Regorafenib monotherapy for previously treated metastatic colorectal cancer. • No explicit inclusion of adverse events, assumed they are captured in utilities • Values were very similar for both arms.