

# Clinical Commissioning Policy Proposition:

**Selective internal radiation therapy (SIRT) in the treatment of chemotherapy refractory and intolerant, unresectable metastatic colorectal cancer (Adults)**

Reference: NHS England: 1740



**Prepared by NHS England Specialised Services Clinical Reference Group for  
Radiotherapy CRG**

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## Contents

1	Executive Summary .....	4
	Equality Statement.....	4
	Plain Language Summary .....	4
2	Introduction .....	7
3	Proposed Intervention and Clinical Indication .....	7
4	Definitions .....	9
5	Aims and Objectives .....	11
6	Epidemiology and Needs Assessment.....	12
7	Evidence Base .....	13
8	Proposed Criteria for Commissioning.....	23
9	Proposed Patient Pathway .....	24
10	Proposed Governance Arrangements.....	24
11	Proposed Mechanism for Funding .....	24
12	Proposed Audit Requirements .....	25
13	Documents That Have Informed This Policy Proposition .....	25
14	Date of Review .....	25
15	References.....	26

# 1 Executive Summary

## Equality Statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities

## Plain Language Summary

### About Colorectal cancer

Colorectal cancer (CRC) includes cancers that develop in the colon (large bowel) and rectum. It is the third most common cancer in the United Kingdom, with around 41,000 new cases diagnosed each year and is more common in people aged over 65 years and in males than females.

Around 25% of people diagnosed with colorectal cancer will develop metastatic disease, which is where the cancer has spread to other parts of the body involving the development of secondary cancers, within six months of the initial diagnosis. This rises to over 50% of people diagnosed with colorectal cancers in time, though this can be several years following diagnosis. In most cases, colorectal cancer spreads to the liver (hepatic metastases) but it may also spread to the lungs, bones and other organs in the body (extrahepatic metastases).

### About current treatments

Metastatic colorectal cancer that has spread to the liver can be treated with surgery (resection), chemotherapy, ablation, radiotherapy and supportive care. Treatment choice largely depends on the extent of metastatic disease.

Where metastatic disease is identified at an early stage with few secondary tumours having developed in the liver, then surgery is almost always the preferred treatment choice. However, most metastatic colorectal cancer is diagnosed at stage where surgery cannot be performed because the cancer is too advanced. Where this is the case, the most common treatment is chemotherapy.

In some cases chemotherapy medicines either don't work or stop working, this is because the cancer develops resistance which is called refractory disease. For some people the side effects of chemotherapy treatments will be so significant that the treatment cannot be tolerated. In both cases, chemotherapy treatment is stopped. Further treatment options are very limited and usually aim to manage symptoms and any side effects of treatment as well as providing pain relief. This type of care is called best supportive care or palliative care.

### **About the new treatment**

Selective internal radiation therapy (SIRT) is a way of giving radiotherapy treatment to cancer in the liver. It involves injecting tiny spheres that contain a radioactive substance into blood vessels in the liver, via a tube (catheter). The spheres become lodged in the small blood vessels around the cancer and deliver radiation directly to the cancer cells which destroys them. The aim of SIRT is to control the growth of the cancer but it is not curative.

In formulating this policy proposition, NHS England has considered the place of SIRT in the treatment of chemotherapy refractory or chemotherapy intolerant, unresectable metastatic colorectal cancer (both liver-only and liver-dominant disease).

### **What we have decided**

NHS England has carefully reviewed the evidence to treat chemotherapy refractory or intolerant, unresectable metastatic colorectal cancer with SIRT and have

concluded that there is sufficient evidence to make the treatment available for adults where the metastatic disease is limited to the liver only.

## 2 Introduction

This document describes the evidence that has been considered by NHS England in formulating a proposal to routinely commission selective internal radiation therapy (SIRT) for chemotherapy refractory or intolerant, unresectable, liver-only metastatic colorectal cancer (adults only).

This document also describes the proposed criteria for commissioning, proposed governance arrangements and proposed funding mechanisms. For the purpose of consultation NHS England invites views on the evidence and other information that has been taken into account as described in this policy proposition.

A final decision as to whether SIRT for chemotherapy refractory or intolerant unresectable, liver-only metastatic colorectal cancer (adults only) will be routinely commissioned will be made by NHS England following a recommendation from the Clinical Priorities Advisory Group.

## 3 Proposed Intervention and Clinical Indication

### Clinical Indication

Colorectal cancer (CRC) includes cancers of the colon and rectum. Around half of all cases of primary CRC will, at some point, develop metastatic disease. The liver is the most common site for metastatic spread (hepatic metastases), but the disease may also spread to the lungs, bones and other organs in the body (extrahepatic metastases).

There may be no symptoms in the early stage of metastases, but in later stages, the cancer can cause the liver to swell or obstruct the normal flow of blood and bile. When this happens, the following symptoms can include, but are not limited to, loss of appetite, weight loss, dark urine, abdominal swelling or bloating and jaundice.

Long-term survival can be achieved in metastatic colorectal cancer (mCRC) if the

metastases are surgically resectable. However, only 10-20% of mCRC cases are resectable because metastatic disease is commonly diagnosed at an advanced stage meaning that surgery cannot be performed. Furthermore, recurrence of disease is common, occurring in up to 75% of patients who are able to undergo resection of colorectal liver metastases; thus, liver metastases remain a life-limiting factor for the majority of patients with mCRC.

Where resection is not possible, mCRC is treated with palliative intent, aiming to prolong life, ensure quality of life and manage pain. The most common palliative treatment option for unresectable mCRC is systemic chemotherapy, however, in some cases biological therapy will be used, either in combination with chemotherapy or on its own. Currently available chemotherapy regimens for mCRC include:

- Folinic acid given with fluorouracil and oxaliplatin (FOLFOX) as a first-line treatment, followed by single agent irinotecan as second-line treatment;
- FOLFOX as a first-line treatment followed by folinic acid given with fluorouracil and irinotecan (FOLFIRI) as a second-line treatment; or
- Capecitabine given with oxaliplatin (XELOX) as a first-line treatment, followed by FOLFIRI as a second-line treatment.

Sometimes chemotherapy treatment must be stopped earlier than planned, either because the cancer is refractory to the medicine, or because the side-effects are so significant that treatment becomes intolerable. Where this is the case, further treatment options are very limited and usually aim to manage symptoms and any side effects of treatment, as well as providing pain relief. This type of care is called best supportive care or palliative care.

### Intervention

SIRT, which may also be called radioembolisation (RE), is a way of giving radiotherapy treatment to cancer in the liver. It involves injecting glass or resin microspheres that contain a radioactive substance into the hepatic arteries via a catheter. The microspheres become lodged in the small blood vessels around the

tumour and deliver radiation directly to the cancer cells, destroying them.

Two different radioactive substances can be used, Yttrium-90 and Holmium-166. Yttrium-90 is a beta emitting isotope with a half-life of 64.2 hours and following administration, 94% of the radiation is delivered in 11 days (Murthy et al. 2008). Holmium-166 is a high-energy beta-emitting isotope with gamma emission and the half-life is 26.8 hours. More than 90% of the radiation is delivered within the first 4 days following the implantation procedure.

Currently, there are two Yttrium-90 microsphere products available to treat mCRC which has spread to the liver in the UK:

- SIR-Spheres®, which are made of resin; and
- TheraSphere®, which are made of glass.

There is only one holmium-166 microspheres available in the UK:

- QuiremSpheres®, which are made of poly-L-lactic acid.

The use of SIRT to treat unresectable colorectal cancer metastases in the liver is supported by Interventional Procedures Guidance (IPG) No. 401 (National Institute of Health and Care Excellence, 2011), which concluded that “the current evidence on the safety of SIRT for non-resectable colorectal metastases in the liver is adequate”. The IPG further noted that the evidence on efficacy of SIRT in chemotherapy-naïve patients was “inadequate in quantity” and that further evidence was needed on overall survival and quality of life for patients receiving SIRT that had previously been treated with chemotherapy.

In 2013, NHS England commissioned a Commissioning through Evaluation (CtE) programme (National Institute of Health and Care Excellence, 2017) to generate further evidence about the impact of SIRT on overall survival in chemotherapy refractory or intolerant mCRC which has spread to the liver.

## 4 Definitions

Ablation – means to destroy and in the context of treating cancer means to destroy the cancer cells. Ablation can be achieved in a number of ways, most commonly it involves the use of extremes of temperature to destroy cancer cells.

Best supportive care – is care which aims to prevent or treat as early as possible the symptoms of a disease and the side effects caused by treatment of a disease. It also aims to maintain psychological and emotional wellbeing. It is sometimes also call palliative treatment.

Biological therapy – is any form of treatment that uses the body's natural abilities, i.e., the immune system, to fight disease or infection.

Cancer – are abnormal cells that divide in an uncontrolled way and can spread elsewhere in the body.

Colorectal cancer – is where cancer first develops in either the colon (bowel) or rectum.

Chemotherapy – is a type of systemic therapy involving the use of medicines to kill the cancer cells. There are many different types of chemotherapy medicines and they all work in a similar way by stopping cancer cells reproducing, which prevents them from growing and spreading in the body. Chemotherapy also affects healthy cells and this can cause side-effects, which will vary depending on the type of cell affected.

Liver-specific progression free survival – the length of time from start of treatment to when the disease gets worse in the liver or death.

Metastasis (or secondary tumour) – the term used if the cancer has spread to other parts of the body.

Overall survival (OS) – the length of time from either diagnosis or start of treatment that the patient is still alive.

Performance status - a recognised system developed by the World Health Organisation and other bodies to describe the general health and daily activity status of patients.

Primary cancer or tumour - is the term used for where in the body that a cancer starts.

Progression free survival (PFS) – the length of time from start of treatment to when the disease gets worse or death.

Radiotherapy - is the safe use of ionising radiation to kill cancer cells with the aim of cure or effective palliation.

Selective internal radiation therapy (SIRT) – the use of microspheres containing a radioactive substance to deliver a targeted dose of radiation to a tumour in order to destroy it.

Systemic therapy – are treatments for cancer using substances that travel through the blood stream to reach and affect cells all over the body. Chemotherapy, immunotherapy and targeted agents are types of systemic therapy.

Time to liver progression – the length of time from start of treatment to when the disease gets worse in the liver. It does not include deaths.

Time to progression (TTP) – the length of time from start of treatment to when the disease gets worse. It does not include deaths.

## 5 Aims and Objectives

This policy proposition considered: the role of SIRT using yttrium-90 microspheres (glass or resin) OR holmium-166 ( $^{166}\text{Ho}$ ) microspheres as part of the treatment pathway for adults with chemotherapy refractory or chemotherapy intolerant

unresectable, liver-only or liver-dominant metastatic colorectal cancer.

The objectives were to:

- Determine the clinical effectiveness, cost effectiveness and safety of using selective internal radiation therapy (SIRT) compared with best supportive care for individuals with unresectable, liver-only or liver-dominant metastatic colorectal cancer who are chemotherapy-refractory or chemotherapy-intolerant and using:
  - glass yttrium-90 microspheres
  - resin yttrium-90 microspheres
  - holmium-166 microspheres
- Determine whether any subgroups of patients with unresectable, liver-only or liver-dominant metastatic colorectal cancer who are chemotherapy-refractory or chemotherapy-intolerant who would gain greater benefit from SIRT using:
  - glass yttrium-90 microspheres
  - resin yttrium-90 microspheres
  - holmium-166 microspheres

## 6 Epidemiology and Needs Assessment

Colorectal cancer (CRC) is the third most common cancer in the UK, with 40,755 new cases diagnosed in 2012, which is projected to rise to 58,119 cases annually by 2035. It is more common in people aged over 65 years (73.1% of new cases) and in males (55.4% of cases) than females. CRC is an important cause of death; there were 16,202 deaths in 2012 and this is expected to increase to almost 24,000 deaths annually by 2035.

Approximately half of all CRC cases will, at some point, go onto develop metastatic disease, usually involving the liver. Around 25% of people present with synchronous metastases, which are metastases that develop within six months of the initial diagnosis. Of these, only 10-20% of cases will be able to have surgical resection; the majority of mCRC cases instead have chemotherapy.

It is estimated that every year around 150 -200 adults treated with chemotherapy for mCRC will either become intolerant of the treatment or will have a cancer that is or becomes refractory to treatment. Of these, it is estimated that approximately 50 cases would be eligible for treatment with SIRT, in accordance with the clinical criteria set out within Section 8.

## 7 Evidence Base

NHS England has concluded that there is sufficient evidence to support a proposal for the routine commissioning of this treatment for the indication (liver only metastatic colorectal cancer).

To develop this policy the following evidence was used :

- The results of evidence reviews undertaken to assess the clinical effectiveness, cost effectiveness and safety of the available SIRT technologies – resin yttrium-90 microspheres, glass yttrium-90 microspheres and holmium-166 microspheres compared with best supportive care; and
- The results of the NHS England SIRT CtE programme.

### **Evidence Reviews**

**1. What is the evidence on clinical effectiveness of using SIRT with yttrium-90 and holmium-166 microspheres compared with best supportive care for individuals with unresectable, liver-dominant metastatic colorectal carcinoma who are chemotherapy-refractory or chemotherapy-intolerant?**

**a) glass yttrium-90 microspheres;**

No evidence was identified directly comparing glass yttrium-90 microspheres with best supportive care.

**b) resin yttrium-90 microspheres;**

Only 3 studies were identified that involved resin yttrium-90 microspheres as a treatment arm for individuals with unresectable, liver-dominant metastatic colorectal carcinoma (Bester et al. 2012; Hendlisz et al. 2010 and Seidensticker et al. 2012).

Hendlisz et al. (2010) was the highest quality study included in this review. It was an open-label, multi-centre (Belgium) randomised phase III trial in patients with unresectable chemotherapy-refractory liver-limited metastatic CRC comparing fluorouracil (FU) protracted intravenous infusion (n=23) to SIR-spheres plus intravenous FU (n=21). For ethical reasons, patients in the control arm with documented progression were permitted to cross over to receive SIRT, 10 patients crossed-over. Patients were followed up for a median of 24.8 months (range 2 – 41). The primary outcome was time to liver progression (TTLP) although the description provided indicated that actually liver-specific progression free survival (LPFS) is reported; patients are censored on death in LPFS and PFS but excluded in TTLP and TTP. SIRT had a significant benefit in controlling liver tumour growth, as measured by LPFS; SIRT & FU - 5.5 months vs. FU - 2.1 months; HR 0.38 (95% CIs 0.28-0.94), p=0.003. The results indicated that there was no significant overall survival (OS) advantage with SIRT; SIRT & FU - 10.0 months vs. FU - 7.3 months; HR 0.92 (0.47-1.78), p=0.80. A significant improvement in PFS (reported as TTP) for the SIRT group was reported, 4.5 vs. 2.1 months; HR 0.51 (0.28-0.94), p=0.03. Although significant improvements were observed in TTLP (LPFS) and TTP (PFS) the study was not powered to detect an overall survival benefit; the study also has several biases that may mask any OS benefit i.e. open-label design, cross-over of patients to SIRT arm and small sample size.

Seidensticker et al. (2012) was a multi-centre (Germany), retrospective comparative study in patients with chemotherapy-refractory liver dominant metastatic colorectal cancer comparing SIRT therapy (n=29) with a matched cohort of patients receiving BSC (n=29). Some patients treated with SIRT (31%) were subsequently able or willing to receive further systemic chemotherapy; exact number of patients who actually received chemotherapy is not provided. The details of the components or

nature of BSC were not provided. Length of follow-up was also not reported. Patients treated with SIRT had a longer median OS of 8.3 months (95% CI 6.6 – 10.2) vs. 3.5 months (95% CI 1.9 – 5.7); HR 0.26 (95% CI 0.15–0.48);  $p < 0.001$ . There is a high risk of bias in this study due to several factors: retrospective, non-randomised and small sample size; this may result in an overestimate of survival benefit in SIRT group.

Bester et al. (2012) was a single-institution (Australia), retrospective comparative study in patients with chemotherapy-refractory liver metastasis comparing SIRT therapy with standard care. The study also included patients with non-CRC primary cancers and some analyses were not stratified for CRC; 14.5% (49/339) of the whole SIRT group were chemo-naïve. In the mCRC group, 224 patients received SIRT therapy and 29 received standard care. 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 naïve. Length of follow-up was not reported. Median OS was improved in the SIRT group compared to standard care (11.9 vs 6.6 months; HR: 0.5, log rank test  $p = 0.001$ ). There is a high risk of bias in this study due to several factors: retrospective, non-randomised, inadequate matching of prognostic factors, small sample size of comparative arm; this may result in an overestimate of survival benefit in SIRT group.

**c) holmium-166 microspheres.**

No evidence was identified directly comparing holmium-166 microspheres with best supportive care.

**2. What is the evidence relating to the safety of SIRT with yttrium-90**

**microspheres and holmium-166 compared with best supportive care for individuals with unresectable, liver-dominant metastatic colorectal carcinoma who are chemotherapy-refractory or chemotherapy-intolerant?**

**a) glass yttrium-90 microspheres;**

No evidence was identified directly comparing glass yttrium-90 microspheres with best supportive care.

**b) resin yttrium-90 microsphere;**

The 3 studies (Bester et al. 2012; Hendlisz et al. 2010 and Seidensticker et al. 2012) that involved resin yttrium-90 microspheres as a treatment arm for individuals with unresectable, liver-dominant metastatic colorectal carcinoma also reported adverse events

Hendlisz et al. (2010) was an open-label, multi-centre (Belgium) randomised phase III trial in patients with unresectable chemotherapy-refractory liver-limited metastatic CRC comparing a protracted intravenous infusion of fluorouracil (FU) (n=23) to SIR-spheres plus intravenous FU (n=21). Ten patients in the control arm with documented progression were permitted to cross over to receive SIRT. Toxicity analysis was conducted in 43 patients (22 in FU group and 21 SIRT & FU group). Two patients (both in FU group) were never treated and so were not evaluated for toxicity. Grade 3 or 4 toxicities were recorded in six patients after FU monotherapy and in one patient after SIRT plus FU treatment (P=0.10).

Seidensticker et al. (2012) was a multi-centre (Germany), retrospective comparative study in patients with chemotherapy-refractory liver dominant metastatic colorectal cancer comparing SIRT therapy (n=29) with a matched cohort of patients receiving BSC (n=29). Some patients treated with SIRT (31%) were subsequently able or willing to receive further systemic chemotherapy; exact number of patients who actually received chemotherapy is not provided. The details of the components or nature of BSC were not provided. Treatment-related adverse events following

radioembolization included: grade 1–2 fatigue (n = 20, 69%) in the first 14 days post-radioembolization; grade 1 mild abdominal pain/nausea (n = 14, 48.3%), and grade 2 gastrointestinal ulceration (n = 3, 10.3%). Three cases (10.3%) of grade 3 radiation-induced liver disease were not deemed to be life-threatening. Adverse events in the comparator arm were not reported.

Bester et al. (2012) was a single-institution (Australia), retrospective comparative study in patients with chemotherapy-refractory liver metastasis comparing SIRT therapy with standard care. The study also included patients with non-CRC primary cancers and some analyses were not stratified for CRC; 14.5% (49/339) of the whole SIRT group were chemo-naïve. In the mCRC group 224 patients received SIRT therapy and 29 standard care. Adverse events occurred in 22% of patients immediately after radioembolization, which were minor abdominal pain, nausea, and vomiting. At the 1-month follow-up after radioembolization, adverse events were minor and easily medically managed; including one case of radiation induced liver disease (RILD). At the 3 month follow-up adverse events were all medically managed, with no deaths within the 3-month follow-up period caused by the radioembolization procedure. There were no known cases of radiation pneumonitis. Adverse events in the supportive care arm were not reported.

**c) holmium-166 microspheres.**

No evidence was identified directly comparing holmium-166 microspheres with best supportive care.

**3. What is the evidence on the cost effectiveness of SIRT with yttrium-90 microspheres and holmium-166 compared with best supportive care for individuals with unresectable, liver-dominant metastatic colorectal carcinoma who are chemotherapy-refractory or chemotherapy-intolerant?**

One study (Pennington et al. 2015) was identified that evaluated the cost-effectiveness of SIRT compared with SC in patients with inoperable chemotherapy-refractory colorectal cancer liver metastases. It used a 3 state partitioned survival

model. Radioembolization using yttrium-90 resin microspheres compared to SC increased overall survival (OS) by a mean of 1.12 life years in the model and resulted in a cost per QALY gained of £28,216 and cost per life year gained of £20,323. The total cost was £35,487 for SIRT and £12,730 for SC, a difference of £22,757. The model uses survival data from an unmatched retrospective comparative study (Bester et al. 2012), which is at risk of bias, and standard care is not defined. 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. The selection of optimistic inputs for SIRT may underestimate the overall cost per QALY and ICER reported in the model. The cost of the SIRT procedure was inadequately explored in the sensitivity analysis. With the highlighted issues of the model the cost-effectiveness estimates cannot be considered reliable. No cost-effectiveness evidence was identified in relation to SIRT with holmium-166.

**4. Does the evidence of clinical and cost-effectiveness identify any subgroups of patients with unresectable, liver-dominant metastatic colorectal carcinoma who are chemotherapy-refractory or chemotherapy-intolerant who would gain greater benefit from using SIRT with yttrium-90 or holmium-166 microspheres compared with best supportive care?**

Neither Bester et al. (2012) or Hendlisz et al. (2010) reported any subgroup analysis that enabled the identification of any patient sub-groups who would gain greater benefit from SIRT compared to BSC.

Seidensticker et al. (2012) conducted multivariate analysis to identify prognostic markers of improved survival; however, patients from both treatment groups (SIRT and BSC) were included and therefore this analysis does not indicate whether any subgroups would gain a greater benefit from using SIRT with yttrium-90 compared with BSC.

No evidence was identified directly comparing holmium-166 microspheres with best supportive care.

### **SIRT CtE programme**

The objective of the CtE programme was to evaluate the clinical and cost-effectiveness of SIRT in patients with unresectable colorectal cancer liver metastases which has progressed following standard chemotherapy (National Institute for Health and Care Excellence, 2017). The single-arm SIRT CtE registry study was carried out in 10 NHS centres in England between December 2013 and March 2017. Data on patients' baseline characteristics, the SIRT procedure, safety, survival, health-related quality of life were collected in a registry. Patients were followed-up for a median of 14.3 months (95% confidence intervals 9.2-19.4).

A total of 399 patients with colorectal cancer treated with SIRT using yttrium-90 (86% resin and 14% glass) microspheres were included in the analysis. 93% of patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, 60% did not have extrahepatic disease, and 78% of patients received 2 or 3 lines of chemotherapy prior to SIRT. Patients required a hospital stay of 1 or 2 nights for the SIRT procedure.

Median overall survival was 7.6 months (95% CIs 6.9-8.3) and survival at 12 months following SIRT was 30%. Median progression-free survival was 3.0 months (95% CIs 2.8-3.1) and median liver-specific progression-free survival was 3.7 months (95% CIs 3.2-4.3). Subgroup analyses (Table 1 and 2) showed that absence of extrahepatic disease, fewer liver tumours, smaller tumour to liver volume percentage, were factors associated with an increased survival benefit (Cedar, 2017).

**Table 1 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						
1 line	32	19	11.3	4.9-17.6	Ref	Ref
2 lines	210	127	7	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)	0.61
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

**Table 2 Kaplan-meier analysis and univariate Cox proportional hazards model of survival by additional baseline characteristics in the colorectal population**

Subgroup	n (pts)	n (events)	Median OS (months)	OS 95% CIs	Hazard ratio (95% CIs)	p-value
Patients without extrahepatic mets AND 1-5 tumours (log-rank p 0.002)						
Yes	64	33	11.3	8.1-14.5	0.562 (0.389-0.814)	0.002
No	315	207	7.3	6.4-8.1		
Patients without extrahepatic mets AND tumour to liver volume of ≤25% (log-rank p 0.002)						
Yes	143	83	9.7	7.4-11.9	0.653 (0.500-0.853)	0.002
No	236	157	6.5	5.6-7.4		
Patients without extrahepatic mets AND 5 or less liver tumours AND tumour to liver volume of ≤25% (log-rank p 0.002)						
Yes	53	27	12.9	9.1-16.6	0.533 (0.356-0.798)	0.002
No	326	213	7.3	6.5-8.1		

Health related quality of life measured using EQ-5D-5L and EQ-VAS remained relatively high and constant before and after the SIRT procedure. A statistically significant reduction in health related quality of life was observed 3 months following SIRT but this was small and not clinically relevant. No significant change was observed at 6 and 9 months, although the number of respondents was small.

Severe complications on the day of treatment were reported in 11 patients (3%). During the follow-up period, 36% of patients experienced an adverse event, of which 8% of the events were grade 3 and above (severe). The most frequently reported adverse events were mild fatigue and abdominal pain.

A new cost-effectiveness model was created using the outputs of the registry. The incremental cost-effectiveness ratio (ICER) for SIRT compared to best supportive care was £85,350 in the base case. 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 best supportive care (£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. Scenario analysis where a longer survival estimate and a lower procedure cost were used with a longer time horizon, based on the published model by Pennington et al. (2015), resulted in a lower ICER of £31,888. This demonstrates the impact of the overall survival and the procedure cost on the model outcomes.

## Conclusion

The evidence review assessing yttrium-90 microspheres identifies one small open label RCT in patients with unresectable chemotherapy-refractory liver-limited metastatic CRC comparing SIRT plus fluorouracil chemotherapy with fluorouracil chemotherapy alone, demonstrated a significant benefit in controlling liver tumour growth, as measured by LPFS. Two non-randomised retrospective studies indicate that SIRT may improve overall survival in patients with unresectable, chemotherapy-refractory or chemotherapy-intolerant, liver-dominant metastatic colorectal carcinoma compared to standard care.

The evidence review assessing holmium-166 microspheres did not identify any studies directly comparing holmium-166 microspheres with best supportive care.

These evidence reviews highlight the lack of well-designed prospective comparative studies of SIRT and BSC to provide reliable evidence of survival outcomes. High quality data would also enable more accurate modelling of the cost-effectiveness of SIRT compared to BSC. There is a need for studies that evaluate the impact of SIRT on patients' quality of life.

The aim of the CtE project was to generate new evidence from real-world settings to enable a judgement on clinical and cost-effectiveness of SIRT in the identified populations. Outcomes data (progression free and overall survival) from SIRT procedures done in the CtE scheme are comparable to those in published evidence and do not show significant benefit compared with best supportive care. The additional register-derived evidence is at risk of bias because of the study design (particular problems being incomplete data submission, lack of validation because of data protection requirements and lack of real world comparators).

New cost modelling, undertaken as part of the CtE project, showed an ICER of £85,350 for SIRT compared with best supportive care. The cost of the SIRT procedure and the survival time were the main drivers in the new cost model. Scenario analysis where a longer survival estimate and a lower procedure cost were used with a longer time horizon, based on the published model by Pennington et al.

(2015), resulted in a lower ICER of £31,888. Subgroup analyses of the register data showed that absence of extrahepatic disease (also termed liver dominant disease), fewer liver tumours, smaller tumour to liver volume percentage, were factors associated with a survival benefit.

## 8 Proposed Criteria for Commissioning

Adults with chemotherapy refractory or chemotherapy intolerant unresectable, liver only metastatic colorectal cancer that meet all of the following criteria will be eligible for treatment with SIRT using resin yttrium-90 microspheres:

- Discussion at a specialist hepatobiliary MDT;
- Histologically confirmed carcinoma with liver-specific metastases not amenable to curative liver surgical resection;
- Unequivocal and measurable CT evidence of liver metastases which are not treatable by surgical resection or local ablation with curative intent;
- Life expectancy > 3 months;
- 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;
- Adequate haematological and hepatic function as follows:
  - serum bilirubin  $\leq 1.5 \times \text{ULN}$ ;
  - absolute neutrophil count  $> 1.5 \times 10^9/\text{L}$ ;
  - platelets  $> 100 \times 10^9/\text{L}$ ;
  - albumin  $\geq 30 \text{ g/L}$ ;
- No evidence of ascites, cirrhosis or portal hypertension;
- No previous portal venous embolisation or previous chemo-embolisation;
- No previous radiotherapy to the upper abdomen or the right lower thorax;
- No extrahepatic metastases;
- Five or fewer liver tumours;
- Percentage tumour to liver volume  $\leq 25\%$ ; and
- World Health Organisation (WHO) performance status 0-1.

## 9 Proposed Patient Pathway

There is a published service specification for SIRT which was developed to support the CtE programme and requires that:

- A multidisciplinary team (MDT) approach must be in place to ensure appropriate patient selection and treatment;
- The specialised MDT must meet the Peer Review cancer standards and offer the full range of liver-directed treatment options for the indications agreed, offering genuine choice between clinically suitable options all cases must be discussed at an appropriate MDT with liver surgery representation;
- Centres should have a minimum of two interventional radiology operators and a minimum of two Administration of Radioactive Substances Advisory Committee (ARSAC) licence holders for SIRT;
- Centres should have adequate MDT, radio-pharmacy and Interventional Radiology capacity to support 10-20 cases per annum;
- Procedures should be performed in an interventional radiology suite that is equipped with cone-beam CT;
- There should be a SIRT nurse co-ordinator to provide individual expert advice and support for the whole SIRT patient pathway; and
- Provide detailed radiation protection advice to patients and their partners.

## 10 Proposed Governance Arrangements

The SIRT service specification describes the governance arrangements for this service. In particular, the Ionising Radiation (Medical Exposure) Regulations (IR(ME)R) 2000. It is mandatory that SIRT practitioners are able to demonstrate the completion and maintenance of suitable training and experience in SIRT.

## 11 Proposed Mechanism for Funding

SIRT, as a form of brachytherapy, is reimbursed through local currencies and pricing

arrangements, in accordance with the National Tariff Payment System.

## **12 Proposed Audit Requirements**

Centres will need to demonstrate audit of clinical outcomes through the British Society of Interventional Radiologists (BSIR) SIRT Registry, or a centre's own collection process with equivalent clinical data, for all SIRT patients treated and these data should be available for evaluation.

## **13 Documents That Have Informed This Policy Proposition**

- Policy Statement: Selective Internal Radiotherapy (SIRT) (reference: B01/PS/a). It is important to note that this policy statement will lapse on publication by NHS England of a clinical commissioning policy for the proposed intervention; and
- Selective Internal Radiotherapy Service Specification (NHS England, 2014).

## **14 Date of Review**

This document will lapse upon publication by NHS England of a clinical commissioning policy for the proposed intervention that confirms whether it is routinely or non-routinely commissioned.

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