NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of selective internal radiation therapy for unresectable colorectal metastases in the liver

Bowel cancer that has spread to other parts of the body is called colorectal metastases. In the liver this can be unresectable (can't be removed using surgery). In this procedure tiny radioactive 'beads' are injected into blood vessels supplying the colorectal metastases, where they become trapped. The beads release radiation directly into the cancer cells. The aim is to destroy the cancer cells while causing as little damage to surrounding healthy tissue as possible.

Contents

Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedure overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in April 2019.

Procedure name

- Selective internal radiation therapy for unresectable colorectal metastases in the liver.

Specialist societies

- Royal College of Radiologists
- British Society of Interventional Radiologists
- British Nuclear Medicine Society
- BASO ~ The Association for Cancer Surgery
- British Society of Gastrointestinal and Abdominal Radiology
- Association of Upper Gastrointestinal Surgeons of Great Britain & Ireland.

Description of the procedure

Indications and current treatment

Colorectal cancer is a common cancer. It generally occurs in people older than 50 years, with the risk increasing with age. About 30% to 50% of patients with colorectal cancer will either have liver metastases at the time of presentation or develop them later during the course of their disease.

Treatment of liver (hepatic) metastases depends on their extent and location. Treatment options for unresectable tumours include thermal ablation techniques,

chemotherapy, different types of arterial embolisation therapy and external beam radiotherapy.

Selective internal radiation therapy (SIRT; also known as radioembolisation) can be used as palliative treatment for unresectable colorectal metastases in the liver. It may also be used as a neoadjuvant treatment in patients being considered for curative treatments such as resection or liver transplantation. It aims to deliver radiation directly into the tumour, minimising the risk of radiation damage to surrounding healthy tissue.

What the procedure involves

SIRT involves delivering microspheres containing radionuclides that emit beta radiation directly into the tumour via the hepatic artery. Under local anaesthesia with fluoroscopic guidance, the radioactive microspheres, which are made of glass, resin or poly(L-lactic acid), are injected into branches of the hepatic artery supplying the tumour. A percutaneous approach through the femoral or radial artery is used. The microspheres are designed to lodge in the small arteries within and surrounding the tumour and release high doses of radiation directly into the tumour. The procedure may be repeated depending on the response.

Outcome measures

The **World Health Organization (WHO)** criteria for tumour response assessment are:

- complete response (CR): disappearance of target tumour
- partial response (PR): more than 50% reduction in tumour size
- no response (NR) or stable disease (SD): less than 50% reduction in tumour size and less than 25% increase in tumour size
- progressive disease (PD): more than 25% increase in tumour size.

Objective response is the aggregation of CR and PR results.

The **Response Evaluation Criteria in Solid Tumours (RECIST)** criteria for tumour response assessment are:

- CR: disappearance of all target lesions
- PR: at least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD

- SD: insufficient shrinkage to qualify for PR or insufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

- PD: at least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of 1 or more new lesions.

National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE)

- Grade 1: mild adverse event
- Grade 2: moderate adverse event
- Grade 3: severe adverse event
- Grade 4: life-threatening or disabling adverse event
- Grade 5: death related to adverse event.

Efficacy summary

Overall survival

First-line SIRT

In an analysis of 3 randomised controlled trials (RCTs) comparing 554 patients who had SIRT plus chemotherapy with 549 who had chemotherapy alone, overall survival was 78% compared with 75% (pooled hazard ratio [HR] 1.04, 95% confidence interval [CI] 0.90 to 1.19, p=0.61). Median survival was 22.6 months (95% CI 21.0 to 24.5) in the SIRT group and 23.3 months (95% CI 21.8 to 24.7) in the chemotherapy alone group.[1]

In a post-hoc analysis of 2 of the 3 RCTs (n=739) analysing the effect of the primary colorectal tumour side, median overall survival in patients with a right-sided primary was 22.0 months (95% CI 18.9 to 25.6) in the SIRT group compared with 17.1 (95% CI 13.9 to 19.9) in the chemotherapy alone group (p=0.008). For patients with a left-sided primary, median overall survival was 24.6 months (95% CI 22.3 to 26.7) in the SIRT group and 26.6 months (95% CI 24.8 to 29.9) in the chemotherapy alone group (p=0.264).[2]

Patients with chemotherapy-refractory colorectal cancer liver metastases

In an RCT of 44 patients comparing SIRT plus chemotherapy with chemotherapy alone, median overall survival was 10.0 and 7.3 months respectively, p=0.80.[3]

In a non-randomised comparative study of 390 patients, 59% (201/339) of patients who had SIRT died during the study period compared with 76% (39/51) of patients who had standard care. Median overall survival was 11.9 months (95% CI 10.1 to 14.9) in patients with colorectal cancer liver metastases who had SIRT compared with 6.6 months in the standard care cohort (p=0.001). On multivariate analysis, SIRT was a significant predictor of overall survival (HR 0.57, 95% CI 0.41 to 0.82, p=0.002).[4]

In a non-randomised comparative study of 58 patients, median overall survival was 8.3 months for patients who had SIRT and 3.5 months for patients who had best supportive care (HR 0.26, 95% CI 0.15 to 0.48, p<0.001). Survival at 3 months was 97% in the SIRT group compared with 59% in the best supportive care group and at 12 months it was 24% compared with 0%.[5]

In a case series of 399 patients, overall survival after SIRT was 7.6 months (95% CI 6.9 to 8.3). Survival rates were 92%, 83%, 30%, 7% and 0% at 3, 6, 12, 24 and 36 months respectively.[6]

In a case series of 606 patients, overall survival was 45%, 19% and 7% at 1, 2 and 3 years respectively.[7]

In a case series of 531 patients, median overall survival was 48.7 months (95% CI 44.2 to 53.2) from diagnosis of the primary tumour, 37.7 months (95% CI 33.7 to 41.7) from diagnosis of hepatic metastases, 10.6 months (95% CI 8.8 to 12.4) from the first SIRT and 17.5 months (95% CI 15.3 to 19.7) from hepatic metastases to SIRT. For patients with no extrahepatic metastases, median overall survival was 14.4 months after SIRT (95% CI 12.7 to 16.1) compared with 6.6 months (95% CI 5.2 to 8.1) for patients with extrahepatic metastases (p<0.001).[8]

Progression-free survival

First-line SIRT

In the 3 RCTs of 1,103 patients, the proportion of patients with observed radiological progression or who died before progression was 86% (474/554) in the SIRT group and 85% (467/549) in the chemotherapy alone group (pooled HR for progression-free survival=0.90, 95% CI 0.79 to 1.02, p=0.11). Median progression-free survival was 11.0 months (95% CI 10.2 to 11.8) compared with 10.3 months (9.7 to 10.9).[1]

In the post-hoc analysis of 739 patients, median progression-free survival in patients with a right-sided primary was 10.8 months (95% CI 9.3 to 12.4) in the SIRT group compared with 8.7 (95% CI 7.8 to 10.9) in the chemotherapy alone group (p=0.056). For patients with a left-sided primary, median progression-free survival was 11.4 months (95% CI 10.1 to 12.6) in the SIRT group and 10.8 months (95% CI 9.9 to 12.3) in the chemotherapy alone group (p=0.351).[2]

Patients with chemotherapy-refractory colorectal cancer liver metastases

In the RCT of 44 patients, median time to progression was 4.5 months in the SIRT group and 2.1 months in the chemotherapy alone group, p=0.03.[3]

In the non-randomised comparative study of 58 patients, median progression-free survival was 5.5 months for patients who had SIRT and 2.1 months for patients who had best supportive care.[5]

In the case series of 399 patients, median progression-free survival was 3.0 months (95% CI 2.8 to 3.1). Median liver-specific progression-free survival was 3.7 months (95% CI 3.2 to 4.3).[6]

Tumour response

First-line SIRT

In the 3 RCTs of 1,103 patients, an objective response (complete or partial) was reported in 72% (400/554) of patients who had SIRT compared with 63% (346/549) of patients who had chemotherapy alone (pooled odds ratio [OR] 1.52, 95% CI 1.18 to 1.96, p=0.0012). The pooled OR for an objective response in the liver was 1.78 (95% CI 1.37 to 2.31, p<0.0001).[1]

Patients with chemotherapy-refractory colorectal cancer liver metastases

In the RCT of 44 patients, a PR or SD was reported in 86% (18/21) of patients who had SIRT compared with 35% (8/23) of patients who had chemotherapy alone.[3]

In the non-randomised comparative study of 58 patients, 41% (12/29) of patients had a PR after SIRT, 17% (5/29) had SD, 38% (11/29) had PD and 1 patient could not be evaluated.[5]

Resectability

First-line SIRT

In the 3 RCTs of 1,103 patients, 17% (94/554) of patients who had SIRT had a hepatic resection during follow up compared with 16% (88/549) of patients who had chemotherapy alone (pooled OR 1.07, 95% CI 0.78 to 1.48, p=0.67).[1]

Patients with chemotherapy-refractory colorectal cancer liver metastases

In the RCT of 44 patients, 1 patient who had SIRT had a tumour that was sufficiently downsized for a right hepatectomy.[3]

Safety summary

Overall

The odds of a patient having a grade 3 or worse adverse event were higher in the SIRT group than in the chemotherapy alone group (pooled OR 1.42, 95% CI 1.09 to 1.85, p=0.0089) in the analysis of 3 RCTs.[1]

After SIRT, 36% (143/399) of patients had an adverse event in the case series of 399 patients; 8% of the events were grade 3 or above.[6]

Death

Treatment-related deaths were reported in 8 patients who had SIRT (3 radiation-induced liver disease, 2 complications of surgery, 1 liver failure, 1 drug-induced pneumonitis and 1 off-target delivery of microspheres) and 3 patients who had chemotherapy alone (1 complications of surgery, 1 neutropenic sepsis and 1 bowel perforation) in the 3 RCTs of 1,103 patients. There were 2 additional deaths caused by hepatic events in the SIRT group after the main safety window until the end of the follow-up period.[1]

Haematological adverse events

Grade 3, 4 and 5 haematological adverse events were reported in 28% (144/507), 17% (86/507) and less than 1% (1/507) of patients who had SIRT and 19% (108/571), 10% (56/571) and less than 1% (1/571) of patients who had chemotherapy alone in the 3 RCTs of 1,103 patients.[1]

Diarrhoea

Grade 3 or 4 diarrhoea was reported in a similar proportion of patients who had SIRT or chemotherapy alone (7% in both groups; 34/507 and 37/571) in the 3 RCTs of 1,103 patients.[1]

Diarrhoea was reported in 2% (10/531) of patients in the case series of 531 patients.[8]

Pulmonary embolism

Grade 3 or 4 pulmonary embolism was reported in 6% (28/507) of patients who had SIRT and 5% (26/571) of patients who had chemotherapy alone in the 3 RCTs of 1,103 patients.[1]

Pulmonary embolism was reported in 1 patient in the case series of 399 patients.[6]

Peripheral neuropathy

Grade 3 or 4 peripheral neuropathy was reported in 4% (18/507) of patients who had SIRT and 6% (33/571) of patients who had chemotherapy alone in the 3 RCTs of 1,103 patients.[1]

Abdominal pain

Grade 3 or 4 abdominal pain was reported in 6% (31/507) of patients who had SIRT and 2% (13/571) of patients who had chemotherapy alone in the 3 RCTs of 1,103 patients.[1]

There were 3 reports of grade 3 or above abdominal pain in the case series of 399 patients.[6] Abdominal pain or discomfort was reported in 34% (182/531) of patients in the case series of 531 patients.[8]

Ascites

Grade 3 ascites was reported in 1% (6/507) of patients who had SIRT and 1% (4/571) of patients who had chemotherapy alone in the 3 RCTs of 1,103 patients.[1]

Ulcer

Gastric ulcer was reported in 2% (12/507) of patients who had SIRT and no patients who had chemotherapy alone in the 3 RCTs of 1,103 patients.[1]

Duodenal or gastric ulcer (grade 3) was reported in 1% (3/339) of patients who had SIRT in the non-randomised comparative study of 390 patients.[4]

Gastrointestinal haemorrhage

Gastrointestinal haemorrhage was reported in 1% (5/507) of patients who had SIRT and less than 1% (1/571) of patients who had chemotherapy alone in the 3 RCTs of 1,103 patients.[1]

Radioembolisation-induced liver disease

Radioembolisation-induced liver disease (grade 3) was reported in 10% (3/29) of patients who had SIRT in the non-randomised comparative study of 58 patients.[5]

Radiation hepatitis was reported in 1% (6/507) of patients who had SIRT and no patients who had chemotherapy alone in the 3 RCTs of 1,103 patients. This includes 2 patients who died.[1]

Hepatic failure

Hepatic failure was reported in less than 1% (2/507) of patients who had SIRT and no patients who had chemotherapy alone in the 3 RCTs of 1,103 patients. This includes 1 patient who died.[1]

Biochemical evidence of liver toxicity

Grade 3 or 4 biological toxicity affecting the following factors was reported in the case series of 531 patients: bilirubin (13%), alkaline phosphatase (9%), albumin (8%), aspartate transaminase (3%) and alanine transaminase (less than 1%).[8]

There were 18 reports of grade 3 or above abnormal laboratory results in the case series of 399 patients.[6]

Fatigue

There were 8 reports of grade 3 or above fatigue in the case series of 399 patients.[6]

Fatigue was reported in 55% (290/531) of patients in the case series of 531 patients.[8]

Other

Hand-foot syndrome (grade 3) was reported in 1 patient who had SIRT in the RCT of 44 patients.[3]

Acute kidney injury (grade 3), bowel obstruction (grade 3), liver abscess (grade 3), skin rash (grade 3), fever (grade 3 or above), delirium or dementia (grade 4) and sepsis (grade 4) were each reported in 1 patient in the case series of 399 patients.[6]

Anecdotal and theoretical adverse events

In addition to safety outcomes reported in the literature, specialist advisers are asked about anecdotal adverse events (events which they have heard about) and about theoretical adverse events (events which they think might possibly occur,

even if they have never happened). For this procedure, specialist advisers did not list any additional anecdotal adverse events. They considered that the following was a theoretical adverse event: non-implantation of SIRT in target organ because of catheter movement (for example, implantation in bowel).

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to SIRT for non-resectable colorectal metastases in the liver. The following databases were searched, covering the period from their start to 26 March 2019: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see the literature search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with unresectable colorectal metastases in the liver.
Intervention/test	Selective internal radiation therapy.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on about 3,100 patients from 4 RCTs (3 were analysed together in a single report [study 1] and 2 of these 3 were also used for a post-hoc analysis, reported in a single study [study 2]), 2 non-randomised comparative studies, and 3 case series.[1–8]

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) are listed in the appendix.

Table 2 Summary of key efficacy and safety findings on selective internal radiation therapy for unresectable colorectal metastases in the liver

Study 1 Wasan HS (2017)

Details

Study type	**3 randomised controlled trials (RCTs): FOXFIRE, SIRFLOX, FOXFIRE-Global**
Country	Australia, Belgium, France, Germany, Israel, Italy, New Zealand, Poland, Portugal, Republic of Korea, Singapore, Spain, Switzerland, Taiwan, UK, US.
Recruitment period	2006 to 2014
Study population and number	**n=1,103** (554 selective internal radiation therapy [SIRT] plus chemotherapy [FOLFOX: leucovorin, fluorouracil, and oxaliplatin] versus 549 chemotherapy alone) **Patients with liver-only or liver-dominant metastatic colorectal cancer**
Age and sex	• SIRT plus chemotherapy: median 63 years (range 28 to 89); 66% (363/554) male • Chemotherapy alone: median 63 years (range 23 to 89); 66% (361/549) male
Patient selection criteria	Patients had to be eligible for systemic chemotherapy as first-line treatment for metastatic colorectal cancer. Inclusion criteria included histologically confirmed colorectal cancer with liver-only or liver-dominant metastases with or without the primary tumour in situ, WHO performance status of 0 or 1, limited extrahepatic disease, age 18 years or over, and life expectancy 3 months or longer. Exclusion criteria included ascites, cirrhosis, or portal hypertension; thrombosis of the main portal vein; and peripheral neuropathy grade 1 or worse.
Technique	All patients had systemic FOLFOX chemotherapy. SIRT therapy used SIR-Spheres Y-90 resin microspheres (Sirtex Medical Limited, Australia).
Follow-up	**Median 43 months**
Conflict of interest/source of funding	The SIRFLOX and FOXFIRE-Global studies were sponsored by Sirtex, who also provided an unrestricted educational grant for the FOXFIRE study. Declaration of interests include grants, personal fees, and non-financial support from companies including Sirtex Medical, Merck, Roche, Amgen, and Pfizer.

Analysis

Follow-up issues: Patients were assessed by CT scan every 8 to 12 weeks until hepatic progression. All patients were followed up until death or for a minimum of 2 years.

Study design issues: Patients were randomly assigned to FOLFOX chemotherapy alone or FOLFOX chemotherapy plus SIRT with minimisation, based on the strata metastasis site (liver only or liver plus extrahepatic metastasis), extent of tumour involvement of the liver (≤25% or >25%), planned use of a biological agent, and investigational centre. Randomisation was done centrally. None of the trials were masked. The primary outcome of the analysis was overall survival, defined as the time from randomisation to death from any cause, with patients who were still alive censored at their last known follow-up date. Secondary outcomes included progression-free survival, liver-specific progression-free survival, health related quality of life, tumour response, liver resection rate, and adverse event profiles. Response Evaluation Criteria in Solid Tumours (RECIST) was used to assess overall and hepatic progression.

Study population issues: Minimisation factors and other baseline characteristics were evenly balanced between treatment groups and between trials. Of the 1,103 patients, 59 (5%) had had previous adjuvant chemotherapy.

Other issues: The authors noted that there were significant changes to the management of metastatic colorectal cancer over the 8-year recruitment period, with the introduction of bevacizumab and epidermal growth factor receptor (EGFR) inhibitors as first-line standards of care, and increased use of liver interventions such as surgery and ablation.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **1,103 (554 versus 549)**

66 (12%) patients in the chemotherapy alone group had SIRT in a later course of treatment, whereas 47 (8%) of patients randomised to SIRT did not have it.

Overall survival

There were 844 (77%) deaths in the intention-to-treat population over the follow-up period (433 [78%] in the chemotherapy plus SIRT group and 411 [75%] in the chemotherapy alone group). **Pooled Hazard ratio (HR)=1.04, 95% CI 0.90 to 1.19, p=0.61**

Median survival time (months):

- Chemotherapy plus SIRT=22.6 (95% CI 21.0 to 24.5)
- Chemotherapy alone=23.3 (95% CI 21.8 to 24.7)

Overall survival in liver-metastasis only group

- Chemotherapy plus SIRT=74% (264/355), median survival time=24.5 months (95% CI 22.3 to 26.3)
- Chemotherapy alone=73% (261/358), median survival time=24.6 months (95% CI 22.1 to 26.4)

Pooled HR=1.00, 95% CI 0.85 to 1.19, p=0.96

Proportion of patients with observed radiological progression or who died before progression

- Chemotherapy plus SIRT=86% (474/554)
- Chemotherapy alone=85% (467/549)

Pooled HR for progression-free survival=0.90, 95% CI 0.79 to 1.02, p=0.11

Median progression-free survival (months)

- Chemotherapy plus SIRT=11.0 (95% CI 10.2 to 11.8)
- Chemotherapy alone=10.3 (9.7 to 10.9)

Proportion of patients in liver-metastasis only group with observed radiological progression or who died before progression

- Chemotherapy plus SIRT=82% (292/355), median survival=11.9 months (95% CI 11.0 to 13.8)
- Chemotherapy alone=83% (297/358), median progression-free survival=11.1 months (95% CI 10.0 to 12.1)

Pooled HR=0.86, 95% CI 0.73 to 1.01, p=0.066

Cumulative incidence of progression in the liver within 12 months

- Chemotherapy plus SIRT=22% (95% CI 19 to 26)
- Chemotherapy alone=39% (95% CI 35 to 43)

Cumulative incidence of progression outside the liver or death before recorded radiological progression within 12 months

- Chemotherapy plus SIRT=33% (95% CI 29 to 37)
- Chemotherapy alone=19% (95% CI 16 to 23)

Proportion of patients in whom first progression was extrahepatic or death occurred before recorded radiological progression

- Chemotherapy plus SIRT=54% (301/554)
- Chemotherapy alone=36% (196/549)

Objective (complete or partial) response

- Chemotherapy plus SIRT=72% (400/554)
- Chemotherapy alone=63% (346/549)

Pooled OR 1.52, 95% CI 1.18 to 1.96, p=0.0012)

Objective response in the liver

Pooled OR 1.78, 95% CI 1.37 to 2.31, p<0.0001)

Proportion of patients who had hepatic resection during follow-up

- Chemotherapy plus SIRT=17% (94/554)
- Chemotherapy alone=16% (88/549)

Pooled OR 1.07, 95% CI 0.78 to 1.48, p=0.67)

Quality of life

Average unadjusted EQ-5D-3L utility scores were not statistically significantly different between treatment groups at any time point except at 2 to 3 months; however, the difference was not clinically meaningful.

Sensitivity analyses excluding all ineligible patients indicated that the findings were robust.

Safety

Adverse events reported in each treatment group (graded using the National Cancer Institute Common Terminology Criteria for Adverse Events) – up to 28 days after the end of protocol chemotherapy or in the first 7 months after randomisation, whichever was earlier

	Chemotherapy plus SIRT, n=507				Chemotherapy only, n=571			
	Grade 1 to 2	Grade 3	Grade 4	Grade 5	Grade 1 to 2	Grade 3	Grade 4	Grade 5
Overall	131 (26%)	239 (47%)	126 (25%)	10 (2%)	189 (33%)	266 (47%)	103 (18%)	11 (2%)
Haematological	109 (21%)	144 (28%)	86 (17%)	1 (<1%)	102 (18%)	108 (19%)	56 (10%)	1 (<1%)
Neutropenia	55 (11%)	115 (23%)	71 (14%)	0	50 (9%)	89 (16%)	48 (8%)	1 (<1%)
Febrile neutropenia	0	25 (5%)	7 (1%)	1 (<1%)	0	11 (2%)	5 (1%)	0
Thrombocytopenia	153 (30%)	37 (7%)	2 (<1%)	0	77 (13%)	6 (1%)	1 (<1%)	0
Leukopenia	41 (8%)	20 (4%)	10 (2%)	0	28 (5%)	10 (2%)	3 (1%)	0
Non-haematological	219 (43%)	218 (43%)	59 (12%)	9 (2%)	265 (46%)	232 (41%)	61 (11%)	10 (2%)
Fatigue	261 (51%)	43 (8%)	0	0	275 (48%)	28 (5%)	0	0
Diarrhoea	189 (37%)	33 (7%)	1 (<1%)	0	256 (45%)	35 (6%)	2 (<1%)	0
Pulmonary embolism	2 (<1%)	4 (1%)	24 (5%)	0	1 (<1%)	7 (1%)	19 (3%)	0
Neuropathy peripheral	273 (54%)	18 (4%)	0	0	307 (54%)	32 (6%)	1 (<1%)	0
Abdominal pain	151 (30%)	30 (6%)	1 (<1%)	0	95 (17%)	13 (2%)	0	0
SIRT-associated	52 (10%)	24 (5%)	3 (1%)	3 (1%)	13 (2%)	9 (2%)	1 (<1%)	0
Ascites	23 (5%)	6 (1%)	0	0	2 (<1%)	4 (1%)	0	0
Blood bilirubin increased	6 (1%)	3 (1%)	0	0	3 (1%)	2 (<1%)	0	0
Gastric ulcer	8 (2%)	3 (1%)	1 (<1%)	0	0	0	0	0
Hyperbilirubinaemia	2 (<1%)	3 (1%)	0	0	1 (<1%)	1 (<1%)	0	0

Gastrointestinal haemorrhage	2 (<1%)	1 (<1%)	2 (<1%)	0	0	0	1 (<1%)	0
Radiation hepatitis	2 (<1%)	2 (<1%)	0	2 (<1%)	0	0	0	0
Duodenal ulcer	4 (1%)	3 (1%)	0	0	1 (<1%)	0	0	0
Pancreatitis	1 (<1%)	2 (<1%)	0	0	0	0	0	0
Hepatic failure	0	1 (<1%)	0	1 (<1%)	0	0	0	0
Jaundice	0	0	0	0	0	2 (<1%)	0	0
Jaundice cholestatic	0	2 (<1%)	0	0	0	0	0	0
Hepatic encephalopathy	0	2 (<1%)	0	0	0	0	0	0
Duodenitis	4 (1%)	1 (<1%)	0	0	0	0	0	0
Portal hypertension	0	1 (<1%)	0	0	1 (<1%)	0	0	0
Duodenal ulcer haemorrhage	0	0	0	0	0	0	1 (<1%)	0
Cholecystitis acute	0	1 (<1%)	0	0	0	0	0	0
Perihepatic abscess	0	1 (<1%)	0	0	0	0	0	0
Gastritis	18 (4%)	0	0	0	4 (1%)	0	0	0
Oesophagitis	2 (<1%)	0	0	0	3 (1%)	0	0	0
Splenomegaly	2 (<1%)	0	0	0	1 (<1%)	0	0	0
Oesophageal ulcer	1 (<1%)	0	0	0	0	0	0	0

There were 8 treatment related deaths in the SIRT group (3 radiation-induced liver disease, 2 complications of surgery, 1 liver failure, 1 drug-induced pneumonitis and 1 off-target delivery of microspheres) and 3 in the chemotherapy alone group (1 complications of surgery, 1 neutropenic sepsis and 1 bowel perforation).

The odds of a patient having a grade 3 or worse adverse event were higher in the SIRT group than in the chemotherapy alone group (pooled OR 1.42, 95% CI 1.09 to 1.85, p=0.0089).

There were 2 additional deaths caused by hepatic events in the SIRT group after the main safety window until the end of the follow-up period.

Abbreviations used: CI, confidence interval; HR, hazard ratio; OR, odds ratio; SIRT, selective internal radiation therapy

Study 2 Gibbs P (2018)

Details

Study type	**Post-hoc analysis of 2 randomised controlled trials (SIRFLOX [SF] and FOXFIRE global [FFG])**
Country	Australia, Belgium, France, Germany, Israel, Italy, New Zealand, Poland, Portugal, Republic of Korea, Singapore, Spain, Switzerland, Taiwan, US
Recruitment period	2006 to 2015
Study population and number	**n=739 (372 SIRT plus chemotherapy, 367 chemotherapy alone)** **Patients with liver-only or liver-dominant metastatic colorectal cancer**
Age and sex	• SIRT plus chemotherapy: mean 62 years; 66% (246/372) male • Chemotherapy alone: mean 62 years; 64% (234/367) male
Patient selection criteria	See study 1 for details (Wasan HS, 2017).
Technique	All patients had systemic FOLFOX chemotherapy. SIRT therapy used SIR-Spheres Y-90 resin microspheres (Sirtex Medical Limited, Australia).
Follow-up	**Median 22.2 months (range 0 to 91)**
Conflict of interest/source of funding	The SIRFLOX and FOXFIRE-Global studies were sponsored by Sirtex, who also provided an unrestricted educational grant for the FOXFIRE study. Declaration of interests include honoraria, grants and personal fees from companies including Sirtex Medical, Merck, Roche, Amgen, and Pfizer.

Analysis

Follow-up issues: Patients were assessed by CT every 8 weeks until disease progression and, after extrahepatic progression, every 12 weeks until hepatic progression. Patients were followed up until death.

Study design issues: Post-hoc analysis of data from 2 randomised controlled trials, in which data on the primary tumour location were collected prospectively. All efficacy measures were assessed in the intent-to-treat population. The main outcome measure was overall survival, stratified by treatment and primary tumour side. Tumour response rate and progression-free survival were determined from serial CT scans using the RECIST.

Study population issues: Of the 739 patients, 179 (24%) had a right-sided primary (RSP), 540 (73%) had a left-sided primary (LSP), 16 (2%) had both and the primary site was not recorded for 4 patients (0.5%). Patients with an RSP were older than those with an LSP (64% compared with 62 years, p=0.002) and a higher proportion were women (43% compared with 32%, p=0.011). Patients randomised to SIRT were less likely to have bevacizumab compared with the control patients (RSP versus LSP; 54% versus 65%, p=0.125 and 51% versus 62%, p=0.014 respectively).

Other issues: Of the 372 patients assigned to SIRT, 33 did not have SIRT (6 with an RSP and 27 with an LSP). Another 31 did not have SIRT to both hepatic lobes (10 with an RSP and 21 with an LSP).

Key efficacy and safety findings

Efficacy

Number of patients analysed: **739 (372 SIRT plus chemotherapy, 367 chemotherapy alone)**

Mortality=74.2% (548/739)

Overall survival and progression-free survival

Primary tumour side	Study cohort	SIRT		Control		p value
		Patients, n	Median, months (95% CI)	Patients, n	Median, months (95% CI)	
Overall survival						
All patients	SF	267	22.6 (21.0 to 25.6)	263	24.5 (21.8 to 26.3)	0.676
	FFG	105	25.9 (23.1 to 28.9)	104	25.0 (22.1 to 28.5)	0.789
	SF + FFG	372	24.3 (21.9 to 25.9)	367	24.6 (22.2 to 26.3)	0.810
RSP mCRC	SF	72	21.7 (16.9 to 25.6)	55	17.1 (13.9 to 19.8)	0.054
	FFG	26	24.5 (19.2 to 28.9)	26	16.6 (9.6 to 22.1)	0.048
	SF + FFG	98	22.0 (18.9 to 25.6)	81	17.1 (13.9 to 19.9)	0.008
LSP mCRC	SF	188	24.4 (21.7 to 26.3)	201	26.4 (24.6 to 30.0)	0.321
	FFG	76	25.9 (22.1 to 31.3)	75	27.4 (24.1 to 33.2)	0.608
	SF + FFG	264	24.6 (22.3 to 26.7)	276	26.6 (24.8 to 29.9)	0.264
Progression-free survival						
All patients	SF	267	10.9 (9.8 to 11.5)	263	10.5 (9.4 to 11.4)	0.563
	FFG	105	11.9 (10.3 to 14.4)	104	11.2 (9.4 to 12.6)	0.127
	SF + FFG	372	11.1 (10.2 to 11.9)	367	10.6 (9.6 to 11.6)	0.193
RSP mCRC	SF	72	9.9 (8.6 to 11.5)	55	8.4 (7.8 to 11.1)	0.084
	FFG	26	11.5 (6.1 to 14.5)	26	9.1 (5.2 to 12.8)	0.394
	SF + FFG	98	10.8 (9.3 to 12.4)	81	8.7 (7.8 to 10.9)	0.056
LSP mCRC	SF	188	11.2 (9.9 to 12.6)	201	10.7 (9.6 to 12.4)	0.849
	FFG	76	11.9 (9.6 to 15.6)	75	11.7 (9.4 to 12.6)	0.143
	SF + FFG	264	11.4 (10.1 to 12.6)	276	10.8 (9.9 to 12.3)	0.351

Objective response rates

	SIRT	Control	p value
RSP	74.5% (73/98)	63.0% (51/81)	0.323
LSP	73.9% (195/264)	69.2% (191/276)	0.263

Resection rates

15% (11/739) of patients had 1 or more partial hepatic resections (11.7% [21/179] RSP and 15.9% [86/540] LSP). Of the 21 RSP patients who had resection, 12 (12.2%) were in the SIRT group and 9 (11.1%) were in the control group.
A multivariate Cox proportional hazards analysis stratified by protocol showed that resection was a statistically significant positive contribution to overall survival for patients with an RSP (hazard ratio 0.67, 95% CI 0.35 to 0.19, p=0.001).

Proportion of patients who had further systemic therapy

	SIRT	Control	p value
RSP	68.4% (67/98)	67.9% (55/81)	0.95
LSP	68.2% (180/264)	77.2% (213/276)	0.019

Safety

Treatment-emergent grade 3 or above adverse events (n=720; 176 RSP, 526 LSP and 18 both or unknown)

- RSP=77.2% of patients who had SIRT compared with 77.4% of control patients (p=1.00)
- LSP=84.4% of patients who had SIRT compared with 71.3% of control patients (p<0.001)

In the SIRT arm, 9 patients died of adverse events (8 LSP and 1 RSP): hepatic failure (n=3), radiation hepatitis (1), intestinal perforation (1), peritonitis (1), hepatic cirrhosis and ascites (1), respiratory failure with dyspnoea (1), febrile neutropenia (1).

Abbreviations used: CI, confidence interval; FFG, FOXFIRE Global; LSP, left-sided primary; mCRC, metastatic colorectal cancer; RSP, right-sided primary; SF, SIRFLOX; SIRT, selective internal radiation therapy

Study 3 Hendlisz A (2010)

Details

Study type	**Randomised controlled trial**
Country	Belgium (3 sites)
Recruitment period	2004 to 2007
Study population and number	**n=44 (21 SIRT plus chemotherapy, 23 chemotherapy alone)** **Patients with liver-limited metastatic colorectal cancer refractory to standard chemotherapy**
Age and sex	Median 62 years (range 45 to 91); 64% (28/44) male
Patient selection criteria	Patients with histologically proven adenocarcinoma of the colon or rectum metastasised to the liver only, not amenable to curative surgery or local ablation and resistant or intolerant to standard chemotherapy. In cases of intolerance leading to previous chemotherapy stop, documentation of progressive disease was needed before study entry. Eligible patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2; were ≥18 years old; had adequate bone marrow function, renal function, and liver function; and were able to give informed consent. Exclusion criteria: pre-existing hepatic disease; extrahepatic disease; clinically significant ascites; more than 20% arteriovenous shunting from liver to lungs; hepatic arterial anatomy that would not allow safe administration of SIRT; partial or total thrombosis of the hepatic artery or main portal vein; prior hepatic arterial infusion with fluorouracil, floxuridine or other chemotherapeutic agent or transarterial embolisation procedure; prior external beam irradiation of the liver; severe chronic or acute disease, concomitant or previous malignancies within 5 years other than basal cell or squamous cell carcinoma of the skin or cervix; and women who were pregnant or breast feeding or who refused to take adequate pregnancy prevention measures.
Technique	All patients had fluorouracil chemotherapy until documented hepatic progression. SIRT therapy used SIR-Spheres Y-90 resin microspheres (Sirtex Medical Limited, Australia).
Follow-up	**Median 24.8 months**
Conflict of interest/source of funding	The study was supported by Sirtex Medical Limited, by provision of yttrium-90 microspheres. One author has received honoraria from Sirtex Medical Limited.

Analysis

Follow-up issues: Physical examination and blood tests were done every 3 weeks. CT scanning was done every 6 weeks until disease progression.

Study design issues: Prospective, multicentre, randomised controlled trial. Randomisation used the minimisation technique, with institution and type of progression before enrolment as stratification factors. There was no blinding. The primary end point was time to liver progression. Adverse events were classified and coded for severity using Common Terminology Criteria for Adverse Events, version 3.0. Objective tumour response was evaluated by local radiology review using RECIST 1.0. All eligible patients were included in efficacy analysis. For the safety analysis, eligible patients not treated were excluded.

Study population issues: Both arms were well balanced for clinical criteria. Most patients had at least 2 hepatic lesions. The median time from diagnosis was 22 months overall.

Other issues: An additional 2 patients were randomised to the SIRT group but were ineligible, 1 because of bone metastases and the other because of technical issues.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **44 (21 SIRT plus chemotherapy, 23 chemotherapy alone)**

Time to liver progression, time to progression overall and overall survival

Time to progression and overall survival	SIRT plus chemotherapy	Chemotherapy alone	Hazard ratio	95% CI	p value
Time to liver progression, median, months					
All progressions considered as events	5.5	2.1	0.38	0.20 to 0.72	0.003
Patients with treatment change censored at the time of change	5.6	2.1	0.35	0.18 to 0.69	0.002
Time to progression, median, months	4.5	2.1	0.51	0.28 to 0.94	0.03
Overall survival, median, months	10.0	7.3	0.92	0.47 to 1.78	0.80

All the patients allocated to chemotherapy alone had disease progression first in the liver. 3 patients in the SIRT group were without documented progression and were censored at 4.3, 6.6 and 26.0 months.

Resectability
The tumour in 1 patient who had SIRT was sufficiently downsized for a right hepatectomy. Extrahepatic disease progression was documented at 1.5 months after surgery.

10 patients in the chemotherapy alone group crossed over to SIRT monotherapy and 6 patients had further systemic treatments.

9 patients in the SIRT group had further systemic treatments.

Best overall hepatic response

Response	SIRT plus chemotherapy		Chemotherapy alone	
	No.	%	No.	%
Partial response	2	10	0	0
Stable disease	16	76	8	35
Progressive disease	2	10	14	61
Non-evaluable	1	5	1	4

Safety

Incidence of adverse events

Event by CTCAE grade	SIRT plus chemotherapy (n=21)			Chemotherapy alone (n=22)		
	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3
Gastrointestinal						
Stomatitis	1	1	0	1	0	1
Diarrhoea	0	0	0	1	0	0
Nausea	4	1	0	0	0	0
Vomiting	2	0	0	2	0	0
Constipation	0	0	0	3	0	0
Anorexia	4	1	0	4	2	1
Gastrointestinal	0	1	0	0	0	0
Pain						
Abdominal pain	3	1	0	2	1	0

Myalgia	2	0	0	1	0	0
Pain other	0	0	0	1	0	0
Constitutional						
Fatigue	4	4	0	2	4	5
Fever	2	1	0	1	2	0
Dermatology						
Skin	0	0	0	0	2	0
Hand-foot syndrome	0	0	1	0	2	0
Pulmonary						
Dyspnoea	0	0	0	0	1	1
Pulmonary	0	0	0	0	0	1
Neurology						
Neurosensorial	2	0	0	0	0	0
Cognitive disturbance	0	1	0	0	1	0
Cardiac arrhythmia	0	0	0	1	0	0
Allergy	0	0	0	0	0	1
Ascites	0	0	0	0	1	0
Thrombocytopaenia	1	0	0	0	0	0
Stomach ulcer, ascites	0	1	0	0	0	0

There were no grade 4 events.

Abbreviations used: CI, confidence interval; SIRT, selective internal radiation therapy

Study 4 Bester L (2012)

Details

Study type	**Non-randomised comparative study**
Country	Australia
Recruitment period	2006 to 2011
Study population and number	**n=390 (339 SIRT [224 colorectal cancer], 51 conservative treatment or best supportive care [29 colorectal cancer])** **Patients with chemotherapy-refractory liver metastases**
Age and sex	• SIRT: median age 67 years (range 27 to 90); 61% (206/339) male • Standard care: median age 66 years (range 27 to 88); 69% (35/51) male
Patient selection criteria	All patients referred for evaluation had radiological evidence on unresectable liver metastases from various primary tumours and no longer qualified for other treatment modalities, such as resection, cryoablation, radiofrequency ablation, or transcatheter arterial chemoembolisation. All patients had had multiple lines of chemotherapy with radiologically proven progressive liver disease or were known or anticipated to have a poor response to chemotherapy. Inclusion criteria included: ECOG score ≤2, Child-Pugh class A or B disease, predicted life expectancy ≥3 months, salvage therapy, liver metastases from primary of any origin, no contraindications, inoperable liver tumours, sufficient hepatic reserve, adequate renal function and blood count, liver-only or liver-dominant disease, tumour burden ≤75% of liver volume, no or limited ascites and no obstruction of the bile duct or extensive portal vein thrombosis, anticipated lung exposure to yttrium-90 radiation ≤30 Gy.
Technique	SIRT: yttrium-90 resin microspheres (Sirtex Medical, Australia) were used, with a femoral or brachial artery catheter. Treatment for bilobar liver disease was done in the same procedure as a single dose to both lobes of the liver or as a divided dose to the left and right lobes. Prophylactic embolisation of gastroduodenal, right gastric and other extrahepatic arteries was done as necessary.
Follow-up	**Not reported**
Conflict of interest/source of funding	One author is a paid consultant for Sirtex Medical, Australia.

Analysis

Follow-up issues: Adverse events were assessed at the time of treatment and at 1- and 3-month intervals after treatment.

Study design issues: Retrospective, single centre, non-randomised comparative study. The control group consisted of patients for whom SIRT was considered unsuitable because of variant hepatic arterial anatomy, extensive hepatopulmonary shunting, or reasons relating to patient consent. These patients were not considered to represent a patient group with more advanced disease and were used as a standard-care comparison cohort. The primary outcome of the study was overall survival, calculated by the Kaplan-Meier method. Survival was measured from the date of SIRT to death or the cut-off date, whichever came first. The cut-off date was the date on which data collection closed (23/02/2011). For the standard care cohort, survival was measured from the time patients were assessed for SIRT eligibility until death or the cut-off date. For the 25 patients who had multiple SIRT sessions, only the first treatment was taken into consideration for data analysis.

Study population issues: The baseline characteristics were similar between the 2 groups. Of the 339 patients in the SIRT group, 224 had colorectal cancer as the primary cancer. Most patients (85%) in this subgroup had an ECOG score of 0, most had 0% to 25% of liver volume replaced by tumour, 87% had bilobar liver disease and 62% did not have extrahepatic disease.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **390 (339 SIRT, 51 standard care)** **Mortality** • SIRT=59.3% (201/339); 59.8% (134/224) in CRC group • Standard care=76% (39/51) **Median overall survival (months)** • Whole SIRT cohort=12.0 (95% CI 10.7 to 14.5) • Whole standard care cohort=6.3 (95% CI 2.6 to 8.9) • CRC SIRT subgroup=11.9 (95% CI 10.1 to 14.9) • CRC standard care subgroup=6.6, log-rank test, p=0.001 • Non-CRC SIRT subgroup=12.7 (95% CI 8.68 to 16.4) • Non-CRC standard care subgroup=3.6, log-rank test, p<0.024 On multivariate analysis, SIRT was a significant predictor of overall survival for the overall treated cohort (p=0.002, hazard ratio [HR] 0.57, 95% CI 0.41 to 0.82). The only other statistically significant prognostic factors that impacted survival in a multivariate model were the extent of hepatic disease (≤25% compared with >25%; HR 1.82, 95% CI 1.2 to 2.7) and previous chemotherapy (HR 1.29, 95% CI 1.5 to 3.5). The primary site of the tumour was not a statistically significant predictor of outcome.	**Adverse events at the time of SIRT (0 to 24 hours) = 22.1% (75/339)** Events were minor (grade 1 abdominal pain, nausea and vomiting). Grade 1 abdominal pain was reported in 15.0% (51/339) of patients. **Adverse events 1 month after SIRT** • Grade 1 abdominal pain=18.3% (62/339) • Grade 1 lethargy=12.1% (41/339) • Grade 2 radiation-induced liver disease=0.3% (1/339) (successfully managed medically) • Grade 2 acalculous cholelithiasis=0.6% (2/339) • Grade 2 gastritis=1.8% (6/339) • Grade 2 ulceration=0.6% (2/339) **Adverse events 3 months after SIRT** • Grade 3 ulceration (duodenal or gastric)=0.9% (3/339) • Grade 2 ulceration=2.4% (8/339) • Grade 3 radiation-induced liver disease=0.3% (1/339) • Grade 2 radiation-induced liver disease=2.7% (9/339) • Grade 2 gallbladder complications=1.8% (6/339) All events were medically managed, with no deaths within the 3-month follow up period caused by SIRT. There were no known cases of radiation pneumonitis.
Abbreviations used: CI, confidence interval; CRC, colorectal cancer; HR, hazard ratio; SIRT, selective internal radiation therapy	

Study 5 Seidensticker R (2012)

Details

Study type	**Non-randomised comparative study**
Country	Germany
Recruitment period	2005 to 2008
Study population and number	**n=58 (29 SIRT, 29 best supportive care)** **Patients with chemotherapy-refractory liver-dominant metastatic colorectal cancer**
Age and sex	• SIRT: mean age 62 years; 76% (22/29) male • Best supportive care: mean age 61 years; 79% (23/29) male
Patient selection criteria	Patients were considered for SIRT if they had extensive liver involvement (≥20% of total liver volume) and none or only nonprogressive extrahepatic deposits. Patients were only considered if they had progressive disease, ineligible for other forms of tumour-directed therapy, and able to give informed consent. Inclusion criteria included adequate renal and haemopoietic function; platelet count >100,000/mm^3; sufficient liver function; hepatic arterial anatomy that would enable safe delivery of microspheres to the liver only; liver-to-lung shunting of <20%; and a patent main portal vein.
Technique	SIRT: yttrium-90 resin microspheres (Sirtex Medical, Australia) were used, with a transfemoral catheter, as a single whole-liver administration or into the lobar arteries as a sequential treatment of each lobe 4 to 8 weeks apart.
Follow-up	**12 months**
Conflict of interest/source of funding	The trial was supported in part by Sirtex Medical Limited, Australia. Two authors received travel fees, and 2 authors received research grants and consultant fees from Sirtex Medical Limited, Australia.

Analysis

Follow-up issues: Patients were given haematological, liver function and blood biochemistry test, and physical examination the day after SIRT. They were monitored by MRI or CT scan at week 6 and every 3 months thereafter until disease progression.

Study design issues: Patients treated prospectively with SIRT were retrospectively paired with controls who had best supportive care only. The clinical records of more than 500 patients from 3 centres were evaluated. Patients were initially matched for prior treatment history and tumour burden and then for the following 4 matching criteria: synchronous versus metachronous metastases, liver involvement, increased alkaline phosphatase and carcinoembryonic antigen ≥200 ng/ml. The first 29 consecutive matching patients identified were included in the analysis. The primary endpoint was overall survival, calculated using the Kaplan-Meier method, from the date of progression of the liver before SIRT or before starting best supportive care assessed radiologically until further progression. Tumour response to SIRT was evaluated by consensus of 2 radiologists using RECIST.

Study population issues: The 2 groups of patients were well matched for all baseline parameters. Of the 29 pairs of patients, 16 on all 4 predefined matching criteria, 11 pairs matched on 3 and 2 pairs matched on 2 criteria. There was no difference in performance status between the groups' Karnofsky index (median 80%). The groups were well matched for treatment history.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **58 (29 SIRT, 29 best supportive care)** **Response after SIRT, assessed by RECIST** • Partial=41.4% (12/29) • Stable=17.2% (5/29) • Progressive disease=37.9% (11/29) The response could not be evaluated in 1 patient because they died from a cerebral stroke 5 weeks after SIRT. **Median progression-free survival (months)** • SIRT=5.5 • Best supportive care=2.1 **Median overall survival (months)** • SIRT=8.3 • Best supportive care=3.5 Hazard ratio (HR) 0.26, 95% CI 0.15 to 0.48, p<0.001 **Survival at 3 months** • SIRT=97% • Best supportive care=59% **Survival at 12 months** • SIRT=24% • Best supportive care=0% In the multivariate analysis, SIRT was the only statistically significant predictor for prolonged survival (HR 0.3, 95% CI 0.16 to 0.55, p<0.001). The extent of liver involvement was associated with an increased risk of death (HR 1.03, 95% CI 1.0 to 1.06, p=0.028)	**Adverse events** • Grade 1 or 2 fatigue in the first 14 days after SIRT=69% (20/29) • Grade 1 abdominal pain and nausea in the first 24 hours after SIRT=48.3% (14/29) • Grade 2 gastrointestinal ulcer=10.3% (3/29) • Grade 3 radioembolisation-induced liver disease=10.3% (3/29) All events were managed medically and were not considered to be life-threatening.
Abbreviations used: CI, confidence interval; HR, hazard ratio; RECIST, response evaluation criteria in solid tumours; SIRT, selective internal radiation therapy	

Study 6 White J (2019)

Details

Study type	**Case series (Registry; NHS England Commissioning through Evaluation Programme)**
Country	UK (10 sites)
Recruitment period	2013 to 2017
Study population and number	**n=399** **Adults with unresectable, chemotherapy-refractory colorectal cancer liver metastases**
Age and sex	Median 66 years; 67% (266/399) male
Patient selection criteria	Inclusion criteria included: histologically confirmed carcinoma with liver-specific or liver-dominant metastases not amenable to curative liver surgical resection; unequivocal and measurable CT evidence of liver metastases not treatable by surgical resection or local ablation with curative intent; World Health Organization performance status 0 to 2; life expectancy more than 3 months; evidence of clinical progression during or after both oxaliplatin-based and irinotecan-based chemotherapy, unless the patient had a specific contraindication to chemotherapy or did not tolerate either regimen; adequate haematological and hepatic function; no central nervous system metastases or bone metastases, but patients were permitted to have limited extrahepatic disease (for example, lung metastases, multiple lymph nodes or low-volume peritoneal disease but the multidisciplinary team must have agreed that the extrahepatic disease was probably not life threatening or a cause for significant morbidity if the liver metastases can be controlled with locally directed therapy; no evidence of ascites or cirrhosis.
Technique	SIR-Spheres (Sirtex Medical Ltd., Australia) resin microspheres (86% of procedures) or Therasphere (Biocompatibles UK Ltd., UK) glass microspheres (14% of procedures) were used. Most patients had SIRT as a single procedure targeting the whole liver. A small proportion (3%) of patients had sequential lobes treated in 2 or more sessions. Administration of concomitant chemotherapy (35% of patients) and post-SIRT chemotherapy (22% of patients) was at the discretion of the treating clinician.
Follow-up	**Median 14.3 months (95% CI 9.2 to 19.4)**
Conflict of interest/source of funding	One author is funded by the NIHR University College London Hospitals Biomedical Research Centre, Cancer Research UK, the CRUK UCL Experimental Medicines Centre and research grants from Sirtex Medical and BTG plc. The same author declares consultancy with Affidea, Astra Zeneca, Boston Scientific, BTG, Cancer Research Technology, DeepMind, Eisai, Sirtex, Terumo and Varian. One author has received lecturing and consultancy honoraria from BTG and Sirtex Medical and 1 author has received honoraria from BTG and Sirtex Medical. Procedures and data collection were funded by NHS England, NICE was commissioned by NHS England to undertake an independent evaluation. Cedar was funded by NICE as an external assessment centre. Cedar's work on the SIRT Commissioning through Evaluation project was funded entirely through a contract with NICE. The SIRT registry was funded by Sirtex Medical.

Analysis

Follow-up issues: Sites were expected to follow up patients every 2 to 3 months after their SIRT procedure until liver progression was confirmed on scan. The progression status of 24 patients (6%) was unknown and the survival status of 20 patients (5%) was unknown.

Study design issues: Prospective, single-arm, observational, multicentre, service-evaluation study. SIRT was provided as routine care at the study centres. The SIRT registry is an online registry hosted by the British Society of Interventional Radiologists. Data relevant to the study were extracted from the registry and transferred to an independent research group for analysis. The primary outcome was overall survival. Secondary outcomes included safety, progression-free survival and liver-specific progression-free survival. Overall survival 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. Typically, the Response Evaluation Criteria for Solid Tumours (RECIST) were used to assess response. Progression-free survival was defined as the duration from the first SIRT procedure to the earliest date of detection of progressive disease by CT, MRI or positron emission tomography scan, or to the date of death if progression was not recorded. Patients with no progressive disease recorded were censored at the most recent date of non-

progression (complete response, partial response or stable disease). Adverse events were recorded using Common Terminology Criteria for Adverse Events. Causality was determined by the treating physician on site.

Study population issues: Most patients had an Eastern Cooperative Oncology Group performance score of 0 or 1 (93%) and most did not have extrahepatic metastatic disease (60%). Almost all patients (98%) had had prior systemic chemotherapy or biologics and 78% had had 2 or 3 lines of prior chemotherapy. There were more than 10 tumours in 44% of patients. The median overall tumour to liver volume ratio was 15% (interquartile range 7% to 27%), reported in 270 patients. Location of the primary tumour was not recorded.

Other issues: High levels of missing data for health-related quality of life meant that reliable conclusions about the impact of SIRT on patient quality of life could not be drawn from this study.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **399**

Overall survival=7.6 months (95% CI 6.9 to 8.3)

Survival rates:

- 3 months=92%
- 6 months=83%
- 12 months=30%
- 24 months=7%
- 36 months=0%

Kaplan-Meier analysis and univariate Cox proportional hazards model of survival by baseline characteristics

Subgroup	n (patients)	n (events)	Median overall survival (months)	95% CI	Hazard ratio (95% CI)	p
Primary tumour *in situ*; log-rank test p=0.079						
Yes	117	82	7.4	6.0 to 8.7	1.28 (0.97 to 1.69)	0.077
No	217	136	8.9	7.4 to 10.3	Reference	Reference
Presence of extrahepatic metastases; log-rank test p=0.021						
Yes	151	100	7.1	5.7 to 8.4	Reference	Reference
No	225	137	8.1	6.9 to 9.2	0.74 (0.57 to 0.96)	0.022
Number of liver tumours; log-rank test p=0.008						
1 to 5	107	58	11.3	8.7 to 13.8	Reference	Reference
6 to 10	50	28	6.7	3.8 to 9.5	1.67 (1.06 to 2.62)	0.027
>10	167	117	7.3	6.2 to 8.3	1.61 (1.17 to 2.21)	0.003
Sex; log-rank test p=0.012						
Female	129	96	6.4	5.2 to 7.7	1.39 (1.07 to 1.80)	0.013
Male	250	144	8.2	7.2 to 9.2	Reference	Reference
Percentage tumour to liver volume; log-rank test p<0.001						
≤25%	226	135	9.4	8.0 to 10.9	Reference	Reference
>25 to 50%	80	57	5.3	4.4 to 6.2	1.96 (1.42 to 2.69)	<0.001
>50%	22	17	5.3	6.8 to 8.2	2.99 (1.79 to 5.01)	<0.001

No statistically significant difference in survival was observed using the covariates of prior chemotherapy lines, ECOG performance status, age and prior liver procedures.

Progression or death=83.0% (331/399); progression=67% (269/399); 16% (62/399) of patients died before progression and 6% (24/399) of patients were censored at the last imaging date when no progression was recorded.

Median progression-free survival=3.0 months (95% CI 2.8 to 3.1)

Liver specific progression or death=75% (299/399), 13% (53/399) of patients were censored and 11% (43/399) were excluded.

Median liver-specific progression-free survival=3.7 months (95% CI 3.2 to 4.3)

Hepatic progression and extrahepatic progression were recorded on the same date in 81% of patients where both dates were recorded. Extrahepatic progression occurred before hepatic progression in 16% of patients.

Safety

35.8% (143/399) of patients had an adverse event during follow up and 8% of the events were grade 3 or above.

Total number of patients with severe day-of-treatment complications and total number of all-cause adverse events and abnormal laboratory value events

Severe day-of-treatment complications	**Number of patients**	
Yes	11 (3%)	
No	375 (94%)	
Missing	13 (3%)	
Adverse event category	**Number of adverse events**	**Number of grade ≥3 adverse events**
Fatigue	89	8
Abdominal pain	58	3
Nausea	22	0
Vomiting	14	0
Fever	10	1
Gastritis	5	0
Gastrointestinal ulcer	1	0
Radioembolisation induced liver disease	1	0
Radiation pneumonitis	0	0
Radiation cholecystitis	0	0
Radiation pancreatitis	0	0
Other	53	7
Total adverse events	253	19
Abnormal laboratory result event category	**Number of events**	**Number of grade ≥3 events**
Aspartate aminotransferase increased	79	0
Alanine aminotransferase increased	73	1
Hypoalbuminaemia	67	4
Hyperbilirubinaemia	44	8
International Normalised Ratio increased	1	0
Neutrophil count decreased	10	3
Platelet count decreased	28	0
Other	51	2
Total abnormal laboratory results events	353	18

The 7 adverse events grade 3 or above categorised as 'other' were: 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 or dementia (grade 4; 70 days after SIRT), pulmonary emboli (grade 4; 47 days after SIRT), sepsis (grade 4; 18 days after SIRT).

Abbreviations used: CI, confidence interval

Study 7 Kennedy A (2017)

Details

Study type	**Case series (Metastatic colorectal cancer liver metastases Outcomes after RadioEmbolisation [MORE] study)**
Country	US (11 sites)
Recruitment period	2002 to 2011
Study population and number	**n=606** **Patients with unresectable colorectal cancer liver metastases**
Age and sex	62% (373/606) male
Patient selection criteria	Patients with advanced liver-only or liver-dominant metastatic colorectal cancer, which was deemed not suitable for surgery, ablation, or systemic therapy, and which had progressed or become refractory to at least 1 line of systemic therapy. Patients had Eastern Cooperative Oncology Group (ECOG) performance status score of up to 2 and untreated life expectancy of at least 12 weeks. Patients with signs of liver failure or compromised bone marrow or pulmonary function were excluded. Under exceptional circumstances and with informed consent, some patients were treated outside the outlined criteria based on the clinical judgment of individual treating physicians.
Technique	Yttrium-90-labelled resin microspheres (SIR-spheres) were used.
Follow-up	**Median 9.5 months (last patient follow up of 125 months)**
Conflict of interest/source of funding	Study was funded by Sirtex Medical Limited, Australia. Three authors received research grants from Sirtex Medical, 2 are consultants to Sirtex Medical, 3 are participants in speakers' bureau for Sirtex Medical and 2 own stock holdings in Sirtex Medical. One author has also served as a consultant for Surefire Medical, XL Sci-Tech and Guerbet.

Analysis

Follow-up issues: Dates of death were obtained for 95% (574/606) of patients.

Study design issues: Retrospective, multicentre, observational study. The main aim of the study was to present an updated survival analysis. Survival was calculated with the first day of SIRT serving as day 0 to the day of death or last follow-up. Kaplan-Meier estimates of overall survival were reported at half-yearly intervals through 5 years. Adverse events were recorded in the study, but they have not been presented in this publication.

Study population issues: Patients had received a median of 2 (range 0 to 6) lines of prior chemotherapy. Most patients (65%) did not have extrahepatic metastatic disease.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **606**

Overall survival

- **1 year=45.0%**
- **2 years=18.9%**
- **3 years=7.0%**

Survival analysis of all patients, stratified by baseline characteristics

Characteristic	n	Survival (months)		P values between subgroups (log-rank)
		Median	95% CI	
All	606	10.0	9.2 to 11.8	
Sex				0.59
Female	233	9.5	8.9 to 12.1	
Male	373	10.4	9.1 to 12.2	
Age				0.26
<70 years	446	10.4	9.2 to 12.0	
≥70 years	160	9.4	8.0 to 12.1	
ECOG performance status				0.004
0	168	11.2	9.2 to 13.1	
1	72	8.5	6.5 to 12.8	
2	14	5.5	2.3 to 12.2	
3	3	5.0	1.3 to 11.0	
Ascites				<0.001
No	563	10.8	9.3 to 12.1	
Yes (controlled)	5	2.4	0.7 to 22.9	
Yes (uncontrolled)	23	5.5	3.8 to 7.4	
Extrahepatic metastases				<0.001
No	393	12.3	11.2 to 13.9	
Yes	213	7.7	6.4 to 8.7	
In-situ primary				0.01
No	522	10.5	9.2 to 12.1	
Yes	78	8.2	6.3 to 12.0	
Metastases				0.015
Metachronous	173	11.3	9.2 to 13.9	
Synchronous	396	9.4	8.7 to 11.1	
Tumour-to-target liver involvement				<0.001
<25%	388	13.1	11.6 to 14.0	
25 to 50%	148	6.7	5.9 to 8.2	
>50%	22	6.5	3.6 to 11.0	
Prior lines of chemotherapy				<0.001
0	35	15.6	9.3 to 21.4	
1	206	13.2	10.9 to 15.5	
2	184	9.1	7.8 to 11.2	
3+	158	8.1	6.4 to 9.3	
Lung shunt				<0.001
≤10%	526	10.8	9.4 to 12.2	
>10%	70	6.8	5.2 to 9.0	

Abbreviations used: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group

Study 8 Hickey R (2016)

Details

Study type	**Case series**
Country	US (8 sites)
Recruitment period	2001 to 2014
Study population and number	**n=531** **Patients with unresectable colorectal cancer liver metastases**
Age and sex	59% (314/531) male
Patient selection criteria	Patients with unresectable metastases from colorectal cancer; imaging-confirmed progressive disease refractory to previous systemic or locoregional therapy; an Eastern Cooperative Oncology Group (ECOG) status of no more than 2; the ability to have angiography and selective visceral catheterisation; and adequate haematology counts and platelets, renal function and liver function. Exclusion criteria included significant extrahepatic disease (life expectancy <3 months); angiographic evidence or ^{99m}Tc-macroaggregated albumin scan evidence of uncorrectable gastrointestinal flow; or an estimated lung dose of more than 30 Gy in a single session.
Technique	Yttrium-90-labelled glass microspheres were used (TheraSphere, BTG International Ltd.). Most patients had lobar or selective radioembolisation at the first treatment. Only 2% of patients had whole-liver treatment in a single setting. Extrahepatic arterial coil embolisation was done in 25% of patients.
Follow-up	**Not reported**
Conflict of interest/source of funding	Six authors are advisers to BTG International Ltd.

Analysis

Follow-up issues: All patients had radiological imaging within 1 month of treatment. Completeness of follow-up is not described.

Study design issues: Retrospective, multicentre, observational study. Median overall survival was calculated from the dates of diagnosis of the primary cancer, hepatic metastases and first SIRT treatment censored to the date of last follow-up. Clinical side effects and biochemical toxicity according to version 4.0 of National Cancer Institute common terminology criteria were recorded at follow-up.

Study population issues: Most patients (63%) were younger than 65 years at the time of treatment, 96% of patients had an ECOG status of 0 or 1, 70% of patients had tumour in no more than 25% of the liver volume and 62% of patients had liver-only disease. 18% of patients had prior hepatic resection, 14% had prior liver ablation and 4% had prior transarterial chemoembolisation. Before SIRT, 56% of patients had had 3 cytotoxic chemotherapeutics, 41% of patients had had 1 or 2 of these agents and 3% had not any. 22% of patients had not had any biological agents, 56% had had 1 biological agent and 22% had had 3 biological agents.

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>Number of patients analysed: 531

Median overall survival (months)
From diagnosis of primary=48.7 (95% CI 44.2 to 53.2)
From diagnosis of hepatic metastases=37.7 (95% CI 33.7 to 41.7)
From first SIRT treatment=10.6 (95% CI 8.8 to 12.4)
From hepatic metastases to SIRT=17.5 (95% CI 15.3 to 19.7)
From SIRT (no extrahepatic metastases, n=329)=14.4 (95% CI 12.7 to 16.1), p<0.001
From SIRT (with extrahepatic metastases, n=202)=6.6 (95% 5.2 to 8.1)
Multivariate analysis for survival<table><tr><th>Category</th><th>Hazard ratio (95% CI)</th><th>p value</th></tr><tr><td>Bilirubin <1.3 mg/dL</td><td>1.23 (0.80 to 1.87)</td><td>0.349</td></tr><tr><td>Albumin >3 g/dL</td><td>0.47 (0.35 to 0.63)</td><td><0.001</td></tr><tr><td>ECOG 0</td><td>0.60 (0.46 to 0.79)</td><td><0.001</td></tr><tr><td>≤2 cytotoxic agents</td><td>0.61 (0.46 to 0.79)</td><td><0.001</td></tr><tr><td>No biologics</td><td>0.93 (0.68 to 1.28)</td><td>0.663</td></tr><tr><td>Tumour burden ≤25%</td><td>0.37 (0.28 to 0.49)</td><td><0.001</td></tr><tr><td>Extrahepatic disease absent</td><td>0.50 (0.38 to 0.64)</td><td><0.001</td></tr><tr><td>Stage IV at diagnosis (American Joint Committee on Cancer criteria)</td><td>0.88 (0.69 to 1.13)</td><td>0.33</td></tr></table></td><td>Clinical side effects
Fatigue=55% (290/531)
Abdominal pain or discomfort=34% (182/531)
Nausea=19% (98/531)
Anorexia=7% (36/531)
Fever or chills=7% (36/531)
Vomiting=6% (32/531)
Diarrhoea=2% (10/531)
Grade 3 or 4 biochemical toxicity – factor affected
Bilirubin=13% (69/531)
Alkaline phosphatase=9% (46/531)
Albumin=8% (40/531)
Aspartate transaminase=3% (18/531)
Alanine transaminase=<1% (3/531)</td></tr>
<tr><td colspan="2">Abbreviations used: CI, confidence interval, SIRT, selective internal radiation therapy</td></tr>
</table>

Validity and generalisability of the studies

- The evidence includes data from RCTs, which included patients from the UK.
- The 3 large RCTs included SIRT as a first-line treatment but most of the other studies used SIRT to treat patients with chemotherapy-refractory disease.
- One of the studies is a post-hoc analysis of data from 2 of the 3 RCTs, to compare results from patients with right or left sided primary tumours.
- One of the studies is a registry-based study from 10 NHS hospitals, which is likely to have a patient population that is representative of the patients to be treated within the NHS.[6]
- Most of the evidence is based on the use of resin microspheres for SIRT, but 2 studies used glass microspheres for some or all of the patients.[6,8]
- Treatment regimens varied between studies.

Existing assessments of this procedure

A Spanish expert panel published recommendations for SIR-Spheres Y-90 resin microspheres in chemotherapy-refractory/intolerant colorectal liver metastases in 2017.[9] The report concluded 'The expert panel recommends the use of SIR-Spheres Y-90 resin microspheres in chemotherapy-refractory and chemotherapy-intolerant patients based on the evidence available today and looks forward to expanding its use into a first line setting once the results of the ongoing Phase III trials are reported.'

The European Society for Medical Oncology (ESMO) consensus guidelines for the management of patients with metastatic colorectal cancer (2016)[10] have the following recommendation on embolisation:

'• For patients with liver-limited disease failing the available chemotherapeutic options

° Radioembolisation with yttrium-90 microspheres should be considered [II, B].

° Chemoembolisation may be also considered as a treatment option [IV, B].

• Radioembolisation (and chemoembolisation) of CLM in earlier treatment lines may be interesting as 'consolidation treatment' but should be limited to clinical trials.'

NHS England published a Clinical Commissioning Policy in December 2018. NHS England will commission selective internal radiation therapy (SIRT) for chemotherapy refractory / intolerant metastatic colorectal cancer in adults in accordance with the criteria outlined in this document. The policy states 'NHS England has carefully reviewed the evidence to treat chemotherapy refractory / intolerant metastatic colorectal cancer with SIRT. We have concluded that there is enough evidence to make the treatment available for adults where the metastatic disease is limited to the liver only.'

Related NICE guidance

Below is a list of NICE guidance related to this procedure.

Interventional procedures

- Selective internal radiation therapy for unresectable primary intrahepatic cholangiocarcinoma. NICE interventional procedures guidance 630 (2018). Available from http://www.nice.org.uk/guidance/IPG630
- Microwave ablation for treating liver metastases. NICE interventional procedures guidance 553 (2016). Available from http://www.nice.org.uk/guidance/IPG553
- Chemosaturation via percutaneous hepatic artery perfusion and hepatic vein isolation for primary or metastatic liver cancer. NICE interventional procedures guidance 488 (2014). Available from http://www.nice.org.uk/guidance/IPG488

- Irreversible electroporation for treating liver metastases. NICE interventional procedures guidance 445 (2013). Available from http://www.nice.org.uk/guidance/IPG445
- Selective internal radiation therapy for primary hepatocellular carcinoma. NICE interventional procedures guidance 460 (2013). Available from http://www.nice.org.uk/guidance/IPG460
- Cryotherapy for the treatment of liver metastases. NICE interventional procedures guidance 369 (2010). Available from http://www.nice.org.uk/guidance/IPG369
- Radiofrequency ablation for colorectal liver metastases. NICE interventional procedures guidance 327 (2009). Available from http://www.nice.org.uk/guidance/IPG327

Technology appraisals

- Cetuximab and panitumumab for previously untreated metastatic colorectal cancer. NICE technology appraisal 439 (2017). Available from http://www.nice.org.uk/guidance/TA439
- Aflibercept in combination with irinotecan and fluorouracil-based therapy for treating metastatic colorectal cancer that has progressed following prior oxaliplatin-based chemotherapy. NICE technology appraisal 307 (2014). Available from http://www.nice.org.uk/guidance/TA307
- Bevacizumab and cetuximab for the treatment of metastatic colorectal cancer. NICE technology appraisal 118 (2007). Available from http://www.nice.org.uk/guidance/TA118

NICE guidelines

- Colorectal cancer: diagnosis and management. NICE clinical guideline 131 (November 2011 Last updated: December 2014). Available from http://www.nice.org.uk/guidance/CG131

Additional information considered by IPAC

Specialist advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by Specialist Advisers, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. Two Specialist Advisor Questionnaires for selective internal radiation therapy for non-resectable colorectal metastases in the liver were submitted and can be found on the NICE website.

Patient commentators' opinions

NICE's Public Involvement Programme will send questionnaires to NHS trusts for distribution to patients who had the procedure (or their carers). When NICE has received the completed questionnaires, these will be discussed by the committee.

Company engagement

A structured information request was sent to 3 companies who manufacture a potentially relevant device for use in this procedure. NICE received 3 completed submissions. These was considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

Issues for consideration by IPAC

- In the studies included in Table 2, 2 brands of CE-marked microspheres were used for the SIRT procedure: SIR-spheres (Sirtex Medical Ltd) and TheraSpheres (Biocompatibles UK Ltd). Both are Y-90 microspheres. A third medical device, QuiremSpheres (Quirem Medical) which uses poly-L-lactic acid microspheres containing holmium-166 has recently been CE marked for

use in SIRT and is available in the UK but none of the studies included in Table 2 report the use of this device for the procedure.

- Ongoing trials:
  - Efficacy Evaluation of TheraSphere Following Failed First Line Chemotherapy in Metastatic Colorectal Cancer (EPOCH); NCT01483027; US, Austria, Belgium, Canada, China, France, Germany, Italy, Republic of Korea, Poland, Singapore, Spain, UK; RCT; n=428; Estimated Study Completion Date September 2019
  - QuiremSpheres Observational Study (Hope166); NCT03563274; Austria, Germany, the Netherlands, Spain; Observational cohort study; n=100; estimated study completion date May 2021
  - CIRSE Registry for SIR-Spheres in France (CIRT-FR) (CIRT-FR); NCT03256994; France; Observational cohort study; n=200; estimated study completion date Feb 2022
  - Yttrium Y 90 Resin Microspheres Data Collection in Unresectable Liver Cancer: the RESIN Study (RESiN); NCT02685631; US; Observational cohort study; n=1,000; estimated study completion date Aug 2021
  - REgistry of Selective Internal Radiation Therapy in TaiwaN (RESIN); NCT03292991; Taiwan; Observational study; n=100; estimated study completion date Dec 2019

References

1. Wasan HS, Gibbs P, Sharma NK et al. (2017) First-line selective internal radiotherapy plus chemotherapy versus chemotherapy alone in patients with liver metastases from colorectal cancer (FOXFIRE, SIRFLOX, and FOXFIRE-Global): a combined analysis of three multicentre, randomised, phase 3 trials. Lancet Oncology 18: 1159-71
2. Gibbs P (2018) Effect of primary tumor side on survival outcomes in untreated patients with metastatic colorectal cancer when selective internal radiation therapy is added to chemotherapy: combined analysis of two randomized controlled studies. Clinical Colorectal Cancer 17: e617-e629
3. Hendlisz A, Van den Eynde M, Peeters M et al. (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: 3687-94
4. Bester L, Meteling B, Pocock N et al. (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: 96-105
5. Seidensticker R, Denecke T, Kraus P et al. (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: 1066-73
6. White J, Carolan-Rees G, Dale M et al. (2019) Analysis of a National Programme for Selective Internal Radiation Therapy for Colorectal Cancer Liver Metastases. Clinical Oncology 31: 58-66
7. Kennedy, A.; Cohn, M.; Coldwell, D. M. et al. (2017) Updated survival outcomes and analysis of long-term survivors from the MORE study on safety and efficacy of radioembolization in patients with unresectable colorectal cancer liver metastases. Journal of Gastrointestinal Oncology 8: 614-24
8. Hickey, R.; Lewandowski, R. J.; Prudhomme, T. et al. (2016) ^{90}Y radioembolization of colorectal hepatic metastases using glass microspheres: Safety and survival outcomes from a 531-patient multicenter study. Journal of Nuclear Medicine 57: 665-71
9. Aranda E, Aparicio J, Bilbao JI et al. (2017) Recommendations for SIR-Spheres Y-90 resin microspheres in chemotherapy-refractory/intolerant colorectal liver metastases. Future Oncology 13 (23): 2065-82

10. Van Cutsem E, Cervantes A, Adam R et al. (2016) ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Annals of Oncology 27: 1386–422

Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	27/03/19	Issue 3 of 12, March 2019
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	27/03/19	Issue 3 of 12, March 2019
HTA database (CRD website)	28/03/19	-
MEDLINE (Ovid)	26/03/19	1946 to March 25, 2019
MEDLINE In-Process (Ovid) & MEDLINE ePubs ahead of print (Ovid)	26/03/19	1946 to March 25, 2019
EMBASE (Ovid)	26/03/19	1974 to 2019 Week 12
BLIC	26/03/19	-

Trial sources searched 25th March 2019

- Clinicaltrials.gov
- ISRCTN
- WHO International Clinical Trials Registry

Websites searched

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- EuroScan
- General internet search

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1	SIRT.tw.
2	(selective* adj4 internal* adj4 radiotherap*).tw.
3	(selective* adj4 internal* adj4 radiation* adj4 therap*).tw.
4	select internal radiotherapy.tw.
5	(select* adj4 internal adj4 radiotherapy).tw.
6	(internal* adj4 radiation* adj4 therap*).tw.

7	(internal* adj4 irradiat*).tw.
8	Brachytherapy/
9	brachytherap*.tw.
10	(radioemboli?ation or radio-emboli?ation).tw.
11	(intravascular adj4 radiation).tw.
12	(local adj4 radioablation).tw.
13	(radionuclide adj4 therap*).tw.
14	(targeted adj4 hepatic adj4 therap*).tw.
15	(transarterial adj4 radiotherap*).tw.
16	or/1-15
17	yttrium/ or exp yttrium isotopes/
18	Yttrium Radioisotopes/
19	(Y-90 or 90-Y or yttrium*).tw.
20	Y-90 radioembolizat*.tw.
21	or/17-20
22	microsphere*.tw.
23	Microspheres/
24	22 or 23
25	21 and 24
26	16 and 25
27	exp Liver Neoplasms/
28	((liver or hepatic* or hepatocellular) adj4 (neoplasm* or cancer* or carcinoma* or adenocarcinom* or tumour* or tumor* or malignan* or metastas* or lesion*)).tw.
29	Cholangiocarcinoma/
30	(hepatoma* or cholangiocarcinoma* or hepatocarcinoma* or HCC).tw.
31	or/27-30
32	26 and 31
33	sirtex.tw.
34	SIR-Spheres.tw.
35	QuiremSphere.tw.
36	TheraSphere.tw.
37	or/33-36
38	32 or 37
39	animals/ not humans/
40	38 not 39

Appendix

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Case reports and case series with fewer than 50 patients have been excluded.

Article	Number of patients/ follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Abbott AM, Kim R, Hoffe SE et al. (2015) Outcomes of Therasphere radioembolization for colorectal metastases. Clinical Colorectal Cancer 14: 146-153	Case series n=68	Yttrium-90 was associated with acceptable overall survival (OS) with minimal morbidity in this series. Minimal exposure to chemotherapy and low hepatic burden of disease were found to be associated with better OS, however, even patients with chemotherapy-refractory disease received a benefit from treatment.	Larger studies are included.
Ahmadzadehfar H, Meyer C, Pieper CC et al. (2015) Evaluation of the delivered activity of yttrium-90 resin microspheres using sterile water and 5 % glucose during administration. EJNMMI Research 5 (no. 1)	Case series n=78	Replacing sterile water with isotonic 5% glucose during administration favourably impacts on the safety of SIRT, eliminates or minimises flow reductions and stasis or reflux during administration of ^{90}Y resin microspheres, improves percentage activity delivered, and reduces peri-procedural pain.	Study focuses on the effect of using glucose instead of water.
Annunziata S, Treglia G, Caldarella C et al. (2014) The role of 18F-FDG-PET and PET/CT in patients with colorectal liver metastases undergoing selective internal radiation therapy with yttrium-90: a first evidence-based review. The scientific world journal 2014; 879469	Review	FDG-PET and PET/CT provide additional information in treatment evaluation of CRLM patients treated with SIRT and may have a role in treatment planning and patient selection. FDG-PET/CT is emerging as good prognostic tool in these patients.	Review focuses on the role of imaging for treatment planning and patient selection.
Atassi B, Bangash AK, Lewandowski RJ et al. (2008) Biliary sequelae following radioembolization with Yttrium-90 microspheres. Journal of Vascular and Interventional Radiology 19:691-697.	Case series n=327 (137 colorectal metastases)	Overall symptomatic or asymptomatic toxicity was seen in 32% (44/137) of patients. 19% (26/137) of patients showed imaging findings related to the biliary tree. 14 had biliary necrosis on imaging. The clinical outcome of biliary necrosis seen on imaging was not reported separately for patients with colorectal metastases.	Study focuses on biliary sequelae.
Badiyan S, Bhooshan N, Chuong MD et al. (2018) Correlation of radiation dose and activity with	Case series n=60	The prescribed activity of 90 Y-resin microspheres may be correlated with radiographic	Larger studies are included.

clinical outcomes in metastatic colorectal cancer after selective internal radiation therapy using yttrium-90 resin microspheres. Nuclear Medicine Communications 39: 915-920	median follow-up=9 months	response by RECIST criteria at 4-6 months post-treatment. For a more accurate prediction of response, a valid dose calculation model based on post-90 Y PET dosimetry is likely needed given the heterogeneous dose delivery seen in SIRT.	
Baltatzis M, Siriwardena AK (2018) Liver resection for colorectal hepatic metastases after systemic chemotherapy and selective internal radiation therapy with Yttrium-90 microspheres: A Systematic Review. Digestive Surgery 1-8	Systematic review n=120	The conversion rate to hepatectomy in previously unresectable patients was 14% (109/802). All studies report a single application of SIRT. The interval from SIRT to surgery ranged from 39 days to 9 months. Overall, there were 4 (3%) deaths after hepatectomy in patients treated by chemotherapy and SIRT.	Review focuses on patients who had a resection after SIRT.
Benson AB 3rd, Geschwind JF, Mulcahy MF et al. (2013) Radioembolisation for liver metastases: results from a prospective 151 patient multi-institutional phase II study. European Journal of Cancer 49: 3122-30	Case series n=151	Median progression-free survival was 2.9 and 2.8 months for colorectal and other primaries, respectively. Median survival from (90)Y treatment was 8.8 months for colorectal and 10.4 months for other primaries.	More recent or larger studies are included.
Bester L, Feitelson S, Milner B et al. (2013) Impact of prior hepatectomy on the safety and efficacy of radioembolization with yttrium-90 microspheres for patients with unresectable liver tumors. American Journal of Clinical Oncology: Cancer Clinical Trials 37: 454-460	Case series n=89	The median overall survival after radioembolisation for hepatectomy patients was 7.8 months, versus 5.8 months for non-hepatectomy patients (p=0.108). The results indicate that radioembolisation is safe to be performed on a remnant liver. Although imaging analysis demonstrated varying responses to radioembolisation when comparing hepatectomy patients to non-hepatectomy patients, overall survival was similar between the 2 groups.	Study focuses on the effect of a previous hepatectomy.
Bester L, Meteling B, Boshell D et al. (2014) Transarterial chemoembolisation and radioembolisation for the treatment of primary liver cancer and secondary liver cancer: A review of the literature. Journal of Medical Imaging and Radiation Oncology 58: 341-352	Review	The data reported in prospective and retrospective studies of radioembolisation as salvage therapy in mCRC (either with or without chemotherapy) appear to demonstrate consistent survival benefits and the delay of disease progression. Some studies have also reported downsizing of tumours in patients with previously unresectable, chemorefractory disease sufficient to enable potentially curative liver resection.	No meta-analysis. More recent studies are included.

		For the first-line treatment of patients with or without extrahepatic metastases, radioembolisation has been shown to augment the treatment response of systemic chemotherapy in mCRC	
Bester L, Meteling B, Pocock N et al. (2013) Radioembolisation with Yttrium-90 microspheres: An effective treatment modality for unresectable liver metastases. Journal of Medical Imaging and Radiation Oncology 57: 72-80	Case series n=339	The survival results, together with the low acute and late toxicity observed in our data and previous studies, support the use of radioembolisation to aid in the local control of unresectable liver metastases in the salvage setting.	A comparative study from the same centre is included.
Bhooshan N, Sharma NK, Badiyan S et al. (2016) Pretreatment tumor volume as a prognostic factor in metastatic colorectal cancer treated with selective internal radiation to the liver using yttrium-90 resin microspheres. Journal of Gastrointestinal Oncology 7: 931-937	Case series n=60 median follow-up=9 months	Patients with metastatic CRC with larger overall pretreatment liver tumour volumes, regardless of number of individual liver lesions, are less likely to have radiographic evidence of stable disease or partial response following SIRT using volumetric response criteria. However, pretreatment volume was not significantly associated with OS, and thus SIRT should be considered for patients with larger pretreatment volumetric tumour burden.	Larger studies are included.
Bishay VL, Biederman DM, Ward TJ et al. (2016) Transradial approach for hepatic radioembolization: initial results and technique. American Journal of Roentgenology 207: 1112-1121	Case series n=318 FU=30 days	Use of the transradial approach for SIRT is safe, feasible, and well tolerated and is associated with high rates of technical success and rare complications.	Study with short term follow-up, focusing on the transradial approach.
Boas FE, Bodei L, Sofocleous CT (2017) Radioembolization of colorectal liver metastases: indications, technique, and outcomes. Journal of Nuclear Medicine 58: 104S-111S	Review	There are 2 types of 90Y microspheres: resin and glass. Because glass microspheres have a higher activity per particle, they can deliver a particular radiation dose with fewer particles, likely reducing embolic effects. Glass microspheres thus may be more suitable when early stasis or reflux is a concern, in the setting of hepatocellular carcinoma with portal vein invasion, and for radiation segmentectomy. Because resin microspheres have a lower activity per particle, more particles are needed to deliver a particular radiation dose. Resin microspheres thus may be	No meta-analysis.

		preferable for larger tumours and those with high arterial flow.	
Burnett NP, Akinwande O, Scoggins CR et al. (2017) Comparison of Yttrium-90 therapy for unresectable liver metastasis: glass versus biocompatible resin microspheres. Journal of Radiation Oncology 6: 101-108	Non-randomised comparative study (glass versus resin) n=119	In colorectal cancer (CRC), mean survival was 16.3 months for SIR-Spheres therapy and 26.8 for TheraSphere therapy (log-rank 0.097). There were no documented severe (grade 3) side effects in the TheraSphere group compared to 14% of patients who had side effects in the SIR-Spheres group. TheraSphere microsphere appears superior to SIR-Spheres in treating non-HCC intrahepatic malignancy. However, patient selection and better multi-disciplinary care may play a role in these differences. Continued studies in combination therapies for all hepatic malignancies is critical to the long-term success and sustainability of Y-90 therapy.	Small study, comparing different types of SIRT.
Chao C, Stavropoulos SW, Mondschein JI et al. (2017) Effect of substituting 50% isovue for sterile water as the delivery medium for sir-spheres: improved dose delivery and decreased incidence of stasis. Clinical Nuclear Medicine 42: 176-179	Case series n=175 procedures	Using dilute contrast as the delivery medium for SIR-Spheres resulted in a significantly greater percentage of the prepared activity administered to the patient with substantially shorter administration time. Termination for stasis occurred less often with dilute contrast. No complications were observed when using dilute contrast, which allowed continuous real-time monitoring of the ^{90}Y microsphere administration.	Study focuses on the use of dilute contrast as the delivery medium.
Chua TC, Bester L, Saxena A et al. (2011) Radioembolization and systemic chemotherapy improves response and survival for unresectable colorectal liver metastases. Journal of Cancer Research and Clinical Oncology 137: 865-873	Case series n=140	Response following treatment was complete in 2 patients (1%), partial in 43 patients (31%), stable in 44 patients (31%), and 51 patients (37%) developed progressive disease. Combining chemotherapy with radioembolisation was associated with a favourable treatment response (p=0.007). The median overall survival was 9 (95% CI 6.4 to 11.3) months with a 1-, 2-, and 3-year survival rate of 42, 22, and 20%, respectively. Primary tumour site (p=0.019), presence of extrahepatic disease (p=0.033), and a favourable treatment response (p<0.001) were identified as independent predictors for survival.	Larger or more recent studies are included.

Cosimelli M, Golfieri R, Cagol P et al. (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: 324-331	Case series n=50	By intention-to-treat analysis using Response Evaluation Criteria in Solid Tumours, 1 patient (2%) had a complete response, 11 (22%) partial response, 12 (24%) stable disease, 22 (44%) progressive disease; 4 (8%) were non-evaluable. Median overall survival was 12.6 months (95% CI, 7.0 to 18.3); 2-year survival was 19.6%.	Larger or more recent studies are included.
Daghir, A. A.; Gungor, H.; Haydar, A. A et al. (2012) Embolisation of the gastroduodenal artery is not necessary in the presence of reversed flow before yttrium-90 radioembolisation. Cardiovascular & Interventional Radiology 35: 839-44	Case series n=92	In patients with reversed gastroduodenal artery (GDA) flow, maintenance of a patent GDA before administration of Y(90) radioembolisation does not increase the risk of toxicity from nontarget dispersal. Therapeutic injection, with careful monitoring to identify early vascular stasis, may be safely performed beyond the origin of the patent GDA. A patent GDA with reversed flow provides forward drive for infused particles and may allow alternative access to the hepatic circulation.	Study focuses on the role of embolising the gastroduodenal artery.
Damm R, Seidensticker R, Ulrich G et al. (2016) Y90 Radioembolization in chemo-refractory metastatic, liver dominant colorectal cancer patients: Outcome assessment applying a predictive scoring system. BMC Cancer 16 (no. 1)	Case series n=106	Median survival of all patients was 6.7 months. Neither age nor prior surgical or systemic therapy nor metastatic spread had an effect on survival. In contrast, hepatic tumour load, Karnofsky index as well as CEA and CA19-9 serums level had a significant influence ($p<0.001$, $p=0.037$, $p=0.023$ and $p<0.001$, respectively).	Small case series, to determine a prognostic score.
Demirelli S, Erkilic M, Oner AO et al. (2015) Evaluation of factors affecting tumor response and survival in patients with primary and metastatic liver cancer treated with microspheres. Nuclear Medicine Communications 36: 340-349	Case series n=54	Technetium-99m macroaggregated albumin single photon emission computed tomography (MAA SPECT) has a predictive value in terms of response to radioembolisation, PFS, and OS. Dosimetry based on Tc-99m MAA SPECT images can be used in the selection of patients and, in particular, to adaptation of treatment plan in selected patients.	Small case series, focusing on imaging.
Evans KA, Richardson MG, Pavlakis N et al. (2010) Survival outcomes of a salvage patient population after radioembolization of hepatic metastases with yttrium-90 microspheres. Journal	Case series n=208 FU=3 months	The median OS was 8.3 months for the whole cohort, 7.9 months for patients with colorectal liver metastases. At the 3-month follow-up, there was an overall adverse event rate of 9%. At the	Larger or more recent studies are included.

of Vascular & Interventional Radiology 21: 1521-6		end of the data collection period, 62 patients were still alive.	
Geisel D, Powerski MJ, Schnapauff D et al. (2014) No infectious hepatic complications following radioembolization with 90Y microspheres in patients with biliodigestive anastomosis. Anticancer Research 34: 4315-21	Case series n=143	Pre-existing bilioenteric anastomoses are not a negative predictive factor for the development of infectious hepatic complications after RE. RE with (90)Y microspheres can be safely performed following careful patient selection.	Study focuses on the impact of biliodigestive anastomoses on infectious hepatic complications after SIRT.
Gil-Alzugaray B, Chopitea A, Inarrairaegui M et al. (2013) Prognostic factors and prevention of radioembolization-induced liver disease. Hepatology 57: 1078-87	Case series n=260	Radioembolisation-induced liver disease appeared only in patients with cirrhosis or in non-cirrhosis patients exposed to systemic chemotherapy prior to SIRT.	Study focuses on techniques to prevent radioembolisation-induced liver disease.
Golfieri R, Mosconi C, Giampalma E. et al. (2015) Selective transarterial radioembolisation of unresectable liver-dominant colorectal cancer refractory to chemotherapy. La Radiologia medica 120: 767-776	Case series n=52 FU=6 months	Disease control rates of target lesions (partial response plus stable disease) at 3- and 6-months follow-up were 59 and 29%, respectively. Target lesions were sufficiently downsized in 2 patients for hepatic resection and in 1 patient for radiofrequency ablation. Median Kaplan-Meier survival was 11.0 months (95% CI 8.0 to 14.0 months) overall and 12.0 months in liver-only disease (+/-lung micro-nodules). Determinants of prolonged survival were response at 3 months (p=0.046), <=5 liver nodules (p=0.004), single-liver-lobe involvement (p=0.037), tumour-to-whole liver ratio <25 % (p=0.021) and absence of extrahepatic metastases (p=0.045). Adverse events possibly related to the nontarget distribution of (90)Y-radioembolisation were grade 1 (90)Y-radioembolisation-induced liver disease (n=1), grade 2 and 3 gastric ulcers (n=2).	Larger studies are included.
Gray B, Van Hazel G, Hope M et al. (2001) Randomised trial of SIR-Spheres plus chemotherapy vs. chemotherapy alone for treating patients with liver metastases from primary large bowel cancer. Ann Oncol 12:1711-1720.	RCT n=70	The combination of a single injection of SIR-Spheres plus HAC is substantially more effective in increasing tumour responses and progression free survival than the same regimen of HAC alone.	Results from larger, more recent RCTs are included.
Inarrairaegui, M.; Bilbao, J. I.; Rodriguez, M. et al. (2010) Liver radioembolization using 90Y resin microspheres in elderly patients:	Case series n=255	In patients with colorectal carcinoma metastatic to the liver, the median overall survival was 10 months (95% CI, 5.2-14.7) for elderly patients and 13 months	Study focuses on outcomes in elderly patients.

tolerance and outcome. Hospital practice 38: 103-9		(95% CI, 7.0-18.9) for younger patients (p=0.3). Elderly patients did not have more toxicity than younger patients treated with SIRT, and survival was similar for each histology. Elderly patients should be considered for SIRT if they otherwise meet the inclusion criteria applicable to younger patients.	
Jakobs TF, Paprottka KJ, Raesler F et al. (2017) Robust evidence for long-term survival with ^{90}Y radioembolization in chemorefractory liver-predominant metastatic colorectal cancer. European Radiology 27: 113-119	Case series n=104	After multiple chemotherapies, many patients still have a good performance status and are eligible for radioembolisation. This single procedure can achieve meaningful survival and is generally well tolerated.	Larger studies are included.
Kennedy AS, Ball DS, Cohen SJ et al. (2015) Hepatic imaging response to radioembolization with yttrium-90-labeled resin microspheres for tumor progression during systemic chemotherapy in patients with colorectal liver metastases. Journal of Gastrointestinal Oncology 6: 594-604	Case series n=195	RECIST 1.0 and RECIST 1.1 imaging responses provide equivalent interpretations in the assessment of hepatic tumors following ^{90}Y-RE. Radiologic lesion responses at 3 months must be interpreted with caution due to the significant proportion of patients with peri-tumoral oedema and necrosis, which may lead to an under-estimation of PR/SD. Nevertheless, 3-month radiologic responses were predictive of prolonged survival.	Study focuses on the impact of imaging artefacts.
Kennedy AS, Ball DS, Cohen SJ et al. (2016) Safety and efficacy of radioembolization in elderly (>= 70 years) and younger patients with unresectable liver-dominant colorectal cancer. Clinical Colorectal Cancer 15: 141-151	Case series n=606	For patients with unresectable liver-dominant mCRC who meet eligibility criteria for radioembolisation, ^{90}Y-radioembolisation microspheres appear to be effective and well-tolerated, regardless of age. Criteria for selecting patients should not include age for exclusion from this potentially beneficial intervention.	A study by the same author is already included.
Kennedy AS, Ball D, Cohen SJ et al. (2017) Baseline hemoglobin and liver function predict tolerability and overall survival of patients receiving radioembolization for chemotherapy-refractory metastatic colorectal cancer. Journal of Gastrointestinal Oncology 8: 70-80	Case series n=606	Review of pre-radioembolisation laboratory parameters may aid in improving median survivals if correctable grade >0 values are addressed before radiation delivery. HGB<10 g/dL is a well-known negative factor in radiation response and is easily corrected. Improving other parameters is more challenging. These efforts are important in optimising treatment response to liver radiotherapy.	A study by the same author is already included.

Kennedy AS, Ball D, Cohen SJ et al. (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: 134-142	Case series n=606	Radioembolization appears to have a favourable risk/benefit profile, even among mCRC patients who had received >=3 prior lines of chemotherapy.	A study by the same author is already included.
Kennedy AS, Coldwell D, Nutting C et al. (2006) Resin 90Y-microsphere brachytherapy for unresectable colorectal liver metastases: modern USA experience. International Journal of Radiation Oncology, Biology, Physics 65:412-425.	Case series n=208 FU=3 months	Complete response=0% (0/208) Partial response=36% (74/208) Stable disease=55% (114/208) Progressive disease=10% (21/208)	Larger or more recent studies are included.
Kucuk ON, Soydal C, Lacin S et al. (2011) Selective intraarterial radionuclide therapy with Yttrium-90 (Y-90) microspheres for unresectable primary and metastatic liver tumors. World Journal of Surgical Oncology 9	Case series n=78	SIRT is a useful treatment method which can contribute to the lengthening of survival times in patients with primary or metastatic unresectable liver malignancies. ~~Also~~Also, F18-FDG PET/CT is seen to be a successful imaging method in evaluating treatment response for predicting survival times in this patient group.	Larger or more recent studies are included.
Kuo JC, Tazbirkova A, Allen R et al. (2014) Serious hepatic complications of selective internal radiation therapy with yttrium-90 microsphere radioembolization for unresectable liver tumors. Asia Pacific Journal of Clinical Oncology 10: 266-272	Case series n=205	Selective internal radiation therapy with radioembolisation was associated with serious hepatic complications with an incidence of 4.9% and a mortality rate of 1.5% in 205 patients from 2 Australian institutions. The risk of serious hepatic toxicity therefore needs to be discussed when counselling patients regarding this potential treatment option.	Larger studies are included.
Kurilova I, Beets-Tan RGH, Ulaner GA et al. (2018) ^{90}Y resin microspheres radioembolization for colon cancer liver metastases using full-strength contrast material. CardioVascular and Interventional Radiology 41: 1419-1427	Case series n=81 Median follow-up=9 months	Administration of ^{90}Y resin microspheres using undiluted non-ionic contrast material in both lines is safe and effective, resulting in lower fluoroscopy radiation dose and shorter infusion time, without evidence of myelosuppression or increased stasis incidence.	Study focuses on the effect of using undiluted non-ionic contrast material.
Lam MGEH, Banerjee A, Louie JD et al. (2014) Splenomegaly-associated thrombocytopenia after hepatic yttrium-90 radioembolization. CardioVascular and Interventional Radiology 37: 1009-1017	Case series n=116	Post-radioembolisation treatment increase of spleen volume is correlated with decreased peripheral platelet count suggesting a mechanism of increased portal hypertension	Study focuses on thrombocytopenia.

		and hypersplenism being responsible.	
Lam MGEH, Banerjee S, Louie JD et al. (2013) Root cause analysis of gastroduodenal ulceration after yttrium-90 radioembolization. CardioVascular and Interventional Radiology 36: 1536-1547	Case series n=247	8 patients (3%) developed a gastroduodenal ulcer. Stasis during injection was the strongest independent risk factor (p=0.004), followed by distal origin of the gastroduodenal artery (p=0.004), young age (p=0.040), and proximal injection of the microspheres (p=0.043). Prolonged administrations, pain during administration, whole liver treatment, and use of resin microspheres also showed interrelated trends in multivariate analysis.	Study focuses on risk factors for gastroduodenal ulcer after SIRT.
Lam MG, Banerjee A, Goris ML et al. (2015) Fusion dual-tracer SPECT-based hepatic dosimetry predicts outcome after radioembolization for a wide range of tumour cell types. European Journal of Nuclear Medicine & Molecular Imaging 42: 1192-201	Case series n=122	Fusion dual-tracer SPECT imaging offers a physiology-based functional imaging tool to predict efficacy and toxicity of radioembolisation. This technique can be refined to define dosing thresholds for specific tumour types and treatments but appears generally predictive even in a heterogeneous cohort.	Study focuses on use of fusion dual-tracer SPECT imaging.
Lam MG, Louie JD, Iagaru AH et al. (2013) Safety of repeated yttrium-90 radioembolization Cardiovascular & Interventional Radiology 36: 1320-8	Case series n=247	8 patients had repeat SIRT. 2 patients died shortly after the second treatment (at 84 and 107 days) with signs and symptoms of REILD. Both patients underwent whole liver treatment twice (cumulative doses 3.08 and 2.66 GBq). The other 6 patients demonstrated only minor toxicities after receiving cumulative doses ranging from 2.41 to 3.88 GBq. All patients experienced objective tumour responses. Repeated RE proved to be the only independent risk factor for REILD in multivariate analysis (odds ratio 9.6; p=0.002). Additionally, the administered activity per target volume (in GBq/L) was found to be an independent risk factor for REILD, but only in whole liver treatments (p=0.033).	Study focuses on the safety of repeated SIRT.
Lewandowski RJ, Minocha J, Memon K et al. (2014) Sustained safety and efficacy of extended-shelf-life (90)Y glass microspheres: long-term follow-up in a 134-patient cohort. European Journal of Nuclear	Case series n=134	This study showed sustained safety and efficacy of extended-shelf-life (90)Y glass microspheres in a larger, 134-patient cohort. The increase in number of microspheres administered theoretically	Study focuses on use of extended shelf-life glass microspheres.

Medicine & Molecular Imaging 41: 486-93		resulted in better tumour distribution of the microspheres without an increase in adverse events.	
Maleux G, Deroose, C, Laenen, A et al. (2016) Yttrium-90 radioembolization for the treatment of chemorefractory colorectal liver metastases: Technical results, clinical outcome and factors potentially influencing survival. Acta Oncologica 55: 486-495	Case series n=71	^{90}Y microsphere radioembolisation for chemorefractory colorectal liver metastases has an acceptable safety profile with a 50% estimated survival after 8 months. Pretreatment high bilirubin, alkaline phosphatase and tumor volume levels were associated with early death.	Larger studies are included.
Meyer C, Aouf A, Sabet A et al. (2014) Early post-treatment FDG PET predicts survival after ^{90}Y microsphere radioembolization in liver-dominant metastatic colorectal cancer. European Journal of Nuclear Medicine and Molecular Imaging 42: 370-376	Case series n=51	The median OS was 7 months (95% CI 5 to 8); early metabolic responders (n=33) survived longer than non-responders ($p<0.001$) with a median OS of 10 months (95% CI 3 to 16) versus 4 months (95% CI 2 to 6). Hepatic tumour burden also had significant impact on treatment outcome ($p<0.001$) with a median OS of 5 months (95% CI, 3 to 7) for patients with >25 % metastatic liver replacement vs 14 months (95% CI 6 to 22) for the less advanced patients. Both factors (early metabolic response and low hepatic tumour burden) remained as independent predictors of improved survival on multivariate analysis.	Larger studies are included.
Nace GW, Steel JL, Amesur N et al. (2011) Yttrium-90 radioembolization for colorectal cancer liver metastases: a single institution experience. International Journal of Surgical Oncology Print 2011: 571261	Case series n=51	Using RECIST criteria, either stable disease or a partial response was seen in 77% of patients. Overall median survival from the time of first 90Y treatment was 10.2 months (95% CI 7.5 to 13.0). The absence of extrahepatic disease at the time of treatment with 90Y was associated with an improved survival, median survival of 17.0 months (95% CI 6.4 to 27.6), compared to those with extrahepatic disease at the time of treatment with 90Y, 6.7 months (95% CI 2.7 to 10.6).	Larger and more recent studies are included.
Narsinh KH, Van Buskirk M, Kennedy AS et al. (2017) Hepatopulmonary shunting: a prognostic indicator of survival in patients with metastatic colorectal adenocarcinoma treated with	Case series n=606	Increased lung shunt fraction (LSF) is an independent prognostic indicator of worse survival in patients undergoing radioembolisation for liver-dominant metastatic colorectal adenocarcinoma. High LSF correlates poorly to other	The same patient population is described in another study included in table 2.

^{90}Y radioembolization. Radiology 282: 281-288		potential markers of tumour size, such as tumour-to-liver volume ratio or serum carcinoembryonic antigen level and does not correlate to the presence of extrahepatic metastases.	
Orwat KP, Beckham TH, Cooper SL et al. (2017) Pretreatment albumin may aid in patient selection for intrahepatic Y-90 microsphere transarterial radioembolization (TARE) for malignancies of the liver. Journal of Gastrointestinal Oncology 8: 1072-1078	Case series n=114 (55 CRC) Median follow-up=6.4 months (range 0 to 86)	Patients with neuroendocrine and breast histology as well as those with better hepatic synthetic function were associated with significantly better survival.	Larger studies are included.
Paprottka KJ, Schoeppe F, Ingrisch M et al. (2017) Pre-therapeutic factors for predicting survival after radioembolization: a single-center experience in 389 patients. European Journal of Nuclear Medicine and Molecular Imaging 44: 1185-1193	Case series n=389	Pre-therapeutic baseline bilirubin and cholinesterase levels, extrahepatic disease and hepatic tumour burden are associated with patient survival after radioembolisation. Such parameters may be used to improve patient selection for radioembolisation of primary or metastatic liver tumours.	Heterogenous patient population.
Paprottka PM, Paprottka KJ, Walter A et al. (2015) Safety of radioembolization with ^{90}yttrium resin microspheres depending on coiling or no-coiling of aberrant/high-risk vessels. CardioVascular and Interventional Radiology 38: 946-956	Case series n=566 procedures	There was no significant difference in delayed toxicity in the coiling versus the no-coiling group. No radioembolisation-induced liver disease was noted after all 566 procedures. Conclusion: Radioembolisation with ^{90}Y resin microspheres is a safe and effective treatment option. Performing radioembolisation without coil embolisation of aberrant vessels prior to treatment could be an alternative for experienced centres.	Study focuses on coiling or no-coiling of aberrant or high-risk vessels before SIRT.
Parakh S, Gananadha S, Allen R et al. (2016) Cholecystitis after yttrium-90 resin microsphere radioembolization treatment: Clinical and pathologic findings. Asian journal of surgery 39: 144-148	Case series n=74	The incidence of symptomatic radiation cholecystitis after radioembolisation is low, and prophylactic cholecystectomy is not routinely recommended for patients undergoing radioembolisation. Radiation cholecystitis should be suspected in patients presenting with symptoms of biliary colic or cholecystitis following radioembolisation.	Small case series, focusing on cholecystitis.
Pardo F, Sangro B, Lee RC et al. (2017) The Post-SIR-Spheres Surgery Study (P4S): retrospective analysis of safety following hepatic resection or	Case series n=100	Post-SIRT, 71 patients were resected and 29 received a liver transplant. Grade 3+ peri/postoperative complications and any grade of liver failure	Study focuses on patients having hepatic resection

transplantation in patients previously treated with selective internal radiation therapy with yttrium-90 resin microspheres. Annals of Surgical Oncology 24: 2465-2473		were experienced by 24 and 7% of patients, respectively. Four patients died <90 days postsurgery; all were trisectionectomies (mCRC: 3; cholangiocarcinoma: 1) and typically had 1 or more previous chemotherapy lines and presurgical comorbidities.	or transplantation after SIRT.
Peterson JL, Vallow LA, Johnson DW et al. (2013) Complications after 90Y microsphere radioembolization for unresectable hepatic tumors: An evaluation of 112 patients. Brachytherapy 12: 573-9	Case series n=112	78 patients (70%) had postradioembolisation syndrome, including fatigue, abdominal pain, nausea, vomiting, anorexia, or fever. Three patients (3%) had a Grade 3 early complication; no Grade 4 or 5 early toxicity occurred. Two patients (2%) had clinically significant liver dysfunction; 13 patients (12%), 27 patients (24%), and 9 patients (8%) had an elevation of bilirubin, aspartate aminotransferase, and alanine aminotransferase, respectively. Eleven patients (10%) had gastrointestinal ulceration, including 2 Grade 3 complications and 1 Grade 4 complication. Cholecystitis occurred in 7 patients (6%), including 2 Grade 3 complications. Grade 2 pancreatitis occurred in 1 patient (1%). No radiation pneumonitis was observed. The cumulative incidence of late Grade 3 or 4 complications at 12 months after radioembolisation was 8%. No Grade 5 toxicity occurred.	Larger studies are included.
Piana PM, Bar V, Doyle L et al. (2014) Early arterial stasis during resin-based yttrium-90 radioembolization: Incidence and preliminary outcomes. Hpb 16: 336-341	Case series n=71	Early stasis occurred in approximately 20% of infusions with similar incidences in hyper- and hypovascular tumours. Whole-liver therapy reduced the incidence of stasis. Stasis did not appear to affect initial imaging outcomes.	Small case series, focusing on arterial stasis.
Piana PM, Gonsalves CF, Sato T et al. (2011) Toxicities after radioembolization with yttrium-90 SIR-spheres: incidence and contributing risk factors at a single center. Journal of Vascular & Interventional Radiology 22: 1373-9	Case series n=81	Mild hepatotoxicity developed frequently after infusion of SIR-Spheres using the body surface area method, with normalization of liver function tests in most patients. Grade 3 or greater toxicities were seen in <10% of infusions. Toxicity was strongly associated with previous intra-arterial therapy.	Larger studies are included.
Pieper CC, Willinek WA, Thomas D. et al. (2016) Incidence and risk	Case series	Early stasis occurred in 103 procedures (25%). Highest	Mixed population of primary and

factors of early arterial blood flow stasis during first radioembolization of primary and secondary liver malignancy using resin microspheres: an initial single-center analysis. European Radiology 26: 2779-89	n=362	incidence and degree of stasis were in breast cancer metastases [43% (20/47); 56% of mean intended dose administered]. Independent risk factors were: metastasized breast cancer (odds ratio [OR] 2.18, p=0.02), liver tumour-burden <25 % and 25-50 % (ORs 5.33, 15.64; p<0.0001), tumour hypovascularity (OR 2.70, p=0.04), previous bevacizumab therapy (OR 2.79, p=0.0009) and concurrent chemotherapy (OR 8.69, p<0.0001).	secondary liver cancers.
Raval M, Bande D, Pillai AK et al. (2014) Yttrium-90 radioembolization of hepatic metastases from colorectal cancer. Frontiers in Oncology 4: 120	review	Yttrium-90 therapy is recommended for chemorefractory patients with liver-only or liver-predominant disease and in patients who do not wish to have systemic chemotherapy. Use of Y-90 therapy in conjunction with standard first line or second line chemotherapy requires more rigorous data and is recommended in a clinical trial setting. The use of Y-90 is not recommended in patients with extensive extra-hepatic disease or extensive bilobar hepatic involvement. Similarly, patients with poor performance status (ECOG PS >2) are not suitable for Y-90 therapy.	No meta-analysis. More recent studies are included.
Roberson Ii JD, McDonald AM, Baden CJ et al. (2016) Factors associated with increased incidence of severe toxicities following yttrium-90 resin microspheres in the treatment of hepatic malignancies. World Journal of Gastroenterology 22: 3006-14	Case series n=58	Severe (grade >= 3) toxicities occurred after 21.5% of the 79 treatments included in the analysis. The most common severe laboratory toxicities were severe alkaline phosphatase (18%), albumin (13%), and total bilirubin (10%) toxicities. Decreased pre-treatment albumin (OR=26.2, p=0.010) and increased pre-treatment international normalized ratio (INR) (OR=17.7, p=0.048) were associated with development of severe hepatic toxicity. Increased pre-treatment aspartate aminotransferase (AST; OR=7.4, p=0.025) and decreased pre-treatment haemoglobin (OR=12.5, p=0.025) were associated with severe albumin toxicity. Increasing pre-treatment model for end-stage liver disease	Larger studies are included.

		(MELD) score (OR=1.8, p=0.033) was associated with severe total bilirubin toxicity. Colorectal adenocarcinoma histology was associated with severe alkaline phosphatase toxicity (OR=5.4, p=0.043).	
Rodriguez-Lago, I.; Carretero, C.; Herraiz, M et al. (2013) Long-term follow-up study of gastroduodenal lesions after radioembolization of hepatic tumors. World Journal of Gastroenterology 19: 2935-40	Case series n=379 procedures	6 patients (1.5%) developed gastrointestinal symptoms and had gastrointestinal lesions as shown by upper endoscopy after 12 weeks. The mean time between radioembolisation and the appearance of symptoms was 5 weeks. Only 1 patient needed endoscopic and surgical treatment. The incidence of gastrointestinal ulcerations was 3.8% (3/80) when only planar images were used for the pre-treatment evaluation. It was reduced to 1% (3/299) when single-photon emission computed tomography (SPECT) images were also done.	Study focuses on gastroduodenal lesions.
Sag AA, Savin MA, Lal NR et al. (2014) Yttrium-90 radioembolization of malignant tumors of the liver: gallbladder effects. American Journal of Roentgenology 202: 1130-5	Case series n=133	Clinically significant radiation-induced cholecystitis occurred in 1 of the 133 patients (0.8%). After radioembolisation, gallbladder imaging abnormalities were found in 99% (84/85) of patients, but none was associated with clinically significant radiation-induced cholecystitis.	Larger studies are included.
Sato KT (2011) Yttrium-90 radioembolization for the treatment of primary and metastatic liver tumors. Seminars in Roentgenology 46: 159-165	Review	This treatment can potentially increase survival and preserve the quality of life for these patients. Ultimately, further study is needed to be able to optimise treatment and establish a proper role for radioembolisation of liver tumours.	No meta-analysis. More recent studies are included.
Sato KT, Lewandowski RJ, Mulcahy MF et al. (2008) Unresectable chemorefractory liver metastases: radioembolization with 90Y microspheres--safety, efficacy, and survival. Radiology 247:507-515.	Case series n=137 (51 colorectal metastases)	49% (25/51) of patients died during follow-up. Median survival was 457 days, and mean survival 416 days. 1- and 2-year survival was 53.7% and 26.7% respectively	Larger or more recent studies are included.
Savin MA, Chehab M, Campbell JM et al. (2015) Yttrium-90 infusion: incidence and outcome of delivery system occlusions during 885 deliveries. Journal of Vascular & Interventional Radiology 26: 1769-76	Case series n=885 procedures	Of 885 90Y microsphere deliveries, 11 resulted in occlusion (1.2%). Five occlusions were associated with contained leakage of radioactive material, and 1 was associated with a spill. Treatment was completed in the	Study focuses on occlusions.

		same day in 10 patients; repeat catheterisation was needed in 5 patients. One patient returned 1 week later to complete treatment. Occlusions were more frequent with deliveries of resin (11/492; 2.2%) versus glass (0/393; 0%) microspheres (p=0.002). Occlusions were more likely to occur within the proximal portion of the delivery apparatus (p=.002). There was no significant relationship with any patient characteristics, and there was no improvement with operator experience. The most common cause of occlusion was resin microsphere delivery device failure.	
Smits ML, van den Hoven AF, Rosenbaum CE et al. (2013) Clinical and laboratory toxicity after intra-arterial radioembolization with (90)y-microspheres for unresectable liver metastases. PLoS ONE 8: e69448	Case series n=59 (30 CRC)	No grade 3-4 clinical toxicity was observed, whereas laboratory toxicity grade 3-4 was observed in 38% of patients. Whole liver treatment in 1 session was not associated with increased laboratory toxicity. Three-months disease control rates for target lesions, whole liver and overall response were 35%, 21% and 19% respectively. Median time to progression was 6.2 months for target lesions, 3.3 months for the whole liver and 3.0 months for overall response. Median overall survival was 8.9 months.	Larger and more recent studies are included.
Sofocleous CT, Violari EG, Sotirchos VS et al. (2015) Radioembolization as a salvage therapy for heavily pretreated patients with colorectal cancer liver metastases: factors that affect outcomes. Clinical Colorectal Cancer 14: 296-305	Case series n=53	Median OS was 12.7 months. Multivariate analysis showed that carcinoembryonic antigen levels >= 90 ng/mL (p=0.004) and microscopic lymphovascular invasion of the primary (p=0.002) were independent predictors of decreased OS. Median LPFS was 4.7 months. At 4 to 8 and 12 to 16 weeks follow-up, most patients (80% and 61%, respectively) according to Response Evaluation Criteria in Solid Tumors (RECIST) had stable disease; additional evaluation using PET Response Criteria in Solid Tumors (PERCIST) led to reclassification in 77% of these cases (response or progression). No deaths were noted within the first 30 days. Within the first 90 days, 4 patients (8%) developed liver	Larger studies are included.

		failure and 5 patients (9%) died, all with evidence of disease progression.	
Stubbs RS, O'Brien I and Correia MM. (2006) Selective internal radiation therapy with 90Y microspheres for colorectal liver metastases: single-centre experience with 100 patients. ANZ Journal of Surgery 76:696-703.	Case series n=100	Selective internal radiation therapy is a very effective and well-tolerated regional treatment for colorectal liver metastases, which should be considered for those with liver-only metastatic disease.	Larger or more recent studies are included.
Sundram FX, Buscombe JR (2017) Selective internal radiation therapy for liver tumours. Clinical Medicine, Journal of the Royal College of Physicians of London 17: 449-453	Review	There is well established clinical benefit evidence and growing research evidence regarding SIRT.	No meta-analysis.
Tchelebi L, Sharma NK (2019) Selective internal radiation therapy in the multidisciplinary management of liver metastases from colorectal carcinoma. Seminars in nuclear medicine 49: 182–8	Review	SIRT has emerged as a safe and effective treatment for patients with liver only or liver-predominant metastases from colorectal cancer. While randomised phase II data is limited in the salvage setting, there is robust data available indicating a survival benefit among these patients, in particular among those who have failed multiple lines of chemotherapy and have limited treatment options remaining.	No meta-analysis.
Tohme S, Sukato D, Nace GW et al. (2014) Survival and tolerability of liver radioembolization: A comparison of elderly and younger patients with metastatic colorectal cancer. Hpb 16: 1110-1116	Case series n=107	Radioembolisation appears to be as well tolerated and effective for the elderly as it is for younger patients with mCRC. Age alone should not be a discriminating factor for the use of radioembolisation in the management of mCRC patients.	Larger or more recent studies are included.
Townsend AR, Chong LC, Karapetis C et al. (2016) Selective internal radiation therapy for liver metastases from colorectal cancer. Cancer Treatment Reviews 50: 148-154	review	There remains a lack of evidence that SIRT improves survival or quality of life in patients with metastatic colorectal cancer. The overall survival results from SIRFLOX combined with FOXFIRE and FOXFIRE Global are awaited.	No meta-analysis. More recent studies are included.
Turkmen C, Ucar A, Poyanli A et al. (2013) Initial outcome after selective intraarterial radionuclide therapy with yttrium-90 microspheres as salvage therapy for unresectable metastatic liver disease. Cancer Biotherapy and Radiopharmaceuticals 28: 534-540	Case series n=61	A subset analysis of colorectal and non-colorectal groups demonstrated median OS rates of 14.0+/-5.8 and 17.0+/-4.8 months, respectively (p=0.543).	Larger studies are included.

Van Hazel GA, Heinemann V, Sharma NK et al. (2016) SIRFLOX: Randomized phase III trial comparing first-line mFOLFOX6 (Plus or Minus Bevacizumab) versus mFOLFOX6 (Plus or Minus Bevacizumab) plus selective internal radiation therapy in patients with metastatic colorectal cancer. Journal of Clinical Oncology 34: 1723-1731	RCT n=530	The addition of SIRT to FOLFOX-based first-line chemotherapy in patients with liver-dominant or liver only metastatic colorectal cancer did not improve PFS at any site but significantly delayed disease progression in the liver. The safety profile was as expected and was consistent with previous studies.	Included in study 1 (Wasan et al., 2017)
Van Hazel G, Blackwell A, Anderson J et al. (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 88:78-85.	RCT n=21	There was a statistically significant improved median survival in the SIRT group (29.4 months) compared with the chemotherapy alone group (12.8 months), hazard ratio 0.33 (95% confidence interval 0.12 to 0.91) (p = 0.025).	Results from a larger, more recent RCT are included.
Ward TJ, Louie JD, Sze, D. Y. (2017) Yttrium-90 radioembolization with resin microspheres without routine embolization of the gastroduodenal artery. Journal of Vascular & Interventional Radiology 28: 246-253	Case series n=62 Median follow-up=134 days	Prophylactic embolisation of the gastroduodenal artery was done in only 2 patients (3%). In 6 treatments (9%), adjunctive embolisation was needed immediately before radioembolisation, and an antireflux microcatheter was used in 14% of treatments. Clinical follow-up was available in 60 of 62 patients. No signs or symptoms of gastric or duodenal ulceration were observed.	Study focuses on embolisation of the gastroduodenal artery.
Ward TJ, Tamrazi A, Lam MG et al. (2015) Management of high hepatopulmonary shunting in patients undergoing hepatic radioembolization. Journal of Vascular & Interventional Radiology 26: 1751-60	Case series n=80	Dose reduction recommendations for high hepatopulmonary shunting (HPSF) may compromise efficacy. Excessive shunting can be reduced by prophylactic catheter-based techniques, which may improve the safety of performing radioembolisation in patients with high HPSF.	Small study, focusing on the management of high hepatopulmonary shunting.