NHS England

Evidence review: selective internal radiation therapy (SIRT) with ytrrium-90 microspheres for unresectable, liver-only or liver-dominant metastatic colorectal carcinoma who are chemotherapy-refractory or chemotherapy-intolerant

First published: Month Year

Updated: Not applicable

Prepared by: Cedar on behalf of NHS England Specialised Commissioning

Contents

Abbreviations

BSC	best supportive care
CI	confidence interval
CR	complete response
CRC	colorectal cancer
CRCLM	colorectal cancer liver metastases
ECOG	Eastern Cooperative Oncology Group
EHM	extrahepatic metastases
FU	fluorouracil
HR	hazards ratio
IPO	Interventional procedure overview
LPFS	liver-specific progression free survival
mCRC	metastatic colorectal cancer
NICE	National Institute for Health and Care Excellence
NR	not reported
OS	overall survival
PD	progressive disease
PFS	progression free survival
PR	partial response
QALY	quality-adjusted life year
RCT	randomised control trial
RE	radioembolization
RESIST	response evaluation criteria in solid tumours
RILD	radiation induced liver disease
SC	standard care
SD	stable disease
SIRT	selective internal radiation therapy
TACE	trans-arterial chemo-embolization
TTLP	time to liver progression
TTP	time to progression
^{90}Y	yttrium-90

1. Introduction

Colorectal cancer (CRC) is a cancer that develops in the colon or rectum. CRC is the third most common cancer in the UK, with 40,755 new cases diagnosed in 2012; this is estimated to rise to 58,119 cases each year by 2035. CRC is more common in people over 65 (73.1% of new cases) and in men (55.4% of cases). CRC is an important cause of death; there were 16,202 deaths in 2012 and this is expected to increase to almost 24,000 deaths in 2035. Metastases are reported in at least half of all CRC cases. CRC most often spreads to the liver (hepatic metastases) but may also spread to the lungs, bones and other organs in the body (extrahepatic metastases).

Long-term survival can be achieved in metastatic colorectal cancer (mCRC) spread to the liver if the metastases are surgically resectable, but only 10-20% of mCRC patients have liver metastases that can be surgically removed at the time of presentation. Furthermore, recurrence of disease is common, occurring in up to 75% of patients who undergo resection of colorectal liver metastases; thus, liver metastases remain a life-limiting factor for the majority of patients with mCRC.

Some patients with unresectable metastases may be suitable for tumour removal using ablation techniques but the majority of these patients are typically treated with systemic chemotherapy in accordance with clinical guideline recommendations. Many patients eventually become insensitive/unresponsive to chemotherapy (chemotherapy-refractory) or cannot tolerate multiple cycles of chemotherapy (chemotherapy-intolerant). Further treatment options in this scenario are limited and disease management is often restricted to best supportive care (BSC) with palliative intent. Other potential options include trans-arterial chemo-embolization (TACE) and external beam liver radiation but there is limited evidence supporting their use and these interventions are currently not recommended in the European Society for Medical Oncology guidelines.

Selective internal radiation therapy (SIRT), which may also be called radioembolisation (RE), is a way of giving radiotherapy treatment for cancer in the liver. SIRT involves injecting tiny beads (resin or glass microspheres), containing a radioactive substance, into the hepatic artery via a catheter. The microspheres become lodged in the small blood vessels around the tumour and deliver radiation directly to the cancer cells and thus destroying them. The purpose of this evidence review is to examine the clinical and cost effectiveness of using SIRT with yttrium-90 microspheres compared with best supportive care for individuals with unresectable, liver-dominant metastatic colorectal carcinoma who are chemotherapy-refractory or chemotherapy-intolerant. Yttrium-90 is a beta emitting isotope with a half-life of 64.2 hours. The emissions from 90Y have an average/maximal penetration range in tissue of 2.5 mm and 11 mm, respectively, thus limiting the damage to surrounding healthy tissue. Following administration, 94% of the radiation is delivered in 11 days (Murthy et al. 2008).

There are two yttrium-90 products currently available in the UK for this indication that were considered for this review: SIR-Spheres (Sirtex Medical) which are resin yttrium-90 microspheres and TheraSphere (Biocompatibles UK) which are glass yttrium-90 microspheres.

The questions that this review aimed to address were:

1. What is the evidence on clinical effectiveness of using selective internal radiation therapy (SIRT) with yttrium-90 microspheres compared with best supportive care for individuals with unresectable, liver-dominant metastatic colorectal carcinoma who are chemotherapy-refractory or chemotherapy-intolerant?
    a) glass yttrium-90 microspheres
    b) resin yttrium-90 microspheres
2. What is the evidence relating to the safety of selective internal radiation therapy (SIRT) with yttrium-90 microspheres compared with best supportive care for individuals with

unresectable, liver-dominant metastatic colorectal carcinoma who are chemotherapy-refractory or chemotherapy-intolerant?

   a) glass yttrium-90 microspheres
   b) resin yttrium-90 microspheres

3. What is the evidence on the cost effectiveness of selective internal radiation therapy (SIRT) with yttrium-90 microspheres compared with best supportive care for individuals with unresectable, liver-dominant metastatic colorectal carcinoma who are chemotherapy-refractory or chemotherapy-intolerant?
   a) glass yttrium-90 microspheres
   b) resin yttrium-90 microspheres
4. Does the evidence of clinical and cost-effectiveness identify any subgroups of patients with unresectable, liver-dominant metastatic colorectal carcinoma who are chemotherapy-refractory or chemotherapy-intolerant who would gain greater benefit from using selective internal radiation therapy (SIRT) with yttrium-90 microspheres compared with best supportive care?

2. Summary of results

Only 3 comparative studies were identified that included SIRT with yttrium-90 microspheres as a treatment arm (Bester et al. 2012; Hendlisz et al. 2010 and Seidensticker et al. 2012). Hendlisz et al. (2010) had the best study methodology being a randomised controlled trial (RCT). However the comparison was between a protracted intravenous infusion of fluorouracil (FU) (n=23) and SIRT with intravenous FU (n=21). The primary outcome was time to liver progression (TTLP) although the description provided indicated that actually liver-specific progression free survival (LPFS) is reported. SIRT had a significant benefit in controlling liver tumour growth, as measured by LPFS; SIRT & FU 5.5 months versus FU 2.1 months; HR 0.38 (95% CIs 0.28-0.94), p=0.003.The results indicated that there was no significant overall survival (OS) advantage with SIRT; SIRT & FU - 10.0 months vs. FU - 7.3 months; HR 0.92 (0.47-1.78), p=0.80. However high rates of cross-over may mask any survival benefit.

Bester et al. (2012) and Seidensticker et al. (2012), n=253 and n=58 respectively, are both non-randomised retrospective studies and therefore at risk of bias, particularly selection bias and variation in outcome measures between groups. Both demonstrated a significant survival benefit with SIRT compared to standard care. However biases in each of the studies raise concern over the reliability of this outcome.

Adverse events were observed in Hendlisz et al. (2010) although these were not significantly different between treatment groups. Adverse events were reported in Bester et al. (2012) and Seidensticker et al. (2012) but were not reported for the standard care group so no comparison could be made to the events experienced in the SIRT groups.

There was a lack of economic evidence for SIRT. A published cost-effectiveness model (Pennington et al. 2015), using survival data from Bester et al. (2012), provided a cost per QALY gained of £28, 216. The data used for this model is subject to bias and some assumptions and inputs used in the model may not be appropriate; this reduces the reliability of the cost-effectiveness estimates.

Without high quality studies it is difficult to fully understand the clinical and cost-effectiveness of SIRT with yttrium-90 microspheres compared to best supportive care in patients with unresectable, chemotherapy-refractory or chemotherapy-intolerant, liver-dominant metastatic colorectal. Studies are required that examine the impact of SIRT on patients' quality of life.

3. Methodology

Literature search

The search conducted for the NICE interventional procedure overview (NICE 2011) of selective internal radiation therapy for non-resectable colorectal metastases in the liver was reviewed and updated or adapted where necessary. As the search for the interventional procedure overview (IPO) covered the period from database commencement to February 2011, searches for this review were conducted to cover the period January 2011 to November 2017. In addition, to identify economic evidence that was not included in the IPO, searches were conducted to identify economic evidence relating to SIRT for unresectable CRCLM. These searches covered the period from database commencement to November 2017 and used an economic filter where appropriate.

A strategy was developed in Ovid Medline (Section 10) and was adapted to the following databases: Medline In-Process; Embase; Cochrane Library (components: CDSR, DARE, CENTRAL, HTA, NHS EED); Pubmed (epub ahead of press only). The manufacturers' websites were searched for additional studies as well as NHS Evidence. The searches were limited to the English language.

Results of all searches were combined in a Reference Manager 12 database together with the references of studies included in the IPO (NICE 2011). The reference lists of any relevant systematic reviews were checked for additional studies.

Study selection

After de-duplication, one reviewer (HM or JW) selected publications that were considered relevant based on titles and/or abstracts using the inclusion and exclusion criteria presented in section 9. In a second selection round, another reviewer (HM or JW) assessed the full text articles for eligibility and selected studies to be included in the review; any uncertainties were discussed and a decision was agreed. Decisions were recorded at each stage.

The review search yielded 1,463 potentially relevant publications, 188 were retained for assessment of eligibility at full-text. Following this assessment 18 were retained for inclusion in the review.

Data extraction

Two reviewers (HM and ER) extracted data from eligible study reports into the evidence summary tables in section 7; these were subsequently checked by the other reviewer.

Quality assessment of evidence

The quality of the evidence was assessed in accordance with the NHS England guidance for conducting evidence reviews and critically appraised using the SURE critical appraisal checklists.

4. Results

The literature search identified 1,463 records. On screening the title and abstracts, 188 were deemed to be relevant and the full text articles of these records were assessed for eligibility using the inclusion and exclusion criteria presented in section 9. Following this assessment 18 publications were retained as being of interest to the review, these comprised of 3 reports of 3 comparative effectiveness studies, 14 reports of 12 non-comparative effectiveness studies and 1 cost-effectiveness study.

There was a paucity of high quality studies evaluating the clinical and cost-effectiveness of

selective internal radiation therapy (SIRT) with yttrium-90 microspheres compared with best supportive care for individuals with unresectable, liver-dominant metastatic colorectal carcinoma who are chemotherapy-refractory or chemotherapy-intolerant. In addition the definition of best supportive care is quite diffuse, most likely as the aim of BSC is to provide palliative care which will be tailored to the patient's need.

The 3 comparative studies that were identified involved SIRT as a treatment arm (Bester et al. 2012; Hendlisz et al. 2010 and Seidensticker et al. 2012); the details of these studies have been provided in this review. The best study design, Hendlisz et al. (2010), was an open-label, multi-centre (Belgium) randomised phase III trial in patients with unresectable chemotherapy-refractory liver-limited metastatic CRC comparing a protracted intravenous infusion of fluorouracil (FU) (n=23) to SIRT plus intravenous FU (n=21). Ten patients (43.5%) in the control arm with documented progression were permitted to cross over to receive SIRT. Bester et al. (2012) was a single-institution (Australia), retrospective comparative study in patients with chemotherapy-refractory liver metastasis comparing SIRT therapy with standard care. The study also included patients with non-CRC primary cancers and some analyses were not stratified for CRC; 14.5% (49/339) of the whole SIRT group were chemo-naive. In the mCRC group 224 patients received SIRT therapy and 29 standard care. Seidensticker et al. (2012) was a multi-centre (Germany), retrospective comparative study in patients with chemotherapy-refractory liver dominant metastatic colorectal cancer comparing SIRT therapy (n=29) with a matched cohort of patients receiving BSC (n=29). Some patients treated with SIRT (31%) were subsequently able or willing to receive further systemic chemotherapy.

As there was a paucity of high quality comparative studies the 12 non-comparative studies have been summarised in the evidence summary tables (section 7); it should be noted that these studies have a high risk of bias and therefore results are only presented in the tables.

Only one study (Pennington et al. 2015) was identified that evaluated the cost-effectiveness of SIRT compared with BSC in patients with inoperable chemotherapy-refractory colorectal cancer liver metastases using a 3 state partitioned survival model

1. What is the evidence on clinical effectiveness of using selective internal radiation therapy (SIRT) with yttrium-90 microspheres compared with best supportive care for individuals with unresectable, liver-dominant metastatic colorectal carcinoma who are chemotherapy-refractory or chemotherapy-intolerant?

a) glass yttrium-90 microspheres;

No evidence was identified that met the inclusion criteria comparing glass yttrium-90 microspheres with best supportive care.

b) resin yttrium-90 microspheres.

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

Hendlisz et al. (2010) was the highest quality study included in this review. It was an open-label, multi-centre (Belgium) randomised phase III trial in patients with unresectable chemotherapy-refractory liver-limited metastatic CRC comparing fluorouracil (FU) protracted intravenous infusion (n=23) to SIR-spheres plus intravenous FU (n=21). For ethical reasons, patients in the control arm with documented progression were permitted to cross over to receive SIRT, 10 patients crossed-over. Patients were followed up for a median of 24.8 months (range 2 – 41). The primary outcome was time to liver progression (TTLP) although the description provided indicated that actually liver-specific progression free survival (LPFS) is reported; patients are censored on death in LPFS and PFS but excluded in TTLP and TTP. SIRT had a significant benefit in controlling liver tumour

growth, as measured by LPFS; SIRT & FU - 5.5 months vs. FU - 2.1 months; HR 0.38 (95% CIs 0.28-0.94), p=0.003. The results indicated that there was no significant overall survival (OS) advantage with SIRT; SIRT & FU - 10.0 months vs. FU - 7.3 months; HR 0.92 (0.47-1.78), p=0.80. A significant improvement in PFS (reported as TTP) for the SIRT group was reported, 4.5 vs. 2.1 months; HR 0.51 (0.28-0.94), p=0.03. Although significant improvements were observed in TTLP (LPFS) and TTP (PFS) the study was not powered to detect an overall survival benefit; the study also has several biases that may mask any OS benefit i.e. open-label design, cross-over of patients to SIRT arm and small sample size.

Seidensticker et al. (2012) was a multi-centre (Germany), retrospective comparative study in patients with chemotherapy-refractory liver dominant metastatic colorectal cancer comparing SIRT therapy (n=29) with a matched cohort of patients receiving BSC (n=29). Some patients treated with SIRT (31%) were subsequently able or willing to receive further systemic chemotherapy; exact number of patients who actually received chemotherapy is not provided. The details of the components or nature of BSC were not provided. Length of follow-up was also not reported. Patients treated with SIRT had a longer median OS of 8.3 months (95% CI 6.6 – 10.2) vs. 3.5 months (95% CI 1.9 – 5.7); HR 0.26 (95% CI 0.15–0.48); p<0.001. There is a high risk of bias in this study due to several factors: retrospective, non-randomised and small sample size; this may result in an overestimate of survival benefit in SIRT group.

Bester et al. (2012) was a single-institution (Australia), retrospective comparative study in patients with chemotherapy-refractory liver metastasis comparing SIRT therapy with standard care. The study also included patients with non-CRC primary cancers and some analyses were not stratified for CRC; 14.5% (49/339) of the whole SIRT group were chemo-naive. In the mCRC group, 224 patients received SIRT therapy and 29 received standard care. Patients in the standard care arm were selected from a population who were assessed for SIRT eligibility but were considered unsuitable due to anatomical contraindications or refusal of consent; they were provided with conservative treatment of continued supportive care. Some baseline characteristics were presented separately for CRC patients treated with SIRT. Baseline characteristics for the CRC-only patients who received standard care were not reported therefore differences could not be assessed. The study reports that 85% of patients were ECOG performance status 0, and 14% of patients treated with SIRT were chemotherapy naive. Length of follow-up was not reported. Median OS was improved in the SIRT group compared to standard care (11.9 vs 6.6 months; HR: 0.5, log rank test p=0.001). There is a high risk of bias in this study due to several factors: retrospective, non-randomised, inadequate matching of prognostic factors, small sample size of comparative arm; this may result in an overestimate of survival benefit in SIRT group.

2. What is the evidence relating to the safety of selective internal radiation therapy (SIRT) with yttrium-90 microspheres compared with best supportive care for individuals with unresectable, liver-dominant metastatic colorectal carcinoma who are chemotherapy-refractory or chemotherapy-intolerant?

a) glass yttrium-90 microspheres;

No evidence was identified that met the inclusion criteria comparing glass yttrium-90 microspheres with best supportive care.

b) resin yttrium-90 microspheres.

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

Hendlisz et al. (2010) was an open-label, multi-centre (Belgium) randomised phase III trial in patients with unresectable chemotherapy-refractory liver-limited metastatic CRC comparing a

protracted intravenous infusion of fluorouracil (FU) (n=23) to SIR-spheres plus intravenous FU (n=21). Ten patients in the control arm with documented progression were permitted to cross over to receive SIRT. Toxicity analysis was conducted in 43 patients (22 in FU group and 21 SIRT & FU group). Two patients (both in FU group) were never treated and so were not evaluated for toxicity. Grade 3 or 4 toxicities were recorded in six patients after FU monotherapy and in one patient after SIRT plus FU treatment (P=0.10).

Seidensticker et al. (2012) was a multi-centre (Germany), retrospective comparative study in patients with chemotherapy-refractory liver dominant metastatic colorectal cancer comparing SIRT therapy (n=29) with a matched cohort of patients receiving BSC (n=29). Some patients treated with SIRT (31%) were subsequently able or willing to receive further systemic chemotherapy; exact number of patients who actually received chemotherapy is not provided. The details of the components or nature of BSC were not provided. Treatment-related adverse events following radioembolization included: grade 1–2 fatigue (n = 20, 69%) in the first 14 days post-radioembolization; grade 1 mild abdominal pain/nausea (n = 14, 48.3%), and grade 2 gastrointestinal ulceration (n = 3, 10.3%). Three cases (10.3%) of grade 3 radiation-induced liver disease were not deemed to be life-threatening. Adverse events in the comparator arm were not reported.

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

3. What is the evidence on the cost effectiveness of selective internal radiation therapy (SIRT) with yttrium-90 microspheres compared with best supportive care for individuals with unresectable, liver-dominant metastatic colorectal carcinoma who are chemotherapy-refractory or chemotherapy-intolerant?

One study (Pennington et al. 2015) was identified that evaluated the cost-effectiveness of SIRT compared with SC in patients with inoperable chemotherapy-refractory colorectal cancer liver metastases. It used a 3 state partitioned survival model. Radioembolization using yttrium-90 resin microspheres compared to SC increased overall survival (OS) by a mean of 1.12 life years in the model and resulted in a cost per QALY gained of £28,216 and cost per life year gained of £20,323. The total cost was £35,487 for SIRT and £12,730 for SC, a difference of £22,757. The model uses survival data from an unmatched retrospective comparative study (Bester et al. 2012), which is at risk of bias, and standard care is not defined.;. The authors assumed that there were equal patient numbers in progression free and progressed states at any point in time which may not be appropriate. The selection of optimistic inputs for SIRT may underestimate the overall cost per QALY and ICER reported in the model. The cost of the SIRT procedure was inadequately explored in the sensitivity analysis. With the highlighted issues of the model the cost-effectiveness estimates cannot be considered reliable.

4. Does the evidence of clinical and cost-effectiveness identify any subgroups of patients with unresectable, liver-dominant metastatic colorectal carcinoma who are chemotherapy-refractory or chemotherapy-intolerant who would gain greater benefit from using selective internal radiation therapy (SIRT) with yttrium-90 microspheres compared

with best supportive care?

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

Seidensticker et al. (2012) conducted multivariate analysis to identify prognostic markers of improved survival (see evidence summary table section 7); however, patients from both treatment groups (SIRT and BSC) were included and therefore this analysis does not indicate whether any subgroups would gain a greater benefit from using SIRT with yttrium-90 compared with BSC.

5. Discussion

Three comparative studies were identified that reported on the clinical effectiveness and adverse events of SIRT when treating patients with unresectable, chemotherapy-refractory or chemotherapy-intolerant, liver-dominant metastatic colorectal carcinoma.

The small RCT (Hendlisz et al. 2010) comparing SIRT plus fluorouracil chemotherapy with fluorouracil chemotherapy alone demonstrated a significant benefit in controlling liver tumour growth, as measured by LPFS; SIRT & FU - 5.5 months vs. FU - 2.1 months; HR 0.38 (95% CI 0.28-0.94), p=0.003. No statistically significant improvement was observed in overall survival (OS) with SIRT (SIRT & FU - 10.0 months vs. FU - 7.3 months; HR 0.92 [0.47-1.78], p=0.80); although the study was not powered to detect an overall survival benefit. For ethical reasons, patients in the control arm were permitted to cross over to receive SIRT which may confounded the OS estimate.No significant difference in severe adverse event rates was observed in the RCT. The most common adverse events in patients treated with SIRT in comparative studies were abdominal pain, fatigue, and nausea.

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

Although there is a paucity of high quality comparative studies that can provide reliable evidence on the efficacy and effectiveness of SIRT, the available data does provide important safety and technical insights.

A published cost-effectiveness model (Pennington et al. 2015), using survival data from Bester et al. (2012), provided a cost per QALY gained of £28, 216. Data used for this model is subject to bias and some model assumptions and inputs may not be appropriate. This raises concern as to the reliability of the cost estimates of SIRT.

6. Conclusion

One small open label RCT in patients with unresectable chemotherapy-refractory liver-limited metastatic CRC comparing SIRT plus fluorouracil chemotherapy with fluorouracil chemotherapy alone, demonstrated a significant benefit in controlling liver tumour growth, as measured by LPFS. Two non-randomised retrospective studies indicate that SIRT may improve overall survival in patients with unresectable, chemotherapy-refractory or chemotherapy-intolerant, liver-dominant metastatic colorectal carcinoma compared to standard care. This evidence review highlights the lack of well-designed prospective comparative studies of SIRT and BSC to provide reliable evidence of survival outcomes. igh quality data would also enable more accurate modelling of the cost-effectiveness of SIRT compared to BSC. There is a need for studies that evaluate the impact of SIRT on patients' quality of life.

7. Evidence Summary Tables

a) Clinical Studies

Use of yttrium-90 microspheres to treat unresectable, chemotherapy refractory liver dominant metastatic colorectal carcinoma comparative studies								
Study reference	**Study Design & Setting**	**Population characteristics**	**Intervention**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Hendlisz 2010	P1 – randomised control trial Multicentre (n=3), Belgium, December 2004 - November 2007	21 RE & FU patients & 23 FU patients Median age (yrs): RE & FU – 62 (46 – 91); FU -62 (45 – 80) Female: RE & FU - 11 (52.4%); FU – 5 (21.7%) Male: RE & FU - 10 (47.6%); FU – 18 (78.3%) Prior chemotherapy lines: NR Chemo naive patients: 0 Prior resection: 7 (24.1%) EHM: 0 Exclusions: pre-existing hepatic disease;	Patients randomly assigned to arm A received protracted intravenous (PIV) infusion of FU 300 mg/m2 days 1 through 14 every 3 weeks until progression. Patients randomly assigned to arm B received RE (SIR-Spheres, Sirtex) plus intravenous FU 225 mg/m2 for 14 days followed by 1 week of rest. Thereafter, patients continued with PIV FU 300 mg/m2 for 14 days every 3 weeks until documented hepatic progression. For ethical reasons, patients in arm A with documented progression were	Median overall survival (months; 95% CI)	RE & FU – 10 (NR) vs. FU - 7.3 (NR) HR 0.92 (0.47-1.78), p=0.80	*7*	Direct	Limitations (author): likely that rapid cross-over of 70% of patients in the FU-only group to receive further therapy, including 10 who received RE with a similar activity as RE & FU group, confounded the survival data Limitations (review team): open-label trial with small numbers so likelihood of bias Funding sources and conflicts of interest: honoraria received by one author from Sirtex Medical Ltd and Sirtex Medical Ltd supplied microspheres.
				Median follow-up (months; range)	24.8 (range 2-41)			
				Median progression free survival (months; 95%)	RE & FU – 4.5 (NR) vs. FU - 2.1 (NR) HR 0.51 (0.28-0.94), p=0.03			
				Median liver-specific progression free survival (months; 95%)	RE & FU - 5.5 (NR) vs. FU - 2.1 (NR) HR 0.38 (0.20-0.72) p=0.003			
				% survival	NR			
				Tumour response	CR: RE & FU –			

		extrahepatic disease; clinically significantly ascites; more than 20% arteriovenous shunting from liver to lungs observed on the 99mTc-MAA scan; hepatic arterial anatomy; partial or total thrombosis of the hepatic artery or main portal vein; prior HAI with FU, FUDR, or other chemotherapeutic agent(s) or transarterial embolization 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; women who were pregnant or breast-feeding or who refused to take adequate pregnancy prevention measures	permitted to cross-over to receive RE at the investigators' discretion.	(RECIST criteria; CR – complete response, PR – partial response, SD – stable response, PD – progressive disease)	0% vs. FU – 0% PR: RE & FU – 10% vs. FU – 0%; SD: RE & FU – 76% vs. FU – 35% PD: RE & FU – 10% vs. FU – 61% *Not evaluated – FU group n=5; RE & FU n=6*			
				Overall response rate	RE & FU – 10% vs. FU – 0%; p=0.22			
				Disease control rate	RE & FU – 86% vs. FU – 35%; P=0.001			
				Quality of life	Not reported			
				Sub-group analysis Not reported				
				Adverse events Toxicity analysis was conducted in 43 patients (22 in FU group and 21 RE & FU group). Two patients (both in FU group) were never treated and so were not evaluated for toxicity. Grade 3 or 4 toxicities were recorded in six patients after FU monotherapy and in one patient after RE plus FU treatment, though not statistically significant (P=0.10)			

Study reference	Study Design & Setting	Population characteristics	Intervention	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
Seidensticker 2012	P1 – retrospective matched comparative study Multicentre (n=3), Germany, June 2005 – March 2008	29 consecutive RE patients & 29 BSC patients Mean age (yrs): RE - 61.9 ± 7.37; BSC - 61.3 ± 8.71 Female: RE - 7 (24.1%); BSC - 6 (20.7%) Male: RE - 22 (75.9%); BSC - 23 79.3% Prior chemotherapy lines: RE - 1 = 0, 2 = 8 (27.6%), 3 = 9 (31%), 4 = 10 (34.5%), 5 = 1 (3.4%), 6 = 1 (3.4%); BSC 1 = 0, 2 = 7 (24.1%), 3 = 11 (37.9%), 4 = 7 (24.1%), 5 = 3 (10.3%), 6 = 1 (3.4%) Chemo naive patients: 0 Prior resection: RE - 7 (24.1%); BSC – 10 (34.5%) EHM: RE - 14 (48.3%); BSC – 14	^{90}Y-resin microspheres (SIR-spheres, Sirtex) were delivered via a temporary transfemoral catheter into the proper hepatic artery as a single whole liver administration or into the lobar arteries as a sequential treatment of each lobe 4–8 weeks apart. All patients were admitted the day before the procedure and typically discharged 2 days later. 31% of SIRT patients were subsequently able or willing to receive further chemotherapy, exact number not given. Detail of BSC not provided.	Median overall survival (months; 95% CI)	RE 8.3 (6.6 – 10.2) vs. BSC 3.5 (1.9 – 5.7), HR 0.3 (95% CI 0.16 – 0.55), p<0.001	7	Direct	Limitations (author): small study size, retrospective study design Limitations (review team): no follow-up data, no confidence intervals for PFS, 31% of SIRT patients were subsequently able or willing to receive further chemotherapy, exact number not given. Detail of BSC not provided. Funding sources and conflicts of interest: supported in part by Sirtex Medical Ltd and authors received travel fees or research grants and consultant fees from Sirtex Medical Ltd.
				Median follow-up (months; range)	Not reported			
				Median progression free survival (months; 95%)	5.5 (NR) vs. 2.1 (NR)			
				Median liver-specific progression free survival (months; 95%)	Not reported			
				% survival	3 months: 97% vs. 59% 12 months: 24% vs. 0%			
				Tumour response (RECIST criteria; CR – complete response, PR – partial response, SD – stable disease, PD –	CR = 0 PR = 12 (42.9%) SD = 5 (17.9%) PD = 11 (39.3%) *1 patient not evaluated*			

		(48.3%) Exclusions: if eligible for other forms of treatment, extensive and progressive extrahepatic deposits		progressive disease)				
				Overall response rate	12 (42.9%)			
				Disease control rate	17 (60.8%)			
				Quality of life	Not reported			
				Sub-group analysis On multivariate analysis the extent of liver involvement was associated with an increased risk of death (HR, 1.03; 95% CI, 1.0–1.06; P = 0.028)				
				Adverse events Treatment-related adverse events following RE included: grade 1–2 fatigue (n = 20, 69%) in the first 14 days post-RE, grade 1 mild abdominal pain/nausea (n = 14, 48.3%), and grade 2 gastrointestinal ulceration (n = 3, 10.3%). Three cases (10.3%) of grade 3 radiation-induced liver disease not deemed life-threatening. AEs not reported for BSC group.				
Study reference	**Study Design & Setting**	**Population characteristics**	**Intervention**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Bester 2012	P1 – retrospective unmatched comparative	224 RE patients & 29 SC patients *Note: Baseline characteristics*	^{90}Y-resin microspheres (SIR-spheres, Sirtex) were administered	Median overall survival (months; 95% CI)	RE group 11.9 (10.1 –14.9) vs. SC group 6.6 (NR), p=0.001 (HR not reported for	6	Direct	Limitations (author): non-randomised, retrospective study, treatment cohort was hetereogenous population

	study Single centre , Australia, Feb 2006 – Feb 2001	*presented for whole group that included non-CRC patients* Median age (yrs): RE group - 67 (27 – 90) & SC group – 66 (27 – 88); CRC group – 67 (27 – 89) Female: RE group – 133 (39.2%); SC group – 16 (31.4%) Male: RE group - 206 (60.8%); SC group – 35 (68.6%) Prior chemotherapy lines: RE group ≥1: 290 (85.6%); SC group ≥1: 47 (92.2%) (incl. non-CRC) Chemo naive patients: RE group – 49 (14.5%) ; SC group – 4 (7.8%) (incl. non-CRC) Prior resection: NR EHM: RE group – 124 (36.6%) ; SC group – 17 (33.3)% (incl. non-CRC) Exclusions: ECOG score > 2, excessive hepatic tumour burden > 75%, and/or compromised	according to standard protocols. Treatment for bilobar liver disease was performed 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.		mCRC group)			Limitations (review team): SC group not matched and comprised of patients deemed unsuitable for RE, SC not fully defined, focus of study was not mCRC so not analyses stratified for mCRC patients and baseline characteristics of SC mCRC patients were not provided. Funding sources and conflicts of interest: Bester is a paid consultant for Sirtex Medical Ltd.
				Median follow-up (months; range)	Not reported			
				Median progression free survival (months; 95%)	Not reported			
				Median liver-specific progression free survival (months; 95%)	Not reported			
				% survival	Not reported			
				Tumour response (RECIST criteria; CR – complete response, PR – partial response, SD – stable disease, PD – progressive disease)	Not reported			
				Overall response rate	Not reported			
				Disease control rate	Not reported			
				Quality of life	Not reported			

		residual liver function		Sub-group analysis Not reported Adverse events Adverse events occurred in 22% of patients immediately after RE, which were minor abdominal pain, nausea, and vomiting. At the 1-month follow-up after RE, adverse events were minor and easily medically managed; including one case of radiation induced liver disease (RILD). At the 3 month follow-up adverse events were all medically managed, with no deaths within the 3-month follow-up period caused by the RE procedure. There were no known cases of radiation pneumonitis. Adverse events in the supportive care arm were not reported.			

Use of yttrium-90 microspheres to treat unresectable, chemotherapy refractory liver dominant metastatic colorectal carcinoma

non-comparative studies

Study reference	Study Design & Setting	Population characteristics	Intervention	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
Paprottka 2017	P1 – retrospective case series Single centre, Germany, January 2013 – February	136 of 389 non-consecutive patients with mCRC Median age (yrs): 64.1 (55.7-70.9) for whole sample	^{90}Y resin microspheres (SIR-Spheres, Sirtex), prescribed activity calculated using the modified body surface area	Median overall survival (months; 95% CI) Median follow-up (months; range)	9.1 (6.4 – 11.8) Not reported for mCRC group	5	Direct	Limitations (author): retrospective case series from single centre Limitations (review team): limited data for mCRC patients, non-consecutive recruitmentFunding sources and conflicts of interest: authors report that study received

	2013	Female: not provided for mCRC group Male: not provided for mCRC group Prior chemotherapy lines: not reported Chemo naive patients: not reported Prior resection: not reported EHM: not provided for mCRC group Exclusions: Patients with limited hepatic reserve, ascites or other clinical signs of liver failure (e.g., bilirubin level >2.0 mg/dL in the absence of a reversible cause; serum albumin <3.0 g/dL), compromised bone marrow or renal function, or other severe co-morbidities were generally considered unsuitable for RE	method based on target tumour and liver volumes for each patient and was administered either in whole-liver, lobar or sequential lobar treatment, according to the tumour burden .	Median progression free survival (months; 95%)	Not reported			no funding and have no conflicts of interest
				Median liver-specific progression free survival (months; 95%)	Not reported			
				% survival	Not reported			
				Tumour response (RECIST criteria; CR – complete response, PR – partial response, SD – stable disease, PD – progressive disease)	Not reported for mCRC group			
				Overall response rate	Not reported for mCRC group			
				Disease control rate	Not reported for mCRC group			
				Quality of life	Not reported			
				Sub-group analysis Not reported				

				Adverse events: not reported				
Study reference	**Study Design & Setting**	**Population characteristics**	**Intervention**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Schmeel 2017	P1 – retrospective case series Single centre, Germany, 2009 - 2014	46 consecutive patients Mean age (yrs): 60.8 ± 10.82 (45-82) Female: 17 (27%) Male: 29 (63%) Prior chemotherapy lines: all had at least 2 lines of IRI and OXA Chemo naive patients: 0 Prior resection: 0 EHM: 21 (46%) Exclusions: not reported	Either ^{90}Y resin (SIR-spheres, SIrtex) or glass (Therаspheres, BTG) microspheres, prescription of activity calculated using the body surface area (BSA) method in patients treated with SIR-Spheres and the MIRD-based method prescribed by the manufacturer in patients receiving TheraSphere, treatment activity administered was 1.66 ± 0.88 GBq (0.4–3.96 GBq) as either whole liver treatment in 24 patients, or by successive RE of initially either the right (six patients) or left liver lobe	Median overall survival (months; 95% CI)	8 (6 -10)	5	Direct	Limitations (author): small, single centre, retrospective study Limitations (review team): exclusion criteria not provided Funding sources and conflicts of interest: no funding received, one author acts as consultant for SIRTEX (manufacturer of SIR-spheres)
				Median follow-up (months; range)	8 (2-48)			
				Median progression free survival (months; 95%)	4 (3 – 5)			
				Median liver-specific progression free survival (months; 95%)	Not reported			
				% survival	Not reported			
				Tumour response (RECIST criteria; CR – complete response, PR – partial response, SD – stable disease, PD – progressive disease)	CR = 0 PR = 8 (17.4%) SD = 14 (30.4%) PD = 24 (52%)			

			(five patients), in eight patients, only the right liver lobe and in three patients only the left liver lobe was treated in a single lobar session.	Overall response rate	8 (17.4%)			
				Disease control rate	22 (47.8%)			
				Quality of life	Not reported			
				Sub-group analysis on multivariate analysis a metastasis of > 4.7cm was significantly associated with an increased risk of death HR=2.985 (1.320 – 6.749), p=0.009				
				Adverse events Not reported				
Study reference	**Study Design & Setting**	**Population characteristics**	**Intervention**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Hickey 2016 (NCT00532740)	P1 – retrospective case series Multicentre (n=8), USA, 2001 – 2014	531 patients Age (yrs): < 65 n=334 (62.9%), ≥ 65 n=197 (37.1%) Female: 217 (40.9%) Male: 314 (59.1%) Prior chemotherapy lines: number of cytotoxic	RE of hepatic metastases of colorectal carcinoma with a glass-based ^{90}Y device (TheraSpheres, BTG). The median radiation dose was 120.2Gy (35-391Gy). Extrahepatic	Median overall survival (months; 95% CI)	10.6 (8.8 – 12.4)	5	Direct	Limitations (author): retrospective nature of the study, variability in the number of treatments that patients received, many patients did not receive all available systemic options Limitations (review team): lack of information about follow-up duration or continuity of patients'' enrolment Funding sources and conflicts of
				Median follow-up (months; range)	Not reported			
				Median progression free survival	Not reported			

		chemotherapy agents: 0 n=15 (3%), 1-2 n=216 (41%), 3 n=295 (56%) Biologic therapy: 0 agents n=114 (21%), 1 n=295 (56%), 2 n=117 (22%), 3 n=4 (<1%), 4 n=1 (<1%) Chemo naive patients: 15 (2.8%) Prior resection: 98 (18.5%) EHM: 202 (38.0%) Exclusions: Patients with significant extrahepatic disease (life expectancy < 3 mo), angiographic evidence or ^{99m}Tcmacroaggregated albumin scan evidence of uncorrectable gastrointestinal flow, or an estimated lung dose of more than 30 Gy in a single session	arterial coil embolization was performed in 25% of patients, nearly all patients underwent lobar or selective RE at the first treatment. Only 2% of patients received whole liver treatment in a single setting.	(months; 95%)				interest: 6 authors of the study are advisors for BTG International Ltd.
				Median liver-specific progression free survival (months; 95%)	Not reported			
				% survival	Not reported			
				Tumour response (RECIST criteria; CR – complete response, PR – partial response, SD – stable disease, PD – progressive disease)	Not reported			
				Overall response rate	Not reported			
				Disease control rate	Not reported			
				Quality of life	Not reported			
				Sub-group analysis Not reported				

				Adverse events Clinical side effects: fatigue n=290 (55%), abdominal pain/discomfort n=182 (34%), nausea n=98 (19%), anorexia n=36 (7%), fever/chills n=36 (7%), vomiting n=32 (6%), diarrhoea n=10 (2%) Grade 3-4 biochemical toxicity: bilirubin n=69 (13%), alkaline phosphatise n=46 (9%), albumin n=40 (8%), aspartate transaminase n=18 (3%), alanine transaminase n=3 (<1%)				
Study reference	**Study Design & Setting**	**Population characteristics**	**Intervention**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Kennedy 2017 (also Kennedy 2015 a & b) MORE study - NCT01815879	P1 – retrospective case series Multi centre (n=11), US, July 2002 – Dec 2011	606 consecutive patients Mean age (yrs): 61.5 (± 12.7) (20.8-91.9) Female: 233 (38.4%) Male: 373 (61.6%) Prior chemotherapy lines: 1 = 206 (35.3%), 2 = 184 (31.6&), 3 ≥ 158 (27.1%) Chemo naive patients: 35 (6.0%) Prior resection: 168 (27.7%)	^{90}Y-resin microspheres (SIR-spheres, Sirtex). Treatment followed the protocol set by the RE Brachytherapy Oncology Consortium. A median of two ^{90}Y-RE procedures (IQR: 1.0) were conducted for each patient	Median overall survival (months; 95% CI)	10 (9.2 – 11.8)	6	Direct	Limitations (author): none reported Limitations (review team): retrospective case series so high risk of bias, difficult study to conduct with population of this type, note this a large study which is a strength Funding sources and conflicts of interest: research grants from Sirtex (manufacturer of SIR-Spheres), authors participated in speakers bureau for Sirtex and hold stock in Sirtex, 2 authors are consultants to Sirtex Medical
				Median follow-up (months; range)	9.5 (9.0 – 11.1)			
				Median progression free survival (months; 95%)	Not reported			
				Median liver-specific progression free survival (months; 95%)	Not reported			
				% survival	6 months: 71.7%			

		EHM: 213 (35.1%) Exclusions: Patients who received glass ^{90}Y microsphere RE for metastatic colorectal liver metastases, with limited hepatic reserve, ascites or other clinical signs of liver failure or compromised bone marrow or pulmonary function; evidence of uncorrectable flow to nontarget sites			12 months: 45.0% 24 months: 18.9% 36 months: 7.0% 48 months: 2.9% 60 months: 2.1%			
				Tumour response (RECIST criteria; CR – complete response, PR – partial response, SD – stable disease, PD – progressive disease)	Not reported			
				Overall response rate	Not reported			
				Disease control rate	Not reported			
				Quality of life	Not reported			
				Sub-group analysis Factors significantly associated with patient survival (P<0.01): included poor ECOG performance status, markers of advanced disease such as increased extent of tumor-to-target liver, involvement, poor baseline liver function, pre-treatment				

				anemia, lung shunt fraction, and number of lines of prior chemotherapy				
				Adverse events Grade ≥3 RE-induced liver disease (REILD) (n=3, 0.5%) and grade ≥3 hepatic failure (n=2, 0.3%) (occurred between 8-90 days following the first treatment). Common grade ≥3 AEs over 184 days follow-up were: abdominal pain = 37 (6.1%), fatigue = 33 (5.5%), hyperbilirubinemia = 31 (5.4%), ascites = 17 (3.6%) and gastrointestinal ulceration = 10 (1.7%)			
Study reference	**Study Design & Setting**	**Population characteristics**	**Intervention**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Maleux 2015	P1 – retrospective case series Single centre, Belgium, January 2005 – January 2014	71 patients Median age (yrs): 62 (42 – 82) Female: 20 (28.2%) Male: 51 (71.8%) Prior chemotherapy lines: 2 - n=27 (38.0%), 3 - n=44 (62.0%) Chemo naive	RE of chemorefractory colorectal liver metastases with resin ^{90}Y microspheres (SIR-spheres, Sirtex). Activity was calculated based on the body surface area method. Median total administered	Median overall survival (months; 95% CI)	8 (7 – 9)	5	Direct	Limitations (author): None reported Limitations (review team): retrospective nature of the study, lack of information about continuity of patients' enrolment and follow-up time (mean, 95% CI) Funding sources and conflicts of interest: funding not stated, authors state no competing interests
				Median follow-up (months; range)	Not reported			
				Median progression free survival (months; 95%)	3			

		patients: 0 Prior liver surgery: 10 (14.1%) EHM: 22 (31.0%) Exclusions: lung shunt fraction of >20%, leakage of ^{99m}Tc-MAA to the gastroduodenal area not correctable by repeat angiography and coil embolization, prior external beam radiotherapy to the liver unknown at the time of angiographic workup and excessive extrahepatic disease (progression between angiographic workup and the SIRT procedure).	activity was 1810MBq (818 – 2454). All bilobar SIRT procedures were performed in one session.	Median liver-specific progression free survival (months; 95%)	4			
				% survival	6 months: 65.2% (55.3 – 73.5) 12 months: 29.5% (23.6 – 35.6) 18 months: 20.2% (16.0 – 24.7) 24 months: 6% (4 - 7)			
				Tumour response (RECIST criteria; CR – complete response, PR – partial response, SD – stable disease, PD – progressive disease)	Not reported			
				Overall response rate	Not reported			
				Disease control rate	Not reported			
				Quality of life	Not reported			

				Sub-group analysis Not reported				
				Adverse events ^{90}Y –related toxicity after the first 30 days after treatment: NCI-CTCAE grade 1 side effects: fatigue (n=39, 55%), fever (n=14, 20%); grade 2: abdominal discomfort (n=33, 47%), nausea (n=5, 7%), diarrhoea (n=6, 9%); grade 3: procedure-related liver insufficiency (two-fold increase in bilirubin level within 30 days after ^{90}Y infusion) (n=3, 4%). ^{90}Y –related toxicity detected later than 30 days after treatment: grade 2: gastric ulcers (n=5, 7%); grade 3 (cirrhosis-like changes in the liver parenchyma): variceal upper gastrointestinal bleeding (n=1, 1.3%), benign, refractory ascites (n=2, 2.6%).				
Study reference	**Study Design & Setting**	**Population characteristics**	**Intervention**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Saxena 2015	P1 - Retrospective case series Single centre, Australia, 2005 – 2013 (note conflicting	302 patients Mean age (yrs): 63.7 ±11.0 Female: 107 (35.4%) Male: 195 (64.6%) Prior chemotherapy	RE with ^{90}Y microspheres (SIR-spheres, Sirtex). Activity of the treatment was adjusted to tumour volume and lung shunting fraction. The mean dose	Median overall survival (months; 95% CI)	10.5 (NR)	5	Direct	Limitations (author): retrospective nature of the study; lack of information on the type of chemotherapeutic regimens used prior and during the study; lack of data on the site of extrahepatic metastases; lack of information in the dataset regarding biochemical toxicity, the incidence of splenic
				Median follow-up (months; range)	7.2 (0.2 – 72.8)			
				Median progression free	Not reported			

	dates in paper, likely population overlap with Bester 2012)	lines: 1 - n=159 (52.7%), 2 - n=91 (30.1%), ≥3 - n=52 (17.2%) Chemo naive patients: 0 Prior resection: 82 (27.2%) EHM: 124 (41.1%) Exclusions: not reported	was 1.73GBq (SD ±0.44, range 0.44 – 2.55). Patients were hospitalised overnight.	survival (months; 95%)				enlargement, platelet drop, the site and the date of hepatic and extrahepatic progression Limitations (review team): The information regarding the time of data collection do not match (abstract and full text), study design is not clear, lack of exclusion criteria Funding sources and conflicts of interest: not reported
				Median liver-specific progression free survival (months; 95%)	Not reported			
				% survival	6 months: 66% 12 months: 42% 18 months: 29% 24 months: 21% 30 months: 17% 36 months: 13% 60 months: 7%			
				Tumour response (RECIST criteria; CR – complete response, PR – partial response, SD – stable disease, PD – progressive disease)	CR = 2 (0.7%) PR = 111 (36.8%) SD = 96 (31.8%) PD = 84 (27.8%)			
				Overall response rate	113 (37.4%)			
				Disease control rate	209 (69.2%)			

				Quality of life	Not reported			
				Sub-group analysis Not reported				
				Adverse event Clinical toxicity n=115 (38%) which included: nausea/vomiting n=79 (26%), nonspecific self-limiting abdominal pain n=54 (n=1 (0.33%).18%), fatigue n=50 (17%), anorexia n=24 (8%), shortness of breath n=21 (7%), gastritis n=4 (1%), gastrointestinal ulceration n=1 (0.33%), radiation-induced lung disease n=1 (0.33%), one death due to radiation hepatitis within first 30 days post-intervention				
Study reference	**Study Design & Setting**	**Population characteristics**	**Intervention**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Kavla 2014	P1 – retrospective case series Single centre , USA, June 2005 – September 2011	45 patients Median age (yrs): 66.7 (41 – 85) Female: 21 (46.7%) Male: 24 (53.3%) Prior chemotherapy lines: patients failed between 1 – 9 chemotherapy regimens, median = 3	RE with ^{90}Y resin microspheres (SIR-spheres, Sirtex) was performed in patients that failed systemic chemotherapy. Microspheres had an average size of 20 to 60µm and carried 50Bq of radioactivity each.	Median overall survival (months; 95% CI)	6.1 (4.9 – 9.1)	5	Direct	Limitations (author): retrospective nature of the study in a single centre, lack of comparison to other therapies available, relatively small sample size, high number of patients with extrahepatic metastatic disease, not all patients underwent PET which affected the survival data Limitations (review team): not clear if patients consecutively treated
				Median follow-up (months; range)	4.9 (0.2 -56.4)			
				Median progression free survival (months; 95%)	Not reported			

		Chemo naive patients: 0 Prior resection: 2 (4.4%) EHM: 22 (48.9%) Exclusions: tumour volume exceeding 70% of the total liver volume, hepatopulmonary shunt of >20% on Tc-99m-MAA scan, main portal vein thrombosis and/or hepatofugal blood flow, direct tumour extension into extrahepatic organs, previous whole-liver external-beam radiation, high risk of extrahepatic perfusion of ^{90}Y spheres (due to hepatic arterial anomalies, significant retrograde reflux of spheres), patients with extensive extrahepatic disease	The activity delivered ranged from 234 – 1762MBq and the median 1082MBq, 22 patients received whole-liver treatment, 23 patients received lobar treatment through the right or the left hepatic artery of which 17 patients received right lobe treatment only, 5 patients received sequential lobar (right followed by left) treatment, and 1 patient received left lobe treatment only. Patients were discharged the same day (n = 30) or the following day (n = 18).	Median liver-specific progression free survival (months; 95%)	Not reported			Funding sources and conflicts of interest: Dr. Kalva was an international proctor for use of SIR-spheres
				% survival	6 months: 53% 12 months: 29%			
				Tumour response (RECIST criteria; CR – complete response, PR – partial response, SD – stable disease, PD – progressive disease)	CR = 0 (0%) PR = 1 (2.4%) SD = 34 (82.9%) PD = 6 (14.6%)			
				Overall response rate	1 (2.4%)			
				Disease control rate	35 (85.4%)			
				Quality of life	Not reported			
				Sub-group analysis Not reported				

				Adverse events Procedure-related acute toxicity (within 6 weeks of treatment): grade 1 n=12 (49%), grade 2 n=4 (9%), grade 3 including pain and fatigue n=4 (8%); toxicity-related symptoms: pain 24%, fatigue 18%, nausea 4%; mild liver dysfunction n=2 (4.4 %)				
Study reference	**Study Design & Setting**	**Population characteristics**	**Intervention**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Schonewolf 2014	P1 - Retrospective case series Single centre, USA, May 2007 - NR	30 patients Mean age (yrs): 61.0 (33.0 – 83.1) Female: 12 (40%) Male: 18 (60%) Mean chemotherapy lines before treatment: 2.1 (0 – 5) Chemo naive patients: 0 Prior resection: NR EHM: NR Exclusions: NR	RE with ^{90}Y-labelled resin microspheres (SIR-spheres, Sirtex). Patients did not receive chemotherapy 2 weeks before and after the treatment. The median activity delivered to the right, left, and whole liver was 25.8, 20.5 and 50.1mCi, respectively.	Median overall survival (months; 95% CI)	9.4 (6.4 – 15.2)	5	Direct	Limitations (author): retrospective approach, small sample size Limitations (review team): lack of the end date of patients recruitment, lack of exclusion criteria, not clear if patients treated consecutively Funding sources and conflicts of interest: one author received grant funding from SIRTEX, no conflicts declared
				Median follow-up (months; range)	7			
				Median progression free survival (months; 95%)	3.2 (1.1 – 7.2)			
				Median liver-specific progression free survival (months; 95%)	Not reported			
				% survival	Not reported			
				Tumour response (RECIST criteria; CR – complete response, PR – partial response,	Not reported			

				SD – stable disease, PD – progressive disease)				
				Overall response rate	Not reported			
				Disease control rate	Not reported			
				Quality of life	Not reported			
				Sub-group analysis Not reported				
				Adverse events Extrahepatic failure n=13/26 (50%), hepatic failure n=6/26 (23%), intrahepatic/extrahepatic failure n=7/26 (27%)				
Study reference	**Study Design & Setting**	**Population characteristics**	**Intervention**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Nace 2011	P1 – retrospective case series Single centre, US, August 2002 – May 2008	51 consecutive patients Median age (yrs): 64 (37 – 83) Female: 16 (31.4%) Male: 35 (68.6%) Prior chemotherapy lines: 1=33 (73%), 2=9 (20%)	^{90}Y-resin microspheres (SIR-spheres, Sirtex) administered via unilobar treatments or for bilobar disease sequential treatments at one-month intervals,	Median overall survival (months; 95% CI)	10.2 (7.5 – 13.0)	5	Direct	Limitations (author): large number of patients with advanced disease, retrospective nature of the study Limiations (review team): small, retrospective, case series so high risk of bias, difficult study to conduct with population of this type, lack of follow-up data Funding sources and conflicts of interest: supported by the NIH
				Median follow-up (months; range)	Not reported			
				Median progression free survival (months; 95%)	Not reported			

		Chemo naive patients: 0 Prior resection: 12 (23.5%) EHM: 28 (58.3%) Exclusions: patients with extrahepatic metastases >10% of total tumour burden and chemotherapy options were available	median dose administered to the target lobe per treatment was 44.4Gy. The median prescribed activity of ^{90}Y administered was 1.10 GBq versus the median activity actually delivered of 0.89GBq.	Median liver-specific progression free survival (months; 95%)	Not reported			Roadmap Multidisciplinary Clinical Research Career Development Award Grants; none of the authors have identified a conflict of interests.
				% survival	Not reported			
				Tumour response (RECIST criteria; CR – complete response, PR – partial response, SD – stable disease, PD – progressive disease)	CR = 0 PR = 4 (12.9%) SD = 20 (64.5%) PD = 7 (22.6%)			
				Overall response rate	4 (12.9%)			
				Disease control rate	24 (77.4%)			
				Quality of life	Not reported			
				Sub-group analysis Those who had received cetuximab prior to ^{90}Y had a significantly decreased median survival as did those who received bevacizumab and cetuximab (P = .001)				

				Adverse events Fatigue, abdominal pain and nausea were most common subjective complaints documented; occurring in 22, 16 and 12% of patients, respectively. Three patients required hospital readmission within 30 days for an upper GI bleed related to oesophageal varices 4 days after treatment, unresolved abdominal pain and need for intravenous narcotics on post procedure day 1, and the development of symptomatic brain metastases. Grade 2 bilirubin toxicity was seen in 5 patients acutely (0–30 days) and 4 patients late (31–90 days). Late grade 3 or 4 toxicity was seen in two patients. The grade 4 toxicity was related to a biliary stricture and resolved with ERCP and stenting.				
Study reference	**Study Design & Setting**	**Population characteristics**	**Intervention**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Cosimelli 2010	P1- prospective case series Multicentre (n=4), Italy , May 2005 - August 2007	50 non-consecutive patients Median age (yrs): 67 (34-85) Female: 13 (26%) Male: 37 (74%) Prior chemotherapy lines: 3 =12 (24%), 4 =25 (50%), 5 =13	Gastroduodenal and right gastric arteries were embolised before hepatic arterial administration of ^{90}Y resin microspheres (SIR-spheres, Sirtex), median activity, 1.7 GBq;	Median overall survival (months; 95% CI)	12.6 (7 – 18.3)	5	Direct	Limitations (author): none reported Limiations (review team): small, retrospective, case series so high risk of bias, unlikely that patients recruited consecutively as subject to MDT review, difficult study to conduct with population of this type Funding sources and conflicts of interest: ^{90}Y resin microspheres
				Median follow-up (months; range)	11.0 (2 - 29)			
				Median progression free survival (months; 95%)	3.7 (2.6 – 4.9)			

		(26%) Chemo naive patients: 0 Prior resection: 12 (24%) EHM: 11 (22%) Exclusions: pregnancy; evidence of local recurrence of primary disease; inflammatory gastrointestinal disease; received previous treatment with hepatic arterial chemotherapy or external beam radiotherapy to the liver	range, 0.9–2.2), 4 patients received RE to a single lobe and 46 received whole-liver treatment, all patients were admitted on the day of the procedure and discharged 1 or 2 days later.	Median liver-specific progression free survival (months; 95%)	Not reported			were provided by Sirtex Medical Limited
				% survival	1 year: 50.4% 2 year: 19.6%			
				Tumour response (RECIST criteria; CR – complete response, PR – partial response, SD – stable disease, PD – progressive disease)	CR = 1 (2.2%) PR = 11 (23.9%) SD = 12 (26.1%) PD = 22 (47.8%) *4 patients not evaluated*			
				Overall response rate	12 (26.1%)			
				Disease control rate	24 (52.2%)			
				Quality of life Quality of life, as measured by cancer- and site-specific questionnaires (EORTC QLQ C30 and EORTC QLQ CR38) in 14 patients at 6 weeks, was not adversely affected by radioembolisation. Six weeks after radioembolisation, as measured using the Hospital Anxiety and Dpression score, patients' anxiety levels were significantly reduced				

				(P<0.01); with no significant change in depression score. Sub-group analysis Not reported Adverse events One patient died 40 days after treatment from acute renal failure and another responding patient died 60 days after treatment due to liver failure. Both deaths were classified as possibly related to treatment. All other adverse events, whether early (within the first 48 h), intermediate (within the first month) or late (2–3 months after treatment) were mild or moderate in nature (WHO grade 1/2 adverse events).				
Study reference	**Study Design & Setting**	**Population characteristics**	**Intervention**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Cianni 2009	P1 - Retrospective case series Single centre, Italy, February 2005 – January 2008	41 patients Mean age (yrs): 61.2 (NR) Female: 11 (26.8%) Male: 30 (73.2%) Prior chemotherapy lines: not clear but likely that at least 3 Chemo naive patients: 0 Prior resection: NR	^{90}Y-resin microspheres (SIR-spheres, Sirtex), two patients received selective lobar treatment, 32 whole-liver treatment, and 7 sequential treatment of the right lobe followed by the left lobe, performed after 30 days to reduce the risk of acute liver toxicity.	Median overall survival (months; 95% CI)	11.6 (NR)	5	Direct	Limitations (author): not reported Limitations (review team): lack of more detailed patients' characteristics (no baseline table), the type of study (retrospective case series) has high risk of bias, the results are not well described e.g. lack of 95% CI, no information on patient enrolment Funding sources and conflicts of interest: not reported
				Median follow-up (months; range)	Not reported			
				Median progression free survival (months; 95%)	9.2 (NR)			
				Median liver-specific progression free	Not reported			

		EHM: 4 (9.76%) Exclusions: Patients with lung shunting >20% and a bilirubin level >1.8 mg/dl.	The dose was calculated based on liver tumoral involvement and the body surface area formula. The mean activity 1.82GBq; all patients were discharged the day after treatment.	survival (months; 95%)				
				% survival	1 month: 41 (100%)			
				Tumour response (RECIST criteria; CR – complete response, PR – partial response, SD – stable disease, PD – progressive disease)	CR = 2 (4.9%) PR = 17 (41.5%) SD = 14 (34.1%) PD = 8 (19.5%)			
				Overall response rate	19 (46.3%)			
				Disease control rate	33 (80.5%)			
				Quality of life	Not reported			
				Sub-group analysis Not reported				
				Adverse events Following the procedure the adverse events included: mild abdominal pain or nausea 12h after the procedure (n=5, 12%), grade 2 cholecystitis after 25 days (n=1, 2.4%), grade 2 gastritis at 4 weeks (n=1, 2.4%) and 6 weeks (n=1, 2.4%) after treatment, grade 4 hepatic failure 40 days after treatment (n=1, 2.4%).				

Study reference	Study Design & Setting	Population characteristics	Intervention	Outcome measures	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
Jakobs 2008	P1 – retrospective case series Single centre, Germany, October 2003 – April 2007	41 non-consecutive patients Mean age (yrs): 61 (37-77) Female: 11 (26.8%) Male: 30 (73.2%) Prior chemotherapy lines: 1 = 3 (7.3%), 2 = 35 (85.4%); mean chemotherapy lines 2.8 (1 – 5) Chemo naive patients: not clear Prior resection: 12 (29.3%) EHM: 7 (17.1%) Exclusions: not provided	^{90}Y – resin microspheres (SIR-spheres, Sirtex) administered in a single whole-liver session for 37 patients, 4 patients received only right lobar treatment. Prophylactic embolization of the gastroduodenal artery was done routinely. Mean activity delivered was 1.9 GBq (0.7-2.8)	Median overall survival (months; 95% CI)	10.5 (NR)	5	Direct	Limitations (author): Small number of patients with PR which may have overestimated median survival Limitations (review team): small, retrospective, case series so high risk of bias, unlikely that patients recruited consecutively as subject to MDT review, difficult study to conduct with population of this type, inclusion criteria provided but not clear if any exclusions, lack of confidence intervals for overall survival Funding sources and conflicts of interest: none
				Median follow-up (months; range)	7.9 (1.3 – 38.3)			
				Median progression free survival (months; 95%)	Not reported			
				Median liver-specific progression free survival (months; 95%)	Not reported			
				% survival	Not reported			
				Tumour response (RECIST criteria; CR – complete response, PR – partial response, SD – stable disease, PD – progressive disease)	CR = 0 PR = 7 (19.4%) SD = 25 (69.4%) PD = 4 (9.8%)			
				Overall response rate	7 (19.4%)			
				Disease control	32 (88.9%)			

				rate				
				Quality of life	Not reported			
				Sub-group analysis None				
				Adverse events 29 patients (71%) reported a mild to moderate postembolization syndrome consisting of right upper quadrant pain. One (2.4%) grade 4 toxicity (treatment-associated cholecystitis), 2 (4.9%) grade 2 toxicity (gastric ulcers), 16 (39%) grade1/2 nausea, 1 (2.4%) grade 3 nausea, 1 (2.4%) minimal ascites. No life-threatening morbidities or treatment-related deaths were observed within a period of 30 days after the procedure.			

b) Economic Studies

Study reference	Model Description	Population characteristics	Intervention	Methods of analysis	Results	Quality of Evidence Score	Applicability	Critical Appraisal Summary
Pennington 2015	A state-transition, cost-effectiveness model comparing SIRT (^{90}Y microspheres) to standard care in	*Characteristics for survival data* 224 SIRT patients & 29 SC patients *Note: Baseline characteristics presented for whole group that included*	^{90}Y-resin microspheres (SIR-spheres, Sirtex) Standard care not defined.	mCRC was modelled using health states to represent pre-progression disease, post-progression disease and death. Outcomes were costs, life years, QALYs,	SIRT using ^{90}Y-resin microspheres compared to SC increased overall survival by a mean of 1.12 life years and resulted in a cost per QALY gained of £28	6	Direct	Limitations (author): PFS and quality of life data not available Limitations (review team): model uses data from retrospective observational study which is likely to favour SIRT. The SC arm was considerably smaller and standard care was not defined.

	patients with liver-dominant, chemotherapy -refractory mCRC.	*non-CRC patients* Median age (yrs): SIRT group - 67 (27 – 90) & SC group – 66 (27 – 88); CRC group – 67 (27 – 89) Female: SIRT group – 133 (39.2%); SC group – 16 (31.4%) Male: SIRT group - 206 (60.8%); SC group – 35 (68.6%) Prior chemotherapy lines: SIRT group ≥1: 290 (85.6%); SC group ≥1: 47 (92.2%) (incl. non-CRC) Chemo naive patients: SIRT group – 49 (14.5%) ; SC group – 4 (7.8%) (incl. non-CRC) Prior resection: NR EHM: SIRT group – 124 (36.6%) ; SC group – 17 (33.3)% (incl. non-CRC) Exclusions: ECOG score > 2, excessive hepatic tumour burden > 75%, and/or compromised residual liver function		cost per life year gained and cost per QALY gained. Survival data from Bester (2012) was extrapolated and used as efficacy data in the model. Procedure costs came from a single hospital. Grade 3 and 4 AE rates came from Hendlisz (2010). As there is no published evidence on the impact of SIRT on HRQoL in this population, utility values were taken from a HTA systematic review and cost-effectiveness model of biologic drugs used after first line therapy (Hoyle et al., 2013).	216 and cost per life year gained of £20,323. The total cost was £35,487 for SIRT and £12,730 for SC, a difference of £22,757.			The authors assumed that there were equal patient numbers in progression free and progressed states at any point in time which may not be appropriate. The cost of SIRT was inadequately explored in the sensitivity analysis. The selection of optimistic inputs for the SIRT arm may underestimate the overall cost per QALY and ICER reported in the model. Funding sources and conflicts of interest: Sirtex funded development of economic model and manuscript, 1 author is an employee of Sirtex and others act as advisors

8. Grade of evidence tables

Use of yttrium-90 microspheres and fluorouracil to treat unresectable, chemotherapy refractory liver limited metastatic colorectal carcinoma versus fluorouracil comparative study					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence** *(results from one study)*
Median overall survival (months; 95% CI)	Hendlisz 2010	7	Direct	B	SIRT & FU – 10 (NR) vs. FU - 7.3 (NR); HR 0.92 (0.47-1.78), p=0.80 There was no significant improvement in overall survival in the SIRT & FU group. This study is at risk of bias which may impact on the reliability of outcomes; patients in the FU only group with documented progression were allowed to cross-over to receive SIRT at the investigators' discretion (n=10, 43.5%), small study (21 SIRT & FU patients vs.23 FU patients) with open-label design.
Median progression free survival (months; 95%)	Hendlisz 2010	7	Direct	B	SIRT & FU – 4.5 (NR) vs. FU - 2.1 (NR); HR 0.51 (0.28-0.94), p=0.03 A significant improvement in PFS was observed in the SIRT & FU group. This study is at risk of bias which may impact on the reliability of outcomes; small study (21 SIRT & FU patients vs.23 FU patients) with open-label design.
Median liver-specific progression free survival (months; 95%)	Hendlisz 2010	7	Direct	B	SIRT & FU - 5.5 (NR) vs. FU - 2.1 (NR); HR 0.38 (0.20-0.72) p=0.003 A significant improvement in PFS was observed in the SIRT & FU group. This study is at risk of bias which may impact on the reliability of outcomes; small study (21 SIRT & FU patients vs.23 FU patients) with open-label design.
Overall response rate *Sum of complete response and partial response*	Hendlisz 2010	7	Direct	B	SIRT & FU – 10% vs. FU – 0%; p=0.22 There was no significant improvement in overall response rate in the SIRT & FU group. This study is subject to several biases that may mask any survival benefit; patients in the FU only group with documented progression were allowed to cross-over to receive SIRT at the investigators' discretion (n=10, 43.5%), small study (21 SIRT & FU patients vs.23 FU patients) with open-label design. Note not all patients were evaluated: FU group n=5; SIRT & FU n=6
Disease control rate *Sum of complete response, partial response and stable*	Hendlisz 2010	7	Direct	B	SIRT & FU – 86% vs. FU – 35%; P=0.001 A significant improvement in the disease control rate was observed in the SIRT & FU group. This study is at risk of bias which may impact on the reliability of outcomes; small study (21 SIRT & FU patients vs.23 FU patients) with open-label design. Note not all patients were evaluated: FU group n=5; SIRT & FU n=6

disease					
Quality of life	No Evidence				
Cost-effectiveness	No Evidence				

Use of yttrium-90 microspheres to treat unresectable, chemotherapy refractory liver dominant metastatic colorectal carcinoma versus supportive care comparative studies

Outcome Measure	Reference	Quality of Evidence Score	Applicability	Grade of Evidence	Interpretation of Evidence *(results from one study)*
Median overall survival (months; 95% CI)	Seidensticker 2012	7	Direct	A	SIRT 8.3 (6.6 – 10.2) vs. BSC 3.5 (1.9 – 5.7); HR 0.3 (95% CI 0.16 – 0.55), p<0.001; Seidensticker et al. 2012 (29 SIRT patients vs. 29 BSC patients). There was a significant survival benefit with ^{90}Y-resin microspheres compared to BSC. This study is subject to several biases that may impact outcomes; it is a matched-pair retrospective study using a small sample (SIRT - n=29; BSC - n=29) with 31% of SIRT patients able or willing to receive further chemotherapy. 2 studies provided overall survival data; both of which are subject to a high risk of bias which may impact on the reliability of outcomes.
	Bester 2012	7	Direct		
Median progression free survival (months; 95%)	Seidensticker 2012	7	Direct	B	SIRT 5.5 (NR) vs. BSC 2.1 (NR). HR not reported This study is subject to several biases that may impact outcomes; it is a matched-pair retrospective study using a small sample (SIRT - n=29; BSC - n=29) with 31% of SIRT patients able or willing to receive further chemotherapy. Confidence intervals were not provided.
Median liver-specific progression free survival (months; 95%)	No Evidence				
Overall response rate *Sum of complete response and partial response*	Seidensticker 2012	7	Direct	B	12 (42.9%) n=28 This study is subject to several biases that may impact outcomes; it is a matched-pair retrospective study using a small sample (SIRT - n=29; BSC - n=29) with 31% of SIRT patients able or willing to receive further chemotherapy.
Disease control rate	Seidensticker	7	Direct	B	17 (60.8%) n=28

Sum of complete response, partial response and stable disease	2012				This study is subject to several biases that may impact outcomes; it is a matched-pair retrospective study using a small sample (SIRT - n=29; BSC - n=29) with 31% of SIRT patients able or willing to receive further chemotherapy.
Cost-effectiveness	Pennington 2015	6	Direct	C	SIRT using ^{90}Y-resin microspheres compared to SC increased overall survival by a mean of 1.12 life years and resulted in a cost per QALY gained of £28, 216 and cost per life year gained of £20,323. The total cost was £35,487 for SIRT and £12,730 for SC, a difference of £22,757. The model uses data from retrospective observational study which is likely to favour SIRT. The SC arm was considerably smaller (SIRT - n=224; SC - n=29) and standard care was not defined. The authors assumed that there were equal patient numbers in progression free and progressed states at any point in time which may not be appropriate. The cost of SIRT was inadequately explored in the sensitivity analysis. The selection of optimistic inputs for SIRT arm may underestimate the overall cost per QALY and ICER reported in the model..

Use of yttrium-90 microspheres to treat unresectable, chemotherapy refractory liver dominant metastatic colorectal carcinoma

non-comparative studies

Outcome Measure	Reference	Quality of Evidence Score	Applicability	Grade of Evidence	Interpretation of Evidence
Median overall survival (months; 95% CI)	Paprottka 2017	5	Direct	B	10 (9.2 – 11.8), Kennedy et al. 2015, n=606 *Overall and stratified survival were estimated by the method of Kaplan and Meier* 12 non-comparative studies provided overall survival data; all these studies are case series which have a high risk of bias.
	Schmeel 2017	5	Direct		
	Hickey 2016	5	Direct		
	Kennedy 2015	6	Direct		
	Maleux 2015	5	Direct		
	Saxena 2015	5	Direct		

	Kavla 2014	5	Direct		
	Schonewolf 2014	5	Direct		
	Nace 2011	5	Direct		
	Cosimelli 2010	5	Direct		
	Cianni 2009	5	Direct		
	Jakobs 2008	5	Direct		
Median progression free survival (months; 95%)	Schmeel 2017	5	Direct	B	3.7 (2.6 – 4.9), Cosimelli 2010, n=50 Five studies provided progression free survival data; all these studies are case series which have a high risk of bias, Cosimelli (2010) had the largest sample size.
	Maleux 2015	5	Direct		
	Schonewolf 2014	5	Direct		
	Cosimelli 2010	5	Direct		
	Cianni 2009	5	Direct		
Median liver-specific progression free survival (months; 95%)	Maleux 2015	5	Direct	C	4 (NR), Maleux 2015, n=71 Only one study provided data for the LPFS outcome which was a case series and therefore has a high risk of bias, confidence intervals were not provided.
Overall response rate *Sum of complete response and partial*	Schmeel 2017	5	Direct	B	113 (37.4%), Saxena 2015, n=302 Seven studies provided overall response rate data; all these studies are case series which have a high risk of bias, Saxena (2015) had the largest sample size
	Saxena 2015	5	Direct		

response	Kavla 2014	5	Direct		
	Nace 2011	5	Direct		
	Cosimelli 2010	5	Direct		
	Cianni 2009	5	Direct		
	Jakobs 2008	5	Direct		
Disease control rate *Sum of complete response, partial response and stable disease*	Schmeel 2017	5	Direct	B	209 (69.2%), Saxena 2015, n=302 Seven studies provided overall response rate data; all these studies are case series which have a high risk of bias, Saxena (2015) had the largest sample size.
	Saxena 2015	5	Direct		
	Kavla 2014	5	Direct		
	Nace 2011	5	Direct		
	Cosimelli 2010	5	Direct		
	Cianni 2009	5	Direct		
	Jakobs 2008	5	Direct		
Quality of life	Cosimelli 2010	5	Direct	C	Only one study, Cosimelli 2010, provided quality of life outcomes. Quality of life, as measured by cancer- and site-specific questionnaires (EORTC QLQ C30 and EORTC QLQ CR38) in 14 patients at 6 weeks, was not adversely affected by radioembolisation. Six weeks after radioembolisation, as measured using the Hospital Anxiety and Dpression score, patients' anxiety levels were significantly reduced (P<0.01); with no significant change in depression score.
Cost-effectiveness	No evidence				

9. Literature Search Terms

Search strategy (terms in bold in the right-hand column were used to construct the search)	
P – Patients / Population Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?	Individuals with **unresectable**, **liver**-only or **liver**-dominant **metastatic colorectal carcinoma** who are chemotherapy-refractory (progression following at least two lines of standard chemotherapy e.g. irinotecan and oxaliplatin based chemotherapy) or chemotherapy-intolerant.
I – Intervention Which intervention, treatment or approach should be used?	**Selective internal radiation therapy** (SIRT) with: a) glass **yttrium-90** microspheres; b) resin **yttrium-90** microspheres.
C – Comparison What is/are the main alternative/s to compare with the intervention being considered?	Best supportive care
O – Outcomes What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission	Critical to decision-making: • Overall survival • Progression free survival • Liver specific progression free survival • Overall response rate • Disease control rate • Adverse events • Quality of life (HRQoL) • Cost effectiveness Any other relevant outcome from included studies.
Assumptions / limits applied to search	
Inclusion Criteria	Patients with liver-only or liver dominant metastatic colorectal carcinoma English language Published studies from 2007 onwards
Exclusion Criteria	Conference abstracts Sample sizes <30 for non-comparative studies Studies in which CRCLM patients are not analysed

	separately

10. Search Strategy

Database: Ovid MEDLINE(R) <1946 to November Week 3 2017>

1 Yttrium/
2 exp Yttrium Radioisotopes/
3 yttrium*.tw.
4 (90Y or Y-90).tw.
5 SIR-Sphere*.tw.
6 TheraSphere*.tw.
7 (sirtex or nordion).tw.
8 SIRT.tw.
9 (selective* adj3 internal* adj3 radiotherap*).tw.
10 (selective* adj3 internal* adj3 radiation* adj3 therap*).tw.
11 (internal* adj3 radiation* adj3 therap*).tw.
12 radioemboli*.tw.
13 or/1-12
14 (liver adj2 metasta*).tw.
15 mCRC.tw.
16 ((unresectable or non-resectable) adj (liver or hepatic) adj (tumo?r* or malignanc*)).tw.
17 (inoperable adj (hepatic or liver) adj tumo?r*).tw.
18 Liver Neoplasms/sc
19 or/14-18
20 13 and 19
21 limit 20 to yr="2011-Current"
22 limit 21 to english language
23 Economics/
24 exp "costs and cost analysis"/
25 Economics, Dental/
26 exp economics, hospital/
27 Economics, Medical/
28 Economics, Nursing/
29 Economics, Pharmaceutical/
30 (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab.
31 (expenditure$ not energy).ti,ab.
32 value for money.ti,ab.
33 budget$.ti,ab.
34 or/23-33
35 ((energy or oxygen) adj cost).ti,ab.
36 (metabolic adj cost).ti,ab.
37 ((energy or oxygen) adj expenditure).ti,ab.
38 or/35-37
39 34 not 38
40 letter.pt.
41 editorial.pt.
42 historical article.pt.
43 or/40-42
44 39 not 43

45	exp animals/ not humans/
46	44 not 45
47	bmj.jn.
48	"cochrane database of systematic reviews".jn.
49	health technology assessment winchester england.jn.
50	or/47-49
51	46 not 50
52	20 and 51
53	22 or 52

11. Evidence selection

- Total number of publications reviewed: 1463
- Total number of publications considered relevant: 188
- Total number of publications selected for inclusion in this briefing: 18 publications - 17 publications of 15 effectiveness studies and 1 publication of a cost-effectiveness study

12. References

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

Cianni, R., Urigo, C., Notarianni, E., Saltarelli, A., Salvatori, R., Pasqualini, V., Dornbusch, T., & Cortesi, E. (2009) Selective internal radiation therapy with SIR-spheres for the treatment of unresectable colorectal hepatic metastases. *Cardiovascular Interventional Radiology.* 32 (6), 1179-1186.

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

Hendlisz, A., Van den Eynde, M., Peeters, M., Maleux, G., Lambert, B., Vannoote, J., De, K.K., Verslype, C., Defreyne, L., Van, C.E., Delatte, P., Delaunoit, T., Personeni, N., Paesmans, M., Van Laethem, J.L., & Flamen, P. (2010) Phase III trial comparing protracted intravenous fluorouracil infusion alone or with yttrium-90 resin microspheres radioembolization for liver-limited metastatic colorectal cancer refractory to standard chemotherapy. *Journal of Clinical Oncology.* 28 (23), 3687-3694.

Hickey, R., Lewandowski, R.J., Prudhomme, T., Ehrenwald, E., Baigorri, B., Critchfield, J., Kallini, J.R., Gabr, A., Gorodetski, B., Geschwind, J.F., Abbott, A., Shridhar, R., White, S.B., Rilling, W.S., Boyer, B., Kauffman, S., Kwan, S., Padia, S.A., Gates, V.L., Mulcahy, M., Kircher, S., Nimeiri, H., Benson, A.B., & Salem, R. (2015) Y90 Radioembolization of Colorectal Hepatic Metastases using Glass Microspheres: Safety and Survival Outcomes from a 531-Patient Multicenter Study. *Journal of Nuclear Medicine.* 57 (5), 665-671.

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

Kalva, S.P., Rana, R.S., Liu, R., Rachamreddy, N., Dave, B., Sharma, A., Ganguli, S., Rabito, C., Kwak, E., & Blaszkowsky, L.S. (2014) Yttrium-90 Radioembolization as Salvage Therapy for Liver Metastases From Colorectal Cancer. *American Journal of Clinical Oncology.* 40 (3), 288-293.

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

Kennedy, A.S., Ball, D.S., Cohen, S.J., Cohn, M., Coldwell, D., Drooz, A., Ehrenwald, E., Kanani, S., Rose, S.C., Nutting, C.W., Moeslein, F.M., Savin, M.A., Schirm, S., Putnam, S.G., III, Sharma, N.K., & Wang, E.A. (2015b) Safety and Efficacy of Radioembolization in Elderly (>/= 70 Years) and Younger Patients With Unresectable Liver-Dominant Colorectal Cancer. *Clinical Colorectal Cancer*. 15 (2), 141-151.

Kennedy, A., Cohn, M., & Coldwell, D. (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 (4), 614-624.

Maleux, G., Deroose, C., Laenen, A., Verslype, C., Heye, S., Haustermans, K., De, H.G., Sagaert, X., Topal, B., Aerts, R., Prenen, H., Vanbeckevoort, D., Vandecaveye, V., & Van, C.E. (2015) Yttrium-90 radioembolization for the treatment of chemorefractory colorectal liver metastases: Technical results, clinical outcome and factors potentially influencing survival. *Acta Oncologica.* 55 (4), 486-495.

Murthy R., Kamat P., Nuñez R. & Salem R. (2008) Radioembolization of yttrium-90 microspheres for hepatic malignancy. *Seminars in Interventional Radiology.* 25(1), 48-57.

Nace, G.W., Steel, J. L., Amesur, N., Zajko, A., Nastasi, B. E., Joyce, J., Sheetz, M., & Gamblin, T.C. (2011) Yttrium-90 radioembolization for colorectal cancer liver metastases: a single institution experience. *International Journal of Surgical Oncology.* doi: 10.1155/2011/571261.

National Institute for Health and Care Excellence. (2011) *Selective internal radiation therapy for non-resectable colorectal metastases in the liver.* Interventional procedures guidance [IPG401]. Available at: https://www.nice.org.uk/guidance/IPG401 [Accessed 7th February 2017].

Paprottka, K. J., Schoeppe, F., Ingrisch, M., Rübenthaler, J., Sommer, N. N., De Toni, E., Ilhan, H., Zacherl, M., Todica, A., & Paprottka, P. M. (2017) Pre-therapeutic factors for predicting survival after radioembolization: a single-center experience in 389 patients. *European Journal of Nuclear Medicine & Molecular Imaging*. 44 (7), 1185-1193.

Pennington, B., Akehurst, R., Wasan, H., Sangro, B., Kennedy, A.S., Sennfält, K., & Bester, L. (2015) Cost-effectiveness of selective internal radiation therapy using yttrium-90 resin microspheres in treating patients with inoperable colorectal liver metastases in the UK. *Journal of Medical Economics*. 18 (10), 797-804.

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

Schmeel, F.C., Simon, B., Luetkens, J.A., Traber, F., Meyer, C., Schmeel, L.C., Sabet, A., Ezziddin, S., Schild, H.H., & Hadizadeh, D.R. (2017) Prognostic value of pretreatment diffusion-weighted magnetic resonance imaging for outcome prediction of colorectal cancer liver metastases undergoing 90Y-microsphere radioembolization. *Journal of Cancer Research & Clinical Oncology*. 143 (8), 1531-1541.

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

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

Specialist Unit for Research Evidence. Critical appraisal checklists. Available at: https://www.cardiff.ac.uk/specialist-unit-for-review-evidence/resources/critical-appraisal-checklists [Accessed 14th February 2018].

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