National Institute for Health and Care Excellence

Draft for consultation

Colorectal cancer (update)

[D2b] Optimal combination and sequence of treatments in patients presenting with metastatic colorectal cancer in the liver not amenable to treatment with curative intent

NICE guideline TBC

Evidence reviews

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Draft for Consultation

These evidence reviews were developed by the National Guideline Alliance hosted by the Royal College of Obstetricians and Gynaecologists

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ISBN:

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Optimal combination and sequence of treatments in patients presenting with metastatic colorectal cancer in the liver not amenable to treatment with curative intent

This evidence review supports recommendations 1.5.5 to 1.5.6.

Review question

What is the optimal combination and sequence of treatments in patients presenting with metastatic colorectal cancer in the liver not amenable to treatment with curative intent?

Introduction

For colorectal cancer with limited liver metastases, surgical resection is typically the treatment of choice. However, many people with metastatic colorectal cancer in the liver are not candidates for surgical resection or local treatment with curative intent because of the extent of their metastases. In these circumstances, other treatment modalities should be considered. The aim of this review is to determine the optimal treatment for people with metastatic colorectal cancer in the liver not amenable to treatment with curative intent.

Summary of the protocol

Please see Table 1 for a summary of the population, intervention, comparison and outcomes (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	Adults with colorectal cancer with metastases in the liver not amenable to treatment with curative intent at presentation Subgroups: • Primary colorectal tumour is symptomatic or asymptomatic • Metastasis is synchronous or metachronous • Performance status/comorbidity score

Intervention	• Ablation
	  ○ Radiofrequency ablation (RFA)
	  ○ Microwave ablation
	  ○ Irreversible Electroporation (IRE)
	• Stereotactic body radiation therapy (SBRT) or stereotactic ablative radiotherapy (SABR)
	• Systemic anti-cancer therapy (SACT)
	• Chemosaturation
	• Transarterial chemoembolization (TACE) (for example irinotecan-loaded drug eluting beads (DEBIRI))

	• Selective internal radiation therapy (SIRT)
Comparison	• Interventions individually or in combination compared against each other • Best supportive care
Outcomes	**Critical** • Liver progression-free survival • Overall survival • Overall quality of life **Important** • Disease-free survival • Treatment-related mortality • Resectability • Any grade 3 or 4 adverse event

For further details see the review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual 2014. Methods specific to this review question are described in the review protocol in appendix A.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy until 31 March 2018. From 1 April 2018, declarations of interest were recorded according to NICE's 2018 conflicts of interest policy. Those interests declared until April 2018 were reclassified according to NICE's 2018 conflicts of interest policy (see Register of Interests).

Clinical evidence

Included studies

Eight randomised controlled trials (RCTs; reported in 7 publications) were included in this review (CLOCC trial [Ruers 2017; Ruers 2012]; DEBIRI trial [Martin 2015]; Fiorentini 2012; FOXFIRE, SIRFLOX, FOXFIRE Global trials [Wasan 2017]; Hendlisz 2010; van Hazel 2004.

The included studies are summarised in Table 2.

The included studies reported on four different comparisons. One RCT compared RFA with SACT to SACT alone (CLOCC trial [Ruers 2017; Ruers 2012]). Two RCTs studied DEBIRI, one comparing DEBIRI with SACT to SACT alone (DEBIRI trial [Martin 2015]) and one comparing DEBIRI to SACT (Fiorentini 2012). Five RCTs compared SIRT with SACT to SACT alone, 4 among chemotherapy-naïve people (FOXFIRE, SIRFLOX, FOXFIRE Global trials [Wasan 2017]; van Hazel 2004) and 1 among people refractory to chemotherapy (Hendlisz 2010).

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review with reasons for their exclusions are provided in appendix K.

Summary of clinical studies included in the evidence review

Summaries of the studies that were included in this review are presented in Table 2.

Table 2: Summary of included studies

Study	Population	Intervention/ Comparison	Outcomes
Comparison 1: RFA + SACT versus SACT alone			
CLOCC trial (Ruers 2017; Ruers 2012) Phase II RCT Austria, Belgium, Egypt, France, Germany, Hungary, Italy, Netherlands, Sweden, UK	N=119 people with nonresectable liver metastases from colorectal adenocarcinoma without extrahepatic disease; all liver lesions could be fully treated by either RFA alone or RFA and resection; WHO performance status <2	RFA + FOLFOX ± bevacizumab versus FOLFOX ± bevacizumab	• Overall survival • Progression-free survival • Postoperative mortality • Postoperative complications • Grade 3 or 4 adverse events
Comparison 2: DEBIRI + SACT versus SACT alone			
DEBIRI trial (Martin 2015) Phase II RCT US	N=72 people with metastatic colorectal cancer to the liver; liver-dominant disease; chemotherapy-naive for their metastatic disease; ECOG performance status ≤2	DEBIRI + FOLFOX + bevacizumab versus FOLFOX + bevacizumab	• Grade 3 or 4 adverse events
Comparison 3: DEBIRI versus SACT			
Fiorentini 2012 Phase III RCT Italy	N=74 people with colorectal cancer with unresectable liver metastasis; no extrahepatic disease; previous chemotherapy completed at least 3 months before protocol therapy	DEBIRI versus FOLFIRI	• Liver progression free survival • Overall survival • Quality of life • Progression-free survival
Comparison 4: SIRT + SACT versus SACT alone			
FOXFIRE, SIRFLOX, FOXFIRE Global trials (Wasan 2017) A combined individual patient	N=1,103 people with colorectal cancer with liver-only or liver-dominant metastases with or without the primary tumour in situ; life	SIRT + FOLFOX ± cetuximab or bevacizumab versus FOLFOX ± cetuximab or bevacizumab	• Progression-free survival • Overall survival • Quality of life • Treatment-related mortality

Study	Population	Intervention/ Comparison	Outcomes
data analysis of 3 phase III RCTs Australia, Belgium, France, Germany, Israel, Italy, New Zealand, Portugal, South Korea, Singapore, Spain, Taiwan, UK, US	expectancy ≥3 months; WHO PS <2 Inclusion/exclusion criteria were similar between the three trials but not identical.		• Resectability • Grade 3 or 4 adverse events
Hendlisz 2010 Phase III RCT Belgium	N=46 people with adenocarcinoma of the colon or rectum metastasised to the liver only; not amenable to curative surgery or local ablation; resistant or intolerant to standard chemotherapy: ECOG performance status ≤2	SIRT + 5-FU versus 5-FU alone	• Liver progression-free survival • Overall survival • Progression-free survival • Grade 3 or 4 adverse events
van Hazel 2004 Phase II RCT Australia	N=21 people with adenocarcinoma of the colorectum and liver metastases that could not be treated by resection or any locally ablative technique; no previous chemotherapy or radiotherapy for the metastases; WHO performance status <3	SIRT + 5-FU/LV versus 5-FU/LV alone	• Overall survival • Treatment-related mortality

DEBIRI: drug-eluting beads loaded with irinotecan; ECOG: Eastern Cooperative Oncology Group; FOLFIRI: leucovorin (folinic acid) + fluorouracil + irinotecan; FOLFOX: leucovorin (folinic acid) + fluorouracil + oxaliplatin; LV: leucovorin (folinic acid); N: number; OS: overall survival; PFS: progression-free survival; PS: performance score; QoL: quality of life; RCT: randomised controlled trial; RFA: radiofrequency ablation; SACT: systemic anti-cancer therapy; SIRT: selective internal radiation therapy; WHO: World Health Organization; 5-FU: 5-fluorouracil

See the full evidence tables in appendix D and the forest plots in appendix E.

Quality assessment of clinical outcomes included in the evidence review

See the clinical evidence profiles in appendix F.

Economic evidence

Included studies

A systematic review of the economic literature was conducted but no economic studies were identified which were applicable to this review question.

Excluded studies

A global search of economic evidence was undertaken for all review questions in this guideline. See Supplement 2 for further information.

Economic model

Economic analysis was planned for this topic in line with the economic plan but is not presented as part of this evidence review. For more information see appendix J.

Evidence statements

Clinical evidence statements

Comparison 1: RFA plus SACT versus SACT alone

Critical outcomes

Liver progression-free survival

No evidence was identified to inform this outcome.

Overall survival

- Moderate quality evidence from 1 RCT (N=119; median follow-up 9.7 years) showed a clinically important better overall survival for people who received RFA plus SACT compared to SACT alone for metastatic colorectal cancer in the liver not amenable to treatment with curative intent.

Quality of life

- Moderate quality evidence from 1 RCT (N=119) showed that health-related quality of life score (measured using EORTC QLQ-C30) temporarily dropped after RFA treatment in people who received RFA plus SACT, otherwise there was no difference in quality of life between people who received RFA plus SACT and those who received SACT alone for metastatic colorectal cancer in the liver not amenable to treatment with curative intent.

Important outcomes

Progression-free survival

- Moderate quality evidence from 1 RCT (N=119; median follow-up 9.7 years) showed a clinically important better progression-free survival for people who received RFA plus SACT compared to SACT alone for metastatic colorectal cancer in the liver not amenable to treatment with curative intent.

Treatment-related mortality

- Moderate quality evidence from 1 RCT (N=119) showed that there was 1 postoperative death in people who received RFA plus SACT and no postoperative deaths in people who received SACT alone for metastatic colorectal cancer in the liver not amenable to treatment with curative intent.

Resectability

No evidence was identified to inform this outcome.

Any grade 3 or 4 adverse event

- Moderate quality evidence from 1 RCT (N=119) showed no clinically important difference in risk of postoperative complications or grade 3 or 4 chemotherapy-related toxicities, apart from an increased risk of hospitalisation for more than 24 hours due to postoperative complications in people who received RFA plus SACT compared SACT alone.

Comparison 2: DEBIRI plus SACT versus SACT alone

Critical outcomes

Liver progression-free survival

- Moderate quality evidence from 1 RCT (N=71) showed that there may be a clinically important better liver progression-free survival in people who received DEBIRI plus FOLFOX plus bevacizumab compared to FOLFOX plus bevacizumab alone for metastatic colorectal cancer in the liver not amenable to treatment with curative intent but there is uncertainty around the estimate.

Overall survival

No evidence was identified to inform this outcome.

Quality of life

No evidence was identified to inform this outcome.

Important outcomes

Progression-free survival

- Moderate quality evidence from 1 RCT (N=71) showed no clinically important difference in progression-free survival in people who received DEBIRI plus FOLFOX plus bevacizumab compared to FOLFOX plus bevacizumab alone for metastatic colorectal cancer in the liver not amenable to treatment with curative intent.

Treatment-related mortality

No evidence was identified to inform this outcome.

Resectability

No evidence was identified to inform this outcome.

Any grade 3 or 4 adverse event

- Moderate quality evidence from 1 RCT (N=71) showed no clinically important difference in risk of grade 3 or 4 adverse events in people who received DEBIRI plus FOLFOX plus bevacizumab compared to FOLFOX plus bevacizumab alone for metastatic colorectal cancer in the liver not amenable to treatment with curative intent.

Comparison 3: DEBIRI versus SACT

Critical outcomes

Liver progression-free survival

- Moderate quality evidence from 1 RCT (N=74) showed a clinically important better liver progression-free survival in people who received DEBIRI compared to FOLFIRI for metastatic colorectal cancer in the liver not amenable to treatment with curative intent.

Overall survival

- Moderate quality evidence from 1 RCT (N=74) showed a clinically important better overall survival in people who received DEBIRI compared to FOLFIRI for metastatic colorectal cancer in the liver not amenable to treatment with curative intent.

Quality of life

- Low quality evidence from 1 RCT (N=74) showed that quality of life physical functioning subscale score (measured using Edmonton Symptom Assessment System [ESAS] was better at 1, 3 and 8 months in people who received DEBIRI compared to those who received FOLFIRI for metastatic colorectal cancer in the liver not amenable to treatment with curative intent.

Important outcomes

Progression-free survival

- Moderate quality evidence from 1 RCT (N=74) showed a clinically important better progression-free survival in people who received DEBIRI compared to FOLFIRI for metastatic colorectal cancer in the liver not amenable to treatment with curative intent.

Treatment-related mortality

No evidence was identified to inform this outcome.

Resectability

No evidence was identified to inform this outcome.

Any grade 3 or 4 adverse event

No evidence was identified to inform this outcome.

Comparison 4: SIRT plus SACT versus SACT alone

Critical outcomes

Liver progression free survival

- High quality evidence from 3 RCTs (N=1,103) showed a clinically important better liver progression-free survival in chemotherapy-naïve people who received SIRT plus SACT compared to SACT alone for metastatic colorectal cancer in the liver not amenable to treatment with curative intent.

- Moderate quality evidence from 1 RCT (N=44) showed a clinically important better liver progression-free survival in people refractory to chemotherapy who received SIRT plus SACT compared to SACT alone for metastatic colorectal cancer in the liver not amenable to treatment with curative intent.

Overall survival

- High quality evidence from 4 RCTs (N=1,124) showed no clinically important difference in overall survival in chemotherapy-naïve people who received SIRT plus SACT compared to SACT alone for metastatic colorectal cancer in the liver not amenable to treatment with curative intent.
- High quality evidence from 3 RCTs (N=958) showed no clinically important difference in overall survival in a subpopulation of chemotherapy-naïve people who received SIRT plus SACT compared to SACT alone for synchronous metastatic colorectal cancer in the liver not amenable to treatment with curative intent.
- Moderate quality evidence from 3 RCTs (N=139) showed no clinically important difference in overall survival in a subpopulation of chemotherapy-naïve people who received SIRT plus SACT compared to SACT alone for metachronous metastatic colorectal cancer in the liver not amenable to treatment with curative intent.
- High quality evidence from 3 RCTs (N=958) showed no clinically important difference in overall survival in a subpopulation of chemotherapy-naïve people with WHO performance status 0 who received SIRT plus SACT compared to SACT alone for metastatic colorectal cancer in the liver not amenable to treatment with curative intent.
- High quality evidence from 3 RCTs (N=958) showed no clinically important difference in overall survival in a subpopulation of chemotherapy-naïve people with WHO performance status 1 who received SIRT plus SACT compared to SACT alone for metastatic colorectal cancer in the liver not amenable to treatment with curative intent.
- Moderate quality evidence from 1 RCT (N=44) showed no clinically important difference in overall survival in people refractory to chemotherapy who received SIRT plus SACT compared to SACT alone for metastatic colorectal cancer in the liver not amenable to treatment with curative intent.

Quality of life

- Moderate quality evidence from 3 RCTs (N=1,103) showed no clinically important difference in health-related quality of life (measured using EQ-5D-3L) at 2-3, 6, 12 and 24 months after randomisation in chemotherapy-naïve people who received SIRT plus SACT compared to SACT alone for metastatic colorectal cancer in the liver not amenable to treatment with curative intent.
- Low quality evidence from 1 RCT (N=21) showed no difference in quality of life (measured using Functional Living Index [FLIC] every 3 months during follow-up) in chemotherapy-naïve people who received SIRT plus SACT compared to SACT alone for metastatic colorectal cancer in the liver not amenable to treatment with curative intent.

Important outcomes

Progression-free survival

- High quality evidence from 3 RCTs (N=1,103) showed that there may be a clinically important better progression-free survival in chemotherapy-naïve people who received SIRT plus SACT compared to SACT alone for metastatic colorectal cancer in the liver not amenable to treatment with curative intent but there is uncertainty around the estimate.
- Moderate quality evidence from 1 RCT (N=44) showed a clinically important better progression-free survival in people refractory to chemotherapy who received SIRT plus SACT compared to SACT alone for metastatic colorectal cancer in the liver not amenable to treatment with curative intent.

Treatment-related mortality

- Moderate quality evidence from 4 RCTs (N=1,099) showed no clinically important difference in treatment-related mortality in people who received SIRT plus SACT compared to SACT alone for metastatic colorectal cancer in the liver not amenable to treatment with curative intent.

Resectability

- Moderate quality evidence from 3 RCTs (N=1,103) showed no clinically important difference in resectability in people who received SIRT plus SACT compared to SACT alone for metastatic colorectal cancer in the liver not amenable to treatment with curative intent.

Any grade 3 or 4 adverse event

- High quality evidence from 3 RCTs (N=1,099) showed a clinically important increase in risk of grade 3 or 4 adverse events in chemotherapy-naïve people who received SIRT plus SACT compared to SACT alone for metastatic colorectal cancer in the liver not amenable to treatment with curative intent.
- Moderate quality evidence from 1 RCT (N=44) showed no clinically important difference in risk of grade 3 or 4 adverse events in people refractory to chemotherapy who received SIRT plus SACT compared to SACT alone for metastatic colorectal cancer in the liver not amenable to treatment with curative intent.

Economic evidence statements

No economic evidence was identified which was applicable to this review question.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

Liver progression-free survival and overall survival were considered critical outcomes for decision making because progression of the liver metastases suggests ineffective treatment, potentially requiring further treatment and affecting overall survival. Quality of life was a critical outcome because of the impact that different treatment options can have on patients' functioning and the potential long term adverse effects.

Progression-free survival, meaning survival without progression anywhere in the body, was an important outcome because it reflects effectiveness of treatment, and can mean additional subsequent treatments can be delivered and may affect overall survival. Resectability was also an important outcome as it indicates that a previously unresectable disease becomes resectable because of effective treatment. Additionally, treatment-related mortality and adverse events were also important outcomes, as they are indicative of the short-term side effects of treatments.

The quality of the evidence

Evidence was available for the comparisons of RFA plus SACT versus SACT alone (comparison 1), DEBIRI plus SACT versus SACT alone (comparison 2), DEBIRI versus SACT (comparison 3), SIRT plus SACT versus SACT alone (comparison 4).No evidence was identified on stereotactic body radiation therapy, stereotactic ablative radiotherapy or chemosaturation. For comparison 1, evidence was available for all of the outcomes apart from liver progression-free survival and resectability. The quality of the evidence was assessed using GRADE and was of moderate quality.

For comparison 2, evidence was available for all outcomes except overall survival, quality of life, treatment-related mortality and resectability. The quality of the evidence was assessed using GRADE and was of moderate quality.

For comparison 3, evidence was available for all outcomes except treatment-related mortality, resectability, and grade 3 or 4 adverse events. The quality of the evidence was assessed using GRADE and was mostly of moderate quality (varying from low to moderate).

Evidence was available for all of the outcomes for comparison 4. The quality of the evidence was assessed using GRADE and was mostly of moderate to high quality (although some evidence was of low quality).

The main reasons for downgrading the quality of the evidence was imprecision of the effect estimate due to small sample sizes and a lack of blinding

Benefits and harms

Surgical resection is usually the treatment of choice for colorectal liver metastases. Assessing resectability is a complex process including anatomical, functional and oncological consideration. Practice is changing and what has historically been considered unresectable might in current practice be considered resectable. Furthermore, unresectable disease might still be curable by other modes of treatment. The differentiation of resectable and unresectable disease, and curable and incurable are changing as techniques evolve.

When surgical resection of colorectal liver metastases is not possible because the metastases are unresectable or because the patient is unfit for surgery, other treatment options have been suggested, including systemic therapy, local ablative techniques, transarterial chemoembolization, selective internal radiation therapy, stereotactic ablative radiotherapy and chemosaturation. The potential benefits on survival should be balanced against potential effects on quality of life, treatment-related mortality and morbidity, and cost.

Evidence from randomised trials on local ablative techniques for colorectal liver metastases is limited. One relatively small phase II trial has compared radiofrequency ablation with systemic therapy to systemic therapy alone. This trial included patients with less than 10 liver metastases considered unresectable at the

time of recruitment (between 2002 and 2007). The results showed that radiofrequency ablation combined with systemic therapy had a beneficial effect on overall survival and progression-free survival while no difference was observed in treatment-related mortality and morbidity. Evidence on quality of life was limited but suggested an initial drop in quality of life scores in the ablation group during the ablative treatment but no difference between the groups later on; however, because of the small sample size no definite conclusions on the effects on quality of life could be drawn. The committee considered this trial to be informative as it is the only trial examining the effectiveness and safety of ablative techniques for colorectal liver metastases but the clinical relevance of it was discussed: at the time of the trial the included population was considered to have unresectable liver metastases whereas at the current time these metastases might be resectable because techniques have evolved.

It was also noted that radiofrequency ablation has been largely replaced by newer local ablative techniques, mainly microwave ablation. While this review did not address the question of whether microwave ablation is comparable to radiofrequency ablation, the committee was aware of the non-randomised studies reported in the NICE interventions procedures guidance on microwave ablation for treating liver metastases (IPG553) which show that compared to radiofrequency ablation microwave ablation has similar survival rates and similar or lower local recurrence rates. For these reasons, the committee agreed that it would not be appropriate to only consider the older local ablation technique of radiofrequency ablation, but local ablative techniques more generally.

Some of the patients in both arms of the trial received bevacizumab as part of their systemic therapy. A NICE technology appraisal on bevacizumab and cetuximab for the treatment of metastatic colorectal cancer (TA118) does not recommend its use as first-line treatment for metastatic colorectal cancer because it was not found to be cost-effective. The trial included people with fewer than 10 liver metastases and in general the population had favourable disease as the survival in the palliative group (systemic treatment only) was around 30% at 5 years, higher than generally expected in people with unresectable colorectal liver metastases. Regardless, the committee agreed that for people whose colorectal liver metastases cannot be surgically resected a combination of systemic therapy and local ablative techniques should be considered.

Transarterial chemoembolization (including DEBIRI) was studied by 2 small RCTs. There was some evidence that DEBIRI improved time to progression in the liver. The committee discussed that improvement in liver progression-free survival would be valuable if it improved overall survival or could replace a course of chemotherapy and potentially hence give a benefit in terms of quality of life and cost. However, little or no benefit was observed on overall survival from DEBIRI and data on quality of life was too limited to draw conclusions. Therefore, the committee agreed that there is not enough evidence to recommend transarterial chemoembolization.

The most robust evidence was available on SIRT. Evidence on SIRT as first-line treatment was available from 4 RCTs, particularly from 3 more recent and larger RCTs where SIRT was given as first-line treatment. Even though SIRT produced a benefit in terms of liver progression there was no benefit on overall survival. There were more grade 3 or 4 adverse events among patients who underwent SIRT. No difference was observed in quality of life, resectability or treatment-related mortality. With no effect on overall survival or quality of life but increased adverse events and costs, the committee agreed that SIRT should not be offered as a first line treatment for people with colorectal liver metastases. The committee was aware of the NICE

interventional procedure guidance on selective internal radiation therapy for non-resectable colorectal metastases in the liver (IPG401) updated in May 2013. At that time, the aforementioned trials on SIRT were still ongoing and while SIRT was found to be safe its effectiveness as a first line treatment was still uncertain. The IPG401 will be updated in due course.

Evidence from one small RCT was available about SIRT for people refractory or intolerant to standard chemotherapy. The evidence was limited but suggested a benefit on liver progression-free survival and progression-free survival but not on overall survival. Because the evidence was limited, the committee was not able to make a recommendation on this. The committee were aware of a NHS England commissioning guidance on SIRT as third-line treatment, which used retrospective data in addition to the small RCT as their evidence base.

No evidence was identified on stereotactic ablative radiotherapy but there are several ongoing trials which have yet to publish their results but which will inform future guidance.

Cost effectiveness and resource use

The addition of RFA to SACT would increase overall survival and progression free survival with no difference to adverse events from treatment. Quality of life, despite being lower in the immediate period following ablation soon recovered to be equal to that of SACT alone. Given the greater overall survival it is likely that the addition of RFA will also increase QALYs.

There would be some initial increase in cost from the addition of RFA although it is likely that most if not all of that will be recouped by reducing or delaying the need for treatment following disease progression. RFA with SACT is already widely used across the NHS and therefore any resource impact from these recommendations are likely to be small.

Other factors the committee took into account

The committee was aware of the EPOCH trial of TheraSphere in patients who had failed first-line chemotherapy for metastatic colorectal cancer. The trial has not yet published any results.

Given the low quality of the published evidence the committee discussed making research recommendations about the effectiveness of chemosaturation and transarterial chemoemoblisation for people with colorectal liver metastases not amenable to local treatment. Following their discussion the committee decided not to make any research recommendations for this topic, partly because it was not a priority in comparison to the other research topics within this guideline and also because of the practical difficulties of recruiting enough participants to complete such a trial within a reasonable time.

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Appendices

Appendix A – Review protocol

Review protocol for review question: What is the optimal combination and sequence of treatments in patients presenting with metastatic colorectal cancer in the liver not amenable to treatment with curative intent?

Table 3: Review protocol for the optimal combination and sequence of treatments in patients presenting with metastatic colorectal cancer in the liver not amenable to treatment with curative intent

Field (based on PRISMA-P)	Content
Review question in guideline	What is the optimal combination and sequence of treatments in patients presenting with metastatic colorectal cancer in the liver not amenable to treatment with curative intent?
Type of review question	Intervention
Objective of the review	To determine the optimal combination and sequence of treatments in patients presenting with metastatic colorectal cancer in the liver not amenable to treatment with curative intent.
Eligibility criteria – population/disease/condition/issue/domain	Adults with colorectal cancer with metastases in the liver not amenable to treatment with curative intent at presentation Subgroups: • Primary colorectal tumour is symptomatic or asymptomatic • Metastasis is synchronous or metachronous • Performance status/comorbidity score

Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	• Ablation
	  ○ Radiofrequency ablation (RFA)
	  ○ Microwave ablation
	  ○ Irreversible Electroporation (IRE)
	• Stereotactic body radiation therapy (SBRT) or stereotactic ablative radiotherapy (SABR)
	• Systemic anti-cancer therapy (SACT)
	• Chemosaturation
	• Transarterial chemoembolization (TACE) (e.g. irinotecan-loaded drug eluting beads (DEBIRI))
	• Selective internal radiation therapy (SIRT)

Eligibility criteria – comparator(s)/control or reference (gold) standard	• Interventions individually or in combination compared against each other • Best supportive care
Outcomes and prioritisation	Critical outcomes: • Liver progression-free survival (minimally important difference [MID]: statistical significance) • Overall survival (minimally important difference [MID]: statistical significance) • Overall quality of life measured using validated scales (MID: published MIDs from literature, see below)

	Important outcomes: • Disease-free survival (MID: statistical significance) • Treatment-related mortality (MID: statistical significance) • Resectability (MID: statistical significance) • Any grade 3 or 4 adverse event (MID: statistical significance) Quality of Life MIDs from the literature: • EORTC QLQ-C30: 5 points • EORTC QLQ-CR29: 5 points • EORTC QLQ-CR38: 5 points • EQ-5D: 0.09 using FACT-G quintiles • FACT-C: 5 points • FACT-G: 5 points • SF-12: > 3.77 for the mental component summary (MCS) and > 3.29 for the physical component summary (PCS) of the Short Form SF-12 (SF-12) • SF-36: > 7.1 for the physical functioning scale, > 4.9 for the bodily pain scale, and > 7.2 for the physical component summary
Eligibility criteria – study design	• Systematic reviews of randomised controlled trials (RCTs) • RCTs • Comparative observational studies will only be considered if eligible RCTs are not available
Other inclusion exclusion criteria	Inclusion: • English-language • All settings will be considered that consider medications and treatments available in the UK • Studies published post 2000 • Observational studies should include multivariate analysis controlling for the following confounding factors: o Age o Synchronous or metachronous o Number of metastases Studies conducted post 2000 will be considered for this review question because the guideline committee considered that some of the treatments were not commercially available before then.
Proposed sensitivity/sub-group analysis, or meta-regression	In case of heterogeneity, the following subgroup analyses will be conducted: • Treatment subtype
Selection process – duplicate screening/selection/ analysis	Sifting, data extraction, appraisal of methodological quality and GRADE assessment will be performed by the systematic reviewer. Resolution of any disputes will be with the senior systematic reviewer and the Topic Advisor. Quality control will be performed by the senior systematic reviewer. Dual sifting will be undertaken for this question for a random 10% sample of the titles and abstracts identified by the search.
Data management (software)	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5).

	'GRADEpro' will be used to assess the quality of evidence for each outcome. NGA STAR software will be used for study sifting, data extraction, recording quality assessment using checklists and generating bibliographies/citations.
Information sources – databases and dates	Potential sources to be searched: Medline, Medline In-Process, CCTR, CDSR, DARE, HTA, Embase Limits (e.g. date, study design): • Apply standard animal/non-English language exclusion • Limit to RCTs and systematic reviews in first instance, but download all results • Dates: from 2000
Identify if an update	Not an update
Author contacts	https://www.nice.org.uk/guidance/indevelopment/gid-ng10060 Developer: NGA
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual
Search strategy – for one database	For details please see appendix B.
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix D (clinical evidence tables) or H (economic evidence tables).
Data items – define all variables to be collected	For details please see evidence tables in appendix D (clinical evidence tables) or H (economic evidence tables).
Methods for assessing bias at outcome/study level	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual Appraisal of methodological quality: The methodological quality of each study will be assessed using an appropriate checklist: • ROBIS for systematic reviews • Cochrane risk of bias tool for RCTs • ROBINS-I for non-randomised studies The quality of the evidence for an outcome (i.e. across studies) will be assessed using GRADE. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis (where suitable)	For details please see section 6.4 of Developing NICE guidelines: the manual
Methods for analysis – combining studies	**Synthesis of data:** Pairwise meta-analysis of randomised trials will be conducted where appropriate.

and exploring (in)consistency	When meta-analysing continuous data, final and change scores will be pooled if baselines are comparable. If any studies report both, the method used in the majority of studies will be analysed. **Minimally important differences:** The guideline committee identified statistically significant differences as appropriate indicators for clinical significance for all outcomes except quality of life for which published MIDs from literature will be used (see outcomes section for more information).
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual. If sufficient relevant RCT evidence is available, publication bias will be explored using RevMan software to examine funnel plots.
Assessment of confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual
Rationale/context – Current management	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by The National Guideline Alliance and chaired by Peter Hoskin in line with section 3 of Developing NICE guidelines: the manual. Staff from The National Guideline Alliance undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see Supplement 1.
Sources of funding/support	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Name of sponsor	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Roles of sponsor	NICE funds The National Guideline Alliance to develop guidelines for those working in the NHS, public health, and social care in England
PROSPERO registration number	Not registered

CCTR: Cochrane Central Register of Controlled Trials; CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; COPM: Canadian Occupational Performance Measure; DARE: Database of Abstracts of Reviews of Effects; DEBIRI: drug eluting beads loaded with irinotecan; EQ-5D: EuroQol five dimensions questionnaire; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 Items; EORTC QLQ-CR29: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire colorectal cancer module (29 items); EORTC QLQ-CR38: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire colorectal cancer module (38 items); FACT-C: Functional Assessment of Cancer Therapy questionnaire (colorectal cancer); FACT-G: Functional Assessment of Cancer Therapy questionnaire (general); FIM: functional independence measure; FAM: functional ability measure; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; IRE: irreversible electroporation; MCS: mental component summary; MID: minimal important difference; NGA: National Guideline Alliance; PCS: physical component summary; RCT: randomised controlled trial; RevMan5: Review Manager version 5; RFA: radiofrequency ablation; RoB: risk of bias; ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions; ROBIS: a tool for assessing risk of bias in systematic reviews; SABR: stereotactic ablative radiotherapy; SACT: systemic anticancer therapy; SBRT: stereotactic body radiation therapy; SD: standard deviation; SF-12: 12-Item Short Form Survey; SF-36:

36-Item Short Form Survey; SIRT: selective internal radiotherapy; TACE: transarterial chemoembolization

Appendix B – Literature search strategies

Literature search strategies for review question: What is the optimal combination and sequence of treatments in patients presenting with metastatic colorectal cancer in the liver not amenable to treatment with curative intent?

A combined search was conducted for the following two review questions:

- What is the optimal combination and sequence of treatments in patients presenting with metastatic colorectal cancer in the liver amenable to treatment with curative intent?
- What is the optimal combination and sequence of treatments in patients presenting with metastatic colorectal cancer in the liver not amenable to treatment with curative intent?

Databases: Embase/Medline

Last searched on: 12/02/2019

#	Search
1	(exp colorectal cancer/ or exp colon tumor/ or exp rectum tumor/) use emez
2	exp colorectal neoplasms/ use ppez
3	((colorect* or colo rect* or colon or colonic or rectal or rectum) adj3 (adenocarcinoma* or cancer* or carcinoma* or malignan* or neoplas* or oncolog* or tumo?r*)).tw.
4	or/1-3
5	liver metastasis/ use emez
6	liver/ use ppez
7	exp neoplasm metastasis/ use ppez
8	6 and 7
9	((Liver or hepatic*) adj3 (disseminat* or metasta* or migrat*)).tw.
10	((colorect* or colo rect* or colon or colonic or rectal or rectum) adj3 (liver metasta* or hepatic* metasta*)).tw.
11	5 or 8 or 9
12	4 and 11
13	10 or 12
14	hepatectomy/ use ppez or segmentectomy/ use emez
15	(Hepatectom* or segmentectom*).tw.
16	(exp liver resection/ or metastasis resection/) use emez
17	Metastasectomy/ use ppez
18	metastasectom*.tw.
19	((liver or hepatic*) adj3 (excis* or metastasectom* or resect* or surg*)).tw.
20	or/14-19
21	exp *antineoplastic agent/ use emez
22	exp antineoplastic agents/ use ppez
23	exp *Antineoplastic Protocols/ use ppez
24	multimodality cancer therapy/ use emez
25	cancer therapy/ use emez
26	exp *chemotherapy/ use emez
27	*cancer combination chemotherapy/ use emez
28	Cancer Vaccines/ use ppez
29	cancer vaccine/ use emez
30	cancer immunotherapy/ use emez
31	exp antibodies, monoclonal/ use ppez or monoclonal antibody/ use emez
32	chemosaturat*.tw.
33	((anti canc* or anticanc* or anticancerogen* or anticarcinogen* or anti neoplas* or antineoplas* or anti tumo?r* or antitumo?r* or cytotoxic*) adj3 (agent* or drug* or protocol* or regimen* or treatment* or therap*)).ti.

#	Search
34	(SACT or chemotherap* or immunotherap* or biological agent* or biological therap*).ti.
35	or/21-34
36	20 and 35
37	((combin* or delay* or simultaneous* or stage*) adj3 (resect* or surg*)).tw.
38	(liver-first or liverfirst).tw.
39	bowel first.tw.
40	or/37-39
41	radiofrequency ablation/ use emez or ablation techniques/ use ppez
42	microwave thermotherapy/ use emez or irreversible electroporation/ use emez or electroporation/ use ppez
43	((percutaneous* or radiofrequen* or radio-frequen* or RF or microwave*) adj3 ablat*).tw.
44	electroporat*.tw.
45	(RFA or MWA or IRE).tw.
46	or/41-45
47	(radiosurgery/ or stereotactic body radiation therapy/ or stereotactic radiosurgery/ or cyberknife/) use emez
48	radiosurgery/ use ppez
49	(Stereotactic* adj2 (irradiation* or RT or radiation* or radioablation* or radiosurg* or radiotherap* or therap* or treat*)).tw.
50	(SBRT or SABRT or SABR or cyberknife or cyber knife).tw.
51	or/47-50
52	chemoembolization/ use emez
53	exp embolization, therapeutic/ use ppez
54	((transarterial or trans-arterial or transcatheter or trans-catheter) adj2 chemoemboli?ation).tw.
55	(irinotecan adj4 beads).tw.
56	(DEBIRI or TACE).tw.
57	or/52-56
58	radioembolization/ use emez
59	radioemboli?ation.tw.
60	((intraarterial or intra-arterial) adj3 brachytherapy).tw.
61	(SIRT or "selective internal radiation therapy").tw.
62	or/58-61
63	limit 35 to yr="2000 - current"
64	limit 57 to yr="2000 - current"
65	limit 62 to yr="2000 - current"
66	36 or 40 or 46 or 51 or 63 or 64 or 65
67	13 and 66
68	limit 67 to (yr="1995 - current" and english language)
69	Letter/ use ppez
70	letter.pt. or letter/ use emez
71	note.pt.
72	editorial.pt.
73	Editorial/ use ppez
74	News/ use ppez
75	exp Historical Article/ use ppez
76	Anecdotes as Topic/ use ppez
77	Comment/ use ppez
78	Case Report/ use ppez
79	case report/ or case study/ use emez
80	(letter or comment*).ti.
81	or/69-80
82	randomized controlled trial/ use ppez
83	randomized controlled trial/ use emez
84	random*.ti,ab.

#	Search
85	or/82-84
86	81 not 85
87	animals/ not humans/ use ppez
88	animal/ not human/ use emez
89	nonhuman/ use emez
90	exp Animals, Laboratory/ use ppez
91	exp Animal Experimentation/ use ppez
92	exp Animal Experiment/ use emez
93	exp Experimental Animal/ use emez
94	exp Models, Animal/ use ppez
95	animal model/ use emez
96	exp Rodentia/ use ppez
97	exp Rodent/ use emez
98	(rat or rats or mouse or mice).ti.
99	or/86-98
100	67 not 99
101	limit 100 to (yr="1995 - current" and english language)
102	limit 101 to yr="1995 - 2012"
103	limit 101 to yr="2013-current"
104	remove duplicates from 102
105	remove duplicates from 103
106	104 or 105

1 **Database: Cochrane Library**

2 Last searched on: 12/02/2019

#	Search
1	MeSH descriptor: [Colorectal Neoplasms] explode all trees
2	((colorect* or colo rect* or colon or colonic or rectal or rectum) near/3 (adenocarcinoma* or cancer* or carcinoma* or malignan* or neoplas* or oncolog* or tumo?r*)):ti,ab,kw
3	#1 or #2
4	MeSH descriptor: [Neoplasm Metastasis] explode all trees
5	MeSH descriptor: [Liver] explode all trees
6	#4 and #5
7	((Liver or hepatic*) near/3 (disseminat* or metasta* or migrat*)):ti,ab,kw
8	((colorect* or colo rect* or colon or colonic or rectal or rectum) near/3 (liver metasta* or hepatic* metasta*)):ti,ab,kw
9	#6 or #7
10	#3 and #9
11	#8 or #10
12	MeSH descriptor: [Hepatectomy] this term only
13	(Hepatectom* or segmentectom*):ti,ab,kw
14	MeSH descriptor: [Metastasectomy] this term only
15	metastasectom*:ti,ab,kw
16	((liver or hepatic*) near/3 (excis* or metastasectom* or resect* or surg*)):ti,ab,kw
17	MeSH descriptor: [Antineoplastic Agents] explode all trees
18	MeSH descriptor: [Antineoplastic Protocols] explode all trees
19	MeSH descriptor: [Cancer Vaccines] explode all trees
20	MeSH descriptor: [Antibodies, Monoclonal] explode all trees
21	chemosaturat*:ti,ab,kw
22	((anti canc* or anticanc* or anticancerogen* or anticarcinogen* or anti neoplas* or antineoplas* or anti tumo?r* or antitumo?r* or cytotoxic*) near/3 (agent* or drug* or protocol* or regimen* or treatment* or therap*)):ti,ab,kw
23	(SACT or chemotherap* or chemosaturat* or immunotherap* or biological agent* or biological therap*):ti,ab,kw

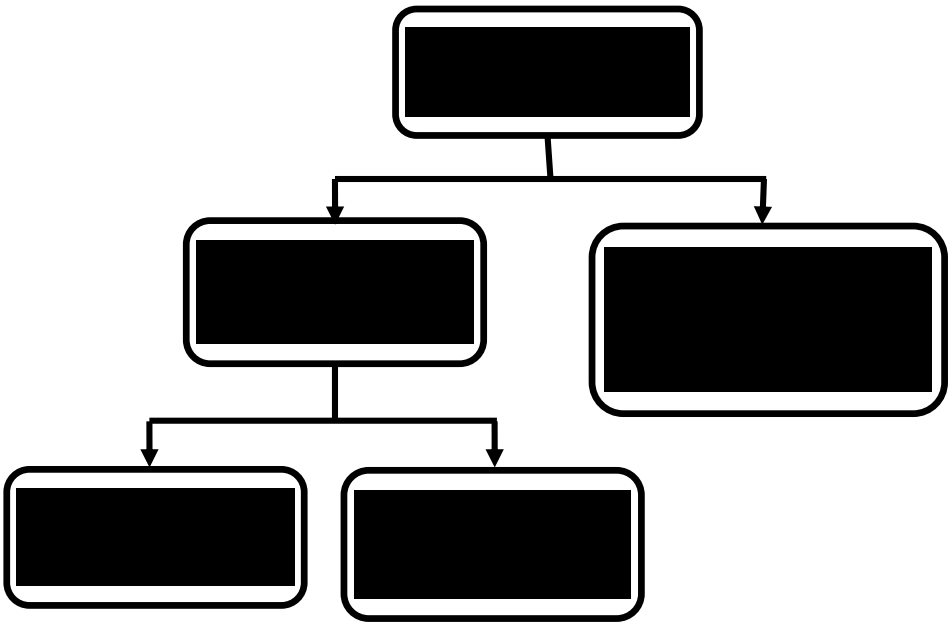
#	Search
24	((combin* or delay* or simultaneous* or stage*) near/3 (resect* or surg*)):ti,ab,kw
25	(liver-first or liverfirst):ti,ab,kw
26	"bowel first":ti,ab,kw
27	MeSH descriptor: [Ablation Techniques] explode all trees
28	((percutaneous* or radiofrequen* or radio-frequen* or RF or microwave*) near/3 ablat*):ti,ab,kw
29	electroporat*:ti,ab,kw
30	(RFA or MWA or IRE):ti,ab,kw
31	MeSH descriptor: [Radiosurgery] this term only
32	(Stereotactic* near/2 (irradiation* or RT or radiation* or radioablation* or radiosurg* or radiotherap* or therap* or treat*)):ti,ab,kw
33	(SBRT or SABRT or SABR or cyberknife or cyber knife):ti,ab,kw
34	MeSH descriptor: [Chemoembolization, Therapeutic] this term only
35	((transarterial or trans-arterial or transcatheter or trans-catheter) near/2 chemoemboli?ation):ti,ab,kw
36	(irinotecan near/4 beads):ti,ab,kw
37	(DEBIRI or TACE):ti,ab,kw
38	radioemboli?ation:ti,ab,kw
39	((intraarterial or intra-arterial) near/3 brachytherapy):ti,ab,kw
40	(SIRT or "selective internal radiation therapy"):ti,ab,kw
41	{or #12-#40}
42	#11 and #41 Publication Year from 1995 to 2018

1
2

Appendix C – Clinical evidence study selection

Clinical study selection for: What is the optimal combination and sequence of treatments in patients presenting with metastatic colorectal cancer in the liver not amenable to treatment with curative intent?

Figure 1: Study selection flow chart



**The literature search was done for 2 review questions at once including the current review and review question 'What is the optimal combination and sequence of treatments in patients presenting with metastatic colorectal cancer in the liver amenable to treatment with curative intent?'. The number of titles and abstracts identified applies for both reviews but all the other numbers are applicable to this specific review only.*

1 Appendix D – Clinical evidence tables

2 Clinical evidence tables for review question: What is the optimal combination and sequence of treatments in patients 3 presenting with metastatic colorectal cancer in the liver not amenable to treatment with curative intent?

4 **Table 4: Clinical evidence tables**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Fiorentini, G., Aliberti, C., Tilli, M., Mulazzani, L., Graziano, F., Giordani, P., Mambrini, A., Montagnani, F., Alessandroni, P., Catalano, V., Coschiera, P., Intra-arterial infusion of irinotecan-loaded drug-eluting beads (DEBIRI) versus intravenous therapy (FOLFIRI) for hepatic metastases from colorectal cancer: Final results of a phase III study, Anticancer Research, 32, 1387-1395, 2012 **Ref Id** 846813 **Country/ies where the study was carried out** Italy **Study type** Phase III RCT **Aim of the study**	**Sample size** N=74 randomised; n=36 allocated to receive drug-eluting beads preloaded with irinotecan (DEBIRI); n=38 allocated to receive systemic irinotecan, fluorouracil and leucovorin (FOLFIRI) **Characteristics** Age in years, mean (range) DEBIRI 64 (44-74) FOLFIRI 63 (42-73) Male sex, n/n DEBIRI 20/36 FOLFIRI 24/38 Liver involvement, n/n ≤25% DEBIRI 26/36 FOLFIRI 26/38 ≤50% DEBIRI 10/36 FOLFIRI 12/38 Metachronous disease, n/n DEBIRI 36/36 FOLFIRI 38/38	**Interventions** DEBIRI consisted of drug eluting beads loaded with irinotecan given twice at 200 mg once a month. Administration of DEBIRI was done using angiography. "A catheter was placed as selectively as possible in order to isolate the blood supply to the metastases and achieve localized chemotherapy. Selective hepatic administration involved embolization of the right or left hepatic arteries separately as they branch from the proper hepatic artery. Highly selective administration involved embolization of branches leading off from the hepatic arteries, preferably the lesion itself or its feeding branches. The size of drug eluting beads was	**Details** Randomisation and allocation concealment Randomisation was stratified by percentage of liver involvement (≤25%, ≤50%), type of prior palliative chemotherapy with/without irinotecan, weight loss in the previous three months, CEA level, KRAS status, and p53 immunohistochemistry. No other details provided. Follow-up/outcomes Primary endpoint was overall survival (time from start of treatment to death from any cause). Secondary endpoints: time to progression (time from start of treatment to documented progression or death	**Results** Time to hepatic progression (liver progression-free survival), median 50 months of follow-up DEBIRI 7 months FOLFIRI 4 months p=0.006 Median overall survival time, median 50 months of follow-up DEBIRI 22 months (95% CI 21 to 23 months) FOLFIRI 15 months (95% CI 12 to 18 months) Overall survival at 2 years DEBIRI 56% FOLFIRI 32% Overall survival at 30 months DEBIRI 34% FOLFIRI 9%	**Limitations** Cochrane risk of bias tool Selection bias Random sequence generation: unclear risk (No details provided.) Allocation concealment: unclear risk (No details provided.) Performance bias Blinding of participants and personnel: unclear/high risk (No blinding.) Detection bias Blinding of outcome assessment: low/high risk (No blinding, depends on the outcome.) Attrition bias Incomplete outcome data: low risk Reporting bias Selective reporting: low risk Other bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
"to compare DEBIRI treatment with irinotecan, fluorouracil and folinic acid (FOLFIRI) given intravenously" **Study dates** December 2006 to December 2008 **Source of funding** Not reported.	Number of metastases, mean (range) DEBIRI 4 (3-10) FOLFIRI 4 (3-10) Performance status, n/n 0-1 DEBIRI 32/36 FOLFIRI 34/38 2 DEBIRI 4/36 FOLFIRI 4/38 Extrahepatic disease, n/n DEBIRI 0/36 FOLFIRI 0/38 2-3 lines of previous chemotherapy DEBIRI 36/36 FOLFIRI 38/38 **Inclusion criteria** Histologically confirmed colorectal cancer with unresectable liver metastasis occupying <50% of the liver parenchyma; no radiological evidence of extrahepatic disease; total bilirubin level of ≤2 × upper limit of normal, with normal haematologic and renal function; previous chemotherapy had been completed at least 3 months before protocol therapy **Exclusion criteria** Patients who had received radiation to the liver; patients	chosen to be 100–300 μm." Patients receiving DEBIRI were closely monitored after the procedures. In order to reduce post-embolization syndrome, intravenous hydration, morphine, anti-emetic and antibiotic prophylaxis were given. Systemic FOLFIRI chemotherapy consisted of intravenous irinotecan, folinic acid and fluorouracil every 2 weeks for 8 times (4 months of treatment). Irinotecan dose of 180 mg/m² on day 1 with folinic acid at 100 mg/m² as a 2 h infusion, followed by bolus of fluorouracil at 400 mg/m² and fluorouracil 600 mg/m² as 22h infusion on days 1 and 2. Ondansetron (8 mg) and dexamethasone (12 mg) were given intravenously on day 1, and loperamide (2 mg) if required, to control nausea, vomiting and diarrhoea.	from any cause), time to hepatic progression (time from start of treatment to documented progression of disease in the liver), time to extrahepatic progression (time from start of treatment to progression outside the liver), decline in quality of life (time from start of treatment to first decline in quality of life). Quality of life was measured before treatment, every 3 months up to 12 months using Edmonton Symptom Assessment System. Statistical analysis Time-to-event analysis done using log-rank tests, Cox proportional hazards model and Kaplan-Meier curves. Differences between categorical variables like toxicities were investigated using Fisher's exact test. Analysis was based on intention-to-treat.	Overall survival at 50 months DEBIRI 15% FOLFIRI 0% p=0.031 Quality of life (Edmonton Symptom Assessment System) "...physical functioning of the DEBIRI patients was better than of those receiving systemic therapy at 1 (p=0.038) and 3 months (p=0.025); this was also performed at 8 months (p=0.025)." Median time to decline in quality of life (time from start of treatment to progression of symptoms or decline in quality of life) DEBIRI 8 months (95% CI 3 to 13 months) FOLFIRI 3 months (95% CI 2 to 4 months) p=0.0002 Time to progression (progression-free survival), median 50 months of follow-up DEBIRI 7 months (95% CI 3 to 11 months)	Other sources of bias: -

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	who had portal vein occlusion or ascites; previous or concurrent malignancy.			FOLFIRI 4 months (95% CI 3 to 5 months) p=0.006 "DEBIRI remained significantly associated with survival when post-progression therapy is considered as a co-variate."	
Full citation Hendlisz, A, Eynde, M, Peeters, M, Maleux, G, Lambert, B, Vannoote, J, Keukeleire, K, Verslype, C, Defreyne, L, Cutsem, E, Delatte, P, Delaunoit, T, Personeni, N, Paesmans, M, Laethem, JI, Flamen, P, 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, 3687-3694, 2010 **Ref Id** 790751 **Country/ies where the study was carried out** Belgium	**Sample size** N=46 randomised; n=23 allocated to SIRT + 5-FU; n=23 allocated to 5-FU alone **Characteristics** Age in years, median (range) SIRT + 5-FU 62 (46-91) 5-FU alone 62 (45-80) Male sex, n/n SIRT + 5-FU 10/21 5-FU alone 18/23 ECOG performance status, n/n 0 SIRT + 5-FU 15/21 5-FU alone 17/23 1 SIRT + 5-FU 5/21 5-FU alone 5/23 2 SIRT + 5-FU 1/21 5-FU alone 1/23 Previous chemotherapy regimen, n/n Irinotecan-based	**Interventions** SIRT + chemotherapy Radioembolization plus protracted intravenous infusion of FU 225 mg/m² for 14 days followed by 1 week of rest. Thereafter, protracted intravenous infusion of FU 300 mg/m² for 14 days every 3 weeks until progression. "The administered activity of 90Y-microspheres was calculated according to the manufacturer's instructions based on the body-surface area and extent of tumor involvement" Chemotherapy alone Protracted intravenous infusion of FU 300 mg/m² days 1 through 14 every 3 weeks until progression. For ethical reasons, patients in chemotherapy	**Details** Randomisation and allocation concealment Randomisation was done using the minimisation technique, stratifying by institution and type of progression before enrolment. No other details provided. Follow-up/outcomes "Physical examination and blood tests were performed every 3 weeks. CT scanning of the chest, abdomen, and pelvis was repeated every 6 weeks until disease progression. Objective tumor response was evaluated by local radiology review using RECIST 1.0. At the investigators' discretion, radiologic	**Results** Liver-progression free survival (event is hepatic progression), median 24.8 months of follow-up SIRT + 5-FU 18/21 5-FU 23/23 HR 0.38 95% CI 0.20 to 0.72, p=0.003 Median time to liver progression SIRT + 5-FU 5.5 months 5-FU 2.1 months Overall survival (event is death from any cause), median 24.8 months of follow-up SIRT + 5-FU n=21, number of events not reported 5-FU n=23, number of events not reported HR 0.92 95% CI 0.47 to 1.78, p=0.8 Median time to death	**Limitations** Cochrane risk of bias tool Selection bias Random sequence generation: unclear risk (Details not reported.) Allocation concealment: unclear risk (Details not reported.) Performance bias Blinding of participants and personnel: unclear/high risk (No blinding.) Detection bias Blinding of outcome assessment: unclear/high risk (Depends on the outcome. No blinding.) Attrition bias Incomplete outcome data: low risk (Intention-to-treat analysis done for survival outcomes.) Reporting bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type Phase III RCT **Aim of the study** To assess "the safety and efficacy of intra-arterial 90Y-resin microspheres in liver-limited mCRC among patients for whom all other evidence-based treatments had failed." **Study dates** December 15 2004 to November 15 2007 **Source of funding** None reported.	SIRT + 5-FU 13/21 5-FU alone 20/23 Oxaliplatin-based SIRT + 5-FU 4/21 5-FU alone 2/23 Other SIRT + 5-FU 4/21 5-FU alone 1/23 Number of liver metastases measures, n/n 1 lesion SIRT + 5-FU 2/21 5-FU alone 1/23 2-4 lesions SIRT + 5-FU 10/21 5-FU alone 10/23 ≥5 lesions SIRT + 5-FU 8/21 5-FU alone 10/23 Not measurable SIRT + 5-FU 1/23 5-FU alone 2/21 Months since diagnosis, median (range) SIRT + 5-FU 8 (2-57) 5-FU 14 (2-60 **Inclusion criteria** Histologically proven adenocarcinoma of the colon or rectum metastasised to the liver only; not amenable to curative surgery or local ablation; resistant or intolerant to standard chemotherapy (5-FU, oxaliplatin, and irinotecan); ECOG performance status of 0 to 2; ≥18 years of	alone group who got disease progression were permitted to cross-over to receive radioembolization at the investigators' discretion.	tumor assessment could be repeated early on the basis of clinical need or suspicion of disease progression." Primary endpoint was time to liver progression (time from randomisation to progression in the liver). Time to progression (time from randomisation to progression at any site or death or loss to follow-up) and overall survival (time from randomisation to death from any cause) were also analysed. Statistical analysis "The distribution of time to event variables was estimated by the nonparametric Kaplan-Meier method. Comparison was made using the log-rank test, and treatment effect was reported by the estimation of a hazard ratio (HR) obtained with Cox regression models."	SIRT + 5-FU 10.0 months 5-FU 7.3 months Progression-free survival (event is progression at any site), median 24.8 months of follow-up SIRT + 5-FU n=21, number of events not reported 5-FU n=23, number of events not reported HR 0.51 95% CI 0.28 to 0.94, p=0.03 Median time to progression SIRT + 5-FU 4.5 months 5-FU 2.1 months Grade 3 or 4 toxicities SIRT + 5-FU 1/21 5-FU 6/22	Selective reporting: low risk Other bias Other sources of bias: - **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	age; adequate bone marrow function (absolute neutrophil count ≥1,000/μL, platelet count ≥100,000/μL), renal function (creatinine <1.5 x upper limit of normal limit [ULN] or creatinine clearance >50 mL/min), and liver function (defined by direct bilirubin <1.0 x ULN; AST, ALT, and alkaline phosphatase levels each <5 x ULN); able to give informed consent. **Exclusion criteria** Pre-existing hepatic disease (cirrhosis > Child-Pugh B, liver abscess, hepatic sarcoidosis or tuberculosis, sclerosing cholangitis); extrahepatic disease; clinically significantly ascites; more than 20% arteriovenous shunting from liver to lungs observed on the 99mTc-MAA scan; hepatic arterial anatomy that would not allow safe administration of 90Y-microspheres; partial or total thrombosis of the hepatic artery or main portal vein; prior HAI with 5-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; pregnancy or				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	breast-feeding; refusal to take adequate pregnancy prevention measures.				
Full citation Martin, R. C. G., Scoggins, C. R., Schreeder, M., Rilling, W. S., Laing, C. J., Tatum, C. M., Kelly, L. R., Garcia-Monaco, R. D., Sharma, V. R., Crocenzi, T. S., Strasberg, S. M., Randomized controlled trial of irinotecan drug-eluting beads with simultaneous FOLFOX and bevacizumab for patients with unresectable colorectal liver-limited metastasis, Cancer, 121, 3649-3658, 2015 **Ref Id** 848468 **Country/ies where the study was carried out** US **Study type** Phase II RCT (DEBIRI trial, NCT00932438) **Aim of the study** "to assess the response and adverse event rates for irinotecan drug-eluting beads (DEBIRI) with folinic acid, 5-fluorouracil, and oxaliplatin (FOLFOX) and bevacizumab as a first-line treatment for	**Sample size** N=72 randomised; n=41 allocated to DEBIRI + FOLFOX ± bevacizumab (intervention); n=30 allocated to FOLFOX ± bevacizumab (control) **Characteristics** Baseline characteristics: Age in years, median Intervention 57 Control 60 Male sex, n/n Intervention 24/40 Control 21/30 Synchronous colon or rectal disease and liver metastasis, % Intervention 53% Control 57% Prior colon surgery, n (%) Intervention 17 (43) Control 13 (45) Prior liver surgery, n Intervention 2 Control 1 CEA, median (range) Intervention 64 (1-12,600) Control 105 (1-16,381)	**Interventions** Intervention group: Modified FOLFOX6 on days 0 to 14, DEBIRI on days 7 to 21 The DEBIRI device was an n-Fil sulfonate–modified, spherical hydrogel device. The treatment was given through a femoral or axillary artery puncture, 1 vial of beads was eluted with the desired amount of irinotecan chemotherapy. Irinotecan was loaded into DEBIRI at 50 mg/mL for a total dose of 100 mg per vial. Most treatments were performed in an outpatient setting. The treating physician determined the number of treatments after re-evaluation with imaging after the 4 cycles of FOLFOX and 2 treatments with DEBIRI, the decision was based on the degree of response, tolerance of combination therapy and quality of life. The use of bevacizumab was left to the discretion of the treating medical oncologist and was based on potential contraindications (for	**Details** Randomisation and allocation concealment "The first 10 enrolled patients were mandated by the Food and Drug Administration to be treated only in the treatment arm (FOLFOX-DEBIRI) for safety and pharmacokinetic studies; it then allowed 60 patients to be randomly assigned to either the treatment arm (30 patients) or the control arm (FOLFOX; 30 patients)." No other details provided. Follow-up/outcomes A triphasic CT scan of the liver within at least 1-2 months of treatment completion. Surgical resectability was assessed after every 4 cycles of systemic chemotherapy (after the 4th, 8th, and 12th cycles). The decision about surgical resection was made by the	**Results** Liver progression-free survival, median 24 months of follow-up Intervention median 17 months (range 12-23 months) Control median 12 months (range 11-24 months) p=0.05 Progression-free survival, median 24 months of follow-up Intervention median 12 months (range 9-15.4 months) Control median 15 months (range 10.4-20 months) p=0.18 Patients with grade 3 or 4 adverse events, n/n Intervention 32/40 Control 18/30	**Limitations** Cochrane risk of bias tool Selection bias Random sequence generation: unclear risk (Details not reported.) Allocation concealment: unclear risk (Details not reported.) Performance bias Blinding of participants and personnel: low/high risk (Patients and treating physicians were not blinded. The study was funded by a company manufacturing DEBIRI and some of the investigators worked as consultants for the company.) Detection bias Blinding of outcome assessment: unclear/high risk (Patients and treating physicians were not blinded. The study was funded by a company manufacturing DEBIRI and some of the investigators worked as consultants for the company. However, tumour response was assessed also by a blinded radiologic review

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
unresectable colorectal liver metastasis" **Study dates** June 2009 to March 2014 **Source of funding** Robert C. G. Martin II and the University of Louisville School of Medicine; Division of Surgical Oncology of the University of Louisville; BTG/Biocompatibles (medical device manufacturer). Some of the authors declare working as consultants for BTG and other companies and receiving grants from the BTG and other companies.	ECOG performance status, n (%) 0 Intervention 17 (44) Control 20 (68) 1 Intervention 20 (50) Control 9 (30) 2 Intervention 3 (6) Control 1 (2) Colon primary in place, n Intervention 12 Control 11 Rectal primary in place, n Intervention 9 Control 6 kRAS mutation, n (%) Intervention 20 (50) Control 10 (30) Presence of extrahepatic disease, n (%) Intervention 22 (55) Control 9 (31) **Inclusion criteria** >18 years of age; have histologically proven colorectal cancer to the liver; chemotherapy-naive for their metastatic disease; liver-dominant disease (≥80% of the tumour body burden being confined to the liver) but <60% liver replacement by the tumour; an ECOG performance status score ≤2	example intact primary tumour with a history of bleeding, recent surgery, and cardiovascular issues). Control group: Same FOLFOX treatment ± bevacizumab	treating surgeon on the basis of established criteria for resectability. The tumour responses for all patients were also assessed by the principal investigator of the study. Statistical analysis Fischer's exact test was used to test the difference between the groups.		with the established RECIST 1.1 criteria or Choi's criteria.) Attrition bias Incomplete outcome data: low risk Reporting bias Selective reporting: high risk of risk (Resectability is listed as one of the main outcomes in the hypothesis but it is not reported in the article.) Other bias Other sources of bias: -

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Exclusion criteria Eligible for curative treatment (resection or radiofrequency ablation); not fitting the inclusion criteria				
Full citation Ruers, T., Punt, C., Van coevorden, F., Pierie, J. P. E. N., Borel-Rinkes, I., Ledermann, J. A., Poston, G., Bechstein, W., Lentz, M. A., Mauer, M., Van Cutsem, E., Lutz, M. P., Nordlinger, B., Verwaal, V. J., Gruenberger, T., Klaase, J., Falk, S., Wals, J., Jansen, R. L., P. Lindner, Mulier, S., Bosscha, K., Jaeck, D., Arnaud, J. P., Smith, D., Sherlock, D., Ammori, B., Gillams, A., El-Serafi, M., Glimelius, B., Hellman, P., Radiofrequency ablation combined with systemic treatment versus systemic treatment alone in patients with non-resectable colorectal liver metastases: A randomized eortc intergroup phase ii study (EORTC 40004), Annals of Oncology, 23, 2619-2626, 2012 **Ref Id** 849478 **Country/ies where the study was carried out**	**Sample size** See Ruers 2017 **Characteristics** **Inclusion criteria** **Exclusion criteria**	**Interventions**	**Details**	**Results**	**Limitations**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type **Aim of the study** **Study dates** **Source of funding**					
Full citation Ruers, T., Van Coevorden, F., Punt, C. J. A., Pierie, J. P. E. N., Borel-Rinkes, I., Ledermann, J. A., Poston, G., Bechstein, W., Lentz, M. A., Mauer, M., Folprecht, G., Van Cutsem, E., Ducreux, M., Nordlinger, B., Pare, A., Verwaal, V. J., Gruenberger, T., Klaase, J., Falk, S., Wals, J., Jansen, R. L., Lindner, P., Mulier, S., Bosscha, K., Jaeck, D., Arnaud, J. P., Smith, D., Sherlock, D., Ammori, B., Gillams, A., El-Serafi, M., Glimelius, B., Hellman, P., Local Treatment of Unresectable Colorectal Liver Metastases: Results of a Randomized Phase II Trial, Journal of the National Cancer Institute, 109 (9) (no pagination), 2017 **Ref Id** 849485 **Country/ies where the study was carried out**	**Sample size** N=119 randomised; n=60 allocated to RFA + systemic therapy; n=59 allocated to systemic therapy alone **Characteristics** Age in years, median (range) RFA + systemic therapy 64 (31-79) Systemic therapy alone 61 (38-79) Male sex, n (%) RFA + systemic therapy 37 (62) Systemic therapy alone 42 (71) WHO performance status, n (%) 0 RFA + systemic therapy 47 (78) Systemic therapy alone 47 (80) 1 RFA + systemic therapy 13 (22) Systemic therapy alone 12 (20) Number of liver metastases, median RFA + systemic therapy 4.0	**Interventions** RFA Hepatobiliary surgeon and the multidisciplinary team decided the strategy (RFA alone or in combination with resection) in order to obtain complete tumour clearance, and the way RFA was done (open surgery, laparoscopically or percutaneously). RFA procedures were carried out according to the manufacturer's guidelines (Radionics, RadioTherapeutics, Rita) by experienced surgeons or radiologists. Systemic therapy (in both arms) FOLFOX 4 (5-FU/leucovorin/oxaliplatin), from October 2005 bevacizumab was added to the regimen. "FOLFOX 4 regimen (oxaliplatin 85 mg/m², LV	**Details** Randomisation and allocation concealment "Randomization was done at the EORTC headquarters with the minimization technique and was stratified for centre, previous chemotherapy for liver metastases, previous adjuvant chemotherapy and route of randomization (before or during surgery). Eligible patients were randomly assigned at a 1:1 ratio to receive RFA plus systemic treatment or systemic treatment alone." (Ruers et al 2012) No other details reported. Follow-up/outcomes	**Results** Overall survival, median 9.7 years of follow-up (event is death from any cause) RFA + systemic therapy 39 events, n=60 Systemic therapy alone 53 events, n=59 HR 0.58 95% CI 0.38 to 0.88, p=0.01 Median overall survival time RFA + systemic therapy 45.6 months 95% CI 30.3 to 67.8 months Systemic therapy alone 40.5 months 95% CI 27.5 to 47.7 months Health-related quality of life (EORTC QLQ-C30) "Based on observed data in the combined treatment	**Limitations** Cochrane risk of bias tool Selection bias Random sequence generation: unclear risk (Details not reported.) Allocation concealment: unclear risk (Details not reported.) Performance bias Blinding of participants and personnel: unclear/high risk (No blinding.) Detection bias Blinding of outcome assessment: low/high risk (No blinding. Bias depends on the outcome.) Attrition bias Incomplete outcome data: low risk (Intention-to-treat analysis done for survival outcomes.) Reporting bias Selective reporting: low risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Austria, Belgium, Egypt, France, Germany, Hungary, Italy, Netherlands, Sweden, UK **Study type** Phase II RCT (EORTC 40004 CLOCC trial, NCT00043004) **Aim of the study** "...to determine the additional value of RFA in patients with non-resecable colorectal metastases confined to the liver, a randomized phase III study was designed by the European Intergroup to compare the efficacy of combination treatment of RFA plus systemic treatment versus systemic treatment alone." (Ruers et al 2012)n= (Due to slow recruitment, the trial was downsized to phase II randomised study.) **Study dates** 16 April 2002 to 20 June 2007 **Source of funding** EORTC; Cancer Research UK; ALM-CAO; Dutch Cancer Foundation; the National Cancer Institute; Kankerbestrijding/KWF; Sanofi-Aventis. Radionics, Radiotherapeutics and Rita provided free RFA needles.	Systemic therapy alone 5.0 Metachronous metastases RFA + systemic therapy 37 (62) Systemic therapy alone31 (53) Time from surgery for primary cancer to randomisation in days, median (range) RFA + systemic therapy 290 (28-1802) Systemic therapy alone 308 (30-2754) Adjuvant chemotherapy for primary cancer, n (%) RFA + systemic therapy 10 (17) Systemic therapy alone 10 (17) Prior chemotherapy for metastatic disease, n (%) RFA + systemic therapy 9 (15) Systemic therapy alone 8 (14) Previous liver surgery for colorectal cancer metastases, n (%) RFA + systemic therapy 9 (15) Systemic therapy alone 10 (17) **Inclusion criteria** 18-80 years old; WHO performance status <2; presented with nonresectable liver metastases from colorectal adenocarcinoma (nonresectability was defined as no possibility to completely resect all tumours); without extrahepatic disease; all liver	200 mg/m², 5-FU bolus 400 mg/m² followed by 600 mg/m² 22-h infusion, every 14 days, or oxaliplatin 85 mg/m², L-folinic acid 175 mg, 5-FU bolus 400 mg/m² followed by 2400 mg/m² 46-h infusion every 14 days or oxaliplatin 85 mg/m² every 14 days and weekly LV 200 mg/m² and 5-FU 2600 mg/m² 24-h infusion, for 6 weeks followed by 1 week of rest). Bevacizumab was administered at 5 mg/kg body weight, once every 2 weeks. Systemic therapy was given for 6 months (in the absence of disease progression or unacceptable toxicity). In case of disease progression, second line chemotherapy based on irinotecan was strongly recommended. In the systemic therapy alone arm, resection was allowed if nonresectable disease converted to resectable during the systemic therapy. RFA was not allowed in this arm at any point.	Tumour response was assessed every 6 weeks during study treatment and every 3 months thereafter for 2 years, after 2 years every 6 months. Follow-up investigations included abdominopelvic CT, chest X-ray and measurement of serum CEA level. Primary endpoint was 30-month survival rate, secondary endpoints were overall survival, progression-free survival and health-related quality of life. Health-related quality of life was assessed with EORTC QLQ-C30 questionnaire at randomisation, and every 6 weeks after start of the systemic therapy until end of study treatment, and thereafter at every standard follow-up assessment. Statistical analysis Intention-to-treat analysis was done for survival outcomes. Kaplan-Meier method and log-rank test were used.	arm, HRQoL scales were impaired after RFA. While a 20-point difference is considered a significant effect, mean global QoL dropped by 27 points. However, recovery to a level at ~10 points below baseline was achieved before the start of systemic treatment (4–8 weeks after RFA). Thereafter, HRQoL scores were similar in both treatment groups, although the limited sample size limits definite conclusions on HRQoL." Progression-free survival, median 9.7 years of follow-up (event is disease progression or death) HR 0.57 95% CI 0.38 to 0.85, p=0.005 Median progression-free survival time RFA + systemic therapy 16.8 months 95% CI 11.0 to 21.9 months	Other bias Other sources of bias: - **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	lesions could be fully treated by either RFA alone or combined treatment of resection of resectable lesions and RFA of the remaining unresectable lesions; number of liver metastases <10; maximum diameter of 4 cm to those treated with RFA; metastatic involvement of the liver ≤50%; adequate bone marrow, liver and renal function. **Exclusion criteria** Presence of the primary tumour; any other malignancy in the past 10 years (expect carcinoma of the cervix in situ or nonmelanoma skin cancer); higher than grade 1 sensory neuropathy; clinically significant cardiovascular disease; uncontrolled hypertension; bleeding disorders or coagulopathy; active infection; any contraindication to the use of 5-FU/leucovorin/oxaliplatin or bevacizumab.			Systemic therapy alone 9.9 months 95% CI 9.1 to 12.9 months Postoperative death* RFA + systemic therapy 1/57 Systemic therapy alone N/A Respiratory failure* RFA + systemic therapy 1/57 Systemic therapy alone N/A Cardiac failure or infarction* RFA + systemic therapy 3/57 Systemic therapy alone N/A Hepatic dysfunction bilirubin >10 mg/dl for 3 days* RFA + systemic therapy 3/57 Systemic therapy alone N/A Renal failure* RFA + systemic therapy 1/57 Systemic therapy alone N/A Intra-abdominal infection (abscess)*	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				RFA + systemic therapy 2/57 Systemic therapy alone N/A Need for reoperation* RFA + systemic therapy 3/57 Systemic therapy alone N/A Hospitalisation for >24h due to complication* RFA + systemic therapy 10/57 Systemic therapy alone N/A Grade 3 or 4 neutropenia* RFA + systemic therapy 14/51 Systemic therapy alone 12/59 Grade 3 or 4 cardiotoxicity* RFA + systemic therapy 5/51 Systemic therapy alone 1/59 Grade 3 or 4 diarrhoea* RFA + systemic therapy 10/51 Systemic therapy alone 10/59	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Grade 3 or 4 vomiting* RFA + systemic therapy 5/51 Systemic therapy alone 4/59 Grade 3 nausea (no grade 4)* RFA + systemic therapy 7/51 Systemic therapy alone 6/59 Grade 3 or 4 other gastrointestinal toxicity* RFA + systemic therapy 4/51 Systemic therapy alone 4/59 Grade 3 or 4 pulmonary toxicity* RFA + systemic therapy 3/51 Systemic therapy alone 1/59 Grade 3 or 4 renal toxicity* RFA + systemic therapy 1/51 Systemic therapy alone 1/59 Grade 3 neuropathy (no grade 4)*	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				RFA + systemic therapy 9/51 Systemic therapy alone 8/59 Grade 3 fatigue (no grade 4)* RFA + systemic therapy 7/51 Systemic therapy alone 4/59 Grade 3 hypertension (no grade 4)* RFA + systemic therapy 2/51 Systemic therapy alone 2/59 *From Ruers et al 2012	
Full citation Van Hazel, G., Blackwell, A., Anderson, J., Price, D., Moroz, P., Bower, G., Cardaci, G., Gray, B., 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, 2004 **Ref Id**	**Sample size** N=21 randomised; n=11 allocated to SIRT + chemotherapy; n=10 chemotherapy alone **Characteristics** Age in years, mean SIRT + chemotherapy 64 Chemotherapy alone 65 Male sex, n/n SIRT + chemotherapy 10/11 Chemotherapy alone 8/10 Extrahepatic disease, n/n SIRT + chemotherapy 2/11	**Interventions** SIRT: A single dose of SIR-Spheres (Sirtex Medical Limited) were administered on the 3rd or 4th day of the second cycle of chemotherapy. "The SIR-Spheres was administered into the hepatic artery via a trans-femoral catheter that was placed under local anaesthetic. In patients where there was more than one hepatic artery supplying blood to	**Details** Randomisation and allocation concealment "Patient registration and randomisation was made by telephoning the independent Australian National Health & Medical Research Council Clinical Trials Centre which randomised patients using a computer based program." Randomisation was	**Results** Overall survival (event is death from any cause) SIRT + chemotherapy 29.4 months Chemotherapy alone 12.8 months HR 0.33 95% CI 0.12 to 0.91, p=0.025 Quality of life (FLIC) "Changes in the quality of life were almost identical in both arms (p=0.96)."	**Limitations** Cochrane risk of bias tool Selection bias Random sequence generation: low risk Allocation concealment: low risk Performance bias Blinding of participants and personnel: unclear/high risk (No blinding.) Detection bias Blinding of outcome assessment: low/high risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
850401 **Country/ies where the study was carried out** Australia **Study type** Phase II RCT **Aim of the study** "to compare the response rate, time to progressive disease (PD), and toxicity of a regimen of systemic fluorouracil/ leucovorin chemotherapy versus the same chemotherapy plus a single administration of SIR-Spheres in patients with advanced colorectal liver metastases." **Study dates** Not reported. **Source of funding** Not reported.	Chemotherapy alone 3/10 Extent of liver metastases >25%, n/n SIRT + chemotherapy 3/11 Chemotherapy alone 3/10 **Inclusion criteria** >18 years of age; histologically proven adenocarcinoma of the colorectum; unequivocal CT scan evidence of liver metastases that could not be treated by resection or any locally ablative technique; not have received chemotherapy or radiotherapy for the liver metastases; have adequate haematologic, hepatic and renal function; no central nervous system metastases; no evidence of cirrhosis, ascites or portal hypertension; WHO performance status <3 **Exclusion criteria** None reported.	the liver, the catheter was repositioned during administration and the total dose of SIR-Spheres was divided into separate aliquots depending on the estimated volume of tumour being supplied by each feeding artery. Patients treated with SIRT were generally kept in hospital overnight and discharged home the following day. As Angiotensin-2 has been shown to increase the microsphere targeting of tumours within the liver, a single bolus of 25 mg of Angiotensin-2 was pulsed into the hepatic artery 30 sec before administering the SIRSpheres." First 5 patients in the SIRT + chemotherapy group received a standard dose of 2.5 GBq of yttiruam-90 activity, for the rest of the patients the dose was calculated based on the patient's body surface and the side of the tumour within the liver according to an equation:	stratified by institution, presence or absence of extrahepatic disease and extent of liver metastases (<25% or >25%). Follow-up/outcomes Follow-up was done every month using serologic tests of haematologic, liver and renal function and CEA and every 3 months including a clinical evaluation and quality of life assessment, CT scans of the abdomen, either an X-ray or a CT scan of the chest. Quality of life was assessed at randomisation and every 3 months after that using a validated 23-item Functional Living Index - Cancer (FLIC) questionnaire. Statistical analysis Time to disease progression and survival curves were constructed using the method of Kaplan–Meier and compared using the logrank test. Intention-to-treat analysis was done.	Treatment-related mortality SIRT + chemotherapy 1/11 Chemotherapy alone 0/10	(Depends on the outcome. No blinding.) Attrition bias Incomplete outcome data: low risk (Intention-to-treat analysis done.) Reporting bias Selective reporting: low risk Other bias Other sources of bias: -

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
		(body surface area in m² - 0.2) + (% of tumour involvement/100). Chemotherapy in both groups: 5-fluorouracil 425 mg/m² per day plus leucovorin 20 mg/m² per day for 5 consecutive days and repeated at 4 weekly intervals. Cycles continued until evidence of unacceptable toxicity, patient request or disease progression.			
Full citation Wasan, H. S., Sharma, N. K., Francis, A., Moschandreas, J., Virdee, P. S., Dutton, P., Love, S., Gebski, V., Gray, A., Adams, R., Bateman, A., Blesing, C., Brown, E., Chau, I., Cummins, S., Cunningham, D., Falk, S., Hadaki, M., Hall, M., Hickish, T., Hornbuckle, J., Lofts, F., Lowndes, S., Mayer, A., Metcalfe, M., Middleton, G., Mills, J., Montazeri, A., Muirhead, R., Polychronis, A., Purcell, C., Ross, P., Sherwin, L., Soomal, R., Swinson, D., Walther, A., Wasan, H., Weaver, A., Wilson, C., Wilson, G., Amin, P., Balosso, J., Boucher, E., Brown, M., Bruch, H. R., Cardaci, G., Chen, Y. J., Chevallier, P., Clarke, S., Coveler, A., Craninx, M.,	**Sample size** Total N=1103; n=554 SIRT + chemotherapy; n=549 chemotherapy alone FOXFIRE: N=364 randomised; n=182 allocated to SIRT + chemotherapy; n=182 allocated to chemotherapy alone SIRFLOX: N=530 randomised; n=267 allocated to SIRT + chemotherapy; n=263 allocated to chemotherapy alone FOXFIRE-Global: N=209 randomised; n=105 allocated to SIRT + chemotherapy; n=104 allocated to chemotherapy alone **Characteristics**	**Interventions** SIRT + systemic FOLFOX chemotherapy versus chemotherapy alone SIRT was administered on day 3 or 4 of the 1st cycle or day 3 or 4 of the 2nd cycle. "We used a hepatic arteriogram and a liver-to-lung breakthrough nuclear medicine scan to assess patient suitability to receive SIRT. We used the patient's body surface area, percentage of tumour involvement, and magnitude of liver-to-lung shunting to establish the activity (GBq) per dosing chart."	**Details** Randomisation and allocation concealment Randomisation was stratified according to metastasis site (liver-only or liver plus extrahepatic metastases), extent of tumour involvement of the liver (≤25% vs >25% measured objectively on baseline CT scan), planned use of a biological agent, and centre. "In FOXFIRE, patients were allocated using minimisation with a probability of 0.8 to the treatment that most reduced the imbalance of the above factors. If there	**Results** Liver progression-free survival, median 43.3 months of follow-up (event is radiological progression in the liver) SIRT + chemotherapy 173/554 Chemotherapy 271/549 HR 0.51 95% CI 0.43 to 0.62, p<0.0001 Overall survival, median 43.3 months of follow-up (event if death from any cause) SIRT + chemotherapy 433/554 Chemotherapy 411/549 HR 1.04 95% CI 0.90 to 1.19, p=0.61	**Limitations** Cochrane risk of bias tool Selection bias Random sequence generation: low risk Allocation concealment: low risk Performance bias Blinding of participants and personnel: unclear/high (No blinding.) Detection bias Blinding of outcome assessment: low/high (Depends on the outcome, high risk of subjective outcomes, low risk for outcomes such as overall survival.) Attrition bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Delanoit, T., Eliadis, P., Ferrante, M., Garofalo, M., Geboes, K., Gehbauer, G., George, B., Gordon, M., Gregory, K., Gulec, S., Hannigan, J., Heinemann, V., Helmberger, T., Isaacs, R., James, P., Karapetis, C., Ko, Y. D., Lammert, F., Liauw, W., Margolis, J., Martin, R., Martoni, A., Marx, G., Moons, V., Nusch, A., Ozer, H., Padia, S., Pavlakis, N., Perez, D., Pluntke, S., Powell, A., Price, T., Ransom, D., Ricke, J., Ridwelski, K., Riera-Knorrenschild, J., Riess, H., Rilling, W., Robinson, B., Rodriguez, J., Sauerbruch, T., Savin, M., Scheidhauer, K., Schneiderman, E., Seeger, G., Segelov, E., Schmueli, E. S., Shannon, J., Shibata, S., Smith, R., Stemmer, S., Stotzer, O., Tatsch, K., Vehling-Kaiser, U., Vogl, T., Whiting, S., Wolf, I., Ades, S., Aghmesheh, M., Angelelli, B., Auber, M., Ayala, H., Beny, A., Bloomgarden, D., Boland, P., Bouche, E., Bowers, C., Bremer, C., Bui, J., Burge, M., Carlisle, J., Casado, A. R., Chai, S., Chuong, M., Cooray, P., Crain, M., De Wit, M., Deleporte, A., Dowling, K., Durand, A., Facchini, F., Faivre, S., Feeney, K., Ferguson, T., Ferru, A., Findlay, M., Fragoso, M., Frenette, G., Frick, J., Ganju, V., Geva, R., Gibbs, P., Granetto, C., Hammel, P.,	Age in years, median (range) SIRT+chemotherapy 63 (28-90) Chemotherapy 63 (23-89) Male sex, n (%) SIRT+chemotherapy 363 (66) Chemotherapy 361 (66) WHO performance status, n (%) 0 SIRT+chemotherapy 354 (64) Chemotherapy 347 (63) 1 SIRT+chemotherapy 198 (36) Chemotherapy 200 (36) Primary tumour site, n (%) Colon SIRT+chemotherapy 421 (76) Chemotherapy 392 (71) Rectum SIRT+chemotherapy 116 (21) Chemotherapy 137 (25) Primary tumour in situ, n (%) SIRT+chemotherapy 278 (50) Chemotherapy 302 (55) Previous adjuvant chemotherapy, n (%) SIRT+chemotherapy 31 (6) Chemotherapy 28 (5) Synchronous metastases, n (%) SIRT+chemotherapy 483 (87) Chemotherapy 475 (87) Extrahepatic disease, n (%) SIRT+chemotherapy 199 (36) Chemotherapy 191 (35)	The oxaliplatin dose was reduced from 85 mg/m² to 60 mg/m² for three cycles from the cycle coinciding with SIRT administration and for two cycles thereafter. Systemic FOLFOX chemotherapy: In FOXFIRE trial - oxaliplatin modified de Gramont chemotherapy (85 mg/m² oxaliplatin infusion over 2 h, L-leucovorin 175 mg or D,L-leucovorin 350 mg infusion over 2 h, and 400 mg/m² bolus fluorouracil followed by a 2400 mg/m² continuous fluorouracil infusion over 46 h) for 12 cycles. Each cycle lasted for 14 days. In SIRFLOX and FOXFIRE-Global trials - modified FOLFOX6 (85 mg/m² oxaliplatin infusion over 2 h, 200 mg leucovorin, and 400 mg/m² bolus fluorouracil followed by a 2400 mg/m² continuous fluorouracil infusion over 46 h) continuing cycles until disease progression or dose-limiting toxicity. Each cycle lasted for 14 days. Biological agents	were equal numbers of patients in each treatment group, then patients were allocated to each treatment with a probability of 0.5. The first 30 treatments were allocated using (simple) block randomisation (using variable block sizes of 2, 4, and 6 in a ratio of 1:2:1). In SIRFLOX and FOXFIRE-Global, an imbalance window of 5 was used; if the treatment imbalance between the two groups was less than 5, the treatment was randomly allocated. If the treatment imbalance reached 5, the next treatment allocation was forced to reduce the imbalance." In FOXFIRE trial, a computer-based randomisation was done centrally at the Oncology Clinical Trials Office. In SIRFLOX and FOXFIRE-Global trials, randomisation was done centrally at the National Health and Medical Research Council	Median survival time SIRT + chemotherapy 22.6 months 95% CI 21.0 to 24.5 months Chemotherapy 23.3 months 95% CI 21.8 to 24.7 months Overall survival, subgroups: WHO performance status 0 SIRT + chemotherapy 265/354 Chemotherapy 249/347 HR 1.03 95% CI 0.86 to 1.22 WHO performance status 1 SIRT + chemotherapy 166/198 Chemotherapy 162/200 HR 1.07 95% CI 0.86 to 1.32 Synchronous disease SIRT + chemotherapy 380/483 Chemotherapy 359/475 HR 1.02 95% CI 0.89 to 1.18 Metachronous disease SIRT + chemotherapy 50/68 Chemotherapy 51/71 HR 0.99 95% CI 0.66 to 1.48	Incomplete outcome data: low risk Reporting bias Selective reporting: low risk Other bias Other sources of bias: -

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Heching, N., Hendlisz, A., Hendrickx, K., Holtzman, M., Issacs, R., Iyer, R., Jackson, C., Kaiser, A., Kaubisch, A., Kim, Y. H., Kroning, H., Liang, J. T., Lim, L., Limentani, S., Liu, J. H., Louafi, S., de Man, M., Masi, G., Matos, M., Monsaert, E., Mosconi, S., Nott, L., Numico, G., O'Donnell, A., Peeters, M., Polus, M., Pracht, M., Ratner, L., Rebischung, C., Sae-Won, H., Sanchez, F., Shani, A., Sharma, N., Singh, M., Singhal, N., Smith, D., Stoltzfus, P., Strickland, A., Taieb, J., Tan, I., Terrebonne, E., Tichler, T., Trogu, A., Underhill, C., Vera-Garcia, R., Walpole, E., Wang, E., Westcott, M., van Hazel, G., Sharma, R. A., 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, The Lancet Oncology, 18, 1159-1171, 2017 **Ref Id** 850602 **Country/ies where the study was carried out** Australia, Belgium, France, Germany, Israel, Italy, New	Extent of liver involvement >25%, n (%) SIRT+chemotherapy 179 (32) Chemotherapy 168 (31) Intention to treat with biological agents, n (%) SIRT+chemotherapy 298 (54) Chemotherapy 299 (54) **Inclusion criteria** Inclusion/exclusion criteria were similar between the three trials but not identical. 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; life expectancy ≥3 months **Exclusion criteria** Ascites; cirrhosis; portal hypertension; thrombosis of the main portal vein; peripheral neuropathy grade 1 or worse	The addition of anti-VEGF or anti-EGFR treatments was at the discretion of the treating physician and doses prescribed were according to local policy at the treating centre. In FOXFIRE trial, patients could receive anti-VEGF (e.g. bevacizumab) or anti-EGFR (e.g. cetuximab) from cycle 1 in the FOLFOX alone group and from cycle 7 onwards in the SIRT + FOLFOX group. In SIRFLOX and FOXFIRE-Global trials, patients could receive bevacizumab from cycle 1 in the FOLFOX alone group and from cycle 4 onwards in the SIRT + FOLFOX group.	Clinical Trials Centre via an interactive voice response system. Follow-up/outcomes CT scan every 8–12 weeks until hepatic progression. Follow-up included clinical assessment; CT of chest, abdomen, and pelvis. "Scans were independently reviewed by Pharmtrace (Berlin, Germany) for overall and hepatic progression in FOXFIRE using Response Evaluation Criteria in Solid Tumors (RECIST; version 1.0) and in SIRFLOX with RECIST (version 1.0) with minor modifications. Independent reviews were not done in FOXFIRE-Global. We assessed all patients for suitability for liver resection at 6 months. After protocol therapy, patients could receive any subsequent treatment as best available care determined by the treating physician. All patients were followed up until death or for a minimum of 2 years."	Quality of life (EQ-5D-3L), mean utility value (scale 0-1, better indicated by higher value) Difference between groups (SIRT + chemotherapy minus chemotherapy), baseline adjusted At 2-3 months -0.021 95% CI -0.04 to -0.001, p=0.038 (SIRT + chemotherapy n=431, chemotherapy n=417) At 6 months -0.019 95% CI -0.045 to 0.007, p=0.144 (SIRT + chemotherapy n=260, chemotherapy n=247) At 12 months -0.023 95% CI -0.050 to 0.004, p=0.096 (SIRT + chemotherapy n=253, chemotherapy n=215) At 24 months -0.013 95% CI -0.069 to 0.044, p=0.664 (SIRT + chemotherapy n=85, chemotherapy n=74)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Zealand, Portugal, South Korea, Singapore, Spain, Taiwan, UK, US **Study type** A combined analysis of 3 multicentre, randomised, phase III trials (FOXFIRE [ISRCTN83867919], SIRFLOX [NCT00724503] and FOXFIRE-Global [NCT01721954] trials) **Aim of the study** To evaluate "the efficacy of combining first-line chemotherapy with SIRT using yttrium-90 resin microspheres in patients with metastatic colorectal cancer with liver metastases". **Study dates** Oct 11 2006 to Dec 23 2014 **Source of funding** Sirtex Medical (company producing SIR-Spheres® Y-90 resin microspheres); University of Oxford.			Health related quality-of-life was assessed during clinic visits by a generic quality of life instrument EQ-5D-3L at baseline, between second and third month after randomisation, at 6 and 12 months and once a year up to 5 years. Primary endpoint of the combined analysis was overall survival (time from randomisation to death from any cause). Secondary endpoints included progression-free survival (time from randomisation to radiological progression or death from any cause), liver-specific progression-free survival (time from randomisation to radiological hepatic progression), health-related quality of life, tumour response, liver resection rate, and adverse events. Statistical analysis Efficacy analysis was done on bases of intention-to-treat. Overall survival and progression-free survival for each trial was analysed using	Progression-free survival, median 43.3. months of follow-up (event is radiological progression or death from any cause) SIRT + chemotherapy 474/554 Chemotherapy 467/549 HR 0.90 95% CI 0.79 to 1.02, p=0.11 Median progression-free survival time SIRT + chemotherapy 11.0 months 95% CI 10.2 to 11.8 months Chemotherapy 10.3 months 95% CI 9.7 to 10.9 months Treatment-related mortality SIRT + chemotherapy 8/571 Chemotherapy 3/507 Resectability SIRT + chemotherapy 94/554 Chemotherapy 88/549 OR 1.07 95% CI 0.78 to 1.48, p=0.67 Grade 3 or 4 adverse events (up to 28 days after the end of protocol chemotherapy or in the first 7 months after	

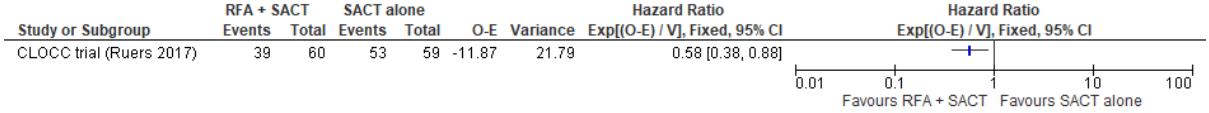
Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
			Kaplan-Meier survival curves, unadjusted log-rank tests, and Cox proportional hazards survival models. "HRs for overall survival and progression-free survival from the individual trials were combined using a two-stage, fixed-effect, inverse-variance weighted individual participant data meta-analysis approach."	randomisation, whichever was earlier) SIRT + chemotherapy 365/507 Chemotherapy 369/571	

5-FU: fluorouracil; ALT: alanine transferase; anti-EGFR: anti epidermal growth factor receptor; anti-VEGF: anti vascular endothelial growth factor; AST: aspartate transaminase; CEA: cardinoembyronic antigen; CI: confidence interval; CT: computer tomography; DEBIRI: drug-eluting beads loaded with irinotecan; ECOG: Eastern Cooperative Oncology Group; EORTC: European Organisation for Research and Treatment of Cancer; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 Items; EQ-5D-3L: EuroQol five dimensions questionnaire, three levels; FLIC: Functional Living Index questionnaire; FOLFIRI: leucovorin (folinic acid), fluorouracil; irinotecan; FOLFOX: leucovorin (folinic acid), fluorouracil, oxaliplatin; FUDR: floxuridine; HAI: hepatic artery infusion; HR: hazard ratio; HRQoL: health-related quality of life; LV: leucovorin (folinic acid); N/A: not applicable; QoL: quality of life; RCT: randomised controlled study; RECIST: Response Evaluation Criteria In Solid Tumors; RFA: radiofrequency ablation; SIRT: selective internal radioation therapy; ULN: upper limit of normal; WHO: World Health Organization

Appendix E – Forest plots

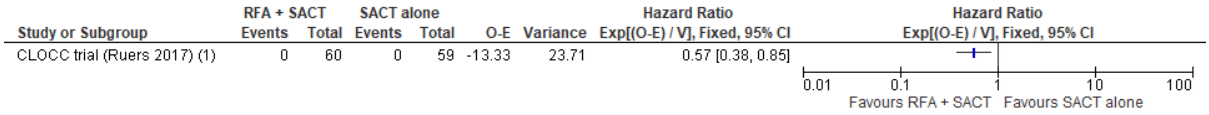
Forest plots for review question: What is the optimal combination and sequence of treatments in patients presenting with metastatic colorectal cancer in the liver not amenable to treatment with curative intent?

Figure 2: Comparison 1: RFA plus SACT versus SACT alone – Overall survival



CI: confidence interval; O-E: observed minus expected; RFA: radiofrequency ablation; SACT: systemic anticancer therapy; V: variance

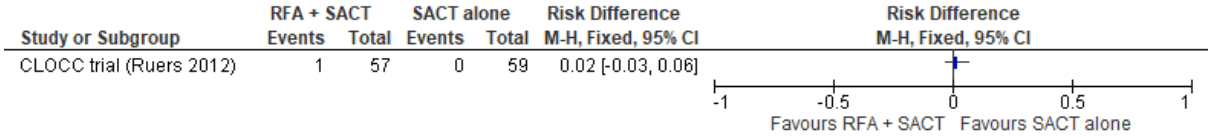
Figure 3: Comparison 1: RFA plus SACT versus SACT alone – Progression-free survival



Footnotes
(1) Number of events not reported.

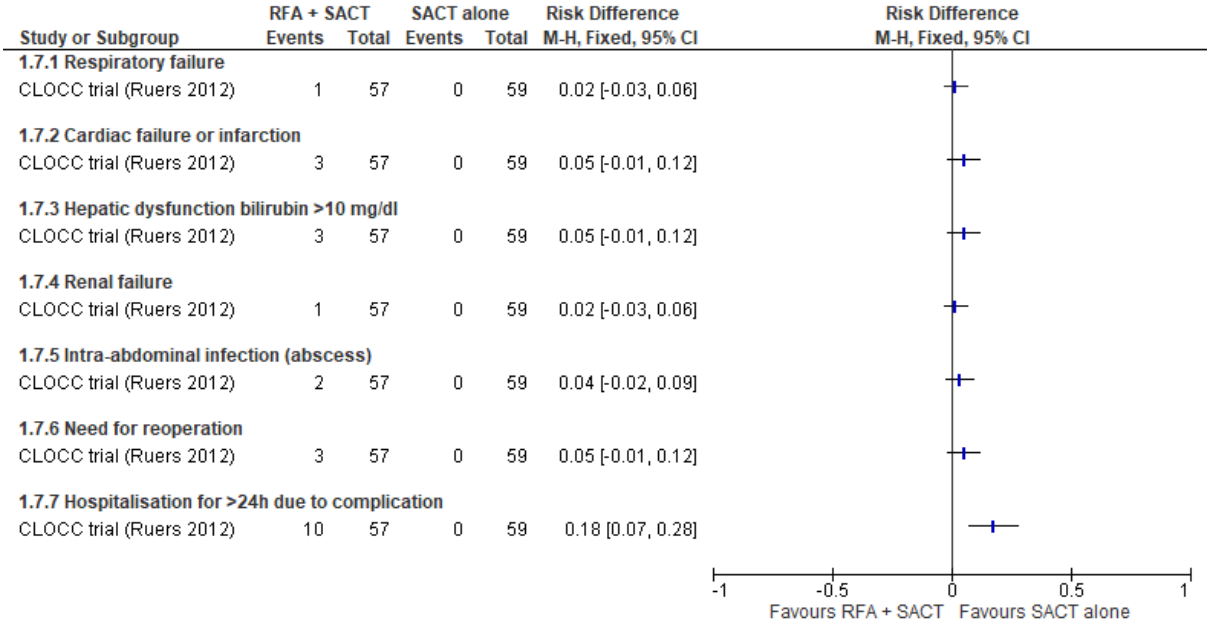
CI: confidence interval; O-E: observed minus expected; RFA: radiofrequency ablation; SACT: systemic anticancer therapy; V: variance

Figure 4: Comparison 1: RFA plus SACT versus SACT alone – Postoperative mortality



CI: confidence interval; M-H: Mantel Haenszel method; RFA: radiofrequency ablation; SACT: systemic anticancer therapy

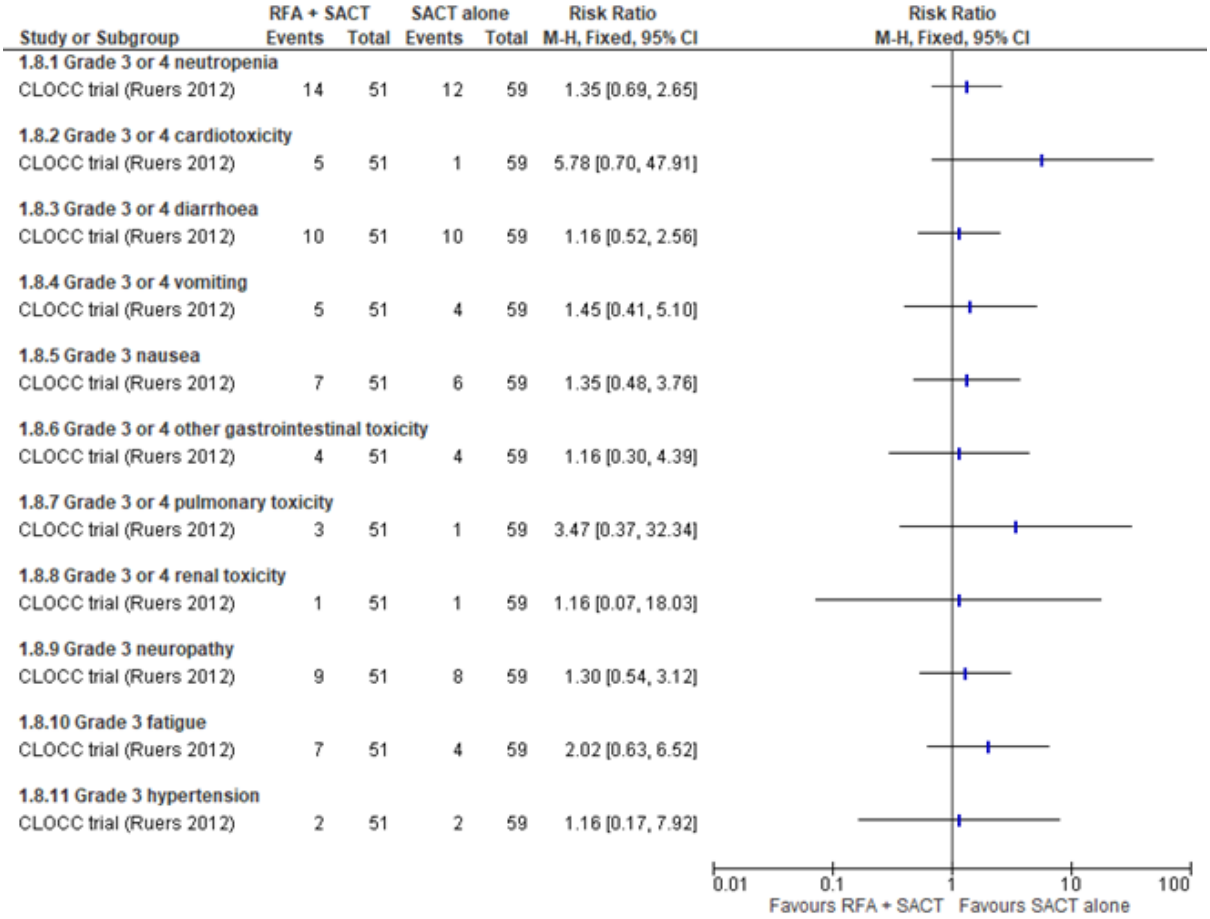
Figure 5: Comparison 1: RFA plus SACT versus SACT alone – Postoperative complications



CI: confidence interval; M-H: Mantel Haenszel method; RFA: radiofrequency ablation; SACT: systemic anticancer therapy

1

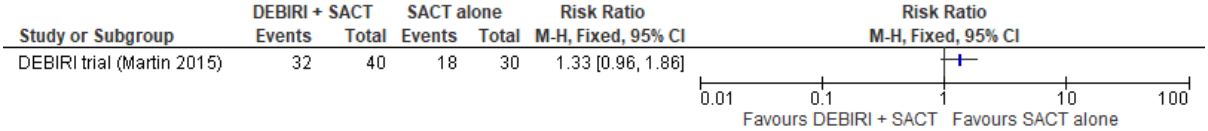
Figure 6: Comparison 1: RFA plus SACT versus SACT alone – Grade 3 or 4 adverse events due to chemotherapy



CI: confidence interval; M-H: Mantel Haenszel method; RFA: radiofrequency ablation; SACT: systemic anticancer therapy

1

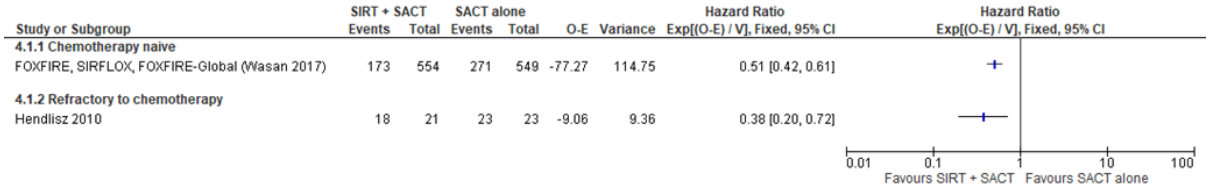
Figure 7: Comparison 2: DEBIRI plus SACT versus SACT alone – Grade 3 or 4 adverse events



CI: confidence interval; DEBIRI: drug-eluting beads loaded with irinotecan; M-H: Mantel Haenszel method; SACT: systemic anticancer therapy

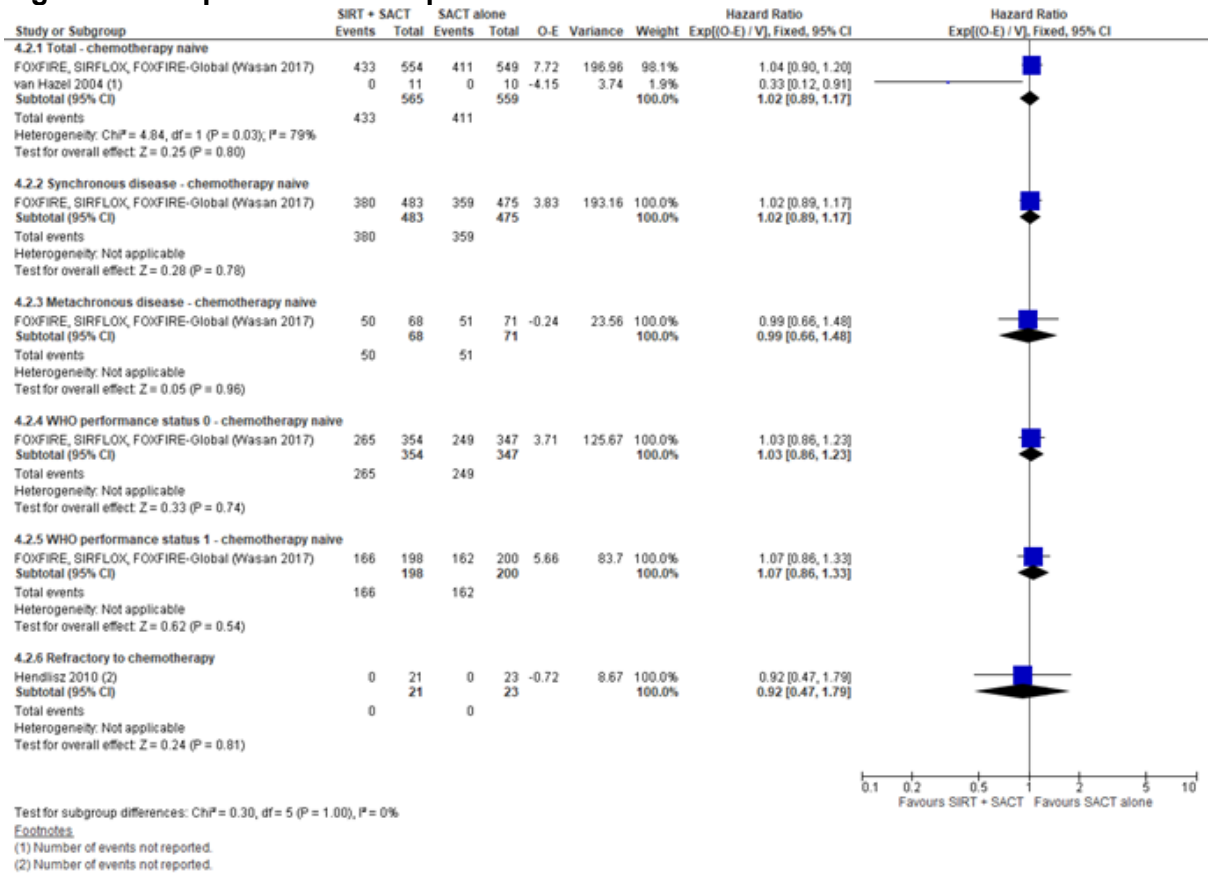
2

Figure 8: Comparison 4: SIRT plus SACT versus SACT alone – Liver progression-free survival



CI: confidence interval; O-E: observed minus expected; SACT: systemic anticancer therapy; SIRT: selective internal radiation therapy; V: variance

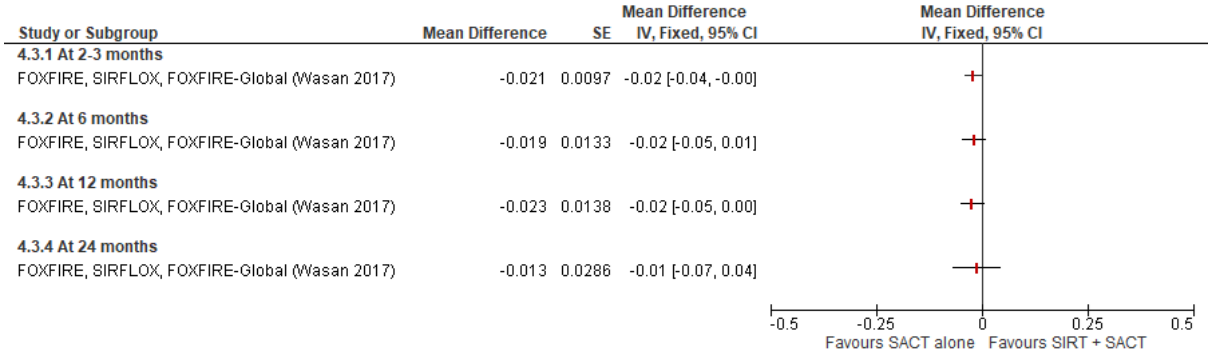
Figure 9: Comparison 4: SIRT plus SACT versus SACT alone – Overall survival



CI: confidence interval; O-E: observed minus expected; SACT: systemic anticancer therapy; SIRT: selective internal radiation therapy; V: variance

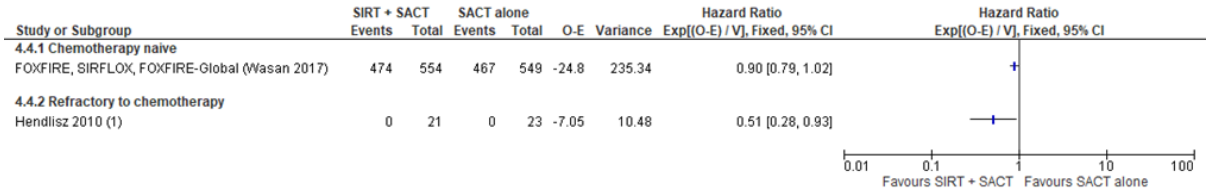
1

Figure 10: Comparison 4: SIRT plus SACT versus SACT alone – Health-related quality of life (EQ-5D-3L; scale 0-1; better indicated by higher values)



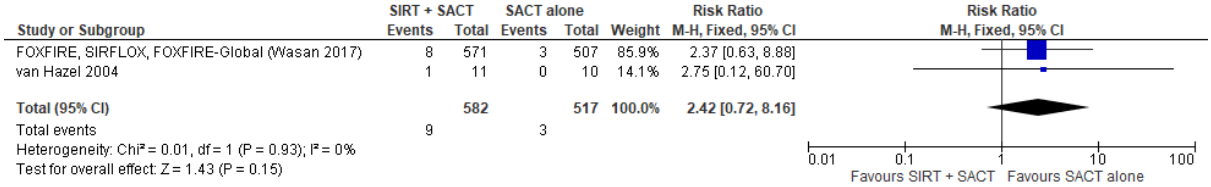
CI: confidence interval; EQ-5D-3L: EuroQol five dimensions questionnaire, three levels; IV: inverse variance; SACT: systemic anticancer therapy; SE: standard error; SIRT: selective internal radiation therapy

Figure 11: Comparison 4: SIRT plus SACT versus SACT alone – Progression-free survival



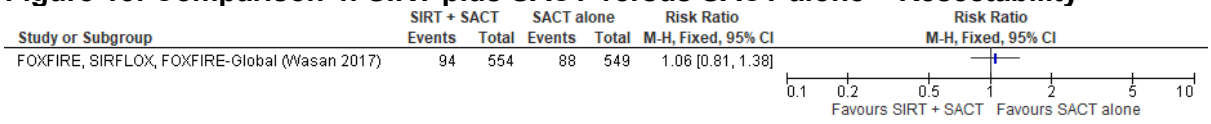
CI: confidence interval; O-E: observed minus expected; SACT: systemic anticancer therapy; SIRT: selective internal radiation therapy; V: variance

Figure 12: Comparison 4: SIRT plus SACT versus SACT alone – Treatment-related mortality



CI: confidence interval; M-H: Mantel-Haenszel method; SACT: systemic anticancer therapy; SIRT: selective internal radiation therapy

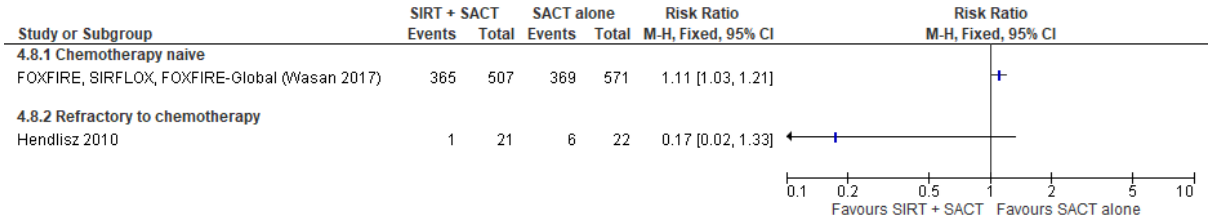
Figure 13: Comparison 4: SIRT plus SACT versus SACT alone – Resectability



CI: confidence interval; M-H: Mantel-Haenszel method; SACT: systemic anticancer therapy; SIRT: selective internal radiation therapy

1

Figure 14: Comparison 4: SIRT plus SACT versus SACT alone – Grade 3 or 4 adverse events



CI: confidence interval; M-H: Mantel-Haenszel method; SACT: systemic anticancer therapy; SIRT: selective internal radiation therapy

1

Appendix F – GRADE tables

GRADE tables for review question: What is the optimal combination and sequence of treatments in patients presenting with metastatic colorectal cancer in the liver not amenable to treatment with curative intent?

Table 5: Clinical evidence profile for comparison 1: RFA plus SACT versus SACT alone for metastatic colorectal cancer in the liver not amenable to treatment with curative intent

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RFA + SACT	SACT alone	Relative (95% CI)	Absolute	Quality	Importance
Liver progression-free survival												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL
Overall survival (follow-up median 9.7 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	39/60 (65%)	53/59 (89.8%)	HR 0.58 (0.38 to 0.88)	At 3 years chemotherapy alone 55%[2], RFA + chemotherapy 71% (59% to 80%)	MODERATE	CRITICAL
Health-related quality of life (EORTC QLQ-C30)												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[1]	none	60	59	-	"HRQoL scales were impaired after RFA. … …mean global QoL dropped by 27 points. However, recovery to a level at ~10 points below baseline was achieved before the start of systemic treatment (4–8 weeks after	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RFA + SACT	SACT alone	Relative (95% CI)	Absolute		
										RFA). Thereafter, HRQoL scores were similar in both treatment groups, although the limited sample size limits definite conclusions on HRQoL."		
Progression-free survival												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	60	59	HR 0.57 (0.38 to 0.86)	At 3 years chemotherapy alone 12%[2], RFA + chemotherapy 30% (16% to 45%)	MODERATE	IMPORTANT
Postoperative mortality												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	1/57 (1.8%)	0/59	Risk difference 2% (-3% to 6%)	20 more per 1000 (from 30 less to 60 more)	MODERATE	IMPORTANT
Resectability												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Postoperative complications - Respiratory failure												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	1/57 (1.8%)	0/59	Risk difference 2% (-3% to 6%)	20 more per 1000 (from 30 less to 60 more)	MODERATE	IMPORTANT
Postoperative complications - Cardiac failure or infarction												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	3/57 (5.3%)	0/59	Risk difference 5% (-1% to 12%)	50 more per 1000 (from 10 less to 120 more)	MODERATE	IMPORTANT
Postoperative complications - Hepatic dysfunction bilirubin >10 mg/dl												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RFA + SACT	SACT alone	Relative (95% CI)	Absolute		
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	3/57 (5.3%)	0/59	Risk difference 5% (-1% to 12%)	50 more per 1000 (from 10 less to 120 more)	MODERATE	CRITICAL
Postoperative complications - Renal failure												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	1/57 (1.8%)	0/59	Risk difference 2% (-3% to 6%)	20 more per 1000 (from 30 less to 60 more)	MODERATE	IMPORTANT
Postoperative complications - Intra-abdominal infection (abscess)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	2/57 (3.5%)	0/59	Risk difference 4% (-2% to 9%)	40 more per 1000 (from 20 less to 90 more)	MODERATE	IMPORTANT
Postoperative complications - Need for reoperation												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	3/57 (5.3%)	0/59	Risk difference 5% (-1% to 12%)	50 more per 1000 (from 10 less to 120 more)	MODERATE	IMPORTANT
Postoperative complications - Hospitalisation for >24h due to complication												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	10/57 (17.5%)	0/59	Risk difference 18% (7% to 28%)	180 more per 1000 (from 70 less to 280 more)	MODERATE	IMPORTANT
Grade 3 or 4 neutropenia												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	14/51 (27.5%)	12/59 (20.3%)	RR 1.35 (0.69 to 2.65)	71 more per 1000 (from 63 fewer to 336 more)	MODERATE	IMPORTANT
Grade 3 or 4 cardiotoxicity												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	5/51 (9.8%)	1/59 (1.7%)	RR 5.78 (0.7 to 47.91)	81 more per 1000 (from 5 fewer to 795 more)	MODERATE	IMPORTANT
Grade 3 or 4 diarrhoea												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RFA + SACT	SACT alone	Relative (95% CI)	Absolute		
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	10/51 (19.6%)	10/59 (16.9%)	RR 1.16 (0.52 to 2.56)	27 more per 1000 (from 81 fewer to 264 more)	MODERATE	IMPORTANT
Grade 3 or 4 vomiting												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	5/51 (9.8%)	4/59 (6.8%)	RR 1.45 (0.41 to 5.1)	31 more per 1000 (from 40 fewer to 278 more)	MODERATE	IMPORTANT
Grade 3 nausea												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	7/51 (13.7%)	6/59 (10.2%)	RR 1.35 (0.48 to 3.76)	36 more per 1000 (from 53 fewer to 281 more)	MODERATE	IMPORTANT
Grade 3 or 4 other gastrointestinal toxicity												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	4/51 (7.8%)	4/59 (6.8%)	RR 1.16 (0.3 to 4.39)	11 more per 1000 (from 47 fewer to 230 more)	MODERATE	IMPORTANT
Grade 3 or 4 pulmonary toxicity												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	3/51 (5.9%)	1/59 (1.7%)	RR 3.47 (0.37 to 32.34)	42 more per 1000 (from 11 fewer to 531 more)	MODERATE	IMPORTANT
Grade 3 or 4 renal toxicity												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	1/51 (2%)	1/59 (1.7%)	RR 1.16 (0.07 to 18.03)	3 more per 1000 (from 16 fewer to 289 more)	MODERATE	IMPORTANT
Grade 3 neuropathy												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	9/51 (17.6%)	8/59 (13.6%)	RR 1.3 (0.54 to 3.12)	41 more per 1000 (from 62 fewer to 287 more)	MODERATE	IMPORTANT
Grade 3 fatigue												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RFA + SACT	SACT alone	Relative (95% CI)	Absolute		
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	7/51 (13.7%)	4/59 (6.8%)	RR 2.02 (0.63 to 6.52)	69 more per 1000 (from 25 fewer to 374 more)	MODERATE	IMPORTANT
Grade 3 hypertension												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	2/51 (3.9%)	2/59 (3.4%)	RR 1.16 (0.17 to 7.92)	5 more per 1000 (from 28 fewer to 235 more)	MODERATE	IMPORTANT

CI: confidence interval; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 Items; HR: hazard ratio; HRQoL: health-related quality of life; QoL: quality of life; RFA: radiofrequency ablation; RR: relative risk; SACT: systemic anticancer therapy
1 Quality of evidence downgraded by 1 because of imprecision of the effect estimate (<300 events for dichotomous outcomes or sample size <400 for continuous outcomes)
2 Survival percentage at 3 years in the control group estimated using 3-year survival data from Ruers 2017
3 Quality of evidence downgraded by 1 because of risk of bias due to no blinding
4 Relative effect not estimable due to 0 events in control arm

Table 6: Clinical evidence profile for comparison 2: DEBIRI plus SACT versus SACT alone for metastatic colorectal cancer in the liver not amenable to treatment with curative intent

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DEBIRI + FOLFOX + bevacizumab	FOLFOX + bevacizumab	Relative (95% CI)	Absolute		
Liver progression-free survival (follow-up median 24 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	41	30	Not reported or estimable	Median time to liver progression: DEBIRI + FOLFOX + Bevacizumab 17 months (range 12-23 months), FOLFOX + Bevacizumab 12 months (11-24 months), p=0.05	MODERATE	CRITICAL
Overall survival												

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**DEBIRI + FOLFOX + bevacizumab**	**FOLFOX + bevacizumab**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
0	No evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL
Overall quality of life												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL
Progression-free survival (follow-up median 24 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	41	30	Not reported or estimable	Median time to progression: DEBIRI + FOLFOX + Bevacizumab 12 months (range 9-15.4 months), FOLFOX + Bevacizumab 15 months (10.4-20 months), p=0.18	MODERATE	IMPORTANT
Treatment-related mortality												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Resectability												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Grade 3 or 4 adverse events												
1	randomised trials	no serious	no serious inconsistency	no serious indirectness	serious[1]	none	32/40 (80%)	18/30 (60%)	RR 1.33 (0.96 to 1.86)	198 more per 1000 (from 24 fewer to 516 more)	MODERATE	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DEBIRI + FOLFOX + bevacizumab	FOLFOX + bevacizumab	Relative (95% CI)	Absolute		
		risk of bias										

CI: confidence interval; DEBIRI: drug-eluting beads loaded with irinotecan; FOLFOX: leucovorin (folinic acid), fluorouracil, oxaliplatin; RR: relative risk
1 Quality of evidence downgraded by 1 because of imprecision of the effect estimate (<300 events for dichotomous outcomes or sample size <400 for continuous outcomes)

Table 7: Clinical evidence profile for comparison 3: DEBIRI versus SACT for metastatic colorectal cancer in the liver not amenable to treatment with curative intent

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DEBIRI	FOLFIRI	Relative (95% CI)	Absolute		
Liver progression-free survival (follow-up median 50 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	36	38	Not reported or estimable	Median time to liver progression: DEBIRI 7 months, FOLFIRI 4 months, p=0.006	MODERATE	CRITICAL
Overall survival (follow-up median 50 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	36	38	Not reported or estimable	Median overall survival time: DEBIRI 22 months (95% CI 21 to 23 months), FOLFIRI 15 months (95% CI 12 to 18 months), p=0.031	MODERATE	CRITICAL
Quality of life (ESAS)												

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**DEBIRI**	**FOLFIRI**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	36	38	-	"...physical functioning of the DEBIRI patients was better than of those receiving systemic therapy at 1 (p=0.038) and 3 months (p=0.025); this was also performed at 8 months (p=0.025)."	LOW	CRITICAL
Progression-free survival (follow-up median 50 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	36	38	Not reported or estimable	Median time to disease progression: DEBIRI 7 months (95% CI 3 to 11 months), FOLFIRI 4 months (95% CI 3 to 5 months), p=0.006	MODERATE	IMPORTANT
Treatment-related mortality												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Resectability												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	IMPORTANT
Grade 3 or 4 adverse event												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DEBIRI	FOLFIRI	Relative (95% CI)	Absolute		
0	No evidence available	-	-	-	-	-	-	-	-	-	-	IMPORTANT

CI: confidence interval; DEBIRI: drug-eluting beads loaded with irinotecan; ESAS: Edmonton Symptom Assessment System; FOLFIRI: leucovorin (folinic acid), fluorouracil, irinotecan; RR: relative risk
1 Quality of evidence downgraded by 1 because of imprecision of the effect estimate (<300 events for dichotomous outcomes or sample size <400 for continuous outcomes)
2 Quality of evidence downgraded by 1 because of risk of bias due to no blinding

Table 8: Clinical evidence profile for comparison 4: SIRT plus SACT versus SACT alone for metastatic colorectal cancer in the liver not amenable to treatment with curative intent

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SIRT + SACT	SACT alone	Relative (95% CI)	Absolute		
Liver progression - chemotherapy-naïve												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	173/554 (31.2%)	271/549 (49.4%)	HR 0.51 (0.42 to 0.61)	At 3 years chemotherapy alone 55%[1], SIRT + chemotherapy 34% (29% to 39%)	HIGH	CRITICAL
Liver progression-free survival - Refractory to chemotherapy												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	18/21 (85.7%)	23/23 (100%)	HR 0.38 (0.2 to 0.72)	Not reported or estimable	MODERATE	CRITICAL
Overall survival - Total – chemotherapy-naïve												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SIRT + SACT	SACT alone	Relative (95% CI)	Absolute		
4	randomised trials	no serious risk of bias	serious[3]	no serious indirectness	no serious imprecision	none	565	559	HR 1.02 (0.89 to 1.17)	At 3 years chemotherapy alone 25%[1], SIRT + chemotherapy 24% (20% to 29%)	MODERATE	CRITICAL
Overall survival - Synchronous disease - chemotherapy naive												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	380/483 (78.7%)	359/475 (75.6%)	HR 1.02 (0.89 to 1.17)	Not reported or estimable	HIGH	CRITICAL
Overall survival - Metachronous disease - chemotherapy naive												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	50/68 (73.5%)	51/71 (71.8%)	HR 0.99 (0.66 to 1.48)	Not reported or estimable	MODERATE	CRITICAL
Overall survival - WHO performance status 0 - chemotherapy naive												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	265/354 (74.9%)	249/347 (71.8%)	HR 1.03 (0.86 to 1.23)	Not reported or estimable	HIGH	CRITICAL
Overall survival - WHO performance status 1 - chemotherapy naive												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	166/198 (83.8%)	162/200 (81%)	HR 1.07 (0.86 to 1.33)	Not reported or estimable	HIGH	CRITICAL
Overall survival - Refractory to chemotherapy												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	21	23	HR 0.92 (0.47 to 1.79)	Not reported or estimable	MODERATE	CRITICAL
Health-related quality of life (EQ-5D-3L, scale 0-1, better indicated by higher values) - At 2-3 months (range of scores: 0-1; Better indicated by higher values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SIRT + SACT	SACT alone	Relative (95% CI)	Absolute		
3	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	431	417	-	MD 0.02 lower (0.04 lower to 0 higher)	MODERATE	CRITICAL
Health-related quality of life (EQ-5D-3L, scale 0-1, better indicated by higher values) - At 6 months (range of scores: 0-1; Better indicated by higher values)												
3	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	260	247	-	MD 0.02 lower (0.05 lower to 0.01 higher)	MODERATE	CRITICAL
Health-related quality of life (EQ-5D-3L, scale 0-1, better indicated by higher values) - At 12 months (range of scores: 0-1; Better indicated by higher values)												
3	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	253	215	-	MD 0.02 lower (0.05 lower to 0 higher)	MODERATE	CRITICAL
Health-related quality of life (EQ-5D-3L, scale 0-1, better indicated by higher values) - At 24 months (range of scores: 0-1; Better indicated by higher values)												
3	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[2]	none	85	74	-	MD 0.01 lower (0.07 lower to 0.04 higher)	LOW	CRITICAL
Quality of life (FLIC)												
1	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[2]	none	11	10	-	"Changes in the quality of life were almost identical in both arms (p=0.96)."	LOW	CRITICAL
Progression-free survival - Chemotherapy naive												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SIRT + SACT	SACT alone	Relative (95% CI)	Absolute		
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	474/554 (85.6%)	467/549 (85.1%)	HR 0.9 (0.79 to 1.02)	At 3 years chemotherapy alone 11%[1], SIRT + chemotherapy 14% (11% to 18%)	HIGH	IMPORTANT
Progression-free survival - Refractory to chemotherapy												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	21	23	HR 0.51 (0.28 to 0.93)	Not reported or estimable	MODERATE	IMPORTANT
Treatment-related mortality												
4	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	9/582 (1.5%)	3/517 (0.58%)	RR 2.42 (0.72 to 8.16)	8 more per 1000 (from 2 fewer to 42 more)	MODERATE	IMPORTANT
Resectability												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	94/554 (17%)	88/549 (16%)	RR 1.06 (0.81 to 1.38)	10 more per 1000 (from 30 fewer to 61 more)	MODERATE	IMPORTANT
Grade 3 or 4 adverse events - Chemotherapy naive												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	365/507 (72%)	369/571 (64.6%)	RR 1.11 (1.03 to 1.21)	71 more per 1000 (from 19 more to 136 more)	HIGH	IMPORTANT
Grade 3 or 4 adverse events - Refractory to chemotherapy												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	1/21 (4.8%)	6/22 (27.3%)	RR 0.17 (0.02 to 1.33)	226 fewer per 1000 (from 267	MODERATE	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SIRT + SACT	SACT alone	Relative (95% CI)	Absolute		
										fewer to 90 more)		

CI: confidence interval; EQ-5D-3L: EuroQol five dimensions questionnaire, three levels; FLIC: Functional Living Index questionnaire; HR: hazard ratio; MD: mean difference; RR: relative risk; SACT: systemic anticancer therapy; SIRT: selective internal radiation therapy; WHO: World Health Organization

1 Survival percentage at 3 years in the control group estimated using 3-year survival data from Wasan 2017

2 Quality of evidence downgraded by 1 because of imprecision of the effect estimate (<300 events for dichotomous outcomes or sample size <400 for continuous outcomes)

3 Quality of evidence downgraded by 1 because of heterogeneity

4 Quality of evidence downgraded by 1 because of risk of bias because of no blinding

Appendix G – Economic evidence study selection

Economic evidence study selection for review question: What is the optimal combination and sequence of treatments in patients presenting with metastatic colorectal cancer in the liver not amenable to treatment with curative intent?

A global search of economic evidence was undertaken for all review questions in this guideline. See Supplement 2 for further information.

Appendix H – Economic evidence tables

Economic evidence tables for review question: What is the optimal combination and sequence of treatments in patients presenting with metastatic colorectal cancer in the liver not amenable to treatment with curative intent?

No economic evidence was identified which was applicable to this review question.

Appendix I – Economic evidence profiles

Economic evidence profiles for review question: What is the optimal combination and sequence of treatments in patients presenting with metastatic colorectal cancer in the liver not amenable to treatment with curative intent?

No economic evidence was identified which was applicable to this review question.

Appendix J – Economic analysis

Economic evidence analysis for review question: What is the optimal combination and sequence of treatments in patients presenting with metastatic colorectal cancer in the liver not amenable to treatment with curative intent?

Economic analysis was planned for this topic in line with the economic plan but is not presented as part of this evidence review. The planned model investigated the addition of radiofrequency ablation (RFA) to systemic anticancer therapy (SACT) compared to SACT alone. It was not possible to get consensus for the structure, inputs and structure, across the committee, for use in an economic model that was both meaningful for making recommendations and had concordance with the identified evidence. This was largely as a result of only 1 trial being identified for this comparison by the accompanying clinical evidence review (Ruers 2017). This study reported outcomes from a trial conducted between 2002 and 2007. The committee highlighted that the differentiation of resectable and unresectable disease, and curable and incurable have changed and are changing as techniques evolve. Consequently, a significant proportion of this trial population would now be eligible for treatments with curative intent either through resection or other treatment. Patients receiving the considered treatments today would likely be older and less fit. Whilst the opinion of the committee was that the addition of RFA would still be beneficial for overall and progression free survival, in line with the low HR estimates from Ruers 2017, it was difficult to estimate the direction or magnitude of any changes in the trial outcomes for use in an economic model as the result of this difference in the patient group.

Given that RFA is not prohibitively expensive and widely available it was likely any economic model would conclude it as a cost effective use of NHS resources when QALYs were valued at £20,000 each.

Appendix K – Excluded studies

Excluded clinical studies for review question: What is the optimal combination and sequence of treatments in patients presenting with metastatic colorectal cancer in the liver not amenable to treatment with curative intent?

Table 9: Excluded studies and reasons for their exclusion

Study	Reason for exclusion
Radiofrequency ablation for the treatment of colorectal metastases in the liver (Structured abstract), Health Technology Assessment Database, 2, 2004	NICE interventional procedure guidance
Selective internal radiation therapy for colorectal metastases in the liver (Structured abstract), Health Technology Assessment Database, 2, 2004	NICE interventional procedure guidance
Abbott, D. E., Cantor, S. B., Hu, C. Y., Aloia, T. A., You, Y. N., Nguyen, S., Chang, G. J. Optimizing clinical and economic outcomes of surgical therapy for patients with colorectal cancer and synchronous liver metastases, Journal of the American College of Surgeons, 215, 262-70, 2012	Population not relevant. Included in review D2a
Abbott, A. M., Parsons, H. M., Tuttle, T. M., Jensen, E. H., Short-term outcomes after combined colon and liver resection for synchronous colon cancer liver metastases: A population study, Annals of Surgical Oncology, 20, 139-147, 2013	Comparison group population not relevant
Abbott, D. E., Sohn, V. Y., Hanseman, D., Curley, S. A., Cost-effectiveness of simultaneous resection and RFA versus 2-stage hepatectomy for bilobar colorectal liver metastases, Journal of Surgical Oncology, 109, 516-520, 2014	Comparison group not relevant
Abdalla, E. K., Vauthey, J. N., Ellis, L. M., Ellis, V., Pollock, R., Broglio, K. R., Hess, K., Curley, S. A., Dale, P. S., Howard, R. J., Henderson, J. M., Bolton, J. S., Stain, S. C., Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases, Annals of Surgery, 239, 818-827, 2004	Unclear if multivariate analysis was done and what variables were included in the model
Abelson, J. S., Michelassi, F., Sun, T., Mao, J., Milsom, J., Samstein, B., Sedrakyan, A., Yeo, H. L. Simultaneous Resection for Synchronous Colorectal Liver Metastasis: the New Standard of Care? Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract, 21, 975-82, 2017	Population not relevant. Included in review D2a
Abramson, R. G., Rosen, M. P., Perry, L. J., Brophy, D. P., Raeburn, S. L., Stuart, K. E., Cost-effectiveness of hepatic arterial chemoembolization for colorectal liver metastases refractory to systemic chemotherapy, Radiology, 216, 485-491, 2000	A health economic model, no relevant clinical data
Abreu de Carvalho, L. F., Scuderi, V., Maes, H., Cupo, P., Geerts, B., Van Bockstal, M., Gremonprez, F., Willaert, W., Pattyn, P., Troisi, R., Ceelen, W., Simultaneous Parenchyma-Preserving Liver Resection, Cytoreductive Surgery and Intraperitoneal Chemotherapy for Stage IV Colorectal Cancer, Acta chirurgica Belgica, 115, 261-267, 2015	Case series, no comparison group
Adam, R., Bhangui, P., Poston, G., Mirza, D., Nuzzo, G., Barroso, E., Ijzermans, J., Hubert, C., Ruers, T., Capussotti, L.,	Observation study, RCT evidence exists and prioritised

Ouellet, J. F., Laurent, C., Cugat, E., Colombo, P. E., Milicevic, M., Is perioperative chemotherapy useful for solitary, metachronous, colorectal liver metastases?, Annals of Surgery, 252, 774-787, 2010	
Agcaoglu, O., Aliyev, S., Karabulut, K., El-Gazzaz, G., Aucejo, F., Pelley, R., Siperstein, A. E., Berber, E., Complementary use of resection and radiofrequency ablation for the treatment of colorectal liver metastases: an analysis of 395 patients, World Journal of Surgery, 37, 1333-1339, 2013	Populations are not similar and would not both be candidates for both approaches compared
Aissou, S., Cartier, V., Hamy, A., Plumereau, F., Aube, C., Lermite, E., Radiofrequency in the Management of Colorectal Liver Metastases: A 10-Year Experience at a Single Center, Surgical technology international, XXIX, 99-105, 2016	Populations are not similar and would not both be candidates for both approaches compared
Akinwande, O., Dendy, M., Ludwig, J. M., Kim, H. S., Hepatic intra-arterial injection of irinotecan drug eluting beads (DEBIRI) for patients with unresectable colorectal liver metastases: A systematic review, Surgical Oncology, 26, 268-275, 2017	A systematic review, included studies checked for relevance
Akinwande, O., Martin, R. C., Hepatic Arterial Therapy for First-Line Treatment of Unresectable Colorectal Liver Metastases: What We Know in the Wake of Two Recent Randomized Control Trials, CardioVascular and Interventional Radiology, 40, 315-317, 2017	This article presents summary of two trials, published separately and considered for inclusion individually
Alexandrescu, S., Diaconescu, A., Ionel, Z., Zlate, C., Grigorie, R., Hrehoret, D., Brasoveanu, V., Dima, S., Botea, F., Ionescu, M., Tomescu, D., Droc, G., Fota, R., Croitoru, A., Gramaticu, I., Buica, F., Iacob, R., Gheorghe, C., Herlea, V., Grasu, M., Dumitru, R., Boros, M., Popescu, I., Comparative Analysis between Simultaneous Resection and Staged Resection for Synchronous Colorectal Liver Metastases - A Single Center Experience on 300 Consecutive Patients, Chirurgia (Bucharest, Romania : 1990), 112, 278-288, 2017	Only univariate analysis performed
Ali, S. M., Pawlik, T. M., Rodriguez-Bigas, M. A., Monson, J. R. T., Chang, G. J., Larson, D. W., Timing of Surgical Resection for Curative Colorectal Cancer with Liver Metastasis, Annals of Surgical Oncology, 25, 32-37, 2018	A systematic review, included studies checked for relevance
Aliyev, S., Agcaoglu, O., Aksoy, E., Taskin, H. E., Vogt, D., Fung, J., Siperstein, A., Berber, E., Efficacy of laparoscopic radiofrequency ablation for the treatment of patients with small solitary colorectal liver metastasis, Surgery (United States), 154, 556-562, 2013	Populations are not similar and would not both be candidates for both approaches compared
Aliyev, S., Agcaoglu, O., Taskin, H. E., Aksoy, E., Vogt, D., Fung, J., Siperstein, A., Berber, E., Resection versus laparoscopic radiofrequency thermal ablation of small solitary colorectal liver metastasis, Journal of Surgical Research. Conference: 8th Annual Academic Surgical Congress of the Association for Academic Surgery, AAS and the Society of University Surgeons, SUS. New Orleans, LA United States. Conference Publication:, 179, 2013	Conference abstract
Allen, P. J., Kemeny, N., Jarnagin, W., DeMatteo, R., Blumgart, L., Fong, Y., Importance of response to neoadjuvant chemotherapy in patients undergoing resection of synchronous colorectal liver metastases, Journal of Gastrointestinal Surgery, 7, 109-15; discussion 116-7, 2003	Observational study, RCT evidence exists and prioritised
Aloia, T. A., Fahy, B. N., A decision analysis model predicts the optimal treatment pathway for patients with colorectal cancer	A decision analysis model using existing clinical data, references checked individually

and resectable synchronous liver metastases, Clinical Colorectal Cancer, 7, 197-201, 2008	
Aloia, T. A., Vauthey, J. N., Loyer, E. M., Ribero, D., Pawlik, T. M., Wei, S. H., Curley, S. A., Zorzi, D., Abdalla, E. K., Nagorney, D. M., Dayton, M. T., Schneider, P. D., Bilchik, A. J., McMasters, K. M., Chapman, W. C., Solitary colorectal liver metastasis: Resection determines outcome, Archives of Surgery, 141, 460-467, 2006	Populations are not similar and would not both be candidates for the approaches compared
Aloia, T., Sebagh, M., Plasse, M., Karam, V., Levi, F., Giacchetti, S., Azoulay, D., Bismuth, H., Castaing, D., Adam, R., Liver histology and surgical outcomes after preoperative chemotherapy with fluorouracil plus oxaliplatin in colorectal cancer liver metastases, Journal of Clinical Oncology, 24, 4983-4990, 2006	Observational study, RCT evidence exists and prioritised
Aloysius, M. M., Zaitoun, A. M., Beckingham, I. J., Neal, K. R., Aithal, G. P., Bessell, E. M., Lobo, D. N., The pathological response to neoadjuvant chemotherapy with FOLFOX-4 for colorectal liver metastases: A comparative study, Virchows Archiv, 451, 943-948, 2007	Observational study, RCT evidence exists and prioritised
Ambiru, S., Miyazaki, M., Ito, H., Nakagawa, K., Shimizu, H., Nakajima, N., Adjuvant regional chemotherapy after hepatic resection for colorectal metastases, British Journal of Surgery, 86, 1025-1031, 1999	Intervention/comparison not relevant
An, H. J., Yu, C. S., Yun, S. C., Kang, B. W., Hong, Y. S., Lee, J. L., Ryu, M. H., Chang, H. M., Park, J. H., Kim, J. H., Kang, Y. K., Kim, J. C., Kim, T. W., Adjuvant chemotherapy with or without pelvic radiotherapy after simultaneous surgical resection of rectal cancer with liver metastases: Analysis of prognosis and patterns of recurrence, International Journal of Radiation Oncology Biology Physics, 84, 73-80, 2012	Intervention/comparison not relevant
Andreou, A., Kopetz, S., Maru, D. M., Chen, S. S., Zimmitti, G., Brouquet, A., Shindoh, J., Curley, S. A., Garrett, C., Overman, M. J., Aloia, T. A., Vauthey, J. N., Adjuvant chemotherapy with FOLFOX for primary colorectal cancer is associated with increased somatic gene mutations and inferior survival in patients undergoing hepatectomy for metachronous liver metastases, Annals of Surgery, 256, 642-650, 2012	Comparison not relevant
Andres, A., Toso, C., Adam, R., Barroso, E., Hubert, C., Capussotti, L., Gerstel, E., Roth, A., Majno, P. E., Mentha, G., A survival analysis of the liver-first reversed management of advanced simultaneous colorectal liver metastases: a LiverMetSurvey-based study, Annals of Surgery, 256, 772-778; discussion 778-779, 2012	Populations are not similar and would not both be candidates for the approaches compared
Antoniou, A, Lovegrove, R E, Tilney, H S, Heriot, A G, John, T G, Rees, M, Tekkis, P, Welsh, F K, Meta-analysis of clinical outcome after first and second liver resection for colorectal metastases (Provisional abstract), Surgery, 141, 9-18, 2007	Intervention/comparison not relevant
Araujo, R. L. C., Gonen, M., Herman, P., Chemotherapy for Patients with Colorectal Liver Metastases Who Underwent Curative Resection Improves Long-Term Outcomes: Systematic Review and Meta-analysis, Annals of Surgical Oncology, 22, 3070-3078, 2015	A systematic review, included studies checked for relevance
Asahara, T., Kikkawa, M., Okajima, M., Ojima, Y., Toyota, K., Nakahara, H., Katayama, K., Itamoto, T., Marubayashi, S., One, E., Yahata, H., Dohi, K., Azuma, K., Ito, K., Studies of postoperative transarterial infusion chemotherapy for liver	Intervention/comparison not of interest

metastasis of colorectal carcinoma after hepatectomy, Hepato-Gastroenterology, 45, 805-811, 1998	
Ayez, N., van der Stok, E. P., de Wilt, H., Radema, S. A., van Hillegersberg, R., Roumen, R. M., Vreugdenhil, G., Tanis, P. J., Punt, C. J., Dejong, C. H., Jansen, R. L., Verheul, H. M., de Jong, K. P., Hospers, G. A., Klaase, J. M., Legdeur, M. C., van Meerten, E., Eskens, F. A., van der Meer, N., van der Holt, B., Verhoef, C., Grunhagen, D. J., Neo-adjuvant chemotherapy followed by surgery versus surgery alone in high-risk patients with resectable colorectal liver metastases: the CHARISMA randomized multicenter clinical trial, BMC Cancer, 15 (1) (no pagination), 2015	Protocol for a RCT
Ayez, N., Van Der Stok, E. P., Grunhagen, D. J., Rothbarth, J., Van Meerten, E., Eggermont, A. M., Verhoef, C., The use of neo-adjuvant chemotherapy in patients with resectable colorectal liver metastases: Clinical risk score as possible discriminator, European Journal of Surgical Oncology, 41, 859-867, 2015	Observational study, RCT evidence exists and prioritised
Bai, H., Huang, X., Jing, L., Zeng, Q., Han, L., The effect of radiofrequency ablation vs. Liver resection on survival outcome of colorectal liver metastases (CRLM): A meta-analysis, Hepato-Gastroenterology, 62, 373-377, 2015	A systematic review, included studies checked for relevance
Bala, M. M., Mitus, J. W., Riemsma, R. P., Wolff, R., Hetnal, M., Kukielka, A., Kleijnen, J., Transarterial (chemo)embolisation versus chemotherapy for colorectal cancer liver metastases, Cochrane Database of Systematic Reviews, 2017 (8) (no pagination), 2017	A protocol for a Cochrane review
Baltatzis, M., Chan, A. K. C., Jegatheeswaran, S., Mason, J. M., Siriwardena, A. K., Colorectal cancer with synchronous hepatic metastases: Systematic review of reports comparing synchronous surgery with sequential bowel-first or liver-first approaches, European Journal of Surgical OncologyEur J Surg Oncol, 42, 159-165, 2016	A systematic review, included studies checked for relevance
Bargellini, I., How does selective internal radiation therapy compare with and/or complement other liver-directed therapies, Future Oncology, 10, 105-109, 2014	Expert review
Belinson, S, Chopra, R, Yang, Y, Shankaran, V, Aronson, N, Local hepatic therapies for metastases to the liver from unresectable colorectal cancer (Structured abstract), Health Technology Assessment Database, 2012	Health Technology Assessment, included studies checked for relevance
Berber, E., Tsinberg, M., Tellioglu, G., Simpfendorfer, C. H., Siperstein, A. E., Resection versus laparoscopic radiofrequency thermal ablation of solitary colorectal liver metastasis, Journal of Gastrointestinal Surgery, 12, 1967-1972, 2008	Populations are not similar and would not both be candidates for the approaches compared
Bernstein, M., Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): A randomized controlled trial, Diseases of the Colon and Rectum, 51, 1306-1307, 2008	Summary of the trial reported by Nordlinger et al 2008
Bester, L., Meteling, B., Pocock, N., Pavlakis, N., Chua, T. C., Saxena, A., Morris, D. L., 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, 2012	Observational study, RCT evidence on radioembolisation available and prioritised

Bhutiani, N., Akinwande, O., Martin, R. C., Efficacy and Toxicity of Hepatic Intra-Arterial Drug-Eluting (Irinotecan) Bead (DEBIRI) Therapy in Irinotecan-Refractory Unresectable Colorectal Liver Metastases, World Journal of Surgery, 40, 1178-1190, 2016	Observational study, RCT evidence on DEBIRI available and prioritised
Bignami, P., Doci, R., Montalto, F., Fissi, S., Di Bartolomeo, M., Gennari, L., Feasibility on intraportal chemotherapy with fluorouracil and folinic acid immediately after hepatic resection for colorectal metastases, Tumori, 81, 96-101, 1995	Intervention/comparison not of interest
Bigourdan, J. M., Faber, B., Rayar, M., Chirpaz, E., Boucher, E., Boudjema, K., Disease-Free Survival after Simultaneous or Delayed Resection of Synchronous Colorectal Liver Metastasis and Primary Cancer, Hepato-Gastroenterology, 61, 1074-1081, 2014	No multivariate analysis on relevant comparison/outcome (effect of timing of resection on survival)
Bijukchhe, S. M., Heping, L., Tao, L., Comparison between simultaneous resection and staged resection of synchronous colorectal cancer with resectable liver metastases: a meta-analysis, European Surgery - Acta Chirurgica Austriaca, 46, 216-225, 2014	A systematic review, included studies checked for relevance
Boame, N., Gresham, G., Jonker, D., Martel, G., Balaa, F., Asmis, T., Use of chemotherapy and radiofrequency ablation to treat colorectal cancer metastases: A retrospective review of the Ottawa Hospital Cancer Centre over 7 years, Current Oncology, 21, e557-e563, 2014	Same population as in Eltawil 2014
Bonney, G. K., Coldham, C., Adam, R., Kaiser, G., Barroso, E., Capussotti, L., Laurent, C., Verhoef, C., Nuzzo, G., Elias, D., Lapointe, R., Hubert, C., Lopez-Ben, S., Krawczyk, M., Mirza, D. F., Role of neoadjuvant chemotherapy in resectable synchronous colorectal liver metastasis; An international multi-center data analysis using LiverMetSurvey, Journal of Surgical Oncology, 111, 716-724, 2015	Observational study, RCT evidence exists and prioritised
Booth, C. M., Nanji, S., Wei, X., Biagi, J. J., Krzyzanowska, M. K., Mackillop, W. J., Surgical resection and peri-operative chemotherapy for colorectal cancer liver metastases: A population-based study, European Journal of Surgical Oncology, 42, 281-287, 2016	No relevant comparison
Brandi, G., De Lorenzo, S., Nannini, M., Curti, S., Ottone, M., Dall'Olio, F. G., Barbera, M. A., Pantaleo, M. A., Biasco, G., Adjuvant chemotherapy for resected colorectal cancer metastases: Literature review and meta-analysis, World Journal of Gastroenterology, 22, 519-533, 2016	A systematic review, included studies checked for relevance
Brouquet, A., Abdalla, E. K., Kopetz, S., Garrett, C. R., Overman, M. J., Eng, C., Andreou, A., Loyer, E. M., Madoff, D. C., Curley, S. A., Vauthey, J. N., High survival rate after two-stage resection of advanced colorectal liver metastases: Response-based selection and complete resection define outcome, Journal of Clinical Oncology, 29, 1083-1090, 2011	Intervention group (resection) and comparison group (chemotherapy) populations different and comparison not relevant
Brouquet, A., Mortenson, M. M., Vauthey, J. N., Rodriguez-Bigas, M. A., Overman, M. J., Chang, G. J., Kopetz, S., Garrett, C., Curley, S. A., Abdalla, E. K., Surgical Strategies for Synchronous Colorectal Liver Metastases in 156 Consecutive Patients: Classic, Combined or Reverse Strategy?, Journal of the American College of Surgeons, 210, 934-941, 2010	Multivariate analysis results on outcomes of interest not reported
Capussotti, L., Ferrero, A., Vigano, L., Ribero, D., Tesoriere, R. L., Polastri, R., Major liver resections synchronous with	No multivariate analysis

colorectal surgery, Annals of Surgical Oncology, 14, 195-201, 2007	
Capussotti, L., Muratore, A., Mulas, M. M., Massucco, P., Aglietta, M., Neoadjuvant chemotherapy and resection for initially irresectable colorectal liver metastases, British Journal of Surgery, 93, 1001-1006, 2006	Observational study, RCT evidence exists and prioritised
Capussotti, L., Vigano, L., Ferrero, A., Lo Tesoriere, R., Ribero, D., Polastri, R., Timing of resection of liver metastases synchronous to colorectal tumor: proposal of prognosis-based decisional model, Annals of surgical oncology : the official journal of the Society of Surgical Oncology, 14, 1143-1150, 2007	No multivariate analysis for relevant comparison and outcome
Carter, S., Martin, Ii R. C. G., Drug-eluting bead therapy in primary and metastatic disease of the liver, Hpb, 11, 541-550, 2009	A systematic review, included studies checked for relevance
Cavallari, A., Vivarelli, M., Bellusci, R., Montalti, R., De Ruvo, N., Cucchetti, A., De Vivo, A., De Raffele, E., Salone, M., La Barba, G., Liver Metastases from Colorectal Cancer: Present Surgical Approach, Hepato-Gastroenterology, 50, 2067-2071, 2003	No relevant comparison
Ceelen, W., Praet, M., Villeirs, G., Defreyne, L., Pattijn, P., Hesse, U., de Hemptinne, B., Initial experience with the use of preoperative transarterial chemoembolization in the treatment of liver metastasis, Acta chirurgica Belgica, 96, 37-40, 1996	No relevant comparison group
Cellini, C., Hunt, S. R., Fleshman, J. W., Birnbaum, E. H., Bierhals, A. J., Mutch, M. G., Stage IV Rectal Cancer with Liver Metastases: Is There a Benefit to Resection of the Primary Tumor?, World Journal of Surgery, 1-7, 2010	Four different populations (who underwent different interventions) compared
Chan, K. M., Wu, T. H., Wang, Y. C., Lee, C. F., Wu, T. J., Chou, H. S., Lee, W. C., Chiang, J. M., Chen, J. S., Clinical relevance of oncologic prognostic factors in the decision-making of pre-hepatectomy chemotherapy for colorectal cancer hepatic metastasis: The priority of hepatectomy, World Journal of Surgical Oncology, 16 (1) (no pagination), 2018	Observational study, RCT evidence exists and prioritised
Chapiro, J., Duran, R., Lin, M. D., Schernthaner, R., Lesage, D., Wang, Z., Savic, L. J., Geschwind, J. F., Early survival prediction after intra-arterial therapies: a 3D quantitative MRI assessment of tumour response after TACE or radioembolization of colorectal cancer metastases to the liver, European Radiology, 25, 1993-2003, 2015	Study about the predictive value of different quantitative MRI, no relevant data presented
Chen, Gq, Li, J, Ding, Kf, A meta-analysis of the safety of simultaneous versus staged resection for synchronous liver metastasis from colorectal cancer (Provisional abstract), Chinese Journal of Gastrointestinal Surgery, 13, 337-341, 2010	Non-English language paper
Chen, J., Li, Q., Wang, C., Zhu, H., Shi, Y., Zhao, G., Simultaneous vs. staged resection for synchronous colorectal liver metastases: A metaanalysis, International Journal of Colorectal Disease, 26, 191-199, 2011	A systematic review, included studies checked for relevance
Chiappa, A., Bertani, E., Zbar, A. P., Foschi, D., Fazio, N., Zampino, M., Belluco, C., Orsi, F., Vigna, P. D., Bonomo, G., Venturino, M., Ferrari, C., Biffi, R., Optimizing treatment of hepatic metastases from colorectal cancer: Resection or resection plus ablation?, International Journal of OncologyInt J Oncol, 48, 1280-1289, 2016	Observational study, no multivariate analysis
Cho, M., Kessler, J., Park, J. J., Lee, A., Gong, J., Singh, G., Chen, Y. J., Ituarte, P. H. G., Fakih, M., A single institute retrospective trial of concurrent chemotherapy with SIR-	Observational study, RCT evidence on SIRT available and prioritised

Spheres versus SIR-Spheres alone in chemotherapy-resistant colorectal cancer liver metastases, Journal of Gastrointestinal Oncology, 8, 608-613, 2017	
Chua, H. K., Sondenaa, K., Tsiotos, G. G., Larson, D. R., Wolff, B. G., Nagorney, D. M., Concurrent vs. staged colectomy and hepatectomy for primary colorectal cancer with synchronous hepatic metastases, Diseases of the Colon and Rectum, 47, 1310-1316, 2004	No multivariate analysis
Chua, T. C., Bester, L., Saxena, A., Morris, D. L., Radioembolization and systemic chemotherapy improves response and survival for unresectable colorectal liver metastases, Journal of Cancer Research and Clinical Oncology, 137, 865-873, 2011	No comparison group
Chua, T. C., Saxena, A., Liauw, W., Kokandi, A., Morris, D. L., Systematic review of randomized and nonrandomized trials of the clinical response and outcomes of neoadjuvant systemic chemotherapy for resectable colorectal liver metastases, Annals of Surgical Oncology, 17, 492-501, 2010	A systematic review, included studies checked for relevance
Chua, Tc, Liauw, W, Chu, F, Morris, Dl, Summary outcomes of two-stage resection for advanced colorectal liver metastases (Provisional abstract), Journal of Surgical OncologyJ Surg Oncol, 107, 211-216, 2013	Review paper about two-stage liver resection, intervention not of interest
Ciferri, E., Bondanza, G. S., Municino, O., Castagnola, M., Gazzaniga, G. M., Colorectal Cancer Metastases: Surgical Indications and Multimodal Approach, Hepato-Gastroenterology, 50, 1836-1846, 2003	Case series, no comparison group
Ciliberto, D., Prati, U., Roveda, L., Barbieri, V., Staropoli, N., Abbruzzese, A., Caraglia, M., Di Maio, M., Flotta, D., Tassone, P., Tagliaferri, P., Role of systemic chemotherapy in the management of resected or resectable colorectal liver metastases: A systematic review and meta-analysis of randomized controlled trials, Oncology Reports, 27, 1849-1856, 2012	A systematic review, included studies checked for relevance
Cirocchi, R., Trastulli, S., Boselli, C., Montedori, A., Cavaliere, D., Parisi, A., Noya, G., Abraha, I., Radiofrequency ablation in the treatment of liver metastases from colorectal cancer, Cochrane database of systematic reviews (Online), 6, CD006317, 2012	A systematic review, includes comparisons not relevant for this review, included studies checked for relevance
Cokmert, S., Ellidokuz, H., Demir, L., Fuzun, M., Astarcioglu, I., Aslan, D., Yilmaz, U., Oztop, I., Survival outcomes of liver metastasectomy in colorectal cancer cases: a single-center analysis in Turkey, Asian Pacific journal of cancer prevention : APJCP, 15, 5195-5200, 2014	No relevant comparison
Conrad, C., Vauthey, J. N., Masayuki, O., Sheth, R. A., Yamashita, S., Passot, G., Bailey, C. E., Zorzi, D., Kopetz, S., Aloia, T. A., You, Y. N., Individualized Treatment Sequencing Selection Contributes to Optimized Survival in Patients with Rectal Cancer and Synchronous Liver Metastases, Annals of Surgical Oncology, 24, 3857-3864, 2017	Results of multivariate analysis not reported for relevant comparisons and outcomes
Correa-Gallego, C., Fong, Y., Gonen, M., D'Angelica, M. I., Allen, P. J., DeMatteo, R. P., Jarnagin, W. R., Kingham, T. P., A Retrospective Comparison of Microwave Ablation vs. Radiofrequency Ablation for Colorectal Cancer Hepatic Metastases, Annals of Surgical Oncology, 21, 4278-4283, 2014	Comparison not of interest

Cucchetti, A., Ercolani, G., Cescon, M., Di Gioia, P., Peri, E., Brandi, G., Pellegrini, S., Pinna, A. D., Safety of hepatic resection for colorectal metastases in the era of neo-adjuvant chemotherapy, Langenbeck's Archives of Surgery, 1-9, 2011	Observational study, RCT evidence exists and prioritised
Curley, S. A., Outcomes after surgical treatment of colorectal cancer liver metastases, Seminars in Oncology, 32, S109-S111, 2005	A summary of the results from a published study (see Abdalla et al 2004)
Curley, S. A., Radiofrequency ablation versus resection for resectable colorectal liver metastases: Time for a randomized trial?, Annals of Surgical Oncology, 15, 11-13, 2008	Editorial
De Haas, R. J., Adam, R., Wicherts, D. A., Azoulay, D., Bismuth, H., Vibert, E., Salloum, C., Perdigao, F., Benkabbou, A., Castaing, D, Comparison of simultaneous or delayed liver surgery for limited synchronous colorectal metastases. British Journal of Surgery, 97, 1279-89, 2010	Population not relevant. Included in review D2a
De Jong, M. C., Pulitano, C., Ribero, D., Strub, J., Mentha, G., Schulick, R. D., Choti, M. A., Aldrighetti, L., Capussotti, L., Pawlik, T. M., Rates and patterns of recurrence following curative intent surgery for colorectal liver metastasis: An international multi-institutional analysis of 1669 patients, Annals of Surgery, 250, 440-447, 2009	No relevant comparison group
De Ridder, J. A. M., Van Der Stok, E. P., Mekenkamp, L. J., Wiering, B., Koopman, M., Punt, C. J. A., Verhoef, C., De Wilt, J. H., Management of liver metastases in colorectal cancer patients: A retrospective case-control study of systemic therapy versus liver resection, European Journal of Cancer, 59, 13-21, 2016	Intervention/comparison not relevant
Dede, K., Mersich, T., Besznyak, I., Zarand, A., Salamon, F., Baranyai, Z., Landherr, L., Jakab, F., Bursics, A., Bevacizumab treatment before resection of colorectal liver metastases: Safety, recovery of liver function, pathologic assesment, Pathology and Oncology Research, 19, 501-508, 2013	No intervention/comparison, no relevant outcomes reported
Des Guetz, G., Mariani, P., Uzzan, B., Neoadjuvant chemotherapy for patients having resection or ablation of liver metastases from colorectal cancer, Cochrane Database of Systematic Reviews, 2018 (1) (no pagination), 2018	Protocol for a Cochrane review
Des Guetz, G., Mariani, P., Uzzan, B., Neoadjuvant chemotherapy for patients having resection or ablation of liver metastases from colorectal cancer, Cochrane Database of Systematic Reviews, (2) (no pagination), 2009	Cochrane review that has been withdrawn in the later updates due to overlap with another review
Dexiang, Z., Li, R., Ye, W., Haifu, W., Yunshi, Z., Qinghai, Y., Shenyong, Z., Bo, X., Li, L., Xiangou, P., Haohao, L., Lechi, Y., Tianshu, L., Jia, F., Xinyu, Q., Jianmin, X., Outcome of patients with colorectal liver metastasis: Analysis of 1,613 consecutive cases, Annals of Surgical Oncology, 19, 2860-2868, 2012	Prognostic data, no relevant intervention/comparison
Dhir, M., Zenati, M. S., Jones, H. L., Bartlett, D. L., Choudry, M. H. A., Pingpank, J. F., Holtzman, M. P., Bahary, N., Hogg, M. E., Zeh, H. J., Geller, D. A., Wallis Marsh, J., Tsung, A., Zureikat, A. H., Effectiveness of Hepatic Artery Infusion (HAI) Versus Selective Internal Radiation Therapy (Y90) for Pretreated Isolated Unresectable Colorectal Liver Metastases (IU-CRCLM), Annals of Surgical Oncology, 25, 550-557, 2018	Hepatic artery infusion not an intervention of interest
Djurisic, I., Nikolic, S., Inic, M., Zegarac, M., Buta, M., Kocic, M., Surgical treatment of colorectal cancer metastases in liver, European Surgery - Acta Chirurgica Austriaca, Conference, 7th	Conference abstract

International European Federation for Colorectal Cancer, EFR Congress - Surgical Congress: Multidisciplinary Treatment of Colorectal Cancer. Vienna Austria. Conference Publication: (var.pagings). 43 (SUPPL. 240) (pp 24), 2011	
Doko, M., Zovak, M., Ledinsky, M., Mijic, A., Peric, M., Kopljar, M., Culinovic, R., Rode, B., Doko, B., Safety of simultaneous resections of colorectal cancer and liver metastases, Collegium Antropologicum, 24, 381-390, 2000	No relevant outcomes
Doughtie, C. A., Edwards, J. D., Philips, P., Agle, S. C., Scoggins, C. R., McMasters, K. M., Martin, R. C. G., Infectious complications in combined colon resection and ablation of colorectal liver metastases, American Journal of Surgery, 210, 1185-1191, 2015	Intervention/comparison not relevant (colon resection with MWA or RFA versus colon resection alone)
Du, J. M., Gong, A. M., Dai, X. N., Wang, F., Weng, W. C., Clinical efficacy of transcatheter arterial chemoembolization combined with DC-CIK in the treatment of colorectal cancer with liver metastasis and its effect on the survival of patients, Biomedical Research (India), 28, 6165-6168, 2017	DK-CIK not used in the UK
Dupre, A., Jones, R. P., Diaz-Nieto, R., Fenwick, S. W., Poston, G. J., Malik, H. Z., Curative-intent treatment of recurrent colorectal liver metastases: A comparison between ablation and resection, European Journal of Surgical Oncology, 43, 1901-1907, 2017	Populations are not similar and would not both be candidates for both approaches compared
Dutton, S. J., Kenealy, N., Love, S. B., Wasan, H. S., Sharma, R. A., FOXFIRE protocol: An open-label, randomised, phase III trial of 5-fluorouracil, oxaliplatin and folinic acid (OxMdG) with or without interventional Selective Internal Radiation Therapy (SIRT) as first-line treatment for patients with unresectable liver-only or liver-dominant metastatic colorectal cancer, BMC CancerBMC Cancer, 14 (1) (no pagination), 2014	Trial protocol, results of the trial published separately (Wasan et al 2017)
Ejaz, A., Semenov, E., Spolverato, G., Kim, Y., Tanner, D., Hundt, J., Pawlik, T. M., Synchronous primary colorectal and liver metastasis: impact of operative approach on clinical outcomes and hospital charges, HPBHpb, 16, 1117-26, 2014	No multivariate analysis on relevant outcomes
Eltawil, K. M., Boame, N., Mimeault, R., Shabanafady, W., Balaa, F. K., Jonker, D. J., Asmis, T. R., Martel, G. Patterns of recurrence following selective intraoperative radiofrequency ablation as an adjunct to hepatic resection for colorectal liver metastases. Journal of Surgical Oncology, 110, 734-8, 2014	Population not relevant. Included in review D2a
Ercolani, G., Cucchetti, A., Cescon, M., Peri, E., Brandi, G., Gaudio, M. D., Ravaioli, M., Zanello, M., Pinna, A. D., Effectiveness and cost-effectiveness of peri-operative versus post-operative chemotherapy for resectable colorectal liver metastases, European Journal of Cancer, 47, 2291-2298, 2011	Health economic model comparing perioperative and postoperative chemotherapy, no new clinical study results
Evrard, S., Becouarn, Y., Fonck, M., Brunet, R., Mathoulin-Pelissier, S., Picot, V., Surgical treatment of liver metastases by radiofrequency ablation, resection, or in combination, European Journal of Surgical Oncology, 30, 399-406, 2004	Population includes patients with non-colorectal cancer. No relevant data for the relevant subpopulation (colorectal liver metastasis) and relevant comparison reported
Evrard, S., Rivoire, M., Arnaud, J. P., Lermite, E., Bellera, C., Fonck, M., Becouarn, Y., Lalet, C., Pulido, M., Mathoulin-Pelissier, S., Unresectable colorectal cancer liver metastases treated by intraoperative radiofrequency ablation with or without resection, British Journal of Surgery, 99, 558-565, 2012	Single-arm study

Eynde, M, Hendlisz, A, Peeters, M, Defreyne, L, Maleux, G, Vannoote, J, Delatte, P, Paesmans, M, Laethem, J, Flamen, P, Prospective randomized study comparing hepatic intra-arterial injection of Yttrium-90 resin-microspheres (HAI-Y90) with protracted IV 5FU (5FU CI) versus 5FU CI alone for patients with liver-limited metastatic colorectal cancer (LMCRC) refractory to standard chemotherapy (CT), Journal of clinical oncology: ASCO annual meeting proceedings, 27, 191, 2009	Conference abstract
Faron, M., Chirica, M., Tranchard, H., Balladur, P., De Gramont, A., Afchain, P., Andre, T., Paye, F., Impact of preoperative and postoperative FOLFOX chemotherapies in patients with resectable colorectal liver metastasis, Journal of Gastrointestinal Cancer, 45, 298-306, 2014	Observational study, RCT evidence exists and prioritised
Fedorowicz, Z., Al-asfoor, A., Lodge, M., Resection versus no intervention or other surgical interventions for colorectal cancer liver metastases, Cochrane Database of Systematic Reviews, (2) (no pagination), 2008	No relevant intervention/comparison in the one included study
Fedorowicz, Zbys, Lodge, Mark, Al-asfoor, Ahmed, Carter, Ben, Resection versus no intervention or other surgical interventions for colorectal cancer liver metastases, Cochrane Database of Systematic Reviews, 2008	Duplicate of 845597
Feng, Q., Wei, Y., Zhu, D., Ye, L., Lin, Q., Li, W., Qin, X., Lyu, M., Xu, J., Timing of hepatectomy for resectable synchronous colorectal liver metastases: For whom simultaneous resection is more suitable - A meta-analysis, PLoS ONE, 9 (8) (no pagination), 2014	A systematic review, included studies checked for relevance
Fiorentini, G, Aliberti, C, Montagnani, F, Tilli, M, Mambrini, A, Giannessi, P, Benea, G, First evaluation of phase III trial of tace adopting polyvinil-alcohol microspheres (PAM) irinotecan (IRI) loaded vs folfiri (CT) for non operable colorectal cancer (CRC) liver metastases, Annals of Oncology, 20, 14, 2009	Conference abstract
Fiorentini, G, Aliberti, C, Tilli, M, Mambrini, A, Turrisi, G, Dentico, P, Benea, G, Evaluation of a phase III clinical trial comparing transarterial chemoembolisation (TACE) using irinotecaN-loaded polyvinyl alcohol micrOsperes (Debiri) vs systemic chemotherapy Folfiri (CT) for the treatment of unresectable metastases to the liver (LM) in patients with advanced colorectal cancer (MCRC), Cardiovascular and interventional radiology., 34, 599, 2011	Conference abstract
Folprecht, G., Grothey, A., Alberts, S., Raab, H. R., Kohne, C. H., Neoadjuvant treatment of unresectable colorectal liver metastases: correlation between tumour response and resection rates, Annals of Oncology, 16, 1311-9, 2005	No relevant comparison
Fossum, C. C., Alabbad, J. Y., Romak, L. B., Hallemeier, C. L., Haddock, M. G., Huebner, M., Dozois, E. J., Larson, D. W., The role of neoadjuvant radiotherapy for locally-advanced rectal cancer with resectable synchronous metastasis, Journal of Gastrointestinal Oncology, 8, 650-658, 2017	Intervention not relevant, population includes people with lung metastases
Fukami, Y., Kaneoka, Y., Maeda, A., Takayama, Y., Onoe, S., Isogai, M., Simultaneous resection for colorectal cancer and synchronous liver metastases, Surgery Today, 46, 176-182, 2016	No multivariate analysis for relevant comparison and outcome
Fukuoka, K., Nara, S., Honma, Y., Kishi, Y., Esaki, M., Shimada, K., Hepatectomy for Colorectal Cancer Liver Metastases in the Era of Modern Preoperative Chemotherapy: Evaluation of	Observational study, RCT evidence exists and prioritised

Postoperative Complications, World Journal of Surgery, 41, 1073-1081, 2017	
Fusco, F, Wolstenholme, J, Gray, A, Chau, I, Dunham, L, Love, S, Roberts, A, Moschandreas, J, Virdee, P, Lewington, V, Wilson, G, Khan, N, Francis, A, Wasan, H, Sharma, R, Selective internal radiotherapy (SIRT) in metastatic colorectal cancer patients with liver metastases: preliminary primary care resource use and utility results from the foxfire randomised controlled trial, Value in health. Conference: ISPOR 20th annual european congress. United kingdom, 20, A445-a446, 2017	Conference abstract
Gavriilidis, P., Sutcliffe, R. P., Hodson, J., Marudanayagam, R., Isaac, J., Azoulay, D., Roberts, K. J., Simultaneous versus delayed hepatectomy for synchronous colorectal liver metastases: a systematic review and meta-analysis, Hpb, 20, 11-19, 2018	A systematic review with different inclusion criteria, included studies checked for relevance
Gazelle, G. S., McMahon, P. M., Beinfeld, M. T., Halpern, E. F., Weinstein, M. C., Metastatic colorectal carcinoma: cost-effectiveness of percutaneous radiofrequency ablation versus that of hepatic resection, Radiology, 233, 729-739, 2004	Health economic analysis of RFA versus resection, no original clinical evidence of relevance
Gibbs, P, Gebski, V, Buskirk, M, Thurston, K, Cade, Dn, Hazel, Ga, Selective Internal Radiation Therapy (SIRT) with yttrium-90 resin microspheres plus standard systemic chemotherapy regimen of FOLFOX versus FOLFOX alone as first-line treatment of non-resectable liver metastases from colorectal cancer: the SIRFLOX study, BMC Cancer, 14, 897, 2014	Study protocol of SIRFLOX trial
Gleisner, A. L., Choti, M. A., Assumpcao, L., Nathan, H., Schulick, R. D., Pawlik, T. M. Colorectal liver metastases: Recurrence and survival following hepatic resection, radiofrequency ablation, and combined resection-radiofrequency ablation. Archives of Surgery, 143, 1204-12, 2008	Population not relevant. Included in review D2a
Goyer, P., Karoui, M., Vigano, L., Kluger, M., Luciani, A., Laurent, A., Azoulay, D., Cherqui, D., Single-center multidisciplinary management of patients with colorectal cancer and resectable synchronous liver metastases improves outcomes, Clinics and Research in Hepatology and Gastroenterology, 37, 47-55, 2013	Comparison not relevant, compares unicentre and multicentre management of colorectal cancer liver metastases
Grande, R., Natoli, C., Ciancola, F., Gemma, D., Pellegrino, A., Pavese, I., Garufi, C., Lauro, L. D., Corsi, D., Signorelli, D., Sperduti, I., Cortese, G., Risi, E., Morano, F., Sergi, D., Signorelli, C., Ruggeri, E. M., Zampa, G., Russano, M., Gamucci, T., Treatment of metastatic colorectal cancer patients 75 years old in clinical practice: A multicenter analysis, PLoS ONE, 11 (7) (no pagination), 2016	Populations compared are not relevant for comparison according to the review, consists of people with both resectable and unresectable liver metastasis
Gray, B., Van Hazel, G., Hope, M., Burton, M., Moroz, P., Anderson, J., Gebski, V., Randomised trial of SIR-Spheres plus chemotherapy vs. chemotherapy alone for treating patients with liver metastases from primary large bowel cancer, Annals of Oncology, 12, 1711-20, 2001	Intervention not of interest
Gruenberger, T, Sorbye, H, Debois, M, Bethe, U, Primrose, J, Rougier, P, Jaeck, D, Finch-Jones, M, Cutsem, E, Nordlinger, B, Tumor response to pre-operative chemotherapy (CT) with FOLFOX-4 for resectable colorectal cancer liver metastases (LM). Interim results of EORTC Intergroup randomized phase III study 40983, Journal of Clinical Oncology, 24, 3500, 2006	Conference abstract
Gugerbauer, J, Warmuth, M, Radiofrequency ablation for hepatocellular carcinoma and colorectal liver metastases	Non-English language paper

(Structured abstract), Health Technology Assessment Database, 2011	
Gulec, S. A., Pennington, K., Wheeler, J., Barot, T. C., Suthar, R. R., Hall, M., Schwartzentruber, D., Yttrium-90 microsphere-selective internal radiation therapy with chemotherapy (Chemo-SIRT) for colorectal cancer liver metastases: An in vivo double-arm-controlled phase II trial, American Journal of Clinical Oncology: Cancer Clinical Trials, 36, 455-460, 2013	Not reported if randomised, therefore presumably not randomised. As there is RCT evidence on SIRT chemotherapy versus chemotherapy alone, non-randomised studies excluded
Gur, I., Diggs, B. S., Wagner, J. A., Vaccaro, G. M., Lopez, C. D., Sheppard, B. C., Orloff, S. L., Billingsley, K. G., Safety and Outcomes Following Resection of Colorectal Liver Metastases in the Era of Current Perioperative Chemotherapy, Journal of Gastrointestinal Surgery, 17, 2133-2142, 2013	No relevant comparison
Gurusamy, K. S., Ramamoorthy, R., Imber, C., Davidson, B. R., Surgical resection versus non-surgical treatment for hepatic node positive patients with colorectal liver metastases, Cochrane Database of Systematic Reviews, 2010	Empty review
Gurusamy, K., Corrigan, N., Croft, J., Twiddy, M., Morris, S., Woodward, N., Bandula, S., Hochhauser, D., Napp, V., Pullan, A., Jakowiw, N., Prasad, R., Damink, S. O., van Laarhoven, C. J. H. M., de Wilt, J. H. W., Brown, J., Davidson, B. R., Liver resection surgery versus thermal ablation for colorectal LiVer MetAstases (LAVA): Study protocol for a randomised controlled trial, Trials, 19 (1) (no pagination), 2018	Study protocol of a RCT (LAVA trial), the trial is currently recruiting
Hamed, O. H., Bhayani, N. H., Ortenzi, G., Kaifi, J. T., Kimchi, E. T., Staveley-O'Carroll, K. F., Gusani, N. J., Simultaneous colorectal and hepatic procedures for colorectal cancer result in increased morbidity but equivalent mortality compared with colorectal or hepatic procedures alone: Outcomes from the National Surgical Quality Improvement Program, Hpb, 15, 695-702, 2013	Comparison groups not relevant, simultaneous resection compared to colorectal resection only (no metastasis) and liver resection only
Han, Y., Yan, D., Xu, F., Li, X., Cai, J. Q., Radiofrequency ablation versus liver resection for colorectal cancer liver metastasis: An updated systematic review and meta-analysis, Chinese Medical Journal, 129, 2983-2990, 2016	A systematic review, included studies checked for relevance
Harmantas, A, Rotstein, L E, Langer, B, Regional versus systemic chemotherapy in the treatment of colorectal carcinoma metastatic to the liver: is there a survival difference? Meta-analysis of the published literature (Structured abstract), Cancer, 78, 1639-1645, 1996	Intervention/comparison not of interest
Hartley, J. E., Lopez, R. A., Paty, P. B., Wong, W. D., Cohen, A. M., Guillem, J. G., Resection of locally recurrent colorectal cancer in the presence of distant metastases: Can it be justified?, Annals of Surgical Oncology, 10, 227-233, 2003	Comparison not relevant, compares outcomes for people with R0 or R1 resection
Hazel, Ga, Gray, Bn, Anderson, J, Randomised phase III trial of SIR-Spheres® plus chemotherapy versus chemotherapy alone in patients with colorectal hepatic metastases, Proceedings of the american society of clinical oncology, 18, 267a, Abstract 1026, 1999	Conference abstract
He, N., Jin, Q. N., Wang, D., Yang, Y. M., Liu, Y. L., Wang, G. B., Tao, K. X., Radiofrequency ablation vs. hepatic resection for resectable colorectal liver metastases, Journal of Huazhong University of Science and Technology, Medical sciences = Hua zhong ke ji da xue xue bao. Yi xue Ying De wen ban =	Populations are not similar and would not both be candidates for both approaches compared

Huazhong keji daxue xuebao. Yixue Yingdewen ban. 36, 514-518, 2016	
Heinemann, V., Ongoing selective internal radiation therapy-based studies in the treatment of liver-dominant metastatic colorectal cancer, Future Oncology, 10, 37-39, 2014	Expert review
Hewes, J. C., Dighe, S., Morris, R. W., Hutchins, R. R., Bhattacharya, S., Davidson, B. R., Preoperative chemotherapy and the outcome of liver resection for colorectal metastases, World Journal of Surgery, 31, 353-364, 2007	Observational study, RCT evidence exists and prioritised
Hillingso, J. G., Wille-jorgensen, P., Staged or simultaneous resection of synchronous liver metastases from colorectal cancer - A systematic review, Colorectal Disease, 11, 3-10, 2009	A systematic review, included studies checked for relevance
Hinz, S., Tepel, J., Roder, C., Kalthoff, H., Becker, T., Profile of serum factors and disseminated tumor cells before and after radiofrequency ablation compared to resection of colorectal liver metastases - A pilot study, Anticancer Research, 35, 2961-2968, 2015	No relevant outcomes
Hirata, M., Comparison between radio frequency ablation therapy and liver resection for liver metastasis from colorectal cancer, Gastroenterology, 152 (5 Supplement 1), S295, 2017	Conference abstract
Hof, J., Joosten, H. J., Havenga, K., De Jong, K. P. Radiofrequency ablation is beneficial in simultaneous treatment of synchronous liver metastases and primary colorectal cancer, PLoS ONE, 13(3), e0193385, 2018	Population not relevant. Included in review D2a
Hof, J., Wertenbroek, M. W., Peeters, P. M., Widder, J., Sieders, E., de Jong, K. P., Outcomes after resection and/or radiofrequency ablation for recurrence after treatment of colorectal liver metastases, The British journal of surgery, 103, 1055-1062, 2016	Two groups are different populations, RFA (unresectable population) and resection groups not comparable
Homayounfar, K., Bleckmann, A., Conradi, L. C., Sprenger, T., Lorf, T., Niessner, M., Sahlmann, C. O., Meller, J., Liersch, T., Ghadimi, B. M., Metastatic recurrence after complete resection of colorectal liver metastases: Impact of surgery and chemotherapy on survival, International Journal of Colorectal Disease, 28, 1009-1017, 2013	Population is people with secondary metastasis, some resectable some unresectable, also no relevant comparison
Homayounfar, K., Liersch, T., Niessner, M., Meller, J., Lorf, T., Becker, H., Ghadimi, B. M., Multimodal treatment options for bilobar colorectal liver metastases, Langenbeck's Archives of Surgery, 395, 633-641, 2010	No intervention/comparison of interest
Hong, K., McBride, J. D., Georgiades, C. S., Reyes, D. K., Herman, J. M., Kamel, I. R., Geschwind, J. F. H., Salvage Therapy for Liver-dominant Colorectal Metastatic Adenocarcinoma: Comparison between Transcatheter Arterial Chemoembolization versus Yttrium-90 Radioembolization, Journal of Vascular and Interventional Radiology, 20, 360-367, 2009	Observational study, RCT evidence on TACE and SIRT available and prioritised
Hu, J. M., Jao, S. W., Hsiao, C. W., Lee, C. C., Chen, C. Y., Chen, T. W., Sung, Y. F., Hsiao, P. C., Wu, C. C., Aggressive surgical resection of the primary tumor without metastasectomy first in stage IV colon cancer with unresectable synchronous liver-only-metastases patients cannot provide the survival benefits compared with chemotherapy first, Journal of Medical Sciences (Taiwan), 36, 85-94, 2016	Intervention/comparison not of interest
Huh, J. W., Cho, C. K., Kim, H. R., Kim, Y. J., Impact of resection for primary colorectal cancer on outcomes in patients	Interventions compared not of interest

with synchronous colorectal liver metastases, Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract, 14, 1258-1264, 2010	
Huh, J. W., Kim, H. C., Park, H. C., Choi, D. H., Park, J. O., Park, Y. S., Park, Y. A., Cho, Y. B., Yun, S. H., Lee, W. Y., Chun, H. K., Is Chemoradiotherapy Beneficial for Stage IV Rectal Cancer?, Oncology (Switzerland), 89, 14-22, 2015	Population includes people with non-hepatic metastasis, interventions not of interest
Hur, H., Ko, Y. T., Min, B. S., Kim, K. S., Choi, J. S., Sohn, S. K., Cho, C. H., Ko, H. K., Lee, J. T., Kim, N. K., Comparative study of resection and radiofrequency ablation in the treatment of solitary colorectal liver metastases, American Journal of Surgery, 197, 728-736, 2009	Populations are not similar and would not both be candidates for both approaches compared
Ihnat, P., Vavra, P., Zonca, P., Treatment strategies for colorectal carcinoma with synchronous liver metastases: Which way to go?, World Journal of Gastroenterology, 22, 7014-7021, 2016	Narrative/expert review
Imai, K., Allard, M. A., Castro Benitez, C., Vibert, E., Sa Cunha, A., Cherqui, D., Castaing, D., Baba, H., Adam, R., Long-term outcomes of radiofrequency ablation combined with hepatectomy compared with hepatectomy alone for colorectal liver metastases. The British Journal of Surgery, 104, 570-9, 2017	Population not relevant. Included in review D2a
Inoue, Y., Fujii, K., Tashiro, K., Ishii, M., Masubuchi, S., Yamamoto, M., Shimizu, T., Asakuma, M., Hirokawa, F., Hayashi, M., Narumi, Y., Uchiyama, K., Preoperative Chemotherapy May Not Influence the Remnant Liver Regenerations and Outcomes After Hepatectomy for Colorectal Liver Metastasis, World Journal of Surgery, 16, 16, 2018	Observational study, RCT evidence exists and prioritised
Inoue, Y., Imai, Y., Osumi, W., Shimizu, T., Asakuma, M., Hirokawa, F., Hayashi, M., Uchiyama, K., What is the optimal timing for liver surgery of resectable synchronous liver metastases from colorectal cancer?, American Surgeon, 83, 45-53, 2017	No multivariate analysis with relevant comparison/outcome (timing of resection on survival)
Jasarovic, D., Stojanovic, D., Mitrovic, N., Stevanovic, D., Resection or radiofrequency ablation of colorectal liver metastasis, Vojnosanitetski Pregled, 71, 542-546, 2014	Populations are not similar and would not both be candidates for both approaches compared
Jatzko, G. R., Lisborg, P. H., Stettner, H. M., Klimpfinger, M. H., Hepatic resection for metastases from colorectal carcinoma - A survival analysis, European Journal of Cancer Part A: General Topics, 31, 41-46, 1995	No relevant comparison group
Jegatheeswaran, S., Mason, J. M., Hancock, H. C., Siriwardena, A. K., The liver-first approach to the management of colorectal cancer with synchronous hepatic metastases: A systematic review, JAMA Surgery, 148, 385-391, 2013	No comparison group considered
Ji, Z. L., Peng, S. Y., Yuan, A. J., Li, P. J., Zhang, W., Yu, Y., Hepatic resection for metastasis from colorectal cancer, Techniques in Coloproctology, 8, S47-S49, 2004	Groups not comparable, populations different (resectable, unresectable etc.)
Kaibori, M., Iwamoto, S., Ishizaki, M., Matsui, K., Saito, T., Yoshioka, K., Hamada, Y., Kwon, A. H., Timing of resection for synchronous liver metastases from colorectal cancer. Digestive Diseases and Sciences, 55, 3262-70, 2010	Population not relevant. Included in review D2a
Kanemitsu, Y., Kato, T., Shimizu, Y., Inaba, Y., Shimada, Y., Nakamura, K., Sato, A., Moriya, Y., A randomized phase II/III trial comparing hepatectomy followed by mFOLFOX6 with hepatectomy alone as treatment for liver metastasis from	Trial protocol

colorectal cancer: Japan Clinical Oncology Group Study JCOG0603, Japanese Journal of Clinical Oncology, 39, 406-409, 2009	
Karanicolas, P. J., Jarnagin, W. R., Gonen, M., Tuorto, S., Allen, P. J., DeMatteo, R. P., D'Angelica, M. I., Fong, Y., Long-term outcomes following tumor ablation for treatment of bilateral colorectal liver metastases, JAMA Surgery, 148, 597-601, 2013	Only univariate analysis done
Karoui, M., Penna, C., Amin-Hashem, M., Mitry, E., Benoist, S., Franc, B., Rougier, P., Nordlinger, B., Influence of preoperative chemotherapy on the risk of major hepatectomy for colorectal liver metastases, Annals of Surgery, 243, 1-7, 2006	Observational study, RCT evidence exists and prioritised
Karoui, M., Roudot-Thoraval, F., Mesli, F., Mitry, E., Aparicio, T., Des Guetz, G., Louvet, C., Landi, B., Tiret, E., Sobhani, I., Primary colectomy in patients with stage IV colon cancer and unresectable distant metastases improves overall survival: results of a multicentric study.[Erratum appears in Dis Colon Rectum. 2011 Oct;54(10):1338 Note: DesGuetz, Gaetan [corrected to Des Guetz, Gaetan]], Diseases of the Colon & Rectum, 54, 930-8, 2011	Intervention/comparison not of interest
Kawaguchi, D., Hiroshima, Y., Matsuo, K., Endo, I., Koda, K., Tanaka, K., Hepatic resection after prehepatectomy chemotherapy for metastatic colorectal cancer: A propensity-matched analysis, Anticancer Research, 36, 4725-4730, 2016	Observational study, RCT evidence exists and prioritised
Kelly, M. E., Spolverato, G., Le, G. N., Mavros, M. N., Doyle, F., Pawlik, T. M., Winter, D. C., Synchronous colorectal liver metastasis: A network meta-analysis review comparing classical, combined, and liver-first surgical strategies, Journal of Surgical Oncology, 111, 341-351, 2015	A systematic review, method of analyses unclear, included studies checked for relevance
Kemeny, M. M., Adak, S., Gray, B., Macdonald, J. S., Smith, T., Lipsitz, S., Sigurdson, E. R., O'Dwyer, P. J., Benson, Iii A. B., Combined-modality treatment for resectable metastatic colorectal carcinoma to the liver: Surgical resection of hepatic metastases in combination with continuous infusion of chemotherapy - An intergroup study, Journal of Clinical Oncology, 20, 1499-1505, 2002	Hepatic arterial infusion not an intervention of interest
Khajanchee, Y. S., Hammill, C. W., Cassera, M. A., Wolf, R. F., Hansen, P. D., Hepatic resection vs minimally invasive radiofrequency ablation for the treatment of colorectal liver metastases: A Markov analysis, Archives of Surgery, 146, 1416-1423, 2011	Health economic analysis, no original clinical data
Khoo, E., O'Neill, S., Brown, E., Wigmore, S. J., Harrison, E. M., Systematic review of systemic adjuvant, neoadjuvant and perioperative chemotherapy for resectable colorectal-liver metastases, Hpb, 18, 485-493, 2016	No meta-analysis, individual studies checked for relevance
Kim, C. W., Lee, J. L., Yoon, Y. S., Park, I. J., Lim, S. B., Yu, C. S., Kim, T. W., Kim, J. C., Resection after preoperative chemotherapy versus synchronous liver resection of colorectal cancer liver metastases: A propensity score matching analysis, Medicine (United States), 96 (7) (no pagination), 2017	Observational study, RCT evidence exists and prioritised
Kim, H., Gill, B., Beriwal, S., Huq, M. S., Roberts, M. S., Smith, K. J., Cost-Effectiveness Analysis of Stereotactic Body Radiation Therapy Compared With Radiofrequency Ablation for Inoperable Colorectal Liver Metastases, International Journal of Radiation Oncology, Biology, Physics, 95, 1175-83, 2016	Health economic analysis comparing SBRT and RFA, no original clinical data

Kim, K. H., Yoon, Y. S., Yu, C. S., Kim, T. W., Kim, H. J., Kim, P. N., Ha, H. K., Kim, J. C., Comparative analysis of radiofrequency ablation and surgical resection for colorectal liver metastases, Journal of The Korean Surgical Society, 81, 25-34, 2011	Populations are not similar and would not both be candidates for both approaches compared
Kim, S. K., Lee, C. H., Lee, M. R., Kim, J. H., Multivariate analysis of the survival rate for treatment modalities in incurable stage IV colorectal cancer, Journal of the Korean Society of Coloproctology, 28, 35-41, 2012	Intervention/comparison not of interest
Kim, W. W., Kim, K. H., Kim, S. H., Kim, J. S., Park, S. J., Kim, K. H., Choi, C. S., Choi, Y. K., Comparison of Hepatic Resection and Radiofrequency Ablation for the Treatment of Colorectal Liver Metastasis, Indian Journal of Surgery, 77, 1126-30, 2015	Populations are not similar and would not both be candidates for both approaches compared
Kirichenko, V, Thai, Nv, Parda, Ds, Stereotactic body radiation therapy (SBRT) versus radiofrequency ablation (RFA) for unresectable colorectal cancer hepatic metastases: a cost-effectiveness analysis, International journal of radiation oncology. Conference: 58th annual meeting of the american society for radiation oncology, ASTRO 2016. United states, 96, S163, 2016	Conference abstract
Ko, S., Jo, H., Yun, S., Park, E., Kim, S., Seo, H. I., Comparative analysis of radiofrequency ablation and resection for resectable colorectal liver metastases, World Journal of Gastroenterology, 20, 525-531, 2014	Populations are not similar and would not both be candidates for both approaches compared
Kobayashi, H., Kotake, K., Sugihara, K., Impact of adjuvant chemotherapy in patients with curatIVely resected stage IV colorectal cancer, Medicine (United States), 94, e696, 2015	Observational study, RCT evidence exists on this comparison
Kornprat, P., Jarnagin, W. R., DeMatteo, R. P., Fong, Y., Blumgart, L. H., D'Angelica, M., Role of intraoperative thermoablation combined with resection in the treatment of hepatic metastasis from colorectal cancer, Archives of Surgery, 142, 1087-1092, 2007	No relevant comparison group
Krishnamurthy, A., Kankesan, J., Wei, X., Nanji, S., Biagi, J. J., Booth, C. M., Chemotherapy delivery for resected colorectal cancer liver metastases: Management and outcomes in routine clinical practice, European Journal of Surgical Oncology, 43, 364-371, 2017	No comparison group
Labori, K. J., Guren, M. G., Brudvik, K. W., Rosok, B. I., Waage, A., Nesbakken, A., Larsen, S., Dueland, S., Edwin, B., Bjornbeth, B. A., Resection of synchronous liver metastases between radiotherapy and definitive surgery for locally advanced rectal cancer: short-term surgical outcomes, overall survival and recurrence-free survival, Colorectal Disease, 19, 731-738, 2017	No relevant comparison group
Lam, V. W. T., Laurence, J. M., Pang, T., Johnston, E., Hollands, M. J., Pleass, H. C. C., Richardson, A. J., A systematic review of a liver-first approach in patients with colorectal cancer and synchronous colorectal liver metastases, Hpb, 16, 101-108, 2014	No relevant comparison group
Lam, Vw, Spiro, C, Laurence, Jm, Johnston, E, Hollands, Mj, Pleass, Hc, Richardson, Aj, A systematic review of clinical response and survival outcomes of downsizing systemic chemotherapy and rescue liver surgery in patients with initially unresectable colorectal liver metastases (Provisional abstract), Annals of Surgical OncologyAnn Surg Oncol, 19, 1292-1301, 2012	No relevant comparison group

Le Souder, E. B., Azin, A., Hirpara, D. H., Walker, R., Cleary, S., Quereshy, F., Considering the cost of a simultaneous versus staged approach to resection of colorectal cancer with synchronous liver metastases in a publicly funded healthcare model, Journal of Surgical Oncology., 2018	No multivariate analysis on relevant outcomes
Leblanc, F., Fonck, M., Brunet, R., Becouarn, Y., Mathoulin-Pelissier, S., Evrard, S., Comparison of hepatic recurrences after resection or intraoperative radiofrequency ablation indicated by size and topographical characteristics of the metastases, European Journal of Surgical Oncology, 34, 185-190, 2008	No multivariate analysis
Lee, B. C., Lee, H. G., Park, I. J., Kim, S. Y., Kim, K. H., Lee, J. H., Kim, C. W., Lee, J. L., Yoon, Y. S., Lim, S. B., Yu, C. S., Kim, J. C., The role of radiofrequency ablation for treatment of metachronous isolated hepatic metastasis from colorectal cancer, Medicine, 95, 2016	Populations are not similar and would not both be candidates for both approaches compared
Lee, H., Heo, J. S., Cho, Y. B., Yun, S. H., Kim, H. C., Lee, W. Y., Choi, S. H., Choi, D. W., Hepatectomy vs radiofrequency ablation for colorectal liver metastasis: A propensity score analysis, World Journal of Gastroenterology, 21, 3300-3307, 2015	Populations are not similar and would not both be candidates for both approaches compared
Lee, K. H., Kim, H. O., Yoo, C. H., Son, B. H., Park, Y. L., Cho, Y. K., Kim, H., Han, W. K., Comparison of radiofrequency ablation and resection for hepatic metastasis from colorectal cancer, The Korean journal of gastroenterology = Taehan Sohwagi Hakhoe chi, 59, 218-223, 2012	Populations are not similar and would not both be candidates for both approaches compared
Lee, W. S., Yun, S. H., Chun, H. K., Lee, W. Y., Kim, S. J., Choi, S. H., Heo, J. S., Joh, J. W., Choi, D., Kim, S. H., Rhim, H., Lim, H. K., Clinical outcomes of hepatic resection and radiofrequency ablation in patients with solitary colorectal liver metastasis, Journal of Clinical Gastroenterology, 42, 945-949, 2008	Populations are not similar and would not both be candidates for both approaches compared
Lehmann, K., Rickenbacher, A., Weber, A., Pestalozzi, B. C., Clavien, P. A., Chemotherapy before liver resection of colorectal metastases: friend or foe?, Annals of Surgery, 255, 237-47, 2012	Single-arm studies included, no relevant comparison
Leung, E. Y. L., Roxburgh, C. S. D., Leen, E., Horgan, P. G., Combined resection and radiofrequency ablation for bilobar colorectal cancer liver metastases, Hepato-Gastroenterology, 57, 41-46, 2010	Observational study, no multivariate analysis
Leung, U., Kuk, D., D'Angelica, M. I., Kingham, T. P., Allen, P. J., DeMatteo, R. P., Jarnagin, W. R., Fong, Y., Long-term outcomes following microwave ablation for liver malignancies, The British journal of surgery, 102, 85-91, 2015	No comparison group, population includes non-colorectal cancer liver malignancies
Li, Y., Bi, X., Zhao, J., Huang, Z., Zhou, J., Li, Z., Zhang, Y., Zhao, H., Cai, J., Simultaneous hepatic resection benefits patients with synchronous colorectal cancer liver metastases, Chinese Journal of Cancer Research, 28, 528-535, 2016	No relevant results reported from multivariate analysis
Li, Yj, Che, Xm, Gan, Jx, Chaudhary, P, Liao, Xh, Zhang, Dj, Bi, Tq, Comparison between simultaneous resection and staged resection for synchronous colorectal liver metastasis: a meta-analysis (Provisional abstract), Journal of Xi'an Jiaotong University (Medical Sciences), 33, 365-369, 2012	Full text not in English
Li, Z. Q., Liu, K., Duan, J. C., Li, Z., Su, C. Q., Yang, J. H., Meta-analysis of simultaneous versus staged resection for synchronous colorectal liver metastases, Hepatology Research, 43, 72-83, 2013	A systematic review, included studies checked for relevance

Lichun, D., Dazhong, Z., Wei Sheng, S., Xiongwei, L., Huaming, S., Lei, X., Jie, Z., Xiangming, C., Clinical observation of laser ablation combined with chemotherapy in postoperative colorectal cancers with liver metastasis, Minerva chirurgica, 72, 18-23, 2017	Observational study, RCT evidence available for ablation and chemotherapy
Lim, C., Doussot, A., Osseis, M., Salloum, C., Gomez Gavara, C., Compagnon, P., Brunetti, F., Calderaro, J., Azoulay, D., Primary Tumor Versus Liver-First Strategy in Patients with Stage IVA Colorectal Cancer: A Propensity Score Analysis of Long-term Outcomes and Recurrence Pattern, Annals of Surgical Oncology, 23, 3024-3032, 2016	Populations are not similar and would not both be candidates for the approaches compared
Liu, W., Zhou, J. G., Sun, Y., Zhang, L., Xing, B. C., The role of neoadjuvant chemotherapy for resectable colorectal liver metastases: A systematic review and meta-analysis, Oncotarget, 7, 37277-37287, 2016	A systematic review, included studies checked for relevance
Liu, Y., Li, S., Wan, X., Li, Y., Li, B., Zhang, Y., Yuan, Y., Zheng, Y., Efficacy and safety of thermal ablation in patients with liver metastases, European Journal of Gastroenterology and Hepatology, 25, 442-446, 2013	Population includes non-colorectal liver malignancies, no subgroup analysis reported comparing relevant interventions
Lorenz, M., Muller, H. H., Staib-Sebler, E., Vetter, G., Gog, C., Petrowsky, H., Kohne, C. H., Relevance of neoadjuvant and adjuvant treatment for patients with resectable liver metastases of colorectal carcinoma, Langenbeck's Archives of Surgery, 384, 328-338, 1999	No relevant comparison
Lubezky, N., Geva, R., Shmueli, E., Nakache, R., Klausner, J. M., Figer, A., Ben-Haim, M., Is there a survival benefit to neoadjuvant versus adjuvant chemotherapy, combined with surgery for resectable colorectal liver metastases?, World Journal of Surgery, 33, 1028-1034, 2009	Observational study, no multivariate analysis
Luo, Y., Wang, L., Chen, C., Chen, D., Huang, M., Huang, Y., Peng, J., Lan, P., Cui, J., Cai, S., Wang, J., Simultaneous Liver and Colorectal Resections Are Safe for Synchronous Colorectal Liver Metastases, Journal of Gastrointestinal Surgery, 14, 1974-1980, 2010	No relevant outcomes reported from multivariate analysis
Lupinacci, R. M., Andraus, W., De Paiva Haddad, L. B., Carneiro Dalbuquerque, L. A., Herman, P., Simultaneous laparoscopic resection of primary colorectal cancer and associated liver metastases: A systematic review, Techniques in Coloproctology, 18, 129-135, 2014	No relevant comparison group
Lyass, S., Zamir, G., Matot, I., Goitein, D., Eid, A., Jurim, O., Combined colon and hepatic resection for synchronous colorectal liver metastases, Journal of Surgical Oncology, 78, 17-21, 2001	Observational study, no adjustments made on statistical analysis for differences between groups
Lykoudis, P. M., O'Reilly, D., Nastos, K., Fusai, G., Systematic review of surgical management of synchronous colorectal liver metastases, British Journal of Surgery, 101, 605-612, 2014	A systematic review, included studies checked for relevance
Makowiec, F., Bronsert, P., Klock, A., Hopt, U. T., Neeff, H. P., Prognostic influence of hepatic margin after resection of colorectal liver metastasis: role of modern preoperative chemotherapy, International Journal of Colorectal Disease, 33, 71-78, 2018	Observational study, RCT evidence exists and prioritised
Malik, H. Z., Farid, S., Al-Mukthar, A., Anthoney, A., Toogood, G. J., Lodge, J. P. A., Prasad, K. R., A critical appraisal of the role of neoadjuvant chemotherapy for colorectal liver metastases: A	Observational study, RCT evidence exists and prioritised

case-controlled study, Annals of Surgical Oncology, 14, 3519-3526, 2007	
Mao, R., Zhao, J. J., Zhao, H., Zhang, Y. F., Bi, X. Y., Li, Z. Y., Zhou, J. G., Wu, X. L., Xiao, C., Cai, J. Q., Non-response to preoperative chemotherapy is a contraindication to hepatectomy plus radiofrequency ablation in patients with colorectal liver metastases, Oncotarget, 8, 75151-75161, 2017	No relevant comparison
Martin, Ii R. C. G., Augenstein, V., Reuter, N. P., Scoggins, C. R., McMasters, K. M., Simultaneous Versus Staged Resection for Synchronous Colorectal Cancer Liver Metastases, Journal of the American College of Surgeons, 208, 842-850, 2009	No relevant outcomes reported from multivariate analysis
Martin, R., Paty, P. B., Fong, Y., Grace, A., Cohen, A., DeMatteo, R., Jarnagin, W., Blumgart, L., Galandiuk, S., Paty, P., Simultaneous liver and colorectal resections are safe for synchronous colorectal liver metastasis, Journal of the American College of Surgeons, 197, 233-242, 2003	No relevant outcomes reported from multivariate analysis
Mayo, S. C., Pulitano, C., Marques, H., Lamelas, J., Wolfgang, C. L., De Saussure, W., Choti, M. A., Gindrat, I., Aldrighetti, L., Barrosso, E., Mentha, G., Pawlik, T. M., Surgical management of patients with synchronous colorectal liver metastasis: A multicenter international analysis. Journal of the American College of Surgeons, 216, 707-18, 2013	Population not relevant. Included in review D2a
McKay, A., Fradette, K., Lipschitz, J., Long-term outcomes following hepatic resection and radiofrequency ablation of colorectal liver metastases, HPB Surgery, 2009, 346863, 2009	Populations are not similar and would not both be candidates for both approaches compared
Mehta, N. N., Ravikumar, R., Coldham, C. A., Buckels, J. A. C., Hubscher, S. G., Bramhall, S. R., Wigmore, S. J., Mayer, A. D., Mirza, D. F., Effect of preoperative chemotherapy on liver resection for colorectal liver metastases, European Journal of Surgical Oncology, 34, 782-786, 2008	Observational study, RCT evidence exists and prioritised
Meijerink, M. R., Puijk, R. S., van Tilborg, A. A. J. M., Henningsen, K. H., Fernandez, L. G., Neyt, M., Heymans, J., Frankema, J. S., de Jong, K. P., Richel, D. J., Prevoo, W., Vlayen, J., Radiofrequency and Microwave Ablation Compared to Systemic Chemotherapy and to Partial Hepatectomy in the Treatment of Colorectal Liver Metastases: A Systematic Review and Meta-Analysis, CardioVascular and Interventional Radiology, 1-16, 2018	A systematic review, included studies checked for relevance
Mima, K., Beppu, T., Chikamoto, A., Miyamoto, Y., Nakagawa, S., Kuroki, H., Okabe, H., Hayashi, H., Sakamoto, Y., Watanabe, M., Kikuchi, K., Baba, H., Hepatic resection combined with radiofrequency ablation for initially unresectable colorectal liver metastases after effective chemotherapy is a safe procedure with a low incidence of local recurrence, International Journal of Clinical Oncology, 18, 847-855, 2013	Population not relevant, this study compares resection versus resection RFA in patients unresectable liver metastasis at presentation that became resectable after chemotherapy
Minagawa, M., Yamamoto, J., Miwa, S., Sakamoto, Y., Kokudo, N., Kosuge, T., Miyagawa, S. I., Makuuchi, M., Selection criteria for simultaneous resection in patients with synchronous liver metastasis, Archives of Surgery, 141, 1006-1012, 2006	No multivariate analysis on relevant outcomes
Minami, Y., Kudo, M., Radiofrequency ablation of liver metastases from colorectal cancer: A literature review, Gut and Liver, 7, 1-6, 2013	Not a systematic review. No comparison group considered
Mitry, E., Fields, A. L. A., Bleiberg, H., Labianca, R., Portier, G., Tu, D., Nitti, D., Torri, V., Elias, D., O'Callaghan, C., Langer, B., Martignoni, G., Bouche, O., Lazorthes, F., Van Cutsem, E.,	Population not relevant. Included in review D2a

Bedenne, L., Moore, M. J., Rougier, P., Adjuvant chemotherapy after potentially curative resection of metastases from colorectal cancer: A pooled analysis of two randomized trials. Journal of Clinical Oncology, 26, 4906-11, 2008	
Moug, S. J., Smith, D., Leen, E., Roxburgh, C., Horgan, P. G., Evidence for a synchronous operative approach in the treatment of colorectal cancer with hepatic metastases: a case matched study. European Journal of Surgical Oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology, 36, 365-70,2010	Population not relevant. Included in review D2a
Muangkaew, P., Cho, J. Y., Han, H. S., Yoon, Y. S., Choi, Y., Jang, J. Y., Choi, H., Jang, J. S., Kwon, S. U., Outcomes of Simultaneous Major Liver Resection and Colorectal Surgery for Colorectal Liver Metastases, Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract, 20, 554-563, 2016	No multivariate analysis for relevant outcomes
Mulier, S., Ni, Y., Jamart, J., Michel, L., Marchal, G., Ruers, T., Radiofrequency ablation versus resection for resectable colorectal liver metastases: Time for a randomized trial?, Annals of Surgical Oncology, 15, 144-157, 2008	A literature review, not systematic, no meta-analysis, comparative studies checked individually for relevance
Nakajima, K., Takahashi, S., Saito, N., Kotaka, M., Konishi, M., Gotohda, N., Kato, Y., Kinoshita, T., Predictive Factors for Anastomotic Leakage after Simultaneous Resection of Synchronous Colorectal Liver Metastasis, Journal of Gastrointestinal Surgery, 16, 821-827, 2012	No comparison group
Nanji, S., Mackillop, W. J., Wei, X., Booth, C. M., Simultaneous resection of primary colorectal cancer and synchronous liver metastases: a population-based study, Canadian journal of surgery, Journal canadien de chirurgie. 60, 122-128, 2017	No multivariate analysis on relevant comparison/outcome
Nasyrov, Ar, Pirtskhalava, Tl, Korovina, IaV, Chemotherapy in patients with non-resectable colorectal cancer metastases to the liver: systemic or regional?, Voprosy onkologii, 57, 192-198, 2011	Non-English language paper
Nelson, R. L., Freels, S., A Systematic Review of Hepatic Artery Chemotherapy after Hepatic Resection of Colorectal Cancer Metastatic to the Liver, Diseases of the Colon and Rectum, 47, 739-745, 2004	No interventions of interest
Nelson, R. L., Freels, S., Hepatic artery adjuvant chemotherapy for patients having resection or ablation of colorectal cancer metastatic to the liver, Cochrane Database of Systematic Reviews, (4) (no pagination), 2009	No interventions of interest
Nicoli, N., Casaril, A., Mangiante, G., Ciola, M., Hilal, M. A., Marchiori, L., Surgical treatment for liver metastases from colorectal carcinoma: Results of 228 patients, Hepato-Gastroenterology, 51, 1810-1814, 2004	Case series, no relevant comparison group
Nigri, G., Petrucciani, N., Ferla, F., La Torre, M., Aurello, P., Ramacciato, G., Neoadjuvant chemotherapy for resectable colorectal liver metastases: what is the evidence? Results of a systematic review of comparative studies, The surgeon : journal of the Royal Colleges of Surgeons of Edinburgh and Ireland, 13, 83-90, 2015	A systematic review, included studies checked for relevance
Nikfarjam, M., Shereef, S., Kimchi, E. T., Gusani, N. J., Jiang, Y., Avella, D. M., Mahraj, R. P., Staveley-O'Carroll, K. F., Survival outcomes of patients with colorectal liver metastases following hepatic resection or ablation in the era of effective	No comparison group

chemotherapy, Annals of Surgical Oncology, 16, 1860-1867, 2009	
Nishioka, Y., Moriyama, J., Matoba, S., Kuroyanagi, H., Hashimoto, M., Shindoh, J., Prognostic Impact of Adjuvant Chemotherapy after Hepatic Resection for Synchronous and Early Metachronous Colorectal Liver Metastases, Digestive Surgery, 35, 187-195, 2018	Observational study, RCT evidence prioritised
Nishiwada, S., Ko, S., Mukogawa, T., Ishikawa, H., Matsusaka, M., Nakatani, T., Kikuchi, E., Watanabe, A., Comparison between percutaneous radiofrequency ablation and surgical hepatectomy focusing on local disease control rate for colorectal liver metastases, Hepato-Gastroenterology, 61, 436-441, 2014	Populations are not similar and would not both be candidates for both approaches compared
Nordlinger, B., Sorbye, H., Glimelius, B., Poston, G. J., Schlag, P. M., Rougier, P., Bechstein, W. O., Primrose, J. N., Walpole, E. T., Finch-Jones, M., Jaeck, D., Mirza, D., Parks, R. W., Collette, L., Praet, M., Bethe, U., Van Cutsem, E., Scheithauer, W., Gruenberger, T., Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. The Lancet, 371, 1007-16, 2008	Population not relevant. Included in review D2a
Nordlinger, B., Sorbye, H., Glimelius, B., Poston, G. J., Schlag, P. M., Rougier, P., Bechstein, W. O., Primrose, J. N., Walpole, E. T., Finch-Jones, M., Jaeck, D., Mirza, D., Parks, R. W., Mauer, M., Tanis, E., Van Cutsem, E., Scheithauer, W., Gruenberger, T., Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): Long-term results of a randomised, controlled, phase 3 trial. The Lancet Oncology, 14, 1208-15, 2013	Population not relevant. Included in review D2a
Oh, S. Y., Kim, D. Y., Kim, Y. B., Suh, K. W., Comparison of oncological outcomes between neoadjuvant and adjuvant chemotherapy combined with surgery for resectable synchronous colorectal liver metastases, Journal of Surgical Research, 182, 257-263, 2013	Observational study, no multivariate analysis
Oshowo, A., Gillams, A. R., Lees, W. R., Taylor, I., Radiofrequency ablation extends the scope of surgery in colorectal liver metastases, European Journal of Surgical Oncology, 29, 244-247, 2003	Case series, no comparison
Oshowo, A., Gillams, A., Harrison, E., Lees, W. R., Taylor, I., Comparison of resection and radiofrequency ablation for treatment of solitary colorectal liver metastases, British Journal of Surgery, 90, 1240-1243, 2003	Populations are not similar and would not both be candidates for both approaches compared
Otto, G., Duber, C., Hoppe-Lotichius, M., Konig, J., Heise, M., Bernhard Pitton, M., Radiofrequency ablation as first-line treatment in patients with early colorectal liver metastases amenable to surgery, Annals of Surgery, 251, 796-803, 2010	Populations are not similar and would not both be candidates for both approaches compared
Ouaissi, M., Moutardier, V., Ramuz, O., Cherki, S., Lelong, B., Turrini, O., Guiramand, J., Delpero, J. R., Preoperative systemic chemotherapy does not modify strategy of liver resection, Hepato-Gastroenterology, 53, 405-408, 2006	Observational study, RCT evidence exists and prioritised
Ouchi, A., Shimizu, Y., Komori, K., Senda, Y., Kinoshita, T., Natsume, S., Ooshiro, T., The role of liver resection after chemotherapy for synchronous colorectal liver metastasis, United European Gastroenterology Journal, 5 (5 Supplement 1), A490-A491, 2017	Conference abstract

Padman, S., Padbury, R., Beeke, C., Karapetis, C. S., Bishnoi, S., Townsend, A. R., Maddern, G., Price, T. J., Liver only metastatic disease in patients with metastatic colorectal cancer: Impact of surgery and chemotherapy, Acta Oncologica, 52, 1699-1706, 2013	Populations compared are not relevant for comparison according to the review, people with resectable (resection group) and unresectable (chemotherapy group) liver metastasis compared
Parc, Y., Dugue, L., Farges, O., Hiramatsu, K., Sauvanet, A., Belghiti, J., Preoperative systemic 5-fluorouracil does not increase the risk of liver resection, Hepato-Gastroenterology, 47, 1703-1705, 2000	No relevant comparison group
Parikh, A. A., Gentner, B., Wu, T. T., Curley, S. A., Ellis, L. M., Vauthey, J. N., Perioperative complications in patients undergoing major liver resection with or without neoadjuvant chemotherapy, Journal of Gastrointestinal Surgery, 7, 1082-1088, 2003	Observational study, RCT evidence exists and prioritised
Park, I. J., Kim, H. C., Yu, C. S., Kim, P. N., Won, H. J., Kim, J. C., Radiofrequency ablation for metachronous liver metastasis from colorectal cancer after curative surgery, Annals of Surgical Oncology, 15, 227-232, 2008	Populations are not similar and would not both be candidates for both approaches compared
Parks, R., Gonen, M., Kemeny, N., Jarnagin, W., D'Angelica, M., DeMatteo, R., Garden, O. J., Blumgart, L. H., Fong, Y., Adjuvant chemotherapy improves survival after resection of hepatic colorectal metastases: analysis of data from two continents, Journal of the American College of Surgeons, 204, 753-61; discussion 761-3, 2007	Observational study, RCT evidence prioritised
Pathak, S., Jones, R., Tang, J. M. F., Parmar, C., Fenwick, S., Malik, H., Poston, G., Ablative therapies for colorectal liver metastases: A systematic review, Colorectal Disease, 13, e252-e265, 2011	A systematic review, included studies checked for relevance
Patrono, D., Paraluppi, G., Perino, M., Palisi, M., Migliaretti, G., Berchialla, P., Romagnoli, R., Salizzoni, M., Posthepatectomy liver failure after simultaneous versus staged resection of colorectal cancer and synchronous hepatic metastases, Il Giornale di chirurgia, 35, 86-93, 2014	Population not relevant. Included in review D2a
Pech, M., Wieners, G., Kryza, R., Dudeck, O., Seidensticker, M., Mohnike, K., Redlich, U., Ruhl, R., Wust, P., Gademann, G., Ricke, J., CT-guided brachytherapy (CTGB) versus interstitial laser ablation (ILT) of colorectal liver metastases: An intraindividual matched-pair analysis, Strahlentherapie und Onkologie, 184, 302-306, 2008	No relevant intervention/comparison, all patients received both CTGB and ILT
Pennington, B., Akehurst, R., Wasan, H., Sangro, B., Kennedy, A. S., Sennfalt, K., Bester, L., 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, 797-804, 2015	Health economic analysis, studies with clinical evidence used in the model checked individually for relevance
Petre, E. N., Sofocleous, C., Thermal ablation in the management of colorectal cancer patients with oligometastatic liver disease, Visceral Medicine, 33, 62-68, 2017	Selective, non-systematic narrative review
Philips, P., Groeschl, R. T., Hanna, E. M., Swan, R. Z., Turaga, K. K., Martinie, J. B., Iannitti, D. A., Schmidt, C., Gamblin, T. C., Martin, R. C., Single-stage resection and microwave ablation for bilobar colorectal liver metastases, The British journal of surgery, 103, 1048-1054, 2016	Intervention/comparison not relevant. The original study compares MWA to resection MWA, in this comparison the populations are different and thus not comparable. The study also compares MWA with or

	without resection to 2-stage hepatectomy (data from other studies), which is not relevant according to the protocol
Philips, P., Scoggins, C. R., Rostas, J. K., McMasters, K. M., Martin, R. C., Safety and advantages of combined resection and microwave ablation in patients with bilobar hepatic malignancies, International Journal of Hyperthermia, 33, 43-50, 2017	Unclear if multivariate analysis done on outcomes of interest and what variables were included in the model
Pinto Marques, H., Barroso, E., De Jong, M. C., Choti, M. A., Ribeiro, V., Nobre, A. M., Carvalho, C., Pawlik, T. M., Peri-operative chemotherapy for resectable colorectal liver metastasis: Does timing of systemic therapy matter?, Journal of Surgical Oncology, 105, 511-519, 2012	Observational study, RCT evidence exists and prioritised
Pommier, R., Ronot, M., Cauchy, F., Gaujoux, S., Fuks, D., Faivre, S., Belghiti, J., Vilgrain, V., Colorectal liver metastases growth in the embolized and non-embolized liver after portal vein embolization: Influence of initial response to induction chemotherapy, Annals of Surgical Oncology, 21, 3077-3083, 2014	Intervention/comparison not relevant
Portier, G., Elias, D., Bouche, O., Rougier, P., Bosset, J. F., Saric, J., Belghiti, J., Piedbois, P., Guimbaud, R., Nordlinger, B., Bugat, R., Lazorthes, F., Bedenne, L., Multicenter randomized trial of adjuvant fluorouracil and folinic acid compared with surgery alone after resection of colorectal liver metastases: FFCD ACHBTH AURC 9002 trial, Journal of Clinical Oncology, 24, 4976-4982, 2006	Population not relevant, included in review D2a
Poulou, L. S., Thanos, L., Ziakas, P. D., Merikas, E., Achimastos, A. L., Gennatas, C., Syrigos, K. N., Thermal ablation may improve outcomes in patients with colorectal liver metastasis: A case-control study, Journal of B.U.ON., 22, 673-678, 2017	Observational study, RCT evidence prioritised
Poultsides, G. A., Bao, F., Servais, E. L., Hernandez-Boussard, T., Dematteo, R. P., Allen, P. J., Fong, Y., Kemeny, N. E., Saltz, L. B., Klimstra, D. S., Jarnagin, W. R., Shia, J., D'Angelica, M. I., Pathologic response to preoperative chemotherapy in colorectal liver metastases: Fibrosis, not necrosis, predicts outcome, Annals of Surgical Oncology, 19, 2797-2804, 2012	Preoperative chemotheraoy vs no preoperative chemotherapy, no outcomes of interest
Poultsides, G. A., Servais, E. L., Saltz, L. B., Patil, S., Kemeny, N. E., Guillem, J. G., Weiser, M., Temple, L. K. F., Wong, W. D., Paty, P. B., Outcome of primary tumor in patients with synchronous stage IV colorectal cancer receiving combination chemotherapy without surgery as initial treatment, Journal of Clinical OncologyJ Clin Oncol, 27, 3379-3384, 2009	No relevant intervention/comparison
Quan, D., Gallinger, S., Nhan, C., Auer, R. A., Biagi, J. J., Fletcher, G. G., Law, C. H. L., Moulton, C. A. E., Ruo, L., Wei, A. C., McLeod, R. S., The role of liver resection for colorectal cancer metastases in an era of multimodality treatment: A systematic review, Surgery (United States), 151, 860-870, 2012	A systematic review, included studies checked for relevance
Rahbari, N. N., Reissfelder, C., Schulze-Bergkamen, H., Jager, D., Buchler, M. W., Weitz, J., Koch, M., Adjuvant therapy after resection of colorectal liver metastases: The predictive value of the MSKCC clinical risk score in the era of modern chemotherapy, BMC Cancer, 14 (1) (no pagination), 2014	No relevant comparison
Reddy, S. K., Parker, R. J., Leach, J. W., Hill, M. J., Burgart, L. J., Tumor histopathology predicts outcomes after resection of colorectal cancer liver metastases treated with and without pre-	No relevant outcomes reported by relevant comparison

operative chemotherapy, Journal of Surgical Oncology, 113, 456-462, 2016	
Reddy, S. K., Pawlik, T. M., Zorzi, D., Gleisner, A. L., Ribero, D., Assumpcao, L., Barbas, A. S., Abdalla, E. K., Choti, M. A., Vauthey, J. N., Ludwig, K. A., Mantyh, C. R., Morse, M. A., Clary, B. M., Simultaneous resections of colorectal cancer and synchronous liver metastases: A multi-institutional analysis, Annals of Surgical Oncology, 14, 3481-3491, 2007	No relevant results reported that were analysed in an appropriate way
Reddy, S. K., Tsung, A., Marsh, J. W., Geller, D. A., Does neoadjuvant chemotherapy reveal disease precluding surgical treatment of initially resectable colorectal cancer liver metastases?, Journal of Surgical Oncology, 105, 55-59, 2012	Preoperative chemotherspy versus no preoperative chemotherapy, no outcomes of interest
Reddy, S. K., Zorzi, D., Lum, Y. W., Barbas, A. S., Pawlik, T. M., Ribero, D., Abdalla, E. K., Choti, M. A., Kemp, C., Vauthey, J. N., Morse, M. A., White, R. R., Clary, B. M., Timing of multimodality therapy for resectable synchronous colorectal liver metastases: A retrospective multi-institutional analysis, Annals of Surgical Oncology, 16, 1809-1819, 2009	Observational study, comparison not of relevance
Reding, D., Pestalozzi, B. C., Breitenstein, S., Stupp, R., Clavien, P. A., Slankamenac, K., Samaras, P., Treatment strategies and outcome of surgery for synchronous colorectal liver metastases, Swiss Medical Weekly, 147 (no pagination), 2017	Unclear if multivariate analysis was conducted on relevant outcome (survival)
Reissfelder, C., Rahbari, N. N., Bejarano, L. U., Schmidt, T., Kortes, N., Kauczor, H. U., Buchler, M. W., Weitz, J., Koch, M., Comparison of various surgical approaches for extensive bilateral colorectal liver metastases, Langenbeck's Archives of Surgery, 399, 481-491, 2014	No relevant intervention/comparison
Reuter, N. P., Woodall, C. E., Scoggins, C. R., McMasters, K. M., Martin, R. C. G., Radiofrequency Ablation vs. Resection for hepatic colorectal metastasis: Therapeutically equivalent?, Journal of Gastrointestinal Surgery, 13, 486-491, 2009	Populations are not similar and would not both be candidates for both approaches compared
Richardson, A. J., Laurence, J. M., Lam, V. W. T., Transarterial chemoembolization with irinotecan beads in the treatment of colorectal liver metastases: Systematic review, Journal of Vascular and Interventional Radiology, 24, 1209-1217, 2013	Systematic review of DEBIRI, individual studies checked for relevance
Riemsma, R. P., Bala, M. M., Wolff, R., Kleijnen, J., Transarterial (chemo)embolisation versus no intervention or placebo intervention for liver metastases, The Cochrane database of systematic reviews, 4, CD009498, 2013	The only study included not relevant for the review
Rosenbaum, C. E. N. M., Verkooijen, H. M., Lam, M. G. E. H., Smits, M. L. J., Koopman, M., Van Seeters, T., Vermoolen, M. A., Van Den Bosch, M. A. A. J., Radioembolization for treatment of salvage patients with colorectal cancer liver metastases: A systematic review, Journal of Nuclear Medicine, 54, 1890-1895, 2013	Systematic review about radioembolization, no relevant comparison group, individual studies checked for relevance
Ruers, T. J., Joosten, J. J., Wiering, B., Langenhoff, B. S., Dekker, H. M., Wobbes, T., Oyen, W. J., Krabbe, P. F., Punt, C. J., Comparison between local ablative therapy and chemotherapy for non-resectable colorectal liver metastases: a prospective study, Annals of surgical oncology : the official journal of the Society of Surgical Oncology, 14, 1161-1169, 2007	Observational study, no adjustments made in analyses for differences between groups
Sabanathan, D., Eslick, G. D., Shannon, J., Use of Neoadjuvant Chemotherapy Plus Molecular Targeted Therapy in Colorectal	Interventions not relevant for this review

Liver Metastases: A Systematic Review and Meta-analysis, Clinical Colorectal Cancer, 15, e141-e147, 2016	
Sabbagh, C., Cosse, C., Ravololoniaina, T., Chauffert, B., Joly, J. P., Mauvais, F., Regimbeau, J. M., Oncological strategies for middle and low rectal cancer with synchronous liver metastases, International Journal of Surgery, Part A. 23, 186-193, 2015	No relevant comparison
Sahajpal, A., Vollmer Jr, C. M., Dixon, E., Chan, E. K., Wei, A., Cattral, M. S., Taylor, B. R., Grant, D. R., Greig, P. D., Gallinger, S., Chemotherapy for colorectal cancer prior to liver resection for colorectal cancer hepatic metastases does not adversely affect peri-operative outcomes, Journal of Surgical Oncology, 95, 22-27, 2007	Observational study, RCT evidence exists and prioritised
Sahay, S. J., Glynne-Jones, R., Davidson, B. R., Current evidence for chemotherapy, chemoradiation, and the liver-first approach for the management of patients with rectal cancer and synchronous liver metastases, Current Colorectal Cancer Reports, 10, 147-156, 2014	Review, no relevant comparative evidence presented
Saif, S., Kielar, A. Z., McInnes, M., Systematic review of 12 years of thermal ablative therapies of non-resectable colorectal cancer liver metastases, Gastrointestinal Intervention, 5, 27-39, 2016	A systematic review, included studies checked for relevance
Sakamoto, K., Honda, G., Beppu, T., Kotake, K., Yamamoto, M., Takahashi, K., Endo, I., Hasegawa, K., Itabashi, M., Hashiguchi, Y., Kotera, Y., Kobayashi, S., Yamaguchi, T., Morita, S., Miyazaki, M., Sugihara, K., Comprehensive data of 3,820 patients newly diagnosed with colorectal liver metastasis between 2005 and 2007: report of a nationwide survey in Japan, Journal of Hepato-Biliary-Pancreatic Sciences, 25, 115-123, 2018	No comparison group
Salvador-Roses, H., Lopez-Ben, S., Planellas, P., Canals, E., Casellas-Robert, M., Farres, R., Ramos, E., Codina-Cazador, A., Figueras, J., Treatment strategies for rectal cancer with synchronous liver metastases: surgical and oncological outcomes with propensity-score analysis, Clinical and Translational Oncology, 20, 221-229, 2018	Populations are not similar and would not both be candidates for the approaches compared
Sangha, B. S., Nimeiri, H., Hickey, R., Salem, R., Lewandowski, R. J., Radioembolization as a Treatment Strategy for Metastatic Colorectal Cancer to the Liver: What Can We Learn from the SIRFLOX Trial?, Current Treatment Options in Oncology, 17 (6) (no pagination), 2016	Ex[pert review and summarises results from the SIRFLOX trial (reported in another publication)
Sasaki, K., Margonis, G. A., Andreatos, N., Kim, Y., Wilson, A., Gani, F., Amini, N., Pawlik, T. M., Combined resection and RFA in colorectal liver metastases: stratification of long-term outcomes, Journal of Surgical Research, 206, 182-189, 2016	Observational study, relevant analysis not adjusted for differences between the groups
Saxena, A., Bester, L., Shan, L., Perera, M., Gibbs, P., Meteling, B., Morris, D. L., A systematic review on the safety and efficacy of yttrium-90 radioembolization for unresectable, chemorefractory colorectal cancer liver metastases, Journal of Cancer Research and Clinical Oncology, 140, 537-547, 2014	Systematic review, individual studies checked for relevance
Scaife, C. L., Curley, S. A., Izzo, F., Marra, P., Delrio, P., Daniele, B., Cremona, F., Gershenwald, J. E., Chase, J. L., Lozano, R. D., Patt, Y. Z., Fornage, B. D., Vauthey, J. N., Woodall, M. L., Gonzalez, K. B., Ellis, L. M., Feasibility of adjuvant hepatic arterial infusion of chemotherapy after radiofrequency ablation with or without resection in patients with	No relevant intervention/comparison

hepatic metastases from colorectal cancer, Annals of Surgical Oncology, 10, 348-354, 2003	
Scartozzi, M., Siquini, W., Galizia, E., Stortoni, P., Marmorale, C., Berardi, R., Fianchini, A., Cascinu, S., The timing of surgery for resectable metachronous liver metastases from colorectal cancer: Better sooner than later? A retrospective analysis, Digestive and Liver Disease, 43, 194-198, 2011	Observational study, RCT evidence exists and prioritised
Schiffman, S. C., Bower, M., Brown, R. E., Martin, R. C., McMasters, K. M., Scoggins, C. R., Hepatectomy is superior to thermal ablation for patients with a solitary colorectal liver metastasis, J Gastrointest SurgJournal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract, 14, 1881-6; discussion 1886-7, 2010	Populations are not similar and would not both be candidates for both approaches compared
Scilletta, R., Pagano, D., Spada, M., Mongiovi, S., Pesce, A., Portale, T. R., Guardabasso, V., Puleo, S., Gruttadauria, S., Comparative analysis of the incidence of surgical site infections in patients with liver resection for colorectal hepatic metastases after neoadjuvant chemotherapy, Journal of Surgical Research, 188, 183-189, 2014	Observational study, RCT evidence exists and prioritised
Scoggins, C. R., Campbell, M. L., Landry, C. S., Slomiany, B. A., Woodall, C. E., McMasters, K. M., Martin, R. C. G., Preoperative chemotherapy does not increase morbidity or mortality of hepatic resection for colorectal cancer metastases, Annals of Surgical Oncology, 16, 35-41, 2009	Observational study, RCT evidence exists and prioritised
Seidensticker, R., Denecke, T., Kraus, P., Seidensticker, M., Mohnike, K., Fahlke, J., Kettner, E., Hildebrandt, B., Dudeck, O., Pech, M., Amthauer, H., Ricke, J., Matched-pair comparison of radioembolization plus best supportive care versus best supportive care alone for chemotherapy refractory liver-dominant colorectal metastases, CardioVascular and Interventional Radiology, 35, 1066-1073, 2012	Observational study, RCT data on radioemobolisation available and prioritised
Shady, W., Petre, E. N., Do, K. G., Gonen, M., Yarmohammadi, H., Brown, K. T., Kemeny, N. E., D'Angelica, M., Kingham, P. T., Solomon, S. B., Sofocleous, C. T., Percutaneous Microwave versus Radiofrequency Ablation of Colorectal Liver Metastases: Ablation with Clear Margins (A0) Provides the Best Local Tumor Control, Journal of Vascular and Interventional Radiology, 29, 268-275.e1, 2018	Comparison not relevant
Shao, Y. C., Chang, Y. Y., Lin, J. K., Lin, C. C., Wang, H. S., Yang, S. H., Jiang, J. K., Lan, Y. T., Lin, T. C., Li, A. F. Y., Chen, W. S., Chang, S. C., Neoadjuvant chemotherapy can improve outcome of colorectal cancer patients with unresectable metastasis, International Journal of Colorectal Disease, 28, 1359-1365, 2013	Intervention/comparison not relevant
Sharma, Ra, Wasan, Hs, Hazel, Ga, Heinemann, V, Sharma, Nk, Taieb, J, Ricke, J, Mills, J, Tait, Np, Boardman, P, Peeters, M, Findlay, Mpn, Virdee, Ps, Moschandreas, J, Gebski, V, Love, S, Gray, A, Gibbs, P, Overall survival analysis of the FOXFIRE prospective randomized studies of first-line selective internal radiotherapy (SIRT) in patients with liver metastases from colorectal cancer, Journal of clinical oncology. Conference: 2017 annual meeting of the american society of clinical oncology, ASCO. United states, 35, 2017	Conference abstract
She, W. H., Chan, A. C., Poon, R. T., Cheung, T. T., Chok, K. S., Chan, S. C., Lo, C. M., Defining an optimal surgical strategy for synchronous colorectal liver metastases: staged versus	Observational study, no multivariate analysis

simultaneous resection?, ANZ Journal of Surgery, 85, 829-33, 2015	
Shetty, S. K., Rosen, M. P., Raptopoulos, V., Goldberg, S. N., Cost-effectiveness of percutaneous radiofrequency ablation for malignant hepatic neoplasms, Journal of Vascular and Interventional Radiology, 12, 823-833, 2001	Health economic analysis, no original clinical data
Silberhumer, G. R., Paty, P. B., Denton, B., Guillem, J., Gonen, M., Araujo, R. L. C., Nash, G. M., Temple, L. K., Allen, P. J., DeMatteo, R. P., Weiser, M. R., Wong, W. D., Jarnagin, W. R., D'Angelica, M. I., Fong, Y., Long-term oncologic outcomes for simultaneous resection of synchronous metastatic liver and primary colorectal cancer, Surgery (United States), 160, 67-73, 2016	Not clear if multivariate analysis conducted for relevant outcome (survival)
Silberhumer, G. R., Paty, P. B., Temple, L. K., Araujo, R. L. C., Denton, B., Gonen, M., Nash, G. M., Allen, P. J., Dematteo, R. P., Guillem, J., Weiser, M. R., D'Angelica, M. I., Jarnagin, W. R., Wong, D. W., Fong, Y., Simultaneous resection for rectal cancer with synchronous liver metastasis is a safe procedure, American Journal of Surgery, 209, 935-942, 2015	No multivariate analysis
Simmonds, P C, Primrose, J N, Colquitt, J L, Garden, O J, Poston, G J, Rees, M, Surgical resection of hepatic metastases from colorectal cancer: a systematic review of published studies (Provisional abstract), British Journal of Cancer, 94, 982-999, 2006	No relevant comparison
Siriwardena, A. K., Chan, A. K. C., Ignatowicz, A. M., Mason, J. M., Sheen, A. J., O'Reilly, D. A., Jamdar, S., Deshpande, R., De Liguori Carino, N., Satyadas, T., Mullamitha, S., Braun, M., Alam, N., Hassan, J., Wilson, G., Treasure, T., Rajashankar, R., Jegatheeswaran, S., Baltatzis, M., McMahon, R., Sethi, R., Hill, J., Smith, D., Smart, C., Khan, A., Kurrimboccus, M., Epstein, J., Reid, F., Siddiqui, K., Aswatha, R., Paraoan, M., Colorectal cancer with Synchronous liver-limited Metastases: The protocol of an Inception Cohort study (CoSMIC), BMJ Open, 7 (6) (no pagination), 2017	A study protocol for a cohort study
Slesser, A. A. P., Chand, M., Goldin, R., Brown, G., Tekkis, P. P., Mudan, S., Outcomes of simultaneous resections for patients with synchronous colorectal liver metastases, European Journal of Surgical Oncology, 39, 1384-1393, 2013	No multivariate analysis
Slesser, A. A. P., Khan, F., Chau, I., Khan, A. Z., Mudan, S., Tekkis, P. P., Brown, G., Rao, S., The effect of a primary tumour resection on the progression of synchronous colorectal liver metastases: An exploratory study, European Journal of Surgical Oncology, 41, 484-492, 2015	Intervention/comparison not relevant
Slesser, A. A. P., Simillis, C., Goldin, R., Brown, G., Mudan, S., Tekkis, P. P., A meta-analysis comparing simultaneous versus delayed resections in patients with synchronous colorectal liver metastases, Surgical Oncology, 22, 36-47, 2013	A systematic review, included studies checked for relevance
Slupski, M., Wlodarczyk, Z., Jasinski, M., Masztalerz, M., Tujakowski, J., Outcomes of simultaneous and delayed resections of synchronous colorectal liver metastases, Canadian journal of surgery, 52, E241-4, 2009	No multivariate analysis
Smith, M. D., McCall, J. L., Systematic review of tumour number and outcome after radical treatment of colorectal liver metastases, British Journal of Surgery, 96, 1101-1113, 2009	No relevant comparative data presented

Smits, M. L. J., van den Hoven, A. F., Rosenbaum, C. E. N. M., Zonnenberg, B. A., Lam, M. G. E. H., Nijsen, J. F. W., Koopman, M., van den Bosch, M. A. A. J., Clinical and Laboratory Toxicity after Intra-Arterial Radioembolization with ⁹⁰Y-Microspheres for Unresectable Liver Metastases, PLoS ONE, 8 (7) (no pagination), 2013	Observational study, RCT evidence prioritised
Son, S. Y., Yi, N. J., Hong, G., Kim, H., Park, M. S., Choi, Y. R., Suh, K. S., Kim, D. W., Jeong, S. Y., Park, K. J., Park, J. G., Lee, K. U., Is neoadjuvant chemotherapy necessary for patients with initially resectable colorectal liver metastases in the era of effective chemotherapy?, Korean Journal of Hepatobiliarypancreatic Surgery, 15, 206-17, 2011	Observational study, RCT evidence exists and prioritised
Song, P., Sheng, L., Sun, Y., An, Y., Guo, Y., Zhang, Y., The clinical utility and outcomes of microwave ablation for colorectal cancer liver metastases, Oncotarget, 8, 51792-51799, 2017	Populations are not similar and would not both be candidates for both approaches compared
Sparchez, Z. A., Mocan, T., Radu, P., Cainap, C., Kacso, G., Seicean, A., Hajjar, N. Al, Outcomes of radiofrequency ablation and microwave ablation in liver metastases: A single center experience, United European Gastroenterology Journal, 4 (5 Supplement 1), A361, 2016	Conference abstract
Spelt, L., Hermansson, L., Tingstedt, B., Andersson, R., Influence of preoperative chemotherapy on the intraoperative and postoperative course of liver resection for colorectal cancer metastases, World Journal of Surgery, 36, 157-163, 2012	Observational study, RCT evidence exists and prioritised
Sperti, E., Faggiuolo, R., Gerbino, A., Magnino, A., Muratore, A., Ortega, C., Ferraris, R., Leone, F., Capussotti, L., Aglietta, M., Outcome of metastatic colorectal cancer: analysis of a consecutive series of 229 patients. The impact of a multidisciplinary approach, Diseases of the Colon & Rectum, 49, 1596-601, 2006	Patient groups compared not relevant for the review
Stang, A., Fischbach, R., Teichmann, W., Bokemeyer, C., Braumann, D., A systematic review on the clinical benefit and role of radiofrequency ablation as treatment of colorectal liver metastases, European Journal of Cancer, 45, 1748-1756, 2009	Systematic review, comparative studies checked individually for relevance
Stattner, S., Jones, R. P., Yip, V. S., Buchanan, K., Poston, G. J., Malik, H. Z., Fenwick, S. W., Microwave ablation with or without resection for colorectal liver metastases, European Journal of Surgical Oncology, 39, 844-849, 2013	Populations are not similar and would not both be candidates for both approaches compared
Stintzing, S., Grothe, A., Hendrich, S., Hoffmann, R. T., Heinemann, V., Rentsch, M., Fuerweger, C., Muacevic, A., Trumm, C. G., Percutaneous radiofrequency ablation (RFA) or robotic radiosurgery (RRS) for salvage treatment of colorectal liver metastases, Acta Oncologica, 52, 971-977, 2013	Observational study, intervention/comparison not relevant
Strowitzki, M. J., Schmidt, T., Keppler, U., Ritter, A. S., Mahmoud, S., Klose, J., Mihaljevic, A. L., Schneider, M., Buchler, M. W., Ulrich, A. B., Influence of neoadjuvant chemotherapy on resection of primary colorectal liver metastases: A propensity score analysis, Journal of Surgical Oncology, 116, 149-158, 2017	Observational study, RCT evidence exists and prioritised
Sturesson, C., Valdimarsson, V. T., Blomstrand, E., Eriksson, S., Nilsson, J. H., Syk, I., Lindell, G., Liver-first strategy for synchronous colorectal liver metastases - an intention-to-treat analysis, Hpb, 19, 52-58, 2017	Populations are not similar and would not both be candidates for the approaches compared
Sutherland, L. M., Williams, J. A. R., Padbury, R. T. A., Gotley, D. C., Stokes, B., Maddern, G. J., Radiofrequency ablation of	No relevant comparative data presented

liver tumors: A systematic review, Archives of Surgery, 141, 181-190, 2006	
Swan, P. J., Welsh, F. K. S., Chandrakumaran, K., Rees, M., Long-term survival following delayed presentation and resection of colorectal liver metastases, British Journal of Surgery, 98, 1309-1317, 2011	No relevant comparison, all groups used bowel surgery first strategy
'T Lam-Boer J, Al Ali, C., Verhoeven, R. H. A., Roumen, R. M. H., Lemmens, V. E. P. P., Rijken, A. M., De Wilt, J. H. W., Large variation in the utilization of liver resections in stage IV colorectal cancer patients with metastases confined to the liver, European Journal of Surgical Oncology, 41, 1217-1225, 2015	No relevant comparison group
Tamandl, D., Gruenberger, B., Klinger, M., Herberger, B., Kaczirek, K., Fleischmann, E., Gruenberger, T., Liver resection remains a safe procedure after neoadjuvant chemotherapy including bevacizumab: A case-controlled study, Annals of Surgery, 252, 124-130, 2010	Intervention/comparison not relevant
Tanaka, K., Murakami, T., Matsuo, K., Hiroshima, Y., Endo, I., Ichikawa, Y., Taguri, M., Koda, K., Preliminary results of 'liver-first' reverse management for advanced and aggressive synchronous colorectal liver metastases: a propensity-matched analysis, Digestive Surgery, 32, 16-22, 2015	Populations are not similar and would not both be candidates for the approaches compared
Tanaka, K., Shimada, H., Matsuo, K., Nagano, Y., Endo, I., Sekido, H., Togo, S., Outcome after simultaneous colorectal and hepatic resection for colorectal cancer with synchronous metastases, Surgery, 136, 650-659, 2004	No comparison group
Tanaka, K., Shimada, H., Nagano, Y., Endo, I., Sekido, H., Togo, S., Outcome after hepatic resection versus combined resection and microwave ablation for multiple bilobar colorectal metastases to the liver, Surgery, 139, 263-273, 2006	Observational study, multivariate analysis done but adjusted data not reported on relevant outcomes
Tanaka, K., Shimada, H., Ueda, M., Matsuo, K., Endo, I., Sekido, H., Togo, S., Perioperative complications after hepatectomy with or without intra-arterial chemotherapy for bilobar colorectal cancer liver metastases, Surgery, 139, 599-607, 2006	Intervention/comparison not relevant
Tang, J. T., Wang, J. L., Fang, J. Y., Meta-analysis: Perioperative regional liver chemotherapy for improving survival and preventing liver metastases in patients with colorectal carcinoma, Journal of Digestive Diseases, 11, 208-214, 2010	Interventions not relevant for the review
Tanis, E., Julie, C., Emile, J. F., Mauer, M., Nordlinger, B., Aust, D., Roth, A., Lutz, M. P., Gruenberger, T., Wrba, F., Sorbye, H., Bechstein, W., Schlag, P., Fisseler, A., Ruers, T., Prognostic impact of immune response in resectable colorectal liver metastases treated by surgery alone or surgery with perioperative FOLFOX in the randomised EORTC study 40983, European Journal of Cancer, 51, 2708-2717, 2015	Reports evidence from EORCT 40004 and 40983 trials, both reported separately in other publications
Tanis, E., Nordlinger, B., Mauer, M., Sorbye, H., Van Coevorden, F., Gruenberger, T., Schlag, P. M., Punt, C. J. A., Ledermann, J., Ruers, T. J. M., Local recurrence rates after radiofrequency ablation or resection of colorectal liver metastases. Analysis of the European Organisation for Research and Treatment of Cancer #40004 and #40983, European Journal of Cancer, 50, 912-919, 2014	Reports evidence from EORCT 40004 and 40983 trials, both reported separately in other publications
Tez, M., Tez, S., Radiofrequency ablation versus resection for resectable colorectal liver metastases: Time for a randomized trial?, Annals of Surgical Oncology, 15, 1804, 2008	Letter to the editor

Thelen, A., Jonas, S., Benckert, C., Spinelli, A., Lopez-Hanninen, E., Rudolph, B., Neumann, U., Neuhaus, P., Simultaneous versus staged liver resection of synchronous liver metastases from colorectal cancer, International Journal of Colorectal Disease, 22, 1269-1276, 2007	No multivariate analysis on relevant outcomes
Topal, B., Tiek, J., Fieuws, S., Aerts, R., Van Cutsem, E., Roskams, T., Prenen, H., Minimally invasive liver surgery for metastases from colorectal cancer: oncologic outcome and prognostic factors, Surgical Endoscopy, 26, 2288-98, 2012	Intervention/comparison not relevant
Townsend, A. R., Chong, L. C., Karapetis, C., Price, T. J., Selective internal radiation therapy for liver metastases from colorectal cancer, Cancer Treatment Reviews, 50, 148-154, 2016	A systematic review, included studies checked for relevance
Townsend, A., Price, T., Karapetis, C., Selective internal radiation therapy for liver metastases from colorectal cancer, Cochrane Database of Systematic Reviews, (4) (no pagination), 2009	A systematic review, included studies checked for relevance
Tsai, C. L., Chung, H. T., Chu, W., Cheng, J. C. H., Radiation therapy for primary and metastatic tumors of the liver, Journal of Radiation Oncology, 1, 227-237, 2012	Expert review, individual studies checked for relevance
Tsai, S., Pawlik, T. M., Outcomes of ablation versus resection for colorectal liver metastases: Are we comparing apples with oranges?, Annals of Surgical Oncology, 16, 2422-2428, 2009	Expert review
Turrini, O., Viret, F., Guiramand, J., Lelong, B., Bege, T., Delpero, J. R., Strategies for the treatment of synchronous liver metastasis, European Journal of Surgical Oncology, 33, 735-40, 2007	No multivariate analysis on relevant outcomes
Ueno, S., Sakoda, M., Kitazono, M., Iino, S., Kurahara, H., Minami, K., Ando, K., Mataki, Y., Maemura, K., Ishigami, S., Natsugoe, S., Is delayed liver resection appropriate for patients with metachronous colorectal metastases?, Annals of Surgical Oncology, 18, 1104-1109, 2011	Intervention/comparison not relevant
Valdimarsson, V. T., Syk, I., Lindell, G., Noren, A., Isaksson, B., Sandstrom, P., Rizell, M., Ardnor, B., Sturesson, C., Outcomes of liver-first strategy and classical strategy for synchronous colorectal liver metastases in Sweden, Hpb, 20, 441-447, 2018	Populations are not similar and would not both be candidates for the approaches compared
Vallance, A. E., van der Meulen, J., Kuryba, A., Charman, S. C., Botterill, I. D., Prasad, K. R., Hill, J., Jayne, D. G., Walker, K., The timing of liver resection in patients with colorectal cancer and synchronous liver metastases: a population-based study of current practice and survival, Colorectal Disease, 16, 16, 2018	Population not relevant, included in review D2a
van Amerongen, M. J., Jenniskens, S. F. M., van den Boezem, P. B., Futterer, J. J., de Wilt, J. H. W., Radiofrequency ablation compared to surgical resection for curative treatment of patients with colorectal liver metastases - a meta-analysis, Hpb, 19, 749-756, 2017	A systematic review, included studies checked for relevance
Van Amerongen, M. J., Van Der Stok, E. P., Futterer, J. J., Jenniskens, S. F. M., Moelker, A., Grunhagen, D. J., Verhoef, C., De Wilt, J. H. W., Short term and long term results of patients with colorectal liver metastases undergoing surgery with or without radiofrequency ablation, European Journal of Surgical Oncology, 42, 523-530, 2016	Population not relevant, included in review D2a
Van Der Pool, A. E., De Wilt, J. H., Lalmahomed, Z. S., Eggermont, A. M., Ijzermans, J. N., Verhoef, C., Optimizing the outcome of surgery in patients with rectal cancer and	No multivariate analysis

synchronous liver metastases, British Journal of Surgery, 97, 383-390, 2010	
Van Dessel, E., Fierens, K., Pattyn, P., Van Nieuwenhove, Y., Berrevoet, F., Troisi, R., Ceelen, W., Defining the optimal therapy sequence in synchronous resectable liver metastases from colorectal cancer: a decision analysis approach, Acta chirurgica Belgica, 109, 317-320, 2009	No relevant clinical data presented
Van Hazel, G. A., Heinemann, V., Sharma, N. K., Findlay, M. P. N., Ricke, J., Peeters, M., Perez, D., Robinson, B. A., Strickland, A. H., Ferguson, T., Rodriguez, J., Kroning, H., Wolf, I., Ganju, V., Walpole, E., Boucher, E., Tichler, T., Shacham-Shmueli, E., Powell, A., Eliadis, P., Isaacs, R., Price, D., Moeslein, F., Taieb, J., Bower, G., Gebski, V., Van Buskirk, M., Cade, D. N., Thurston, K., Gibbs, P., 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, 2016	Data from SIRFLOX trial included in Wasan 2017 which is included. No additional relevant outcomes reported in this publication
van Iersel, L. B. J., Koopman, M., van de Velde, C. J. H., Mol, L., van Persijn van Meerten, E. L., Hartgrink, H. H., Kuppen, P. J. K., Vahrmeijer, A. L., Nortier, J. W. R., Tollenaar, R. A. E. M., Punt, C., Gelderblom, H., Management of isolated nonresectable liver metastases in colorectal cancer patients: A case-control study of isolated hepatic perfusion with melphalan versus systemic chemotherapy, Annals of Oncology, 21, 1662-1667, 2010	Observational study, intervention/comparison not relevant
van Tilborg, A. A. J. M., Scheffer, H. J., de Jong, M. C., Vroomen, L. G. P. H., Nielsen, K., van Kuijk, C., van den Tol, P. M. P., Meijerink, M. R., MWA Versus RFA for Perivascular and Peribiliary CRLM: A Retrospective Patient- and Lesion-Based Analysis of Two Historical Cohorts, CardioVascular and Interventional Radiology, 39, 1438-1446, 2016	Comparison not relevant
Vargas, G. M., Parmar, A. D., Sheffield, K. M., Tamirisa, N. P., Brown, K. M., Riall, T. S., Impact of liver-directed therapy in colorectal cancer liver metastases, Journal of Surgical Research, 191, 42-50, 2014	No relevant comparison
Vassiliou, I., Arkadopoulos, N., Theodosopoulos, T., Fragulidis, G., Marinis, A., Kondi-Paphiti, A., Samanides, L., Polydorou, A., Gennatas, C., Voros, D., Smyrniotis, V., Surgical approaches of resectable synchronous colorectal liver metastases: Timing considerations, World Journal of Gastroenterology, 13, 1431-1434, 2007	Intervention/comparison not relevant (one-stage versus two-stage hepatectomy)
Veereman, G., Robays, J., Verleye, L., Leroy, R., Rolfo, C., Van Cutsem, E., Bielen, D., Ceelen, W., Danse, E., De Man, M., Demetter, P., Flamen, P., Hendlisz, A., Sinapi, I., Vanbeckevoort, D., Ysebaert, D., Peeters, M., Pooled analysis of the surgical treatment for colorectal cancer liver metastases, Critical Reviews in Oncology/Hematology, 94, 122-135, 2015	Included studies/reviews, checked for relevance
Vente, M. A. D., Wondergem, M., van der Tweel, I., van den Bosch, M. A. A. J., Zonnenberg, B. A., Lam, M. G. E. H., van het Schip, A. D., Nijsen, J. F. W., Yttrium-90 microsphere radioembolization for the treatment of liver malignancies: A structured meta-analysis, European Radiology, 19, 951-959, 2009	No comparison group
Verhoef, C., Van Der Pool, A. E. M., Nuyttens, J. J., Planting, A. S. T., Eggermont, A. M. M., De Wilt, J. H. W., The 'liver-first	No comparison group

approach' for patients with locally advanced rectal cancer and synchronous liver metastases, Diseases of the Colon and Rectum, 52, 23-30, 2009	
Vigano, L., Karoui, M., Ferrero, A., Tayar, C., Cherqui, D., Capussotti, L., Locally advanced mid/low rectal cancer with synchronous liver metastases, World Journal of Surgery, 35, 2788-2795, 2011	Compares simultaneous versus staged resections, but n=4 in staged group
Virdee, P. S., Moschandreas, J., Gebski, V., Love, S. B., Francis, E. A., Wasan, H. S., van Hazel, G., Gibbs, P., Sharma, R. A., Protocol for Combined Analysis of FOXFIRE, SIRFLOX, and FOXFIRE-Global Randomized Phase III Trials of Chemotherapy +/- Selective Internal Radiation Therapy as First-Line Treatment for Patients With Metastatic Colorectal Cancer, JMIR Research Protocols, 6, e43, 2017	Protocol for a pooled analysis of RCTs, results reported in a separate publication
Vogel, A., Gupta, S., Zeile, M., von Haken, R., Bruning, R., Lotz, G., Vahrmeijer, A., Vogl, T., Wacker, F., Chemosaturation Percutaneous Hepatic Perfusion: A Systematic Review, Advances in Therapy, 33, 2122-2138, 2017	Included studies checked for relevance
Vogl, T. J., Farshid, P., Naguib, N. N., Darvishi, A., Bazrafshan, B., Mbalisike, E., Burkhard, T., Zangos, S., Thermal ablation of liver metastases from colorectal cancer: radiofrequency, microwave and laser ablation therapies, La Radiologia medica, 119, 451-461, 2014	Expert review, no comparison group
Vogl, T. J., Lahrsow, M., Albrecht, M. H., Hammerstingl, R., Thompson, Z. M., Gruber-Rouh, T., Survival of patients with non-resectable, chemotherapy-resistant colorectal cancer liver metastases undergoing conventional lipiodol-based transarterial chemoembolization (cTACE) palliatively versus neoadjuvantly prior to percutaneous thermal ablation, European Journal of Radiology, 102, 138-145, 2018	Observational study, RCT evidence on TACE available and prioritised
Vogl, T. J., Naguib, N. N. N., Zangos, S., Eichler, K., Hedayati, A., Nour-Eldin, N. E. A., Liver metastases of neuroendocrine carcinomas: Interventional treatment via transarterial embolization, chemoembolization and thermal ablation, European Journal of Radiology, 72, 517-528, 2009	Population unclear, no comparison group
Vozdvizhenskiy, M., Solovov, V., Orlov, A., Multidisciplinary approach in the treatment of patients with the primary unresectable hepatic metastasis of colorectal cancer: Seven years' single-center experience, HPB, Conference, 11th International Congress of the European-African Hepato-Pancreato-Biliary Association. Manchester United Kingdom. Conference Publication: (var.pagings). 18 (SUPPL. 2) (pp e691), 2016	Conference abstract
Wang, B., Qian, Y. B., Jin, W., Song, X. Y., Liu, Y. Q., Efficacy and safety of simultaneous vs staged operation for synchronous colorectal liver metastases: A meta-analysis, World Chinese Journal of Digestology, 3349-3355, 2014	Non-English language paper
Wang, Z. M., Chen, Y. Y., Chen, F. F., Wang, S. Y., Xiong, B., Peri-operative chemotherapy for patients with resectable colorectal hepatic metastasis: A meta-analysis, European Journal of Surgical Oncology, 41, 1197-1203, 2015	Included studies checked for relevance
Weber, J. C., Bachellier, P., Oussoultzoglou, E., Jaeck, D., Simultaneous resection of colorectal primary tumour and synchronous liver metastases, British Journal of Surgery, 90, 956-962, 2003	No multivariate analysis on relevant comparison/outcome

Wei, A. C., Kachura, J. R., Radiofrequency ablation in the treatment of isolated liver metastases from colorectal cancer, Cochrane Database of Systematic Reviews, (1) (no pagination), 2007	A review protocol
Welsh, F. K., Chandrakumaran, K., John, T. G., Cresswell, A. B., Rees, M., Propensity score-matched outcomes analysis of the liver-first approach for synchronous colorectal liver metastases, The British journal of surgery, 103, 600-606, 2016	Populations are not similar and would not both be candidates for the approaches compared
Weng, M., Zhang, Y., Zhou, D., Yang, Y., Tang, Z., Zhao, M., Quan, Z., Gong, W., Radiofrequency Ablation versus Resection for Colorectal Cancer Liver Metastases: A Meta-Analysis, PLoS ONE, 7 (9) (no pagination), 2012	A systematic review, included studies checked for relevance
White, R. R., Avital, I., Sofocleous, C. T., Brown, K. T., Brody, L. A., Covey, A., Getrajdman, G. I., Jarnagin, W. R., Dematteo, R. P., Fong, Y., Blumgart, L. H., D'Angelica, M., Rates and patterns of recurrence for percutaneous radiofrequency ablation and open wedge resection for solitary colorectal liver metastasis, Journal of Gastrointestinal Surgery, 11, 256-263, 2007	Populations are not similar and would not both be candidates for both approaches compared
Wieners, G., Pech, M., Hildebrandt, B., Peters, N., Nicolaou, A., Mohnike, K., Seidensticker, M., Sawicki, M., Wust, P., Ricke, J., Phase ii feasibility study on the combination of two different regional treatment approaches in patients with colorectal "liver-only" metastases: Hepatic interstitial brachytherapy plus regional chemotherapy, CardioVascular and Interventional Radiology, 32, 937-945, 2009	Intervention/comparison not relevant
Wieser, M., Sauerland, S., Arnold, D., Schmiegel, W., Reinacher-Schick, A., Peri-operative chemotherapy for the treatment of resectable liver metastases from colorectal cancer: A systematic review and meta-analysis of randomized trials, BMC Cancer, 10 (no pagination), 2010	A systematic review, included studies checked for relevance
Wimmer, K., Schwarz, C., Szabo, C., Bodingbauer, M., Tamandl, D., Mittlbock, M., Kaczirek, K., Impact of Neoadjuvant Chemotherapy on Clinical Risk Scores and Survival in Patients with Colorectal Liver Metastases, Annals of Surgical Oncology, 24, 236-243, 2017	A study about predictive value of risk scores, no relevant data
Worni, M., Mantyh, C. R., Akushevich, I., Pietrobon, R., Clary, B. M., Is There a Role for Simultaneous Hepatic and Colorectal Resections? A Contemporary View from NSQIP, Journal of Gastrointestinal Surgery, 16, 2074-2085, 2012	No relevant comparison, compares simultaneous bowel and liver resection to bowel resection only and liver resection only
Wu, Y. Z., Li, B., Wang, T., Wang, S. J., Zhou, Y. M., Radiofrequency ablation Vs hepatic resection for solitary colorectal liver metastasis: A meta-analysis, World Journal of Gastroenterology, 17, 4143-4148, 2011	A systematic review, included studies checked for relevance
Yamamura, T, Yabe, K, Oka, H, Kouzuma, T, Kawahara, H, Wakayama, T, Sugiura, A, Hagiwara, M, Ohdate, K, Miyajima, N, Maeda, C, Okamura, R, Miyahara, T, Moriyama, Y, Yamaguchi, S, Gunji, A, Final results of a randomized clinical trial of adjuvant intraportal chemotherapy for colorectal cancer: intraportal Chemotherapy for Colorectal Cancer Group, Gan to kagaku ryoho. Cancer & chemotherapy, 29, 1765-1771, 2002	Non-English language paper
Yan, T. D., Chu, F., Black, D., King, D. W., Morris, D. L., Synchronous resection of colorectal primary cancer and liver metastases, World Journal of Surgery, 31, 1496-1501, 2007	No multivariate analysis

Yang, B., Li, Y., A comparative study of laparoscopic microwave ablation with laparoscopic radiofrequency ablation for colorectal liver metastasis, Journal of B.U.ON., 22, 667-672, 2017	Comparison not relevant
Yang, P. C., Lin, B. R., Chen, Y. C., Lin, Y. L., Lai, H. S., Huang, K. W., Liang, J. T., Local Control by Radiofrequency Thermal Ablation Increased Overall Survival in Patients with Refractory Liver Metastases of Colorectal Cancer, Medicine (United States), 95 (14) (no pagination), 2016	Populations are not similar and would not both be candidates for both approaches compared
Yazici, P., Akyuz, M., Yigitbas, H., Dural, C., Okoh, A., Aydin, N., Berber, E., A comparison of perioperative outcomes in elderly patients with malignant liver tumors undergoing laparoscopic liver resection versus radiofrequency ablation, Surgical Endoscopy and Other Interventional Techniques, 31, 1269-1274, 2017	Population includes people with non-colorectal liver malignancy
Yin, Z., Liu, C., Chen, Y., Bai, Y., Shang, C., Yin, R., Yin, D., Wang, J., Timing of hepatectomy in resectable synchronous colorectal liver metastases (SCRLM): Simultaneous or delayed?, Hepatology, 57, 2346-2357, 2013	A systematic review, included studies checked for relevance
Yoshidome, H., Kimura, F., Shimizu, H., Ohtsuka, M., Kato, A., Yoshitomi, H., Furukawa, K., Mitsuhashi, N., Takeuchi, D., Iida, A., Miyazaki, M., Interval period tumor progression: Does delayed hepatectomy detect occult metastases in synchronous colorectal liver metastases?, Journal of Gastrointestinal Surgery, 12, 1391-1398, 2008	Population not relevant, included in review D2a
Yoshioka, R., Hasegawa, K., Mise, Y., Oba, M., Aoki, T., Sakamoto, Y., Sugawara, Y., Sunami, E., Watanabe, T., Kokudo, N., Evaluation of the safety and efficacy of simultaneous resection of primary colorectal cancer and synchronous colorectal liver metastases, Surgery (United States), 155, 478-485, 2014	No comparison group
Yu, Q., Zhang, L., Fan, S., Huang, L., Wang, X., Xindun, C., The significance of transarterial chemoembolization combined with systemic chemotherapy for patients with KRAS wild-Type unresectable metachronous colorectal carcinoma with liver metastases, Journal of Cancer Research and Therapeutics, 12, C205-C211, 2016	Observational study, RCT evidence available on TACE
Zeman, M., Maciejewski, A., Poltorak, S., Kryj, M., Evaluation of outcomes and treatment safety of patients with metastatic colorectal cancer to the liver with estimation of prognostic factors, Polski Przeglad Chirurgiczny, 85, 333-339, 2013	No relevant outcomes for relevant comparisons
Zhu, D., Zhong, Y., Wei, Y., Ye, L., Lin, Q., Ren, L., Ye, Q., Liu, T., Xu, J., Qin, X., Effect of neoadjuvant chemotherapy in patients with resectable colorectal liver metastases, PLoS ONE, 9 (1) (no pagination), 2014	Observational study, RCT evidence exists and prioritised
Zhu, G. Q., You, J., Shi, K. Q., He, S. Y., Wang, L. R., Chen, Y. P., Braddock, M., Zheng, M. H., Systematic review with network meta-analysis: Adjuvant chemotherapy for resected colorectal liver metastases, Medicine (United States), 94, e379, 2015	Interventions and comparisons not relevant

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Appendix L – Research recommendations

Research recommendations for review question: What is the optimal combination and sequence of treatments in patients presenting with metastatic colorectal cancer in the liver not amenable to treatment with curative intent?

No research recommendations were made for this review question.