National Institute for Health and Care Excellence

Draft for consultation

Colorectal cancer (update)

[D2a] Treatment for metastatic colorectal cancer in the liver 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:

Contents

1

Optimal combination and sequence of treatments in patients presenting with metastatic colorectal cancer in the liver amenable to treatment with curative intent

This evidence review supports recommendations 1.5.3 to 1.5.4.

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?

Introduction

Surgical resection is the standard mode of treatment for colorectal liver metastases. However, questions have been raised on whether it is better to do a simultaneous or staged resection of the primary tumour and the liver metastases, if chemotherapy is beneficial in addition to liver resection, and whether treatment methods other than surgical resection could be used to treat colorectal liver metastasis. The aim of this review is to find out what is the optimal combination and sequence of treatments in patients with metastatic colorectal cancer in the liver 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 amenable to treatment with curative intent at presentation Subgroups: Primary colorectal tumour is • symptomatic or asymptomatic • right colon or left colon/rectum Metastasis is: • synchronous or metachronous
Intervention	1) Simultaneous resection (bowel and liver) 2) Liver surgery before or after systemic anti-cancer therapy (SACT) 3) Ablation (microwave, IRE, RFA) 4) SABR (SBRT, cyber-knife)
Comparison	1) Staged resection (bowel resection first or liver resection first) 2) Liver surgery without SACT 3) Resection or SABR 4) Resection or ablation

Outcomes	Critical • Liver progression-free survival • Overall survival • Overall quality of life Important • Disease-free survival • Treatment-related mortality • Any grade 3 or 4 adverse event

IRE: irreversible electroporation; RFA: radiofrequency ablation; SABR: stereotactic ablative radiotherapy; SACT: systemic anticancer therapy; SBRT: stereotactic body radiation therapy

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

Three randomised controlled trials (RCTs; reported in 4 publications) and 18 retrospective cohort studies were included in this review (Abbott 2012; Abelson 2017; Bartolini 2018; De Haas 2010; Eltawil 2014; EORTC 40983 trial [Nordlinger 2013; Nordlinger 2008]; FFCD trial and ENG trial [Mitry 2008]; FFCD trial only [Portier 2006]; Gleisner 2008; Hof 2018; Imai 2017; Karibori 2010; Masuda 2018; Mayo 2013; Moug 2010; Patrono 2014; Vallance 2018; van Amerongen 2016; van der Poel 2018; Wang 2018; Yoshidome 2008).

The included studies are summarised in Table 2.

Twelve retrospective cohort studies compared simultaneous resection of the colorectal tumour and liver metastases to staged resection (mainly colorectal resection first) (Abbott 2012; Abelson 2017; Bartolini 2018; De Haas 2010; Hof 2018; Karibori 2010; Mayo 2013; Moug 2010; Patrono 2014; Vallance 2018; van der Poel 2018; Yoshidome 2008). Three RCTs compared chemotherapy in addition to surgery to surgery alone (EORTC 40983 trial [Nordlinger 2013; Nordlinger 2008]; FFCD trial and ENG trial [Mitry 2008]; FFCD trial only [Portier 2006]). Five retrospective cohort studies compared ablation with resection to resection alone (Eltawil 2014; Gleisner 2008; Imai 2017; Masuda 2018; van Amerongen 2016) and one retrospective cohort study compared ablation alone to resection alone (Wang 2018).

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.

1 Summary of clinical studies included in the evidence review

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

3 **Table 2: Summary of included studies**

Study	Population	Intervention/ Comparison	Outcomes
Comparison 1: Simultaneous resection versus staged resection			
Abbott 2012 Retrospective cohort study US	N=60 people who underwent colorectal and liver resection for colorectal cancer with synchronous liver metastases to the liver with curative intent	Simultaneous resection versus staged resection (RFA was sometimes used if resection was not feasible)	• Overall survival • Disease-free survival
Abelson 2017 Retrospective cohort study US	N=1088 people who underwent an open or laparoscopic colorectal resection for colorectal cancer and a liver resection for secondary malignancy of the liver at the time of or within 6 months before or after the colorectal resection	Simultaneous resection versus staged resection	• Grade 3 or 4 adverse events
Bartolini 2018 Retrospective cohort study Italy	N=39 people who undergoing liver resection (potentially curative) for first recurrence of colorectal cancer (“liver only” first metastasization from colorectal cancer). According to timing of metastasis presentation/treatment , patients were divided into 3 groups: “synchronous combined surgery” that included patients who underwent combined surgery for primary tumor and liver metastasis, 'synchronous bowel first' that included patients with metastatic disease from the beginning of their neoplastic history but liver metastases were not treated during colorectal surgery	Simultaneous resection versus staged (colorectal resection first). RFA was used in a small number of people.	• Progression-free survival • Overall survival

Study	Population	Intervention/ Comparison	Outcomes
De Haas 2010 Retrospective cohort study France	N=52 people with synchronous colorectal liver metastases treated with limited hepatectomy (<3 segments) and resection of the primary tumour with curative intent	Simultaneous resection versus staged (colorectal resection first)	• Treatment-related mortality • Post-operative complications
Hof 2018 Retrospective cohort study Netherlands	N=226 people with synchronous colorectal liver metastases who underwent a radical resection of the colorectal cancer and a radical resection and/or ablation of the liver metastases; complete R(0) resection	Simultaneous resection versus staged (colorectal resection first)	• Overall survival
Kaibori 2010 Retrospective cohort study Japan	N=74 people with synchronous colorectal liver metastases undergoing complete R(0) resection	Simultaneous resection versus staged resection (colorectal resection first)	• Progression-free survival
Mayo 2013 Retrospective cohort study Italy, Portugal. Switzerland, US	N=1,004 people with colorectal cancer and synchronous liver metastases who underwent surgery with curative intent for both primary cancer and metastases	Simultaneous resection versus staged resection (mostly colorectal resection first)	• Overall survival
Moug 2010 Retrospective cohort study UK	N=64 people with colorectal cancer and hepatic metastases that underwent either simultaneous or staged surgery	Simultaneous resection versus staged resection (colorectal resection first)	• Treatment-related mortality • Grade 3 or 4 adverse events
Patrono 2014 Retrospective cohort study Italy	N=106 people with colorectal cancer and synchronous liver metastases who underwent liver resection	Simultaneous resection versus staged resection (colorectal resection first)	• Overall survival
Vallance 2018 Retrospective cohort study UK	N=396 people with colorectal cancer and synchronous liver-limited metastases undergoing elective colorectal cancer and liver resection	Simultaneous resection versus staged resection (colorectal resection first)	• Overall survival

Study	Population	Intervention/ Comparison	Outcomes
van der Poel 2018 Retrospective cohort study Belgium, Netherlands	N=122 (after propensity score matching) people undergoing combined laparoscopic resection of liver metastases and colorectal cancer or laparoscopic colorectal cancer resection alone.	Simultaneous resection versus staged resection (colorectal resection first)	• Treatment-related mortality
Yoshidome 2008 Retrospective cohort study Japan	N=137 people with synchronous colorectal liver metastases undergoing resection	Simultaneous resection versus staged resection (colorectal resection first)	• Progression-free survival
Comparison 2: Surgery and SACT versus surgery alone			
EORTC 40983 trial (Nordlinger 2013; Nordlinger 2008) Phase III RCT Australia, Austria, Belgium, France, Germany, Hong Kong, Italy, Norway, Sweden, the Netherlands, UK	N=364 people with colorectal cancer and 1-4 liver metastases that were resectable; no detectable extrahepatic tumours; WHO performance status 0-2; no previous chemotherapy with oxaliplatin	Perioperative FOLFOX before and after surgery (6 + 6 cycles) versus surgery alone	• Overall survival • Disease-free survival • Treatment-related mortality
FFCD trial and ENG trial (Mitry 2008; Portier 2006 [FFCD trial only]) A combined individual patient data analysis of 2 phase III RCTs Belgium, Canada, France, Italy, Switzerland	N=302 people with colorectal cancer; free of clinically detectable disease by complete R(0) surgical resection of the primary tumour; ≤4 metastases located in a single location (liver or lung); negative resection margins by histologic examination; ECOG performance status 0-2; no previous chemotherapy except adjuvant treatment of their primary tumour	Postoperative 5-FU + leucovorin (6 cycles) versus surgery alone	• Overall survival • Disease-free survival • Grade 3 or 4 adverse events
Comparison 3: Ablation ± resection versus resection alone			
Eltawil 2014 Retrospective cohort study Canada	N=174 people with colorectal cancer liver metastases who underwent liver resection	Liver resection with RFA versus resection alone	• Overall survival • Disease-free survival
Gleisner 2008 Retrospective cohort study	N=247 people with colorectal liver metastases who were operated on with	Liver resection with RFA versus resection alone	• Overall survival • Disease-free survival

Study	Population	Intervention/ Comparison	Outcomes
US	curative intent; undergoing their first liver-directed therapy; RFA performed during open laparotomy		
Imai 2017 Retrospective cohort study France	N=124 people with colorectal liver metastases undergoing curative hepatectomy	Liver resection with RFA versus resection alone	• Progression-free survival • Overall survival • Disease-free survival • Post-operative mortality • Grade 3 or 4 adverse events
Masuda 2018 Retrospective cohort study Japan, US	N=717 people who underwent hepatic resection alone or hepatic resection with RFA.	Resection only versus resection + RFA	• Overall survival
van Amerongen 2016 Retrospective cohort study Netherlands	N=628 people who received partial hepatic resection or a combination of both RFA and resection in one session for curative treatment of colorectal liver metastases	Liver resection with RFA versus resection alone	• Overall survival • Disease-free survival
Wang 2018 Retrospective cohort study China	N=138 (after propensity score matching) people with ≤3 tumors, well-located tumor size of ≤ 5 cm, and absence of uncontrolled extrahepatic disease	RFA alone versus resection alone	• Overall survival

5-FU: fluorouracil; ECOG: Eastern Cooperative Oncology Group; FOLFOX: leucovorin (folinic acid) + fluorouracil + oxaliplatin; N: number; R(0): complete tumour resection margin; RCT: randomised controlled trial; RFA: radiofrequency ablation; WHO: World Health Organization

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 D.

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

The cost effectiveness of simultaneous versus staged resection in patients presenting with metastatic colorectal cancer in the liver amenable to treatment with curative intent?

See appendix J for the full report of the economic analysis.

This economic analysis aims to estimate the outcomes, patient quality of life and costs of a simultaneous approach to resection compared to a staged approach in patients with colorectal cancer presenting with liver metastases.

Methods

Population

The model considers patients with colorectal cancer presenting with liver metastases where surgical resection of both the primary cancer and the metastases is considered the most appropriate treatment option.

Intervention and comparator

Two approaches to the surgical resection of the cancer were considered in the economic model:

Staged Approach: This approach consists of 2 surgical operations, 1 for the resection of the primary colorectal cancer and 1 for the resection of the liver metastases.

Simultaneous Approach: This approach involves 1 surgical operation to resect both the primary colorectal cancer and the liver metastases.

Model Structure

A partitioned survival analysis was developed to estimate the expected life expectancy, quality adjusted life years (QALYs) and costs associated with the 2 approaches considered by this economic analysis. A partitioned survival analysis divides the model cohort between different health states based on survival curves derived for overall survival (OS) and disease-free survival (DFS) derived from the accompanying clinical evidence review. The expected OS and DFS are then calculated from the area under the respective curves

Model parameters

Clinical inputs

Socioeconomic and demographics variables

The model assumed a uniform age of the cohort of 60 years of age based and 60% male.

Overall and disease-free survival

Survival curves for the economic model were estimated entirely from the accompanying clinical evidence report. Two models were reported one which adjusted for biases in the survival estimates identified in the clinical evidence review and one which used the reported values.

Adverse events

The proportion of adverse events for either approach was taken from the accompanying clinical evidence review.

Perioperative period

Perioperative period in the study was estimated from one US costing study a retrospective study at 1 US hospital. The studied reported a median length of stay of 7 days for the simultaneous approach and 13 days (total across both resections) for the staged approach.

Resource use and costs

Cost of resection and resection related complications

All resection costs were taken from NHS Reference Costs 2016/17.

To estimate the cost of the resections in the simultaneous approach it was not appropriate to combine the 2 costs as undertaken for the staged approach. This is because both sets of costs would include costs for pre-assessment, surgical preparation, anaesthesia, time in surgical theatre and many other items that can be 'shared' between the 2 procedures by combining them To estimate the cost for the simultaneous approach the cost of the staged approach was adjusted using data on total operative time and length of stay in hospital. Abbott 2012, identified in the accompanying clinical evidence review, estimated that total operating time in the simultaneous approach was 144 minutes shorter compared to the staged approach. This was converted into a cost using estimates of the cost of operating theatre time

Length of stay in hospital also differed between the 2 arms of the model with simultaneous approach resulting in 6 less days in hospital as discussed above. This mean cost was then multiplied by the reduction in days and subtracted from the procedure cost for the staged approach. This was in addition to the adjustment for operative time.

Resource use and cost of further treatment

All patients who have disease recurrence will go on to receive further treatment or if not appropriate palliative care. Of those patients with recurrent disease who go on to receive further treatment three broad types of treatment were identified by the committee-hepatic resection, extrahepatic resection and chemotherapy.

The proportion of patients going on to receive further treatment was taken from a UK cost utility study comparing operable to non-operable treatments for liver metastases. Costs for both hepatic and extrahepatic resection were again taken from NHS Reference Costs.

For disease recurrence, which was considered not amenable to resection, patients received systemic chemotherapy treatment. Two chemotherapy regimens were used by the economic model which were considered to cover the majority of chemotherapy received in the NHS for this patient group following inoperable disease recurrence-FOLFOX and FOLFIRI. Costs were taken from the 'Drug and Pharmaceutical Electronic Market Information Tool' (eMit) for all drug components. Administration costs were taken from NHS Reference Costs 2016.

Cost of palliative care

Given the relatively short life expectancy of the model cohort and that the majority of patients would die as a result of their disease a one off cost of palliative care was applied to the entirety of the cohort during their final year of life. This is to represent the increase in resource use experienced during the final months of a patient's life.

Quality of life

Quality of life weights for the model were taken from previous cost-effectiveness study of patients (identical in age to our cohort) with rectal cancer.

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis was also conducted to assess the combined parameter uncertainty in the model.

Results

Base-case results

The base case results of the analysis are shown in Table 3. The results show an increase in life expectancy of half a year with the simultaneous approach corresponding to a 0.28 QALY increase compared to the staged approach. The simultaneous approach also led to reduction in costs just below £2,500. In the base-case analysis the simultaneous approach dominated (was both cost saving and health increasing).

Table 3: Base-case results

Strategy	Life Expectancy (year)		Cost		QALYs		ICER (cost per QALY)
	Total	Incremental	Total	Incremental	Total	Incremental	
Staged	3.80		£31,749	-	3.22	-	-
Simultaneous	4.30	0.51	£29,282	*-£2,467*	3.51	*0.28*	**Dominant**

ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years

When the unadjusted results of the accompanying clinical evidence review are used to inform the economic model and adjustments for survival have not been made to account for individuals who only received the first resection life expectancy is now higher in the staged group (potentially for reasons discussed above) with an associated higher QALY as well (Table 4). The simultaneous approach remains cost saving (even more so given the larger number of liver resections in the staged approach). If a £20,000 per QALY threshold is considered, in line with Developing NICE guidelines: the manual, the reduction in costs would not justify the decrease in QALYs, that is, only £16,506 is saved for every QALY forgone.

Table 4: Results of the economic model using values reported in the accompanying clinical evidence review

Strategy	Life Expectancy (year)		Cost		QALYs		ICER (cost per QALY)
	Total	Incremental	Total	Incremental	Total	Incremental	
Staged	4.62		£33,942	-	3.79	-	-
Simultaneous	4.30	0.51	£29,282	*-£4,660*	3.51	*-0.28*	£16,506

ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years

Probabilistic Sensitivity Analysis

Base-case assumptions

The results of 10,000 runs of the PSA are shown using ICER scatterplots and cost-effectiveness acceptability curves (CEAC). The ICER scatter plots show the incremental costs and QALYs associated with each of the 10,000 runs of the PSA along with the mean

result. The CEAC graphs show the probability of each strategy being considered cost-effective at the various cost-effectiveness thresholds on the x axis.

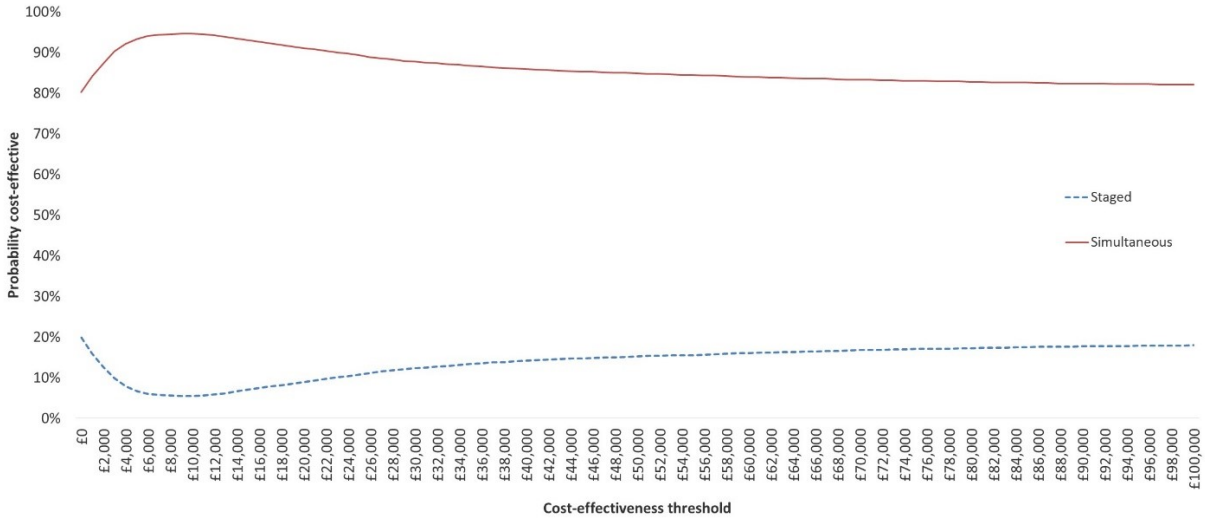
Figure 1 presents the probabilistic results of the base case analysis. Of these 10,000 iterations over 75% of them are health improving (to the right of the Y-axis) and over 80% are cost decreasing (below the X-axis) with the majority of iterations being both cost saving and health increasing.

Figure 1: ICER scatterplot base case results

CE: cost effectiveness; ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years

Figure 2 presents the CEAC for the base case results. The probability that the simultaneous approach is the preferred option is 80% at a cost effectiveness ratio of £0 i.e. where the cheapest option is preferred. At £20,000 threshold there is a 86% probability of the simultaneous approach being the preferred option. This remains above 80% beyond values above the £100,000 threshold. For no threshold does a staged approach become the preferred option.

Figure 2: Cost effectiveness acceptability curve base case results



Clinical evidence review values results

When results from the clinical evidence review are used to inform the economic model there is a greater degree of uncertainty around the results (Figure 3). When these inputs are

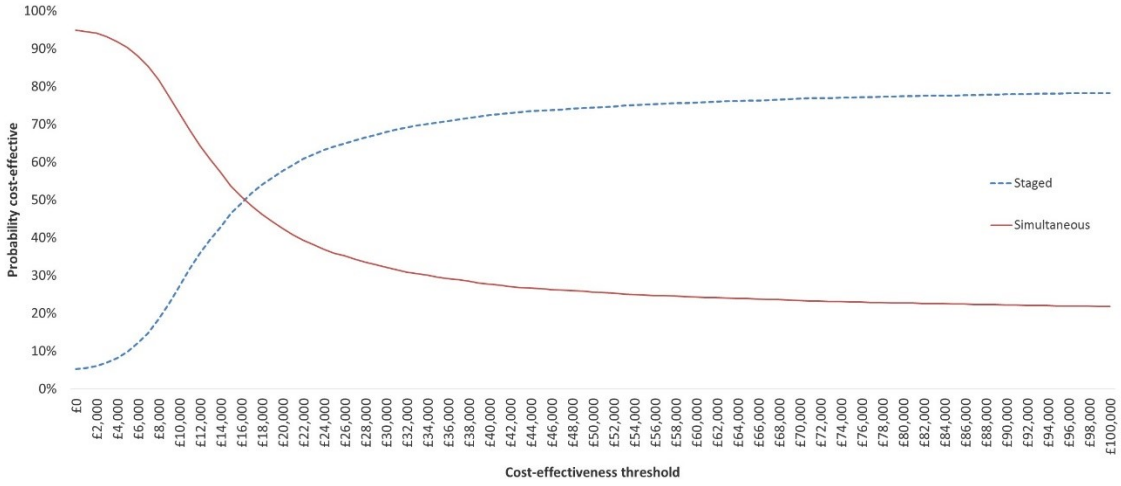
considered a greater number of iterations show the simultaneous approach as cost saving (94%) but with less than 20% of iterations being health improving.

Figure 3: ICER scatterplot clinical evidence review inputs

CE: cost effectiveness; ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years

The CEAC for this analysis shows uncertainty around the preferred option (Figure 4). At the £20,000 threshold 42% showed the simultaneous approach to be cost effective although as shown by the cost effectiveness plane the majority of these would also be health decreasing. As the threshold increases the probability of the staged approach being the most cost effective option also increases. The threshold at which the CEACs cross and we are indifferent between the two options is £17,000 per QALY.

Figure 4: Cost effectiveness acceptability curve clinical evidence review inputs



Conclusions

Both versions of the model gave differing results. The base-case results, where survival in the staged approach had been adjusted, showed the simultaneous approach as both health improving and cost saving. This conclusion was robust to both probabilistic and deterministic sensitivity analysis. The secondary analysis using survival estimates from the accompanying

clinical evidence review presented the simultaneous approach as health decreasing and cost decreasing but not cost effective although the PSA highlighted considerable uncertainty around this conclusion.

Evidence statements

Clinical evidence statements

Comparison 1: Simultaneous resection versus staged resection

Critical outcomes

Liver-progression free survival

- Very low quality evidence from 3 retrospective cohort studies (N=250) showed no clinically important difference in liver-progression free survival between people who underwent simultaneous resection or staged resection for metastatic colorectal cancer in the liver.

Overall survival

- Low to very low quality evidence from 8 retrospective cohort studies (N=2031) showed no clinically important difference in overall survival between people who underwent simultaneous resection or staged resection for metastatic colorectal cancer in the liver.

Quality of life

No evidence was identified to inform this outcome.

Important outcomes

Disease-free survival

- Very low quality evidence from 2 retrospective cohort studies (N=196) showed mixed results for disease-free survival. Evidence from 1 study showed no clinically important difference in disease-free survival between people who underwent simultaneous resection or staged resection for metastatic colorectal cancer in the liver. Evidence from another study showed a clinically important worse disease-free survival for people who underwent simultaneous resection compared to those who underwent staged resection for metastatic colorectal cancer in the liver.

Treatment-related mortality

- Very low quality evidence from 2 retrospective cohort studies (N=238) showed that there were no clinically important differences in treatment-related mortality (postoperative mortality, 30-day or 60-day) between people who underwent simultaneous resection or staged resection for metastatic colorectal cancer in the liver.

Any grade 3 or 4 adverse event

- Very low quality evidence from 1 retrospective cohort study (N=64) showed no clinically important difference in grade 3 or 4 adverse events between people who underwent simultaneous resection or staged resection for metastatic colorectal cancer in the liver.
- Very low quality evidence from 2 retrospective cohort studies (N=1,552) showed no clinically important difference in major events within 30 days (myocardial infarction, stroke, pulmonary embolism, shock, in-hospital death), return to operating theatre, anastomotic leak, acute liver failure, or liver abscess between people who underwent simultaneous resection or staged resection for metastatic colorectal cancer in the liver.

- Very low quality evidence from 2 retrospective cohort studies (N=1,552) showed no clinically important difference in likelihood of readmission within 30 days in people who underwent simultaneous resection compared to those who underwent staged resection for metastatic colorectal cancer in the liver.
- Very low quality evidence from 1 retrospective cohort study (N=52) showed no clinically important difference in postoperative complications between people who underwent simultaneous resection or staged resection for metastatic colorectal cancer in the liver.

Comparison 2: Surgery and SACT versus surgery alone

Critical outcomes

Liver-progression free survival

No evidence for a specific outcome

Overall survival

- Moderate quality evidence from 2 RCTs (N=666) pooled together showed that there may be a clinically important better overall survival for people who received chemotherapy in addition to surgery compared to those who underwent surgery alone for metastatic colorectal cancer in the liver but there is uncertainty around the estimate. However, pooling the results might not be appropriate because the chemotherapy regimens in these two RCTs were different in terms of 1) the timing of the chemotherapy and 2) the chemotherapy drugs used. In one RCT (N=302) the patients received fluorouracil (5-FU) and leucovorin (folinic acid) postoperatively and in the other RCT (N=364) the patients received FOLFOX (leucovorin, fluorouracil and oxaliplatin) pre- and post-operatively. If the RCTs are considered individually, there was no clinically important difference in overall survival in people who received chemotherapy in addition to surgery compared to those who underwent surgery alone for metastatic colorectal cancer in the liver.

Quality of life

No evidence was identified to inform this outcome.

Important outcomes

Disease-free survival

- Moderate quality evidence from 2 RCTs (N=666) pooled together showed that there is a clinically important better disease-free survival for people who received chemotherapy in addition to surgery compared to those who underwent surgery alone for metastatic colorectal cancer in the liver. However, pooling the results might not be appropriate because the chemotherapy regimens in these two RCTs were different in terms of 1) the timing of the chemotherapy and 2) the chemotherapy drugs used. In one RCT (N=302) the patients received fluorouracil (5-FU) and leucovorin (folinic acid) postoperatively and in the other RCT (N=364) the patients received FOLFOX (leucovorin, fluorouracil and oxaliplatin) pre- and post-operatively. If the RCTs are considered individually, the evidence showed that there may be a clinically important better disease-free survival in people who received chemotherapy in addition to surgery compared to those who underwent surgery alone for metastatic colorectal cancer in the liver but there is uncertainty around the estimate.

Treatment-related mortality

- Moderate quality evidence from 1 RCT (N=364) showed no clinically important difference in treatment-related mortality between people who received chemotherapy in addition to

surgery and those who underwent surgery alone for metastatic colorectal cancer in the liver.

Any grade 3 or 4 adverse event

- Moderate quality evidence from 1 RCT (N=166) showed that around 25% of the people who received chemotherapy in addition to surgery had grade 3 or 4 chemotherapy-related adverse events compared to 0% in those who had surgery alone for metastatic colorectal cancer in the liver.

Comparison 3: Ablation ± resection versus resection alone

Critical outcomes

Liver-progression free survival

- Very low quality evidence from 1 retrospective cohort study (N=124) showed no clinically important difference in liver disease-free survival between people who underwent liver resection and RFA and those who underwent resection alone for metastatic colorectal cancer in the liver.

Overall survival

- Very low quality evidence from 4 retrospective cohort studies (N=1,177) showed mixed results. Evidence from 2 studies (N=298) showed no clinically important difference in overall survival between people who underwent liver resection and RFA and those who underwent resection alone for metastatic colorectal cancer in the liver. However, evidence from 2 other studies (N=879) showed a clinically important worse overall survival in people who underwent liver resection and RFA compared to those who underwent resection alone for metastatic colorectal cancer in the liver.
- Very low quality evidence from 1 retrospective cohort study (N=149) showed no clinically important benefit in overall survival for high risk patients who underwent liver resection alone compared to those who underwent liver resection + RFA for metastatic colorectal cancer in the liver.
- Very low quality evidence from 1 retrospective cohort study (N=568) showed no clinically important benefit in overall survival for low risk patients who underwent liver resection alone compared to those who underwent liver resection + RFA for metastatic colorectal cancer in the liver.
- Very low quality evidence from 1 retrospective cohort study (N=138) showed no clinically important difference in overall survival between people who received RFA alone and those who underwent resection alone for metastatic colorectal cancer in the liver.

Quality of life

No evidence was identified to inform this outcome.

Important outcomes

Disease-free survival

- Very low quality evidence from 4 retrospective cohort studies (N=1,177) showed mixed results. Evidence from 3 studies (N=930) showed no clinically important difference in disease-free survival between people who underwent liver resection and RFA and those who underwent resection alone for metastatic colorectal cancer in the liver. However, evidence from 1 study (N=247) showed a clinically important worse disease-free survival in people who underwent liver resection and RFA compared to those who underwent resection alone for metastatic colorectal cancer in the liver.

Treatment-related mortality

- Very low quality evidence from 1 retrospective cohort study (N=124) showed no clinically important difference in 90-day mortality between people who received RFA in addition to resection and those who underwent resection alone for metastatic colorectal cancer in the liver.

Any grade 3 or 4 adverse event

- Very low quality evidence from 1 retrospective cohort study (N=124) showed no clinically important difference in grade 3 or 4 adverse events between people who received RFA in addition to resection and those who underwent resection alone for metastatic colorectal cancer in the liver.

Comparison 4: SABR versus resection or ablation

No evidence was identified to inform this comparison.

Economic evidence statements

A bespoke economic model was created for this topic to investigate the cost effectiveness of a simultaneous compared to a staged approach to resection. The study took a UK NHS+PSS perspective and was informed by evidence identified in the accompanying clinical evidence review. Two models were created one using the survival outcomes from the clinical evidence review and another where the inputs had been adjusted to account for biases in these estimates. The adjusted analysis showed a simultaneous approach to be both cost saving and health improving. This result was robust to sensitivity analysis with a greater than 85% probability of being cost effective at a £20,000 per QALY threshold. The analysis using the results from the clinical evidence review showed a simultaneous approach to be cost saving but also health decreasing with a staged approach being the preferred option at a £20,000 per QALY threshold. There was however large uncertainty around this conclusion. For both analyses a simultaneous approach was cost saving under the majority of iterations during the probabilistic sensitivity analysis.

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.

Disease-free survival, meaning survival without disease recurrence or progression anywhere in the body, was an important outcome because it reflects effectiveness of treatment, and can mean additional treatments and affect overall survival. 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 comparison of simultaneous versus staged resection, for which evidence was available on all outcomes except quality of life; surgery and SACT versus surgery alone, for which evidence was available for all outcomes except liver-progression free survival and quality of life; and ablation (with or without resection) versus resection alone, for which evidence was available on all other outcomes except quality of life.

No evidence was identified on stereotactic body radiation therapy or stereotactic ablative radiotherapy.

The quality of the evidence was assessed using GRADE and varied from very low to moderate quality.

Only observational evidence was available for comparing simultaneous resection to staged resection and comparing ablation with or without resection to resection alone. The evidence was mostly of very low quality, varying from very low to low. The main reason for downgrading the quality of the evidence was imprecision of the effect estimate due to small sample sizes or risk of bias due to lack of adequate controlling for confounding factors. Even when baseline characteristics between the groups were controlled for (usually through multivariate regression or propensity score matching), there were serious concerns about the comparability of the groups included in these retrospective studies as the committee thought that there were underlying clinical reasons why one patient received treatment X and another received treatment Y. For example, in the included studies local ablation in addition to resection was largely done because some metastases were unresectable.

Because of the serious concerns about the comparability of the groups included in these retrospective studies, and the differences between studies in their criteria for resectability their results were not pooled in meta-analysis.

For comparing liver resection with SACT to liver resection alone RCT evidence was available and it was of moderate quality. The main reason for downgrading the quality of the evidence was imprecision of the effect estimate due to small sample sizes.

Benefits and harms

There was some evidence that simultaneous resection worsened liver progression-free survival, however, evidence from more studies showed no difference in overall survival or disease-free survival. No difference was seen in treatment-related mortality and morbidity. Because there was not enough evidence to show that one approach was better than the other, the patient's perspective on the effect of each approach on quality of life is particularly important to guide clinicians. No quality of life evidence was available, however, it can be assumed that if simultaneous resection is feasible it would also be preferred by patients in order to avoid having to go through two major surgeries with waiting time in between.

The committee agreed that there are problems with comparability of the patient groups in the included studies. In some cases a staged resection was done because a simultaneous resection was not possible due to clinical reasons, therefore, the groups were not similar enough to be truly comparable.

Due to the low quality of the evidence paired with the inconclusive evidence on which approach is better, the committee agreed that it cannot recommend one approach over the other. Instead, the decision should be based on a careful consideration by a multidisciplinary team consisting of experts in both colorectal and liver surgeries.

Moderate quality evidence from three RCTs suggested that SACT in addition to liver resection was beneficial in terms of disease-free survival and possibly overall survival compared to liver resection alone. Chemotherapy increased the rate of treatment-related adverse events with around a quarter of patients in one trial having grade 3 or 4 adverse events due to chemotherapy. There was no evidence on quality of life, however, considering the adverse effects that chemotherapy might cause, it could be assumed that quality of life might be impaired as a result of chemotherapy, at least in the short-term. The potential gain in survival should therefore be balanced with the potential effect on quality of life and morbidity.

The RCTs were different in terms of chemotherapy regimen used (oxaliplatin-based FOLFOX versus 5-FU and leucovorin without oxaliplatin) and the timing of administering the chemotherapy (before and after resection versus after resection only). This makes it more difficult to draw definitive conclusions from the evidence when the RCTs are pooled together while individually they lack statistical power.

Additional caution is needed when interpreting the evidence because the included RCTs are relatively old. For example, patient population has since changed because more synchronous disease is detected currently due to improvements in detection. Having a synchronous versus metachronous disease can make a big difference in terms of treatment effectiveness and survival but unfortunately the available data did not allow that type of analysis. In addition, the regimens used in the RCTs are somewhat outdated and more options for chemotherapy are available in current practice. If the RCTs would be conducted at current time, the committee would expect to see a bigger difference in survival.

Taking into consideration these different aspects of the evidence, the committee agreed that chemotherapy should be considered for people who are suitable for liver resection.

Local ablative techniques have been suggested as an alternative to surgical resection for people not fit for surgery and with potentially less mortality and morbidity associated with major surgery. The LAVA randomised trial was established to compare these two approaches, however, the trial was discontinued due to poor recruitment of patients. With no RCT evidence available on the effectiveness and safety of local ablative technique as an alternative to resection, observational studies were sought. Very low quality observational evidence from retrospective cohort studies was available comparing local ablation in combination with liver resection versus liver resection alone, or comparing local ablation alone to liver resection alone. The committee had major concerns about the usefulness of this data because the comparability of the groups in these studies. For most patients in the ablation group, ablation was only used because resection was not possible due to patient fitness or clinical reasons. Therefore, the ablation group would likely have more advanced disease or be less likely to achieve good outcome.

Cost effectiveness and resource use

The committee considered 2 versions of a bespoke economic model to investigate the cost effectiveness of a staged versus simultaneous approach to resection, 1 using the results of the clinical evidence review and another where the inputs had been adjusted to account for biases in the clinical evidence around survival. The adjusted analysis showed a simultaneous approach to be both cost saving and health improving. This result was robust to sensitivity analysis with a greater than 85% probability of being cost effective at a £20,000 per QALY threshold. The analysis using the results from the clinical evidence review showed a simultaneous approach to be cost saving but also health decreasing with a staged approach being the preferred option at a £20,000 per QALY threshold. There was uncertainty around this conclusion. For both analyses a simultaneous approach was cost saving under the majority of iterations during the probabilistic sensitivity analysis.

The committee was of the opinion that a simultaneous approach was unlikely to be health decreasing and the survival difference (although not statistically significant) identified in the clinical evidence review was most likely a result of selection bias. Given this the committee concluded that a simultaneous approach was likely a cost effective use of resources. However, with uncertainty around the clinical inputs and the potential for harm, either through a less effective approach or through inefficient use of resources, the committee did not feel it appropriate to recommend one approach over the other.

The committee acknowledge the majority of the clinical evidence was retrospective observational studies with the previously discussed weaknesses. Given the importance of this parameter for informing economic decisions the confidence with which they could make

this conclusion was reduced. The committee considered that it was unlikely there would be future high quality evidence for this clinical topic as they consider it would be difficult to recruit to a staged arm of any RCT with patients' preferences being towards one operation with a shorter total hospital stay.

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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 amenable to treatment with curative intent?

Table 5: Review protocol for the optimal combination and sequence of treatments in patients presenting with metastatic colorectal cancer in the liver amenable to treatment with curative intent

Field (based on PRISMA-P)	Content
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?
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 amenable to treatment with curative intent.
Eligibility criteria – population/disease/condition/issue/domain	Adults with colorectal cancer with metastases in the liver amenable to treatment with curative intent at presentation Subgroups: Primary colorectal tumour is • symptomatic or asymptomatic • in the right colon or left colon/rectum Metastasis is • synchronous or metachronous
Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	1) Simultaneous resection (bowel and liver) 2) Liver surgery before or after systemic anti-cancer therapy (SACT) 3) Ablation (microwave, IRE, RFA) 4) SABR (SBRT, cyber-knife)
Eligibility criteria – comparator(s)/control or reference (gold) standard	1) Staged resection (bowel resection first or liver resection first) 2) Liver surgery without SACT 3) a) Resection b) SABR 4) a) Resection b) Ablation Intervention 1 versus comparison 1, intervention 2 versus comparison 2 etc.
Outcomes and prioritisation	Critical outcomes: • Liver progression-free survival (MID: statistical significance) • Overall survival (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) • 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 and > 3.29 for the physical component summary 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 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 1995
	• Observational studies should include multivariate analysis controlling for the following confounding factors:
	  ○ Age
	  ○ Synchronous or metachronous
	  ○ Number of metastases
	
	Studies conducted post 1995 will be considered for this review question because the guideline committee considered that treatment techniques have evolved and evidence prior to 1995 would no longer be relevant.

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 1995
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 and exploring (in)consistency	**Synthesis of data:** Pairwise meta-analysis of randomised trials will be conducted where appropriate.

	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: methods.
Sources of funding/support	The NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Name of sponsor	The NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Roles of sponsor	NICE funds the NGA 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; DARE: Database of Abstracts of Reviews of Effects; 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); GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; IRE: irreversible electroporation; MID: minimal important difference; NGA: National Guideline Alliance; RCT: randomised controlled trial; RFA: radiofrequency ablation; 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

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 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

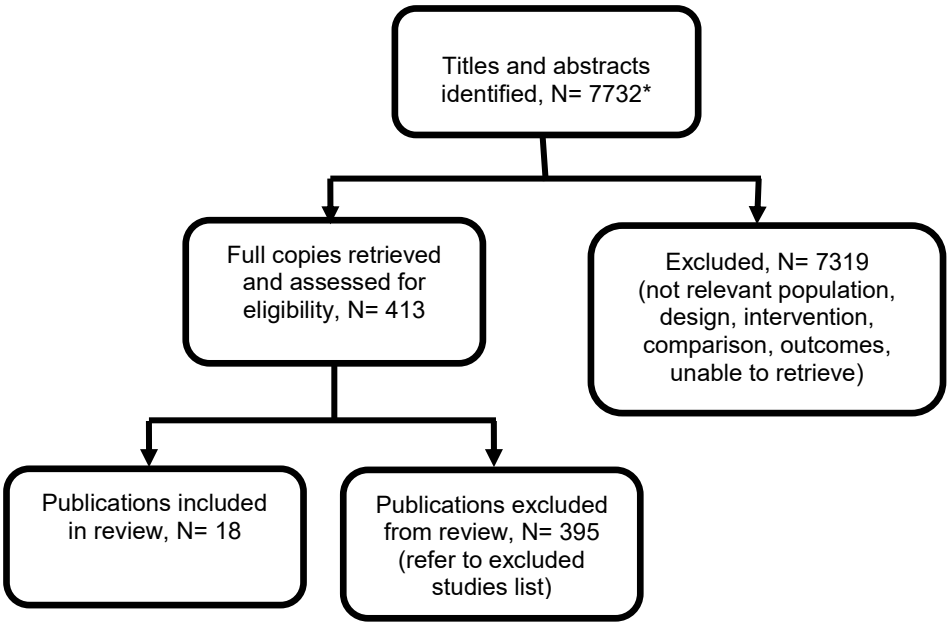
#	Search
24	((combin* or delay* or simultaneous* or stage*) near/3 (resect* or surg*)):ti,ab,kw
25	(liver-first or liverfirst):ti,ab,kw
26	"bowel first":ti,ab,kw
27	MeSH descriptor: [Ablation Techniques] explode all trees
28	((percutaneous* or radiofrequen* or radio-frequen* or RF or microwave*) near/3 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 amenable to treatment with curative intent?

Figure 5: 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 not 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.*

Appendix D – Clinical evidence tables

Clinical evidence tables for 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?

Table 6: Clinical evidence tables

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation 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, 262-270, 2012 **Ref Id** 845486 **Country/ies where the study was carried out** US **Study type** Retrospective cohort study **Aim of the study** To "… evaluate outcomes and economic implications of	**Sample size** N=60 simultaneous resection; n=84 staged resection **Characteristics** Age in years, median (IQR) Simultaneous 58 (46-64) Staged 53 (46-61) Male sex, n (%) Simultaneous 40 (67) Staged 49 (58) Primary tumour locations, n (%) Colon Simultaneous 26 (43) Staged 31 (37) Rectum Simultaneous 34 (57) Staged 53 (63) Type of liver resection, n (%) Minor (<3 segments) Simultaneous 40 (67) Staged 21 (25) Major (≥3 segments) Simultaneous 20 (33) Staged 63 (75) ≤5 liver metastases, n (%) Simultaneous 55 (92) Staged 57 (68)	**Interventions** Simultaneous or staged resections were all done at the same centre, with curative intent. RFA was sometimes used if resection was not feasible (the resulting liver remnant would be too low in volume).	**Details** Patient data was accessed from an institutional database. "Overall survival was calculated from the date of operation to the date of death. Recurrence-free survival was calculated from the date of operation to the date of cancer recurrence, either locoregional or systemic, or the date of death from another cause. Statistical analysis Survival was analysed using the Kaplan-Meier method. "Multivariable Cox regression analysis with backward stepwise selection was performed to evaluate the association of variables on overall and recurrence-free survival. Final model variables were surgical strategy, body mass index, type of liver resection, and number of liver metastases. These variables were chosen based on their significance on univariate analysis and/or their importance in surgical decision making and their potential influence on	**Results** Overall survival, median 36 months of follow-up Simultaneous n=60 Staged n=84 Adjusted HR 1.4 95% CI 0.74 to 2.65, p=0.3 Recurrence-free survival, median 36 months of follow-up Simultaneous n=60 Staged n=84 Adjusted HR 1.3 95% CI 0.62 to 1.75, p=0.88	**Limitations** ROBINS-I checklist for non-randomised studies of interventions Pre-intervention Bias due to confounding: Moderate risk of bias (Confounding expected, but controlled for) Bias in selection of participants into the study: Low risk of bias At intervention Bias in classification of interventions: Low risk of bias Post-intervention Bias due to deviations from intended interventions: Low risk of bias Bias due to missing data: Low risk of bias Bias in measurement of outcomes: Low risk of bias Bias in selection of the reported result: Low risk of bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
simultaneous and staged resections." **Study dates** 1993 to 2010 **Source of funding** American Society of Clinical Oncology Conquer Cancer Foundation; the National Institutes of Health	Preoperative chemotherapy Simultaneous 46 (77) Staged 52 (62) Preoperative radiotherapy, n (%) Simultaneous 21 (35) Staged 33 (39) **Inclusion criteria** Patients undergoing colorectal and hepatic resection for colorectal cancer with synchronous metastases to the liver; tumours resected with curative intent. **Exclusion criteria** Colorectal recurrence in the primary site; metachronous hepatic metastases; complete resection not performed.		postoperative morbidity and mortality."		
Full citation 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, 975-982, 2017 **Ref Id** 789136	**Sample size** N=1088 simultaneous resection; n=342 staged resection (n=309 bowel first, n=33 liver first) **Characteristics** Age, mean (SD) Simultaneous 59 (14) Staged 57 (12) Male sex, n (%) Simultaneous 551 (51) Staged 177 (52) Minimally invasive surgery, n (%) Colorectal resection Simultaneous 129 (12) Staged 81 (24) Liver resection Simultaneous 129 (12) Staged 19 (6) Liver procedure, n (%) Partial hepatectomy	**Interventions** Staged resection (colorectal or liver resection first, followed by liver or colorectal resection within 6 months, respectively) and simultaneous colorectal and liver resection during the same hospitalization."	**Details** Patients' data was accessed from a New York State Department of Health Statewide Planning and Research Cooperative System database. "Patients were identified using International Classification of Diseases, Ninth Revision, and Clinical Modification (ICD-9-CM) diagnosis codes." Primary endpoint was major events at 30-day follow-up (including in-hospital mortality, acute myocardial infarction, stroke, pulmonary embolism and shock). For the staged group, two separate 30-day follow-ups were considered, after each resection. Secondary endpoints were 30-day readmission, reoperation, procedure-related complications, surgical site infection, anastomotic	**Results** Major events within 30 days (myocardial infarction, stroke, pulmonary embolism, shock, and in-hospital death) Simultaneous n=1086 Staged n=341 Adjusted OR 0.72 95% CI 0.47 to 1.12, p=0.14 Readmission at 30 days Simultaneous n=1086 Staged n=341 Adjusted OR 0.71 95% CI 0.52 to 0.99, p=0.04 Return to operating theatre Simultaneous n=1086 Staged n=341 Adjusted OR 0.81 95% CI 0.41 to 1.59, p=0.53	**Limitations** ROBINS-I checklist for non-randomised studies of interventions Pre-intervention Bias due to confounding: Moderate risk of bias (Confounding expected, but controlled for) Bias in selection of participants into the study: Low risk of bias At intervention Bias in classification of interventions: Low risk of bias Post-intervention Bias due to deviations from intended interventions: Low risk of bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out US **Study type** Retrospective cohort study **Aim of the study** To "… provide an updated analysis of surgical utilization for patients presenting with synchronous colorectal liver metastasis and a comparison of real-world post-operative outcomes between staged and simultaneous resections." **Study dates** 2005 to 2014 **Source of funding** None reported.	Simultaneous 935 (86) Staged 236 (69) Total hepatic lobectomy Simultaneous 153 (14) Staged 106 (31) "When comparing patients who underwent staged resection, patients who underwent simultaneous resection were older (59.2 vs. 57.4 years, p = 0.03) and more likely to undergo partial hepatectomy (85.9 vs. 68.9%, p < 0.01).A significantly lower proportion of colorectal resections were performed using minimally invasive surgery in the simultaneous resection group compared to the staged group (11.9 vs. 23.7%, p < 0.01)" **Inclusion criteria** Patients who underwent an open or laparoscopic colorectal resection for colorectal cancer and a liver resection for secondary malignancy of the liver at the time of or within 6 months before or after the colorectal resection. **Exclusion criteria:** None reported.		leak, acute hepatic failure, liver abscess, transfusion, prolonged length of stay, high hospital charges, discharge status, and trend in annual number of surgeries. Statistical analysis "A generalized linear mixed model, accounting for hospital clustering as random effects, was adopted to compare outcomes across groups, using patients undergoing staged resection as the reference group. The model was adjusted for patient demographics, surgery year, comorbidities, use of minimally invasive surgical, extent of liver resection, and primary tumor location."	Anastomotic leak Simultaneous n=1086 Staged n=341 Adjusted OR 1.29 95% CI 0.86 to 1.92, p=0.21 Acute liver failure Simultaneous n=1086 Staged n=341 Adjusted OR 0.38 95% CI 0.08 to 1.72, p=0.21 Liver abscess Simultaneous n=1086 Staged n=341 Adjusted OR 1.93 95% CI 0.79 to 4.71, p=0.15	Bias due to missing data: Low risk of bias Bias in measurement of outcomes: Low risk of bias Bias in selection of the reported result: Low risk of bias
Full citation Bartolini, I., Ringressi, M. N., Melli, F., Risaliti, M., Brugia, M., Mini, E., Batignani, G., Bechi, P., Boni, L., Taddei, A., Analysis of prognostic factors for resected synchronous	**Sample size** N = 70 Synchronous combined surgery n=25; Synchronous "bowel first" n=14; metachronous n=31 **Patient characteristics**	**Interventions** "According to timing of metastasis presentation/treatment, patients were divided into 3 groups: "synchronous combined surgery" that included patients who underwent	**Details** Data collection: Data on patients undergoing liver resection (potentially curative) for first recurrence of colorectal ("liver only" first metastasization from colorectal) from February 2006 to February 2018 at a single unit.	Data extracted from multivariate analyses only Timing of metastases presentation/treatment - Overall effect p = 0.053; synchronous 'combined surgery' = ref treatment; synchronous 'bowel first'	**Limitations** Risk of bias assessed using the ROBINS-I checklist for non-randomised studies of interventions Pre-intervention

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
and metachronous liver metastases from colorectal cancer, Gastroenterology Research and Practice, 2018 (no pagination), 2018 **Ref Id** 983195 **Country/ies where the study was carried out:** Italy **Study type:** Prospective, single-centre observational study **Aim of the study:** To identify clinicopathological factors affecting disease-free (DFS) and overall survival (OS) in patients undergoing potentially curative liver resection for colorectal metastasis **Study dates:** February 2006 - February 2018 **Source of funding:** Not reported.	Age (years, range): Synchronous combined surgery 68 (34–85); synchronous 'bowel first' 75 (46–82); Metachronous 70 (52–85); total 69.5 (34–85), p = 0.730 Sex (n, %): Male -Synchronous combined surgery n=15 (60%), synchronous 'bowel first' n=9 (64.3%), metachronous n=16 (51.6%), total n=40 (57.1%); female - synchronous combined surgery n=10 (40%), synchronous 'bowel first' n=5 (35.7%), metachronous n=15 (48.4%); total n=30 (42.9%), p = 0.683 Bowel obstruction (n, %): Synchronous combined surgery 5 (20%); Synchronous 'bowel first- 7 (50%); Metachronous 7 (22.6%); total 19 (27.1%), p = 0.097 Site of primary tumor (n, %): Right colon - Synchronous combined surgery 8 (32%), Synchronous 'bowel first' 2 (14.3%); Metachronous 11 (35.5%); total 21 (30%); Left colon - Synchronous combined surgery 17 (68%), Synchronous 'bowel first' 12 (85.7%), metachronous 20 (64.5%), total 49 (70%), p = 0.343 Chemotherapy before liver surgery: Synchronous combined surgery 2 (8%); Synchronous 'bowel first' 11 (78.6%), metachronous 20 (64.5%), total 33 (47%), p <0.0001 **Inclusion criteria:** Consecutive patients undergoing liver resection (potentially curative) for first	combined surgery for primary tumor and liver metastasis, 'synchronous bowel first' that included patients with metastatic disease from the beginning of their neoplastic history but liver metastases were not treated during colorectal surgery, and “metachronous” that included patients who developed liver metastasis after colorectal cancer surgery. The decision to perform combined or delayed surgery in synchronous presentation with or without any perioperative chemotherapy was discussed during Hospital Tumor Board meetings. Patient’s conditions (i.e., comorbidities, bowel obstruction) and wishes, number, dimension, and position of the liver metastases at preoperative examination (confirmed or not at surgery time) were taken into account. Preoperative workup included triple phase-contrast enhanced computed tomography (CT) scan and	Patients’ data were prospectively collected into a database which was retrospectively reviewed. Outcomes: Overall survival (time between day of liver surgery and date of death) Disease-free survival (time between day of liver surgery and the diagnosis of any site of recurrence of disease or until the date of death or the last visit for alive patients). Clavien Dindo III-IV complications Follow-up: 10 years. Retrieval of follow-up data was completed including the revision of any available medical records and phone call interviews. Statistical analysis: Cox regression	HR = 2.8, p = 0.025; metachronous HR = 1.1, p = 0.895. Timing of metastases presentation/treatment - Overall effect p = 0.0008; synchronous 'combined surgery' = ref treatment; synchronous 'bowel first' HR =1.9, p = 0.219; metachronous HR = 0.5, p = 0.067.	Bias due to confounding: Low risk of bias Bias in selection of participants into the study: Low risk of bias Bias in classification of interventions: Low risk of bias Post-intervention Bias due to deviations from intended interventions: Low risk of bias Bias due to missing data: Moderate risk of bias. Multivariate analyses did not include histopathological parameters such as number of resected lesions, maximum diameter, liver margin status, etc; due to the aim of including patients undergoing RFA in the analyses. Bias in measurement of outcomes: Low risk of bias Bias in selection of the reported result: Low risk of bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	recurrence of colorectal (“liver only” first metastasization from colorectal) from February 2006 to February 2018 at a single unit. Patients undergoing intraoperative radiofrequency ablation (RFA) with a curative intent were also included. **Exclusion criteria:** Patients with a primary rectal squamocellular carcinoma were excluded.	pancolonoscopy. Liver volume assessment was performed when indicated. Magnetic resonance and positron emission tomography (PET) scan were used to rule out doubtful cases. Intraoperative ultrasound sonography (IOUS) was routinely used during liver surgery. Follow-up was done according to a standardized scheduled program including CT scan or abdominal ultrasound, colonoscopy, and blood test examination. It could be modified according to oncologist’s indications."			
Full citation 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, 1279-1289, 2010 **Ref Id** 846441	**Sample size** Case-matched groups n=26 simultaneous; n=26 staged **Characteristics** Case-matched groups: Age in years, mean (SD) Simultaneous 60 (8) Staged 60 (8) Male sex, n/n Simultaneous 17/26 Staged 17/26 Number of liver metastases, n (%) 1 Simultaneous 15 (58) Staged 15 (58) 2-3	**Interventions** Simultaneous resection of colorectal tumour and liver metastases versus delayed hepatectomy (staged resection), both with curative intent "Simultaneous colorectal and liver resection was considered when both the primary tumour and all metastatic disease could be resected curatively, generally in patients with limited liver disease necessitating a limited hepatectomy (fewer than	**Details** Patient data was accessed from a prospectively collected database. Postoperative follow-up consisted of history, physical examination, serum tumour markers, liver function parameters, abdominal ultrasound 1 month after surgery and every 4 months thereafter. Abdominal and thoracic CT was performed every 8 months. Statistical analysis "To obtain highly comparable groups, a one-to-one case match was performed within the total study population, whereby each patient who had undergone a simultaneous colorectal and hepatic resection was matched with a patient in	**Results** Overall survival at 3 years Simultaneous 67% (n=26) Staged 76% (n=26) p=0.78 Progression-free survival at 1 and 2 years Simultaneous 29% and 13% (n=26) Staged 73% and 52% (n=26) p=0.007 60-day mortality Simultaneous 0/26 Staged 0/26 Postoperative morbidity*	**Limitations** ROBINS-I checklist for non-randomised studies of interventions Pre-intervention Bias due to confounding: Moderate risk of bias (Confounding expected, but controlled for) Bias in selection of participants into the study: Low risk of bias At intervention Bias in classification of interventions: Low risk of bias Post-intervention

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out France **Study type** Retrospective cohort study **Aim of the study** To "… compare simultaneous colorectal and hepatic resection with a delayed strategy in patients who had a limited hepatectomy (fewer than three segments)." **Study dates** 1990 to 2006 **Source of funding** None reported.	Simultaneous 7 (27) Staged 7 (27) >3 Simultaneous 4 (15) Staged 4 (15) Bilateral liver metastases, n (%) Preoperative chemotherapy Simultaneous 7 (27) Staged 7 (27) Maximum size of liver metastases in mm, mean (SD) Simultaneous 38 (33) Staged 41 (21) Preoperative chemotherapy, n (%) Simultaneous 8 (31) Staged 24 (92) **Inclusion criteria** Patients with synchronous colorectal liver metastases (diagnosed before or during primary tumour surgery); treated with a limited hepatectomy (<3 liver segments) **Exclusion criteria** Patients scheduled for a two-stage hepatectomy; patients with major hepatectomy (3 or more liver segments resected)	three liver segments). In addition, patients had to be without general contraindications to a combined surgical strategy (such as cardiovascular or pulmonary co-morbidity) and with no complications from the primary tumour (bowel obstruction, perforation or haemorrhage). All treatment decisions were taken during a multidisciplinary staff meeting that included surgeons, medical oncologists and radiologists." "If a simultaneous resection strategy was chosen, first the liver resection was performed, representing the non-contaminated part of the procedure, followed by resection of the primary colorectal tumour, which involved a higher risk of septic contamination. If indicated, hepatic resection was combined with radiofrequency ablation and/or cryosurgery."	whom hepatectomy had been delayed. The following matching criteria were used: age, sex, number (categorized as one, two or three, or more than three) and distribution (unilateral or bilateral) of CLMs at diagnosis." Survival was analysed using the Kaplan-Meier method and log-rank test.	Simultaneous 2/26 Staged 8/26 *Including colorectal anastomotic leak, hepatic complications, general complications	Bias due to deviations from intended interventions: Low risk of bias Bias due to missing data: Low risk of bias Bias in measurement of outcomes: Low risk of bias Bias in selection of the reported result: Low risk of bias
Full citation Eltawil, K. M., Boame, N.,	**Sample size** N=174 total; n=24 treated with resection and RFA;	**Interventions**	**Details**	**Results**	**Limitations**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
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, 734-738, 2014 **Ref Id** 846678 **Country/ies where the study was carried out** Canada **Study type** Retrospective cohort **Aim of the study** To "… analyze the patterns of recurrence following intraoperative radiofrequency ablation (RFA) combined with hepatic resection for patients with colorectal liver metastases" **Study dates** January 2003 to December 2009 **Source of funding** "The Liver and	n=150 treated with resection without RFA **Characteristics** "The median age was significantly lower in the RFA/resection group compared to the resection only group. Chemotherapy was used in a majority of cases, although a greater proportion of RFA/ resection patients had neoadjuvant therapy (79% vs. 43%, P=0.18). Patients who underwent RFA /resection had a greater number of total liver lesions (median of 2 vs. 1 resected lesions, P=0.01; plus median of 1 ablated lesion in RFA/resection)." **Inclusion criteria** "(1) patients who underwent liver resection for CLM with curative intent; (2) histologically proven colorectal carcinoma; (3) the absence of disseminated metastatic disease on preoperative imaging (except lung and/or primary tumor site recurrence where there was also an anticipation to curatively address these lesions); and (4) age >18 years." **Exclusion criteria** None reported.	"Typically, the use of RFA in combination with resection was confined to (1) patients in whom complete resection of disease leaving sufficient hepatic parenchyma to support post-resection liver function was judged borderline or not possible, and (2) patients with tumors localized in the liver in such a way that complete resection was judged overly morbid. The decision to utilize RFA for otherwise resectable lesions was individualized, and took into account various patient-level (age, comorbidities, BMI, underlying liver parenchyma, number of cycles, and type of chemotherapy) and tumor-level factors (size, response to chemotherapy, proximity to major vessels, and/or bile ducts). The decision was based on the surgeon's judgment regarding the perceived morbidity of resection for a given patient in the context of his/her comorbidities, and residual liver size and quality."	Patient data was accessed from the institutional database. Primary endpoint was disease recurrence in the liver. Secondary endpoint was overall survival and recurrence-free survival. Statistical analysis Survival was analysed using the Kaplan-Meier method with log-rank test. Multivariate Cox regression models were constructed, variables were included in the model if they reached a p<0.2 in the univariate regression. Variables with p<0.2 in the univariate analysis: age, pre-operative CEA, primary site, neoadjuvant chemotherapy, median size of metastases, no of resected metastases.	Overall survival, median 35 months of follow-up Resection with RFA n=24 Resection alone n=150 Adjusted HR 1.02 95% CI 0.55 to 1.88, p=0.95 Recurrence-free survival, median 35 months of follow-up Resection with RFA n=24 Resection alone n=150 Adjusted HR 1.51 95% CI 0.94 to 4.42, p=0.08	ROBINS-I checklist for non-randomised studies of interventions Pre-intervention Bias due to confounding: Moderate risk of bias (Confounding expected, but controlled for) Bias in selection of participants into the study: Low risk of bias At intervention Bias in classification of interventions: Low risk of bias Post-intervention Bias due to deviations from intended interventions: Low risk of bias Bias due to missing data: Low risk of bias Bias in measurement of outcomes: Low risk of bias Bias in selection of the reported result: Low risk of bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Pancreas Unit, Ottawa Hospital, receives unrestricted funding for clinical and administrative support from Sanofi."					
Full citation 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, 1204-1212, 2008 **Ref Id** 847034 **Country/ies where the study was carried out** US **Study type** Retrospective cohort **Aim of the study** "To evaluate outcome following resection alone, combined resection-RFA, and RFA alone."	**Sample size** N=55 resection with RFA; n=192 resection alone **Characteristics** Median age 61 years (IQR 53-69.5) Male sex 169/258 Synchronous disease 71/258 "Patients who underwent resection alone were more likely to have larger tumors (median size, 3.5 cm; IQR, 2.0-5.0 cm) vs patients who underwent resection-RFA (median size, 2.5 cm; IQR, 1.9-4.0 cm) (P=.02). In contrast, patients who underwent resection alone had fewer hepatic metastases (median, 1 metastasis; IQR, 1-2 metastases) than patients who underwent resection-RFA (median, 5 metastases; IQR, 3-6 metastases) (P<.001). Among patients who underwent resection alone, 58.3% had solitary tumors (P<.001). Preoperative systemic chemotherapy was less commonly administered to patients before resection alone (38.0%) vs before resection-RFA (65.5%) (P<.001)." **Inclusion criteria** Patients "… with colorectal liver metastases who were operated on with curative intent were	**Interventions** "Radiofrequency ablation of hepatic lesions was performed at the time of laparotomy according to a standardized treatment algorithm. Intraoperative ultrasonography was used to insert needles into the lesions to be treated by RFA. Radiofrequency ablation was administered using an RFA generator (RITA Model 1500X; Rita Medical Systems, Inc, Fremont, California) with an enhanced device (Starburst XL or XLi, Rita Medical Systems, Inc) wherever applicable." Patients were treated with RFA in combination with resection when "at least 1 hepatic tumor was considered unresectable because of location of the disease, inadequate liver remnant, proximity of tumor to major vascular structures, or the presence of medical	**Details** Patient data accessed from a prospective institutional database. Endpoints of interest were systemic and hepatic recurrence, overall survival and disease-free survival. Statistical analysis - Kaplan-Meier method and log-rank test were used for survival outcomes. "To adjust for relative intergroup differences in known risk factors for disease-free and overall survival, a matched control analysis was performed. Patients who underwent RFA with or without resection (ie, cases) were matched 1:1 with patients who underwent resection alone (ie, controls). Matching was moderately successful in identifying cohorts of patients with comparable age, sex, primary tumor characteristics, and metastatic levels of hepatic disease burden (ie, similar number and size of liver lesions)." Because not all factors that were different among the treatment groups were able to be matched a multivariate Cox regression model was used. "Variables that were significant on	**Results** Overall survival Resection with RFA n=55 Resection alone n=192 Adjusted HR 2.82 95% CI 1.64 to 4.85 Disease-free survival Resection with RFA n=55 Resection alone n=192 Adjusted HR 2.09 95% CI 1.28 to 3.42	**Limitations** ROBINS-I checklist for non-randomised studies of interventions Pre-intervention Bias due to confounding: Moderate risk of bias (Confounding expected, but controlled for) Bias in selection of participants into the study: Low risk of bias At intervention Bias in classification of interventions: Low risk of bias Post-intervention Bias due to deviations from intended interventions: Low risk of bias Bias due to missing data: Low risk of bias Bias in measurement of outcomes: Low risk of bias Bias in selection of the reported result: Low risk of bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates January 1 1999 to August 30 2006 **Source of funding** None reported.	included in the study. In addition, only patients undergoing their first liver-directed therapy were included. Similarly, only RFA treatments that were performed at the time of open laparotomy were included." **Exclusion criteria** Patients "…who underwent percutaneous or laparoscopic-assisted RFA were excluded."	comorbidities that precluded major hepatic resection. Tumors were considered for RFA if near a major hepatic vein branch but not if adjacent to major biliary structures near the liver hilum."	univariate analysis or variables that were unbalanced among the treatment groups were included in the final multivariate model."		
Full citation 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) (no pagination), 2018 **Ref Id** 847352 **Country/ies where the study was carried out** Netherlands **Study type** Retrospective cohort study **Aim of the study** To "… analyze short-term and long-term outcome of RFA in	**Sample size** N=106 simultaneous resection; n=120 staged resection (bowel resection first) **Characteristics** Age in years, mean (SD) Simultaneous 62 (12) Colorectal first 62 (9) Male sex, n (%) Simultaneous 37 (53) Colorectal first 34 (49) Extent of liver surgery, n (%) ≥3 segments Simultaneous 25 (36) Colorectal first 27 (39) 1-2 segments Simultaneous 13 (19) Colorectal first 14 (20) RFA or wedge resection Simultaneous 32 (46) Colorectal first 29 (41) RFA as part of treatment, n (%) RFA + resection Simultaneous 19 (30) Colorectal first 11 (16) RFA only Simultaneous 11 (16)	**Interventions** Simultaneous resection of the colorectal cancer and liver metastases versus colorectal cancer resection first followed by a resection of the liver metastases. "During all simultaneous procedures, intraoperative RFA was performed under ultrasound guidance, using the RF 3000 TM Radio Frequency Ablation System." "Most patients who underwent the colorectal-first procedure are treated for colorectal cancer in a primary hospital. Another reason for not performing simultaneous surgery is comorbidity or large liver resections (>70% of liver volume). In simultaneous procedures, we always performed the liver procedure first and the	**Details** Patient data was accessed from a prospectively collected database of all patients with colorectal liver metastases in the study hospital. Statistical analysis For survival, Kaplan-Meier method was used with log-rank test. "In order to compare survival, a propensity score matching was used to reduce the influence of selection bias." "Covariates used for matching were location of the primary tumor, type of colorectal surgery, major/minor liver surgery, type of liver procedure, sex, age, neoadjuvant chemotherapy and clinical risk score"	**Results** Overall survival at 5 years Simultaneous 43.8% Colorectal first 43.0% Median survival time Simultaneous 48.9 months 95% CI 42.8 to 55.0 months Colorectal first 55.2 months 95% CI 41.7 to 68.7 months p=0.223 Overall survival was not added to Forest plots as the Kaplan Meier curves cross indicating the log-rank test / HR would not be useful.	**Limitations** ROBINS-I checklist for non-randomised studies of interventions Pre-intervention Bias due to confounding: Moderate risk of bias (Confounding expected, but controlled for) Bias in selection of participants into the study: Low risk of bias At intervention Bias in classification of interventions: Low risk of bias Post-intervention Bias due to deviations from intended interventions: Low risk of bias Bias due to missing data: Low risk of bias Bias in measurement of outcomes: Low risk of bias Bias in selection of the reported result: Low risk of bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
simultaneous treatment. A secondary aim was to compare simultaneous resection with the colorectal-first approach." **Study dates** 2000 to 2016 **Source of funding** The authors received no funding.	Colorectal first 14 (20) Low clinical risk score (0-2) Simultaneous 37 (53) Colorectal first 36 (51) Diameter of liver metastasis in cm, median (IQR) Simultaneous 2.5 (2.5) Colorectal first 3.0 (3.5) Neoadjuvant chemotherapy, n (%) Simultaneous 35 (50) Colorectal first 32 (46) Primary tumour in rectal site, n (%) Simultaneous 36 (51) Colorectal first 34 (49) Bilobar liver disease, n (%) Simultaneous 23 (33) Colorectal first 32 (46) **Inclusion criteria** Patients with synchronous colorectal liver metastases who underwent a radical resection of the colorectal cancer and a radical resection and/or ablation of the liver metastases; tumour-free resection margin (R0) **Exclusion criteria** None reported.	colorectal surgery second."			
Full citation 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	**Sample size** N=31 liver resection with RFA; n=93 liver resection alone **Characteristics** Age in years, median (range) Resection + RFA 59 (33-73) Resection alone 58 (29-81) Male sex, n/n	**Interventions** "If removal of all tumours could not be achieved by single hepatectomy, specific techniques, such as RFA and/or portal vein embolization, were added."	**Details** Data collection Patient data accessed from a prospectively collected database. Follow-up "After treatment, all patients underwent regular follow-up to monitor serum CEA and CA19-9 levels, and imaging studies,	**Results** Intrahepatic disease-free survival, median 36 months of follow-up Resection + RFA n=31 Resection alone n=93 HR 1.10 95% CI 0.65 to 1.79, p=0.705	**Limitations** ROBINS-I checklist for non-randomised studies of interventions Pre-intervention Bias due to confounding: Moderate ri sk of bias (Confounding

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
ablation combined with hepatectomy compared with hepatectomy alone for colorectal liver metastases, The British journal of surgery, 104, 570-579, 2017 **Ref Id** 847465 **Country/ies where the study was carried out** France **Study type** Retrospective cohort study **Aim of the study** To "… evaluate the therapeutic efficacy of RFA in combination with hepatectomy in comparison with hepatectomy alone in patients with CRLM using a propensity score-matched analysis." **Study dates** 2001 to 2012 **Source of funding** None reported.	Resection + RFA 20/31 Resection alone 60/93 Synchronous disease, n (%) Resection + RFA 27 (87) Resection alone 85 (91) Preoperative chemotherapy, n (%) Resection + RFA 30 (97) Resection alone 88 (95) **Inclusion criteria** Patients "…. who underwent hepatectomy for CRLM between 2001 and 2012 at Hôpital Universitaire Paul Brousse, Villejuif, France." **Exclusion criteria** Patients "who underwent repeat surgery or non-curative surgery (liver R2 resection and/or extrahepatic disease or primary tumour not resected) were excluded."	"Hepatectomy combined with RFA was in principle performed in patients with no more than three contralateral liver metastases, with a maximum tumour diameter in the remnant liver of less than 30 mm. If complete treatment was impossible by one-stage hepatectomy, even when combined with portal embolization or RFA, two-stage hepatectomy was considered."	including ultrasonography and abdominal and thoracic CT (alternately) to detect any intrahepatic or distant recurrence." Overall survival was defined as the time from the date of hepatic resection to death or last follow-up. Disease-free survival was defined as the time from resection to first recurrence or death. Intrahepatic disease-free survival was defines as the time from date of resection and first intrahepatic recurrence. Statistical analysis "To overcome bias caused by uneven distribution of prognostic factors between groups, a propensity score analysis with 1:3 matching was used. Matching was done based on propensity scores, including 12 variables that had P <0·300 (age, primary N category, primary tumour location, timing of liver metastases, distribution of liver metastases, initial unresectability, preoperative chemotherapy, number of tumours at hepatectomy, presence of concomitant extrahepatic disease, portal vein embolization, 2-step approach, and major hepatectomy involving at least 3 segments)." Survival was analysed using the Kaplan-Meier method and log-rank test.	Overall survival, median 36 months of follow-up Resection + RFA n=31 Resection alone n=93 HR 1.16 95% CI 0.59 to 2.19, p=0.649 Disease-free survival, median 36 months of follow-up Resection + RFA n=31 Resection alone n=93 HR 0.96 95% CI 0.60 to 1.50, p=0.865 90-day mortality Resection + RFA 1/31 Resection alone 0/93 Grade ≥3 postoperative complications Resection + RFA 6/31 Resection alone 22/93	expected, but controlled for) Bias in selection of participants into the study: Low risk of bias At intervention Bias in classification of interventions: Low risk of bias Post-intervention Bias due to deviations from intended interventions: Low risk of bias Bias due to missing data: Low risk of bias Bias in measurement of outcomes: Low risk of bias Bias in selection of the reported result: Low risk of bias
Full citation Kaibori, M., Iwamoto, S., Ishizaki, M., Matsui, K., Saito, T.,	**Sample size** N=32 simultaneous; n=42 staged (delayed liver resection) **Characteristics**	**Interventions** Simultaneous resection versus staged resection (delayed liver resection)	**Details** Patient data was accessed from medical records. "All of the patients who survived were	**Results** Hepatic disease-free survival at 5 years Simultaneous n=32 43.2%	**Limitations** ROBINS-I checklist for non-randomised studies of interventions

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Yoshioka, K., Hamada, Y., Kwon, A. H., Timing of resection for synchronous liver metastases from colorectal cancer, Digestive Diseases and Sciences, 55, 3262-3270, 2010 **Ref Id** 847643 **Country/ies where the study was carried out** Japan **Study type** Retrospective cohort study **Aim of the study** To compare surgical outcomes and long-term survival after simultaneous or delayed resection of liver metastasis and to investigate the factors influencing hepatic disease-free survival. **Study dates** February 1993 to March 2007 **Source of funding** None reported.	Age in years, mean (SD) Simultaneous 62 (9.3) Staged 65 (9.9) Male sex, n/n Simultaneous 17/32 Staged 27/42 Primary tumour in rectum, n/n Simultaneous 5/32 Staged 14/42 Adjuvant chemotherapy, n/n Simultaneous 0/32 Staged 25/42 **Inclusion criteria** Patients with synchronous colorectal liver metastases undergoing complete R(0) resection. **Exclusion criteria** None reported.		followed-up after discharge with physical examination, liver function tests, ultrasound, CT, or MRI being performed at least every 3 months to check for intrahepatic recurrence, and chest radiographs to detect pulmonary metastasis. Chest X-ray films and CT scans were obtained every 3 months and 6 months, respectively." Statistical analysis - Survival was analysed using the Kaplan-Meier method with log-rank test. "All of the variables that were significant according to univariate analysis were then examined using Cox's proportional hazards model to identify those variables with an independent influence on hepatic disease-free survival."	Staged n=42 59.5% HR 3.72 95% CI 1.49 to 9.26, p=0.0049	Pre-intervention Bias due to confounding: Moderate risk of bias (Confounding expected, but controlled for) Bias in selection of participants into the study: Low risk of bias At intervention Bias in classification of interventions: Low risk of bias Post-intervention Bias due to deviations from intended interventions: Low risk of bias Bias due to missing data: Low risk of bias Bias in measurement of outcomes: Low risk of bias Bias in selection of the reported result: Low risk of bias
Full citation Masuda, T., Margonis, G. A., Andreatos, N., Wang, J., Warner, S., Mirza, M. B., Angelou, A.,	**Sample size** N = 717. Patients with tumors <4 (n=568): Hepatic resection only n=520; hepatic resection + RFA n =48	Hepatic resection only vs heaptic resection + RFA. At Johns Hopkins University, hepatic resection + RFA was	Details Data collection: Data for included patients were collected via two institutions. Information on	**Results** Data extracted from multivariate analyses only	**Limitations** Risk of bias assessed using the ROBINS-I checklist for non-

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Damaskos, C., Garmpis, N., Sasaki, K., He, J., Imai, K., Yamashita, Y. I., Wolfgang, C. L., Baba, H., Weiss, M. J., Combined hepatic resection and radio-frequency ablation for patients with colorectal cancer liver metastasis: A viable option for patients with a large number of tumors, Anticancer Research, 38, 6353-6360, 2018 **Ref Id** 983402 **Country/ies where the study was carried out**: Japan and US. **Study type:** Retrospective observational analysis conducted in two centres **Aim of the study:** To compare overall survival of patients who had hepatic resection plus RFA versus hepatic resection only according to number of tumours (with the presence of <4 lesions defined as	**Patient characteristics** Patients with tumors <4 (n=568; hepatic resection n=520; hepatic resection + RFA n=48): Age, mean: Hepatic resection 59.8±12.5; hepatic resection + RFA 57.6±12.0, p = 0.23 Gender: Male - Hepatic resection 311 (59.8%); Hepatic resection + RFA 31 (64.6%); Female - hepatic resection 209 (40.2%); hepatic resection + RFA 17 (35.4%), , p = 0.54 Primary tumor location: Colon - hepatic resection 378 (72.7%); hepatic resection + RFA 41 (85.4%); Rectum - hepatic resection 142 (27.3%); hepatic resection + RFA 7 (14.6%), p = 0.06 Primary N status: Negative - hepatic resection 168 (32.3%); hepatic resection + RFA 16 (33.3%); Positive - hepatic resection 352 (67.7%); hepatic resection 32 (66.7%), p = 0.87 Concurrent primary tumor resection: Yes - hepatic resection 117 (22.5%); hepatic resection + RFA 9 (18.8%); No - hepatic resection 403 (77.5%); hepatic resection + RFA 39 (81.2%), p = 0.71 KRAS mutation (data obtained from 397 patients): Mutant - hepatic resection 136 (38.3%); hepatic resection + RFA 15 (35.7%); Wild -	selected when at least one hepatic tumor was considered unresectable because of its location, inadequate liver remnant, proximity of tumor to major vascular structure, or presence of medical comorbidities that precluded major hepatic resection. At Kumamoto University, hepatic resection + RFA was performed in patients with initially unresectable multiple metastases and had already received chemotherapy for CRLM.	preoperative patient characteristics including age, gender, primary tumor location (colon vs. rectum), primary lymph node metastasis (N) status, concurrent primary tumor resection, KRAS mutation status, serum carcinoembryonic antigen (CEA) level, presence of extrahepatic metastasis, administration of preoperative chemotherapy, size of the largest liver metastasis and number of CRLM were collected for each included patient. Data on tumor size and number were obtained with the aid of preoperative CT or MRI; information on the size and number of tumors treate with hepatic resection and RFA was also collected, based on the findings of pathology. Patients' survival data after hepatic resection were obtained. " Outcomes: Overall survival Follow-up: 120 months Statistical analysis: Kaplan Meier and log rank test	OS: Pre-operative prognostic factors for patients with tumors ≥4 (n=149) (not clear how poor prognosis was defined) Combination of RFA (Yes): HR 1.03 (95% CI 0.54 to 1.96), p = 0.93 Primary N (positive): HR 1.98 (95% CI 1.02 to 3.86), p = 0.044 KRAS mutation (mutant): HR 4.02 (95% CI 1.91 to 8.40), p <0.001 Extrahepatic metastasis (present): HR 4.93 (95% CI 2.04 to 11.9), <0.001 Preoperative chemotherapy (Yes): HR 2.92 (95% CI 0.92 to 9.26), p = 0.07 Preoperative prognostic factors for patients with tumors <4 (n=568). Combination of RFA (Yes): HR 1.89 (95% CI 1.24 to 2.87), p = 0.003 Primary N (positive): HR 1.27 (95% CI 0.91 to 1.78), p = 0.16 CEA (≥30 ng/ml): HR 2.12 (95% CI 1.51 to 2.98), p <0.001	randomised studies of interventions Pre-intervention Bias due to confounding: Low risk of bias Bias in selection of participants into the study: Low risk of bias Bias in classification of interventions: Low risk of bias Post-intervention Bias due to deviations from intended interventions: Low risk of bias Bias due to missing data: Low risk of bias Bias in measurement of outcomes: Low risk of bias Bias in selection of the reported result: Low risk of bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
small number and the presence of ≥4 liver lesions as big number); furthermore, factors associated with poor survival among patients with <4 and ≥4 liver lesions were also assessed. **Study dates:** January 2000 - January 2015 **Source of funding:** Not reported	hepatic resection 219 (61.7%); hepatic resection + RFA 27 (64.3%), p = 0.87 CEA (ng/ml - data obtained from 347 patients):hepatic resection 36.6±127.2; hepatic resection + RFA 22.6±52.4, p = 0.48 Extrahepatic metastasis: Present - hepatic resection 50 (9.6%); hepatic resection + RFA 4 (8.3%); Absent - hepatic resection 470 (90.4%); hepatic resection + RFA 44 (91.7%), p >0.99 Preoperative chemotherapy: Yes - hepatic resection 353 (67.9%); hepatic resection 42 (87.5%); No - hepatic resection 167 (32.1%); hepatic resection + RFA 6 (12.5%), p = 0.005 Tumor size (cm): hepatic resection 3.2±2.3; hepatic resection + RFA 2.8±1.7, p = 0.20 Tumor number, median (IQR): hepatic resection 1 (1-2); hepatic resection + RFA 2 (2-3), p <0.001 Patients with tumors ≥4 (n=149; hepatic resection n=81; hepatic resection + RFA n=68): Age, mean: hepatic resection 56.9±12.4; hepatic resection + RFA 58.7±10.6, p = 0.37 Gender: Male - hepatic resection 45 (55.6%); hepatic resection + RFA 43 (63.2%); Female: hepatic resection			Extrahepatic metastasis (present): HR 1.84 (95% CI 1.15 to 2.93), p = 0.01 Preoperative chemotherapy (Yes): HR 1.45 (95% CI 1.03 to 2.05), p = 0.03 Prognosis of patients without extrahepatic metastases and with ≥4 hepatic lesions who underwent hepatic resection + RFA vs. hepatic resection alone. 5 year OS (patients with extrahepatic metastases excluded from analysis): Hepatic resection + RFA (n=61) 34.0% vs hepatic resection alone (n=75) 35.4% (p=0.66).	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	36 (44.4%); hepatic resection + RFA 25 (36.8%), p = 0.40 Primary tumor location: Colon - hepatic resection 58 (71.6%); hepatic resection + RFA 56 (82.4%); Rectum - hepatic resection 23 (28.4%); hepatic resection + RFA 12 (17.6%), p = 0.17 Primary N status: Negative - hepatic resection 30 (37.0%); hepatic resection + RFA 22 (32.4%); Positive - hepatic resection 51 (63.0%); hepatic resection + RFA 46 (67.6%), p = 0.61 Concurrent primary tumor resection: Yes - hepatic resection 20 (24.7%); hepatic resection + RFA 10 (14.7%); No - hepatic resection 61 (75.3%); hepatic resection + RFA 58 (85.3%), p = 0.008 KRAS mutation (Data obtained from 97 patients): Mutant - hepatic resection 17 (33.3%); hepatic resection + RFA 20 (43.5%); Wild - hepatic resection 34 (66.7%); hepatic resection + RFA 26 (56.5%), p = 0.40 CEA (ng/ml - data obtained from 82 patients):hepatic resection 134.4±831.8; hepatic resection + RFA 28.6±89.4, p = 0.33 Extrahepatic metastasis: Present - hepatic resection 6 (7.4%); hepatic resection + RFA 7 (10.3%); Absent - hepatic resection 75 (92.6%); hepatic resection 61 (89.7%), p = 0.57				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Preoperative chemotherapy: Yes - hepatic resection 66 (81.5%); hepatic resection + RFA 61 (89.7%); No - hepatic resection 15 (18.5%); hepatic resection + RFA 7 (10.3%), p = 0.17 Tumor size (cm): hepatic resection 3.1±2.4; hepatic resection + RFA 2.8±1.6, p = 0.45 Tumor number, median (IQR): hepatic resection 5 (4-7); hepatic resection + RFA 5 (4-10), p = 0.10 **Inclusion criteria:** Not reported specifically. **Exclusion criteria:** Not reported specifically.				
Full citation 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, 707-718, 2013	**Sample size** N=329 simultaneous resection; n=675 staged resection (n=647 colorectal first; n=28 liver first) **Characteristics** Age in years, median (SD) Simultaneous 60 (30) Colorectal first 61 (18) Liver first 58 (12) Male sex, n (%) Simultaneous 185 (56) Colorectal first 396 (61) Liver first 17 (61) Primary cancer in rectum, n (%) Simultaneous 91 (28) Colorectal first 170 (26) Liver first 15 (54) Bilateral hepatic disease, n (%)	**Interventions** Simultaneous resection of colorectal cancer and liver metastases versus staged resection (mainly colorectal first)	**Details** Patient data was accessed from a multi-institutional database. No details are provided about follow-up. Statistical analysis: Survival was analysed using the Kaplan-Meier method and log-rank test and multivariate Cox regression analysis.	**Results** Overall survival, median 34 months of follow-up Simultaneous n=329 Staged n=675 Adjusted HR 1.08 95% CI 0.88 to 1.31, p=0.472	**Limitations** ROBINS-I checklist for non-randomised studies of interventions Pre-intervention Bias due to confounding: Moderate ri sk of bias (Confounding expected, but controlled for) Bias in selection of participants into the study: Low risk of bias At intervention Bias in classification of interventions: Low risk of bias Post-intervention Bias due to deviations from intended

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref Id 848512 **Country/ies where the study was carried out** Italy, Portugal, Switzerland, US **Study type** Retrospective cohort study **Aim of the study** To "… investigate the surgical management and outcomes of patients with primary colorectal cancer and synchronous liver metastasis." **Study dates** October 1982 to June 2011 **Source of funding** None reported.	Simultaneous 124 (38) Colorectal first 240 (38) Liver first 16 (64) >2 hepatic metastases, n (%) Simultaneous 112 (35) Colorectal first 14 (58) Liver first 199 (33) Size of metastases in cm, median (SD) Simultaneous 3.0 (2.7) Colorectal first 3.5 (3.1) Liver first 3.0 (2.4) Extrahepatic metastases, n (%) Simultaneous 47 (7) Colorectal first 69 (11) Liver first 1 (4) **Inclusion criteria** Patients with colorectal cancer and synchronous liver metastases who underwent surgery with curative intent for both primary cancer and metastases. "If the patient had extrahepatic colorectal metastasis, the extrahepatic disease had to be surgically addressed with curative intent either at the time of the hepatic operation or at another date for the patient to be included in the study cohort." **Exclusion criteria** Previous hepatic resections or ablations of the colorectal liver metastases; patients undergoing ablation only.				interventions: Low risk of bias Bias due to missing data: Low risk of bias Bias in measurement of outcomes: Low risk of bias Bias in selection of the reported result: Low risk of bias
Full citation Mitry, E., Fields, A. L. A., Bleiberg, H.,	**Sample size** N=302 randomised;	**Interventions** "FU 400 mg/m² administered	**Details** Randomisation and allocation concealment	**Results** Overall survival	**Limitations** Cochrane risk of bias tool

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
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., 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, 4906-4911, 2008 **Ref Id** 844662 **Country/ies where the study was carried out** Belgium, Canada, France, Italy, Switzerland **Study type** Two phase III RCTs (Federation Francophone de Cancerologie Digestive Trial 9002/Association de Chirugie Hepato-Biliare et de Transplantation Hepatique/Association Universitaire de	n=148 allocated to adjuvant chemotherapy; n=154 allocated to surgery alone **Characteristics** Age in years, median (range) Adjuvant chemotherapy 63 (35-77) Surgery alone 62 (20-82) Male sex, n (%) Adjuvant chemotherapy 80 (58) Surgery alone 89 (64) Age ≥70 years, n (%) Adjuvant chemotherapy 28 (20) Surgery alone 29 (21) Primary tumour in rectum, n (%) Adjuvant chemotherapy 49 (36) Surgery alone 51 (36) Prior chemotherapy, n (%) Adjuvant chemotherapy 39 (28) Surgery alone 38 (28) Site of metastases, n (%) Liver Adjuvant chemotherapy 130 (94) Surgery alone 131 (94) Lung Adjuvant chemotherapy 7 (5) Surgery alone 6 (4) Unknown Adjuvant chemotherapy 1 (1) Surgery alone 3 (2) Number of metastases, median (range) Adjuvant chemotherapy 1 (1-7) Surgery alone 1 (1-4) ≥2 metastases, n (%) Adjuvant chemotherapy 46 (33)	intravenously once daily for 5 days plus DL-leucovorin 200 mg/m² administered intravenously for 5 days (FFCD) or FU 370 mg/m² plus L-leucovorin 100 mg/m² for 5 days (ENG), both given for six cycles at 28-day intervals. Adjuvant chemotherapy started between 10 and 35 days after surgery in the FFCD trial, whereas randomization had to occur within 49 days from surgery and treatment had to begin within 7 days from randomization in the ENG trial."	FFCD trial: randomisation was stratified by the number of metastases (1 or ≥2), maximum size of metastases (≤5 or >5 cm), disease-free interval between primary tumour resection and liver progression (≤1 or >1 year), and prior adjuvant chemotherapy (yes or no). ENG trial: randomisation was stratified by treatment centre, number of metastases (1 or ≥2), disease-free interval between primary tumour resection and liver progression (><6 or ≥6 months), site of resected metastatic disease (liver or lung), and prior adjuvant chemotherapy (yes or no). No other details provided. Follow-up/outcomes Monthly follow-up during the adjuvant chemotherapy treatment. Follow-up visits included taking history, physical examination, assessment of performance status, full blood count, serum biochemistry (and CEA level in the FFCD trial). In the FFCD trial: thereafter evaluation every 3 months until 2 years after randomisation, thereafter yearly including history, physical examination, chest X-ray (chest CT as indicated), abdominal ultrasound, and CEA level. In the ENG trial: thereafter an assessment at 9 months and 12 months from randomisation, then every 6 months until 5 years from randomisation, then yearly,	HR 1.32 95% CI 0.95 to 1.82, p=0.095 (chemotherapy as reference, when calculated* as surgery alone as reference HR 0.76 95% CI 0.55 to 1.05) Median overall survival time Adjuvant chemotherapy 62 months 95% CI 45.2 months to not reached Surgery alone 47.3 months 95% CI 40.6 to 57.2 months Progression-free survival HR 1.32 95% CI 1.00 to 1.76, p=0.058 (chemotherapy as reference, when calculated* as surgery alone as reference HR 0.76 95% CI 0.56 to 1.00) Median progression-free survival time Adjuvant chemotherapy 27.9 months 95% CI 21.0 to 41.9 months Surgery alone 18.8 months 95% CI 14.7 to 23.8 months Grade 3 or 4 adverse events (in FFCD trial)** Adjuvant chemotherapy 20/86 Surgery alone N/A *Calculated by the NGA technical team.	Selection bias Random sequence generation: unclear risk (Details not reported.) Allocation concealment: unclear risk (Not reported.) Performance bias Blinding of participants and personnel: unclear/high risk (No blinding.) Detection bias Blinding of outcome assessment: unclear/high risk (No blinding. Risk of bias depends on the outcomes.) Attrition bias Incomplete outcome data: low risk Reporting bias Selective reporting: low risk Other bias Other sources of bias: - **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Recherche en Chirurgie Vasculaire trial [FFCD trial]; EORTC Trial 40923/National Cancer Institute of Canada Clinical Trials Group Trial CO.7/Gruppo Italiano di Valutazione Interventi in Oncologia CO.3 trial [ENG trial]) **Aim of the study** To "... evaluate the benefit of postoperative chemotherapy with bolus FU plus leucovorin compared with surgery alone after potentially curative resection of metastases from colorectal cancer." **Study dates** Decemeber 1991 to Decemeber 2001 (FFCD trial) and February 1994 to January 1998 (ENG trial) **Source of funding** Association pour la Recherche en Oncologie Digestive	Surgery alone 44 (31) Disease-free interval between primary tumour resection and diagnosis of metastatic disease >1 years, n (%) Adjuvant chemotherapy 78 (57) Surgery alone 80 (57) **Inclusion criteria** Histologically proven colorectal cancer; free of clinically detectable disease by R0 surgical resection of the primary tumour; ≤4 metastases located in a single location (FFCD trial: liver; ENG trial: liver or lung); negative resection margins by histologic examination; ECOG performance status 0-2; <76 years of age (FFCD trial); biologic tests compatible with chemotherapy administration; no primary cancer of any other site; no previous chemotherapy except adjuvant treatment of their primary tumour (ENG trial: minimum of 6 months between cessation of chemotherapy and diagnosis of metastatic disease; FFCD trial: adjuvant chemotherapy finished before diagnosis of metastatic disease); no uncontrolled medical condition that would be aggravated by treatment; adequate contraception, not pregnant or breastfeeding. **Exclusion criteria** Distant lymph nodes, including metastases to the porta hepatis or mediastinal nodes; metastases to other organs		including history, physical examination, chest X-ray (chest CT if indicated), and abdominal ultrasound/CT/MRI. Primary endpoint in the FFCD trial was disease-free survival at 2 years and in the ENG trial overall survival. Secondary endpoint in the FFCD trial was overall survival and in the ENG trial disease-free survival. Disease-free survival calculated from the date of metastases resection to date of proven recurrence or death from any cause; overall survival was calculated from the date of metastases resection to death from any cause. Statistical analysis Survival estimates analysed with Kaplan Meier method and log-rank test. Cox proportional hazard regression stratified by trial, variables included in the model: age, performance status, treatment group, number of metastases, maximum size of metastases, previous chemotherapy, disease-free interval)	**From Portier et al 2006 reporting FFCD trial only.	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation 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, Eur J Surg OncolEuropean journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology, 36, 365-70, 2010 **Ref Id** 911447 **Country/ies where the study was carried out** UK **Study type** Retrospective matched cohort study **Aim of the study** To "… determine short and long term patient outcomes, this study cased matched patients undergoing synchronous procedures to patients undergoing staged procedures."	**Sample size** n=32 simultaneous resection; n=32 staged resection **Characteristics** Age in years, mean (range) Simultaneous 69 (53-79) Staged 67 (37-82) Male sex, n/n Simultaneous 18/32 Staged 21/32 Clinical risk score, median (range) Simultaneous 2 (1-3) Staged 2 (0-5) RFA, n/n Simultaneous 5/32 Staged 1/32 Chemotherapy/radiotherapy (neoadjuvant or adjuvant), n/n Simultaneous 13/32 Staged 17/32 **Inclusion criteria** Consecutive patients "… with colorectal cancer and hepatic metastases that underwent a synchronous operative approach...were individually case matched with patients that had undergone a staged approach." "Patients were case matched according to: age; sex; ASA grade (American Society of Anesthesiologists); type of hepatic resection and type of colonic resection." **Exclusion criteria** None reported.	**Interventions** Simultaneous resection versus staged resection (colorectal resection first) "The patients in the staged group had their colonic resection performed at another hospital and were subsequently referred to this unit for treatment of their hepatic metastases." "The criteria for selection for synchronous surgery have been documented previously and included: fitness for anaesthesia; expected margin negative resection (R0) of the primary disease; no unresectable extrahepatic disease and adequate predicted volume of hepatic remnant post resection."	**Details** Not clearly reported where patient data was accessed but presumably from an institutional medical records database. Follow-up "Postoperatively, patients entered the departmental surveillance programme. This consisted of serial examination and contrast-enhanced CT at six months, then at yearly intervals, up until five years after their operation. Colonoscopies were performed at one year, three years and five years after colonic resection. Patients that had undergone RFA had one additional scan at 6 weeks to allow confirmation of complete necrosis." Statistical analysis - Groups were matched according to age, sex, ASA grade, type of hepatic resection and type of colonic resection. No information about statistical analysis reported. Survival was compared using log-rank test.	**Results** Overall survival at 5 years Simultaneous 21% Staged 24% Median survival time Simultaneous 39 months Staged 42 months p=0.838 Perioperative mortality Simultaneous 0/32 Staged 0/32 Grade 3 complications Simultaneous 1/32 Staged 0/32	**Limitations** ROBINS-I checklist for non-randomised studies of interventions Pre-intervention Bias due to confounding: Serious risk of bias (Groups were matched according age, sex, ASA grade and type of surgery but no adjustment was made on certain potentially important variables such as extent or number of liver metastases) Bias in selection of participants into the study: Moderate risk of bias (Not clearly reported, difficult to assess) At intervention Bias in classification of interventions: Low risk of bias Post-intervention Bias due to deviations from intended interventions: Low risk of bias Bias due to missing data: Low risk of bias Bias in measurement of outcomes: Moderate risk of bias (Definitions of outcomes not described) Bias in selection of the reported result: Serious risk of bias (Unclear and limited reporting)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates Not reported. **Source of funding** "No funding was received for this study."					
Full citation 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, 1007-1016, 2008 **Ref Id** 848901	**Sample size** See Nordlinger 2013 **Characteristics** **Inclusion criteria** **Exclusion criteria**	**Interventions**	**Details**	**Results**	**Limitations**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out **Study type** **Aim of the study** **Study dates** **Source of funding**					
Full citation 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	**Sample size** N=364 randomised; n=182 allocated to perioperative chemotherapy; n=182 allocated to surgery alone. **Characteristics** Age in years, median (range) Perioperative chemotherapy 62 (29-79) Surgery alone 64 (25-78) Male sex, n (%) Perioperative chemotherapy 127 (70) Surgery alone 114 (63) Metachronous liver metastases, n (%) Perioperative chemotherapy 121 (66) Surgery alone 115 (63) Time from diagnosis of primary cancer to diagnosis of liver metastases 2 or more years, n (%) Perioperative chemotherapy 49 (27) Surgery alone 43 (24) Previous adjuvant chemotherapy for primary cancer (without oxaliplatin), n (%) Perioperative chemotherapy 78 (43)	**Interventions** Perioperative chemotherapy. Six cycles of FOLFOX4 (each cycle lasted for 14 days, subsequent cycle starting on day 15): oxaliplatin 85 mg/m², folinic acid 200 mg/m² DL form or 100 mg/m² L form on days 1-2 plus bolus, and fluorouracil 400 mg/m² bolus and 600 mg/m² continuous 22h infusion before and after surgery.	**Details** Randomisation and allocation concealment. Randomisation was done with a minimisation method via a web-based randomisation system at the EORTC coordinating data centre, accessed by authorised investigators. Randomisation was stratified according to centre, previous adjuvant chemotherapy to primary surgery for colorectal cancer, and a risk score developed previously by Nordlinger and colleagues. Follow-up/outcomes Follow-up was done every 3 months for 2 years after the end of the treatment and every 6 months thereafter, including chest radiography, abdominal ultrasound or CT scan, and CEA level. Primary endpoint was progression-free survival (time from randomisation to either progressive or recurrent disease, surgery if metastases were	**Results** Overall survival, median 8.5 years of follow-up (event is death from any cause) Perioperative chemotherapy 107 events, n=182 Surgery alone 114 events, n=182 HR 0.88 95% CI 0.68 to 1.14, p=0.34 Median overall survival Perioperative chemotherapy 61.3 months 95% CI 51.0 to 83.4 months Surgery alone 54.3 months 95% CI 41.9 to 79.4 months Progression-free survival, median 8.5 years of follow-up Perioperative chemotherapy 136 events, n=182 Surgery alone 139 events, n=182	**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 (No blinding. Risk of bias depends on the outcome.) 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
Oncology, 14, 1208-1215, 2013 **Ref Id** 848902 **Country/ies where the study was carried out** Australia, Austria, Belgium, France, Germany, Hong Kong, Italy, Norway, Sweden, the Netherlands, UK **Study type** Phase III RCT (EORTC 40983, NCT00006479) **Aim of the study** To study "… the combination of perioperative chemotherapy and surgery compared with surgery alone for patients with initially resectable liver metastases from colorectal cancer". **Study dates** October 10 2000 to July 5 2004 **Source of funding** European Organisation for Research and Treatment of Cancer, Norwegian and Swedish Cancer Societies, Cancer Research UK, Ligue	Surgery alone 76 (42) **Inclusion criteria** 18-80 years old; WHO performance status ≤2; histologically proven colorectal cancer; 1-4 liver metastases that were resectable; no detectable extrahepatic tumours; primary tumour had to be either previously resected (R0 resection) or judged to be resectable (in case of synchronous metastases). **Exclusion criteria** Previous chemotherapy with oxaliplatin; any history with cancer in the past 10 years (except non-melanoma skin cancer or in-situ cervix cancer); major hepatic insufficiency; an absolute neutrophil count <1.5x10^9/l; serum creatinine more than twice the upper limit of normal; grade >1 of common toxicity criteria for peripheral neuropathy; uncontrolled congestive heart failure; angina pectoris; hypertension; arrhythmia; history of significant neurological or psychiatric disorders, active infection; pregnant or breastfeeding.		deemed not resectable, or death from any cause). Secondary endpoints were overall survival (time from randomisation to death from any cause), tumour resectability and tumour response. Statistical analysis Survival was estimated with the Kaplan-Meier method and log-rank test. Intention-to-treat analysis was done.	HR 0.81 95% CI 0.64 to 1.02, p=0.068 Median progression-free survival Perioperative chemotherapy 20.0 months 95% CI 15.0 to 27.6 months Surgery alone 12.5 months 95% CI 9.7 to 17.7 months Treatment-related mortality Perioperative chemotherapy 3/182 Surgery alone 3/182	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Nationale Contre Cancer, US National Cancer Institute, Sanofi-Aventis (pharmaceutical company which also offered free oxaliplatin supplies).					
Full citation 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 **Ref Id** 849099 **Country/ies where the study was carried out** Italy **Study type** Retrospective cohort study **Aim of the study** To "… assess the incidence and risk factros of PHLF (posthepatectomy liver failure) after	**Sample size** N=46 simultaneous resection; n=60 staged resection. **Characteristics** Age in years, mean (SD) Simultaneous 64 (12) Staged 61 (9) Male sex, n/n Simultaneous 24/46 Staged 37/60 Primary cancer in rectum, n (%) Simultaneous 8 (17) Staged 13 (22) Extrahepatic metastases, n (%) Simultaneous 7 (15) Staged 6 (10) ≥3 hepatic metastases, n (%) Simultaneous 13 (28) Staged 28 (47) Metastasis diameter >5 cm, n (%) Simultaneous 17 (37) Staged 19 (32) Preoperative chemotherapy (before liver resection), n (%) Simultaneous 13 (28) Staged 51 (85)	**Interventions** Simultaneous resection of colorectal cancer and liver metastases versus staged resection (colorectal first). Simultaneous resection was proposed to all patients regardless of the location of the primary tumour, except in 5 patients who were considered unfit for simultaneous surgery because of age and comorbidities and underwent staged resection. Apart from these 5, all other patients in the staged resection group were patients who underwent colorectal resection in another hospital before being referred to the study hospital for liver resection. During simultaneous resection, the primary colorectal cancer was resected first, colonic	**Details** Patient data was accessed from an institutional database. Overall survival and disease-free survival were calculated from the rate of liver resection. Statistical analysis Survival was analysed using a multivariate Cox regression model, "propensity score was entered as a covariate to adjust for the differences in patients' characteristics between the treatment groups".	**Results** Overall survival at 3 years Simultaneous 55%; Staged 56%, p=0.802	**Limitations** ROBINS-I checklist for non-randomised studies of interventions Pre-intervention Bias due to confounding: Moderate ri sk of bias (Confounding expected, but controlled for) Bias in selection of participants into the study: Low risk of bias At intervention Bias in classification of interventions: Low risk of bias Post-intervention Bias due to deviations from intended interventions: Low risk of bias Bias due to missing data: Low risk of bias Bias in measurement of outcomes: Low risk of bias Bias in selection of the reported result: Low risk of bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
simultaneous vs staged resection of colorectal cancer and hepatic metastases" **Study dates** February 1997 to June 2012 **Source of funding** None reported.	Major hepatectomy, n (%) Simultaneous 22 (48) Staged 42 (70) **Inclusion criteria** Consecutive patients with colorectal cancer and synchronous liver metastases who underwent liver resection **Exclusion criteria** None reported.	anastomosis was done after hepatic resection was completed.			
Full citation 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 **Ref Id** 849222 **Country/ies where the study was carried out** **Study type**	**Sample size** See Mitry 2008 **Characteristics** **Inclusion criteria** **Exclusion criteria**	**Interventions**	**Details**	**Results**	**Limitations**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study **Study dates** **Source of funding**					
Full citation 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 **Ref Id** 850356 **Country/ies where the study was carried out** UK **Study type** Retrospective cohort study **Aim of the study** To "… describe temporal trends and inter-hospital variation in surgical strategy, and to compare longterm survival in a	**Sample size** N=198 simultaneous resection; n=198 staged resection (colorectal resection first). (In the study, n=259 simultaneous resection; n=1301 colorectal resection first in total, however, relevant analysis was conducted between groups that were matched according to baseline characteristics, n shown above) **Characteristics** Characteristic in the whole cohort (characteristics of the matched cohort not reported) Age <60 years, n %) Simultaneous 73 (28) Colorectal first 397 (31) Age >70 years, n (%) Simultaneous 105 (41) Colorectal first 432 (33) Male sex, n (%) Simultaneous 141 (54) Colorectal first 814 (63) Primary site rectum, n (%) Simultaneous 54 (21) Colorectal first 315 (24) Charlson comorbidity score ≥2, n (%) Simultaneous 28 (11) Colorectal first 100 (8)	**Interventions** Simultaneous resection versus colorectal resection first (the study also included a group who underwent liver resection first, however, no relevant results are presented comparing liver first to simultaneous, therefore, data from this group has not been included here)	**Details** Patient data was accessed from National Bowel Cancer Audit (NBOCA). This data was linked to the Hospital Episodes Statistics database. "The NBOCA collects data on all patients with newly diagnosed colorectal cancer in England." Statistical analysis "The potential biases to the survival analysis associated with differences in patient characteristics were accounted for by propensity score matching. Propensity score matching can reduce biases associated with multivariable regression modelling because it restricts the comparison to only those patients eligible for either approach" Survival was compared using the Kaplan-Meier method with log-rank test. Cox regression analysis was performed on the matched cohort.	**Results** Overall survival: Simultaneous n=198; Colorectal first n=198, HR 0.92 (95% CI 0.801 to 1.06).	**Limitations** ROBINS-I checklist for non-randomised studies of interventions Pre-intervention Bias due to confounding: Moderate risk of bias (Confounding expected, but controlled for) Bias in selection of participants into the study: Low risk of bias At intervention Bias in classification of interventions: Low risk of bias Post-intervention Bias due to deviations from intended interventions: Low risk of bias Bias due to missing data: Low risk of bias Bias in measurement of outcomes: Low risk of bias Bias in selection of the reported result: Serious risk of bias (Limited reporting on the matched cohort, for example, no sample sizes are reported.)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
propensity score-matched analysis" **Study dates** 1 January 2010 to 31 December 2015 **Source of funding** Healthcare Quality Improvement Partnership	ASA grade 3/4, n (%) Simultaneous 71 (30) Colorectal first 234 (19) Major liver resection, n (%) Simultaneous 40 (15) Colorectal first 535 (41) **Inclusion criteria** Patients with colorectal cancer and synchronous liver-limited metastases undergoing elective colorectal cancer and liver resection **Exclusion criteria** Emergency colorectal cancer surgery; extrahepatic disease at diagnosis				
Full citation 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 **Ref Id** 850362	**Sample size** N=98 resection + RFA; n=534 resection alone **Characteristics** Age in years, median (range) Resection + RFA 64 (37-82) Resection alone 65 (31-89) Male sex, n (%) Resection + RFA 63 (64) Resection alone 343 (64) Neoadjuvant chemotherapy, n (%) Resection + RFA 71 (72) Resection alone 170 (32) "Patients were more frequently categorized as ASA class II in combination group as compared to ROG (resection only group), making the average ASA classification of these patients lower (P=0.04). However, there was no further difference in the total presence of	**Interventions** "The main reason to perform RFA was a limited future liver remnant, e.g., excessive loss of parenchyma due to resection because of multifocal disease or ill located lesions which would provide a disproportionate parenchyma loss compared to the tumor size." "With the use of ultrasound, a Cool-Tip(Covidien, Boulder, CO, USA) was placed in the target lesion to achieve complete ablation with a 1 cm margin. Depending on the size of the lesion, a single probe (lesions	**Details** Data collection - Patient data was accessed from a prospective institutional database. Follow-up - Clinical examination and CEA level measurement were done every 4 months. Imaging (ultrasound, CE-CT of chest and abdomen) was performed in different schedule in the two study centres. In one centre: normally every 4 months in the first year, every 6 months for the second year and annually thereafter. In the second centre: every 3 months in the first 3 years, and every 6 months for the next 2 years (up to 5 years). Disease-free survival was defined as the time between hepatic treatment and first disease recurrence. Overall survival was defined as the time between treatment and death.	**Results** Overall survival Resection + RFA n=98 Resection alone n=534 Adjusted HR 1.55 95% CI 1.07 to 2.25, p=0.02 Disease-free survival Resection + RFA n=98 Resection alone n=534 Adjusted HR 1.01 95% CI 0.73 to 1.39, p=0.95	**Limitations** ROBINS-I checklist for non-randomised studies of interventions Pre-intervention Bias due to confounding: Serious risk of bias (Confounding expected and controlled for but certain important potential confounders were not included in the multivariate model) Bias in selection of participants into the study: Low risk of bias At intervention Bias in classification of interventions: Low risk of bias Post-intervention Bias due to deviations from intended

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out Netherlands **Study type** Retrospective cohort study **Aim of the study** To "… compare hepatic resection with or without neo-adjuvant chemotherapy in combination with RFA to conventional hepatic resection with regard to complications, disease-free survival and overall survival." **Study dates** January 2000 to May 2013 **Source of funding** None reported.	comorbidities between the two groups (P=0.91). Patients from combination group had a significantly higher number of liver metastases (P=0.001), a higher risk profile (CRS 3-5, P=0.00119) and received more neoadjuvant chemotherapy as compared to the patients in resection only group (P=0.001)." Adjuvant chemotherapy, n (%) Resection + RFA 17 (18) Resection alone 61 (12) Tumour size in cm, median (range) Resection + RFA 3 (0.2-15) Resection alone 3 (0.2-18) Tumour number, median (range) Resection + RFA 4 (2-10) Resection alone 1 (1-11) **Inclusion criteria** Patients who received partial hepatic resection or a combination of both RFA and resection in one session for curative treatment of colorectal liver metastases. **Exclusion criteria** Patients with recurrent colorectal liver metastases after previous resection; extrahepatic disease; missing follow-up data; two-stage operations; only RFA treatment; simultaneous resection of the primary tumour and liver metastases.	less than 2 cm) or a needle cluster of three probes (lesions larger than 2 cm) was used."	Statistical analysis - Survival was analysed using the Kaplan-Meier method and log-rank test. Multivariate Cox regression model was used. Variables included in the model were variables/characteristics that were significantly different between the two groups: neoadjuvant chemotherapy, ASA classification and Fong CRS.		interventions: Low risk of bias Bias due to missing data: Low risk of bias Bias in measurement of outcomes: Low risk of bias Bias in selection of the reported result: Low risk of bias
Full citation van der Poel, M. J., Tanis, P. J., Marsman, H. A.,	**Sample size** N = 122. A total of 1020 LCR were included in the study period and used for matching. After	**Interventions** Combined laparoscopic resection of liver metastases and	**Details**	**Outcomes**	**Limitations**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Rijken, A. M., Gertsen, E. C., Ovaere, S., Gerhards, M. F., Besselink, M. G., D'Hondt, M., Gobardhan, P. D., Laparoscopic combined resection of liver metastases and colorectal cancer: a multicenter, case-matched study using propensity scores, Surgical Endoscopy, 01, 01, 2018 **Ref Id** 983852 **Country/ies where the study was carried out:** Belgium, Netherlands **Study type:** Retrospective propensity score-matched study (multi-centre) **Aim of the study:** To determine whether combined laparoscopic resection of liver metastases and colorectal cancer (LLCR) increases postoperative morbidity in comparison with laparoscopic colorectal cancer	matching, 61 LLCR could be compared with 61 LCR." LLCR n = 61; LCR n = 61 Patient characteristics Male sex: LLCR 37 (61); LCR 34 (56), p = 0.719 Age, mean (SD): LLCR 64 (11.6); LCR 64 (13.1), p = 0.949 BMI, kg/m2, median (IQR): LLCR 25.8 (23.4–28.1); LCR 25.2 (23.7–28.5), p = 0.958 ASA grade: ASA 1 - LLCR 15 (25), LCR 14 (23); ASA 2 - LLCR 33 (54), LCR 36 (59); ASA 3 - LLCR 12 (20), LCR 9 (15); ASA 4 - LLCR 1 (2) 2, LCR (3), p = 0.988 Location primary: Rectum - LLCR 12 (20), LCR 18 (30); Sigmoid - LLCR 27 (44), LCR 23 (38); Left colon - LLCR 4 (7), LCR 4 (7); Transverse colon - LLCR 0, LCR 2 (3); Right colon - LLCR 18 (30), LCR 14 (23), p = 0.378 Neoadjuvant chemotherapy: LLCR 12 (20); LCR 5 (8), p = 0.039 Neoadjuvant radiotherapy: LLCR 9 (15), LCR 7 (12), p = 0.687 Type of resection primary: Low anterior resection/sigmoid resection - LLCR 37 (61), LCR 35 (57); Abdominoperineal resection - LLCR 3 (5), LCR 4 (7); Left colectomy - LLCR 4 (7), LCR 4 (7); Right colectomy LLCR 15 (25), LCR 17	colorectal cancer (LLCR) vs laparoscopic colorectal cancer resection (LCR) alone. "The primary tumor was diagnosed based on colonoscopy. Liver metastases were assessed with abdominal computed Surgical technique LLCR mostly started with the liver resection, thereby being able to decide on liver resection only in case a more extensive liver resection than planned based on preoperative imaging was required or more blood loss than expected. Laparoscopic liver resection was performed with the patient in supine position (or semiprone for liver resection of lesions in posterosuperior segments) and the surgeon in between the patient's legs using three to four trocars in the upper abdomen. Laparoscopic ultrasound was used for detection of potentially occult lesions and to determine the plane of transection. Parenchymal transection was performed by usingan ultrasonic dissection or bipolar sealing device alone or	Data collection: Data collected from each centres prospectively collected databases of patients undergoing LLCR or LCR between 2006 and 2017. 61 LLCR patients were matched in a 1:1 ratio using a caliper of 0.1 to LCR alone patients. Outcomes: Treatment related mortality Grade 3 or 4 complications (Clavien-Dindo, including anastomotic leak - diagnosis based on clinical and radiological parameters, including any abscess occurring at the anastomosis, leakage of contrast fluid on imaging, endoscopically proven leakage or clinically suspect leakage requiring a reoperation). Other outcome parameters included operative time, intraoperative blood loss, need for conversion, (to laparotomy, hand-assisted or hybrid technique), reason for conversion (e.g., adhesions, bleeding, inadequate access to the lesion, inadequate progress or other), need for a stoma, resection margins (R0 = tumor free, R1 = microscopic tumor involvement, R2 = macroscopic tumor involvement), pathology reported TNM stage of primary tumor, postoperative hospital stay, readmission (reason and timing) and 30-day mortality." Follow-up: Perioperative period.	30-day mortality: LLCR 0; LCR 1 (2), p = 1.0 Peroperative incidents, Oslo classification: p = 0.237 None: LLCR 52 (85); LCR 56 (92) Grade 1: LLCR 6 (10); LCR 4 (7) Grade 2: LLCR 3 (5); LCR 1 (2) Grade 3: LLCR 0; LCR 0 Stoma, p = 0.317 None: LLCR 51 (84); LCR 46 (75) Double loop ileostomy: LLCR 4 (7); LCR 7 (12) End ileostomy: LLCR 2 (3); LCR 0 End colostomy: LLCR 4 (7); LCR 8 (13) Severe complications: LLCR 9 (15); LCR 13 (21), p = 0.481 Anastomotic leakage: LLCR 5 (8); LCR 4 (7), p = 1.0 Blood loss, ml, median (IQR): LLCR 200 (100–700); LCR 75 (5–200), p = 0.011	Risk of bias assessed using the ROBINS-I checklist for non-randomised studies of interventions Pre-intervention Bias due to confounding: Low risk of bias Bias in selection of participants into the study: Low risk of bias Bias in classification of interventions: Low risk of bias Post-intervention Bias due to deviations from intended interventions: Low risk of bias Bias due to missing data: Low risk of bias Bias in measurement of outcomes: Low risk of bias Bias in selection of the reported result: Low risk of bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
resection (LCR) alone. **Study dates:** Patients treated between 2006 and 2017 were included **Source of funding:** Not reported	(28); Subtotal colectomy - LLCR 2 (3), LCR 1 (2), p = 0.686 Pathology primary tumor: T0 - LLCR 2 (3), LCR 0; T1 - LLCR 2 (3), LCR 2 (3); T2 - LLCR 3 (5), LCR 8 (13); T3 - LLCR 46 (75), LCR 42 (69); T4 - LLCR 8 (13), LCR 9 (15); N+ -LLCR 48 (79), LCR 46 (75) , p = 0.931 **Inclusion criteria:** All patients undergoing LLCR or LCR at one of four centres between 2006 and 2017. No further details reported. **Exclusion criteria:** Not reported.	together with cavitron ultrasonic surgical aspirator (CUSA), with additional haemostasis using bipolar diathermy. Pedicle clamping during laparoscopic liver resection (Pringle manoeuver) was not standard practice. A laparoscopic 60-mm stapler was used to transect the portal pedicle and hepatic vein in case of a left lateral sectionectomy. Additional trocars were placed if necessary for laparoscopic colorectal surgery. A Pfannenstiel or vertical umbilical incision were mostly used for specimen extraction, followed by either an intra- or extracorporeal anastomosis. CT scans with triphasic contrast enhancement and/or liver-specific double-contrast magnetic resonance imaging. To rule out extrahepatic disease, CT-chest and, in selected patients, positron emission tomography scans were used. Prior to surgery, patients were discussed in a multidisciplinary team meeting attended by both liver and	Statistical analysis: Wilcoxin signed rank test, paired T test, McNemar test.	Conversion: LLCR 3 (5); LCR 5 (8), p = 0.687 Readmission: LLCR 7 (12); LCR 8 (13), p = 1.0 Postoperative stay, days, median (IQR): LLCR 6 (5–9); LCR 7 (4–13), p = 0.164 Resection margins, R0: LLCR 57 (93); LCR 61 (100), p = 0.125	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
		colorectal surgeons, gastroenterologists, medical oncologists, radiologists, radiotherapists and pathologists. Based on grading, size and location of the tumor (neo)adjuvant chemo- and/ or radiotherapy regimens were considered according to national guidelines. During work-up, a simultaneous resection was planned when both colorectal primary and liver metastases wereconsidered resectable with curative intention, and the condition of the patient, judged by both the anesthesiologist and surgeon, was considered sufficient. Resectability was defined as the ability to achieve complete resection of the primary tumor as well as all metastases without the need for additional procedures, thus excluding patients with extrahepatic metastases. During the study period, patients requiring major liver resections and patients with liver lesions close to the portal pedicle or hepatic veins were not considered			

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
		candidates for a simultaneous resection. Major liver resection was defined as any resection of 3 or more segments.Emergency colorectal resection because of bowel obstruction or perforation was also a contra-indication for LLCR. Simultaneous resections were usually performed by a single surgeon trained in both colorectal and liver surgery and discussed within the units liver surgery team. A decision regarding the surgical approach (laparoscopic or open) was made independently of the indication for surgery and was based on the patient's performance status and location and size of both the primary tumor and metastases."			
Full citation Wang, L. J., Zhang, Z. Y., Yan, X. L., Yang, W., Yan, K., Xing, B. C., Radiofrequency ablation versus resection for technically resectable colorectal liver metastasis: A propensity score	**Sample size** N = 138 (after propensity score matching). RFA n = 46, hepatic resection n = 98. Patient characteristics Sex: Male/female - hepatic resection 58/34; RFA 29/17, p = 1.000 Age (years): hepatic resection 58.0 (51.0–65.8); RFA 58.5 (50.8–67.0), p = 0.492	**Interventions** Hepatic resection vs RFA	**Details** Data collection: Data collected from 428 consecutive patients who underwent RFA or resection for CRLM at a single centre between November 2010 and December 2015. 1:2 "nearest neighbor" match paradigm was used. Patients were matched using a caliper of 0.15 in each group.	**Results** Liver PFS Local recurrence rate: Resection 6.5%; RFA 15.2%; p = 0.099 Intrahepatic recurrence rate (de novo): Resection 11.9%; RFA 36.9%, P = 0.001	**Limitations** Risk of bias assessed using the ROBINS-I checklist for non-randomised studies of interventions Pre-intervention Bias due to confounding: Low risk of bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
analysis, World Journal of Surgical Oncology, 16 (1) (no pagination), 2018 **Ref Id** 983863 **Country/ies where the study was carried out:** China **Study type:** Retrospective propensity score matched analysis (single centre) **Aim of the study:** To compare recurrence rates and prognosis between resectable CRLM patients receiving either hepatic resection or RFA **Study dates:** November 2010 to December 2015 **Source of funding:** National Natural Science Foundation of China, Beijing Municipal Science & Technology Commission	Preoperative CEA (ng/mL): hepatic resection 6.7 (2.9–22.3); RFA 5.4 (3.2–12.9), p = 0.731 Location of primary cancer (Colon/rectum): hepatic resection 58/34; RFA 30/16, p = 0.802 Timing of metastasis (Synchronous/metachronous): hepatic resection 70/22; RFA 31/15, p = 0.277 T stage (T4/T1–3): hepatic resection 30/62; RFA 16/30, p = 0.798 N stage (N0/N+): hepatic resection 31/61; RFA 16/30, p = 0.899 Median diameter (mm): hepatic resection 30.0 (18.5–35.8); RFA 22.5 (16.8–36.3), p = 0.249 No. of tumors (1/2–3): hepatic resection 75/17; RFA 37/9, p = 0.878 Location of liver metastasis (Unilobar/bilobar): hepatic resection 73/19, RFA 42/4, p = 0.076 Neoadjuvant chemotherapy (Yes/no): hepatic resection 34/58; RFA 22/24, p = 0.220 Extrahepatic disease (Yes/no): hepatic resection 4/88; RFA 5/41, p = 0.160 Comorbidities: Hypertension - hepatic resection 14, RFA 5; Diabetes - hepatic resection 8, RFA 1; Cardiac - hepatic resection 5, RFA		Outcomes: Liver progression free survival, overall survival, disease-free survival Follow-up: All follow-ups ended in July 2018, and the median follow-up was 44 months (range, 6–96 months). Patients were evaluated by contrast-enhanced computed tomography (CE-CT) or MR) at 1 month after resection or RFA procedure. Then, CEA test, MRI of the abdomen, CT of the chest, and MRI or CT of the pelvis were repeated every 3 months for 2 years and every 6 months thereafter. Recurrences were typically identified radiologically. Local recurrence was defined as tumor growth at the treatment site. Intrahepatic recurrence was defined as new liver lesions emerging at a non-treatment site. Systemic recurrence was defined as tumors at both hepatic and extrahepatic sites, including recurrence at the site of the primary tumor. Statistical analysis: Inter-group differences were analysed using the chi-square test, Fisher's exact test, or Student's t test, as appropriate. Survival data were analyzed using the Kaplan-Meier method and the log-rank test. Variableswith a univariate p value of < 0.1 were entered into the Cox regression model for multivariate analysis.	Hepatic recurrence rate: Resection 32.6%; RFA 69.6%, p < 0.001. Systemic recurrence rate: Resection 39.1%; RFA 26.1%, p = 0.129). Time to local recurrence: Not significant, p = 0.083. (Resection n=6; RFA n=6) Overall survival "1 year OS: Resection 97.8%; RFA 95.7% 2 year OS: Resection 83.6%; RFA 91.3% 3 year OS Resection 66.8%; RFA 71.6% Median OS (Kaplan-Meier analyses): Resection 74 months; RFA 59 months p = 0.484 RFA/resection (n=46/n=92):19 vs 21; Relative risk 1.198 (95% CI 0.453 to 1.778), p = 0.494 Median DFS (all patients): Resection 22 months; RFA 14 months (p = 0.032). Median DFS (patients with a tumour size of ≤ 3 cm): Resection 24 months; RFA 21 months (p = 0.41).	Bias in selection of participants into the study: Low risk of bias Bias in classification of interventions: Low risk of bias Post-intervention Bias due to deviations from intended interventions: Low risk of bias Bias due to missing data: Low risk of bias Bias in measurement of outcomes: Low risk of bias Bias in selection of the reported result: Low risk of bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	3; Cerebrovascular - hepatic resection 5, RFA 2; Pulmonary or others - hepatic resection 2, RFA 4, p = 0.232 **Inclusion criteria:** Patients with ≤3 tumors, well-located tumor size of ≤ 5 cm, and absence of uncontrolled extrahepatic disease. Preoperative images were retrospectively viewed to confirm that the patient had technically resectable disease (feasibility of complete macroscopic resection to maintain at least 30% future liver remnant). **Exclusion criteria:** Patients with recurrent CRLM after previous resection or RFA, patients who received both RFA and resection in one session, and those who received palliative treatment.			Time to systemic recurrence: Not significant, p = 0.478 (Resection n=18; RFA n=11) RFA/resection (n=46/n=92): Relative risk 1.661 (95% CI 1.085 to 2.543), p = 0.020	
Full citation 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	**Sample size** N=116 simultaneous resection (up to year 2003); n=21 staged resection (from year 2004 onwards) **Characteristics** Male sex Simultaneous 71/116 Staged 12/21 Median age in the staged group 66 years (range 41-75 years) No other characteristics reported. **Inclusion criteria** Patients with synchronous colorectal liver metastases undergoing resection.	**Interventions** Simultaneous resection of colorectal cancer and liver metastases versus staged resection (delayed liver resection) The study hospital strategy was to have simultaneous resection up to 2003 and from 2004 onwards the hospital strategy was to have two separate resections.	**Details** Patient data accessed from the institutional database. Follow-up "Tumor markers such as carcinoembryonic antigen and carbohydrate antigen 19-9 were determined every 3 months. Ultrasonography, thoracoabdominal CT, or total colonoscopy was performed to examine recurrence." No other details provided. Statistical analysis"Hepatic disease-free survival was calculated by the Kaplan–Meier method, and comparisons were performed using the log-rank test.	**Results** Hepatic recurrence-free survival - Simultaneous n=116; Staged n=21; HR 4.74 (95% CI 1.72 to 13.1), p=0.003	**Limitations** ROBINS-I checklist for non-randomised studies of interventions Pre-intervention Bias due to confounding: Serious risk of bias (Confounding expected, but controlled for but unclear which variables were included in the final model and why) Bias in selection of participants into the study: Low risk of bias At intervention Bias in classification of interventions: Low risk of bias

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Surgery, 12, 1391-1398, 2008 **Ref Id** 850821 **Country/ies where the study was carried out** Japan **Study type** Retrospective cohort study **Aim of the study** To "… examine the changes in metastatic lesions during the interval period and to determine whether the delayed hepatic resection reduces the hepatic recurrence in patients with synchronous CRLM (colorectal liver metastases)." **Study dates** March 1985 to December 2006 **Source of funding** None reported.	**Exclusion criteria** None reported.		Multivariate analysis was performed using the Cox proportional hazards model." Not clearly reported which variables were included in the multivariate model and how these variables were selected. At least the following variables were included in the model: primary nodal involvement, tumour side, number of metastases, and time of resection.		Post-intervention Bias due to deviations from intended interventions: Low risk of bias Bias due to missing data: Low risk of bias Bias in measurement of outcomes: Low risk of bias Bias in selection of the reported result: Serious risk of bias (unclear reporting, not clear if the relative effect reported is hazard ratio.)

ASA: American Society of Anesthesiologists; BMI: body mass index; CA19-9: carbohydrate antigen 19-9; CEA: carcinoembryonic antigen; CI: confidence interval; CLM or CRLM: colorectal liver metastases; CRC: colorectal cancer; CRS: clinical risk score; (CE-)CT: (contrast enhanced) computed tomography; DFS: disease-free suruval; DL-leucovorin: dextro-levogyre form of leucovorin; ECOG: Eastern Cooperative Oncology Group; ENG trial: European Organisation for Research and Treatment of Cancer/National Cancer Institute of Canada Clinical Trials Group/Gruppo Italiano di Valutazione Interventi in Oncologia trial; EORTC: European Organisation for Research and Treatment of Cancer; FFCD trial: Federation Francophone de Cancerologie Digestive trial 9002; FOLFOX: leucovorin (folinic acid), fluorouracil, oxaliplatin; FU: fluorouracil; HR: hazard ratio; ICD-9-CM: International Classification of Diseases, Ninth Revision, and Clinical Modification diagnosis codes; IOUS: intraoperative ultrasound sonography; IQR: interquartile range; KRAS: Kirsten rat gene homolog; LCR: laparoscopic resection of colorectal cancer; LLCR: laparoscopic resection of liver metastases and colorectal caner; L-leucovorin: levogyre form of leucovorin; MRI: magnetic resonance imaging; N: number; NBOCA: National Bowel Cancer Audit; NGA: National Guidleine Alliance; OR: odds ratio; OS: overall survival; PET: positron emission tomography; PHLF: posthepatectomy liver failure; PFS: progression free survival; R0: tumour-free resection margin; R1: microscopic

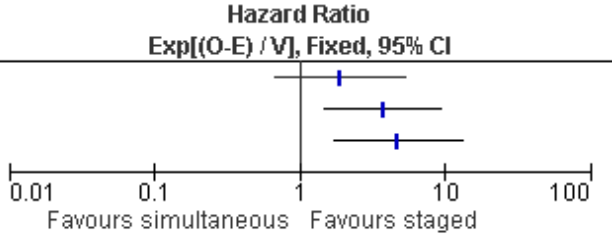
residual tumour in the resection margin; R2: macroscopic residual tumour in the resection margin; RCT: randomised controlled trial; RFA: radiofrequency ablation; ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions; ROG: resection only group; SD: standard deviation; 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 amenable to treatment with curative intent?

Figure 6: Comparison 1: Simultaneous resection versus staged resection – Liver progression-free survival

	Simultaneous		Staged				Hazard Ratio
Study or Subgroup	Events	Total	Events	Total	O-E	Variance	Exp[(O-E) / V], Fixed, 95% CI
Bartolini 2018	0	25	0	14	2.32	3.62	1.90 [0.68, 5.32]
Kaibori 2010 (1)	0	32	0	42	6.05	4.6	3.73 [1.49, 9.29]
Yoshidome 2008 (2)	0	116	0	21	5.8	3.73	4.73 [1.72, 13.06]

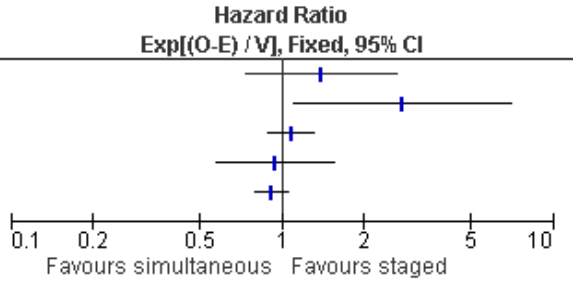


Footnotes
(1) Number of events not reported.
(2) Number of events not reported.

CI: confidence interval; O-E: observed minus expected; V: variance

Figure 7: Comparison 1: Simultaneous resection versus staged resection – Overall survival

	Simultaneous		Staged				Hazard Ratio
Study or Subgroup	Events	Total	Events	Total	O-E	Variance	Exp[(O-E) / V], Fixed, 95% CI
Abbott 2012 (1)	0	60	0	84	3.18	9.44	1.40 [0.74, 2.65]
Bartolini 2018	0	25	0	14	4.62	4.49	2.80 [1.11, 7.06]
Mayo 2013 (2)	0	329	0	675	7.47	97.07	1.08 [0.89, 1.32]
Patrono 2014	30	46	32	60	-0.84	15.48	0.95 [0.58, 1.56]
Vallance 2018 (3)	0	198	0	198	-16.32	195.76	0.92 [0.80, 1.06]

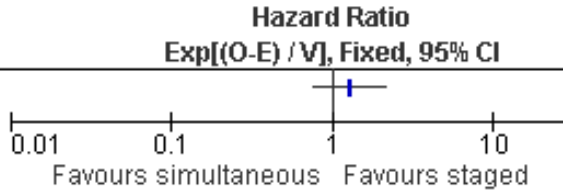


Footnotes
(1) Number of events not reported.
(2) Number of events not reported.
(3) Number of events not reported.

CI: confidence interval; Exp: expected; O-E: observed minus expected; V: variance

Figure 8: Comparison 1: Simultaneous resection versus staged resection – Disease-free survival

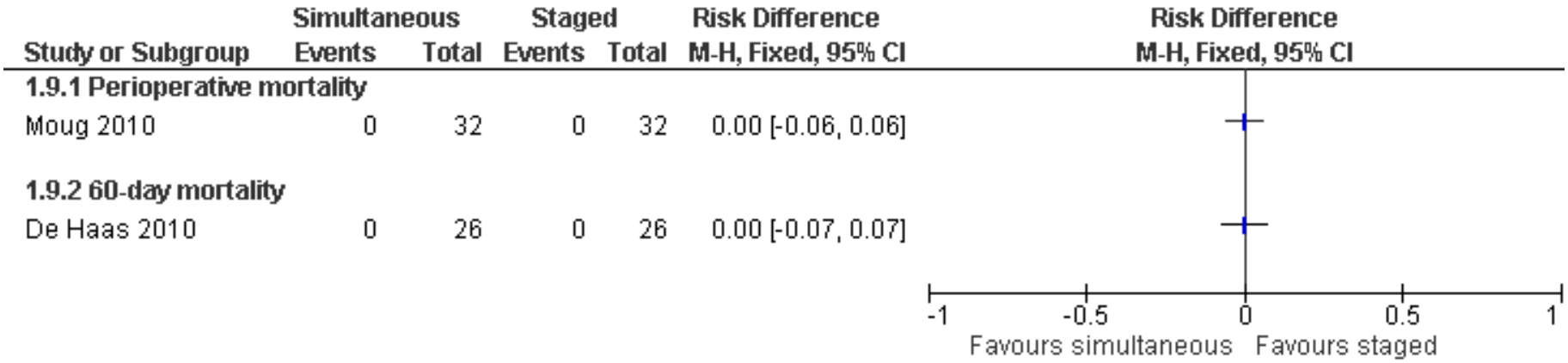
	Simultaneous		Staged				Hazard Ratio
Study or Subgroup	Events	Total	Events	Total	O-E	Variance	Exp[(O-E) / V], Fixed, 95% CI
Abbott 2012 (1)	0	60	0	84	3.74	14.27	1.30 [0.77, 2.18]



Footnotes
(1) Number of events not reported.

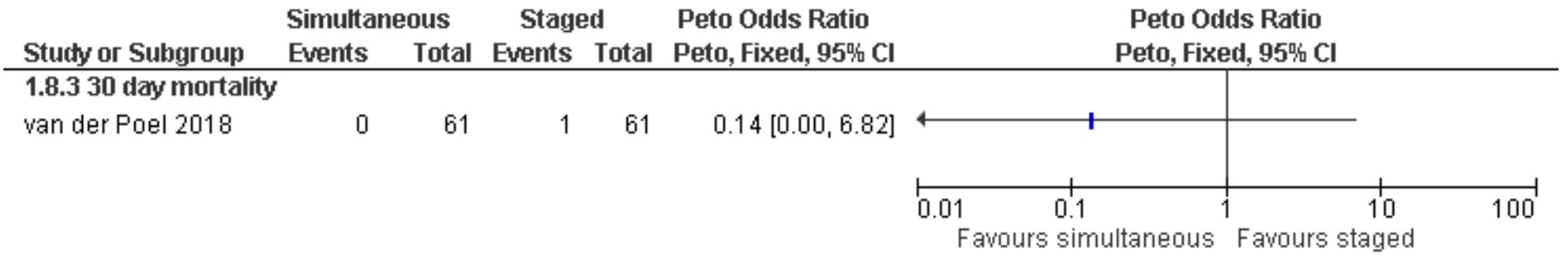
CI: confidence interval; O-E: observed minus expected; V: variance

Figure 9: Comparison 1: Simultaneous resection versus staged resection –Treatment-related mortality



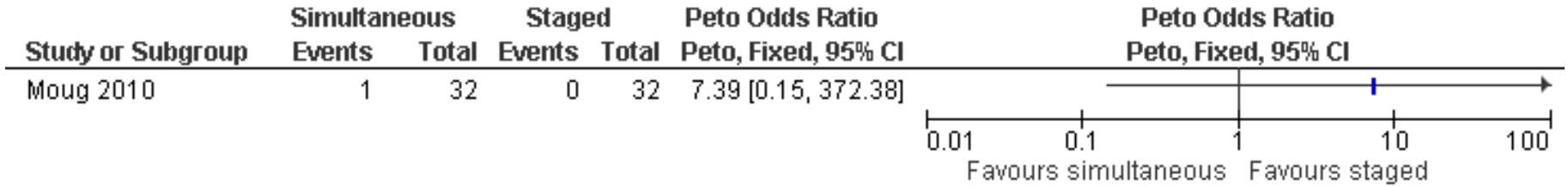
CI: confidence interval; M-H: Mantel Haenszel method

Figure 10: Comparison 1: Simultaneous resection versus staged resection –Treatment-related mortality



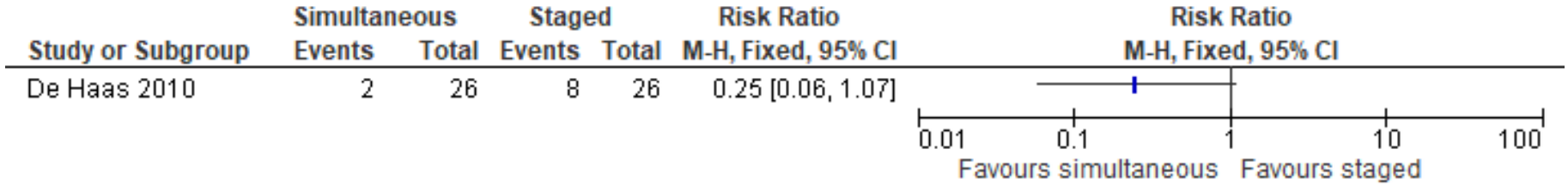
CI: confidence interval

Figure 11: Comparison 1: Simultaneous resection versus staged resection – Grade 3 or 4 adverse events



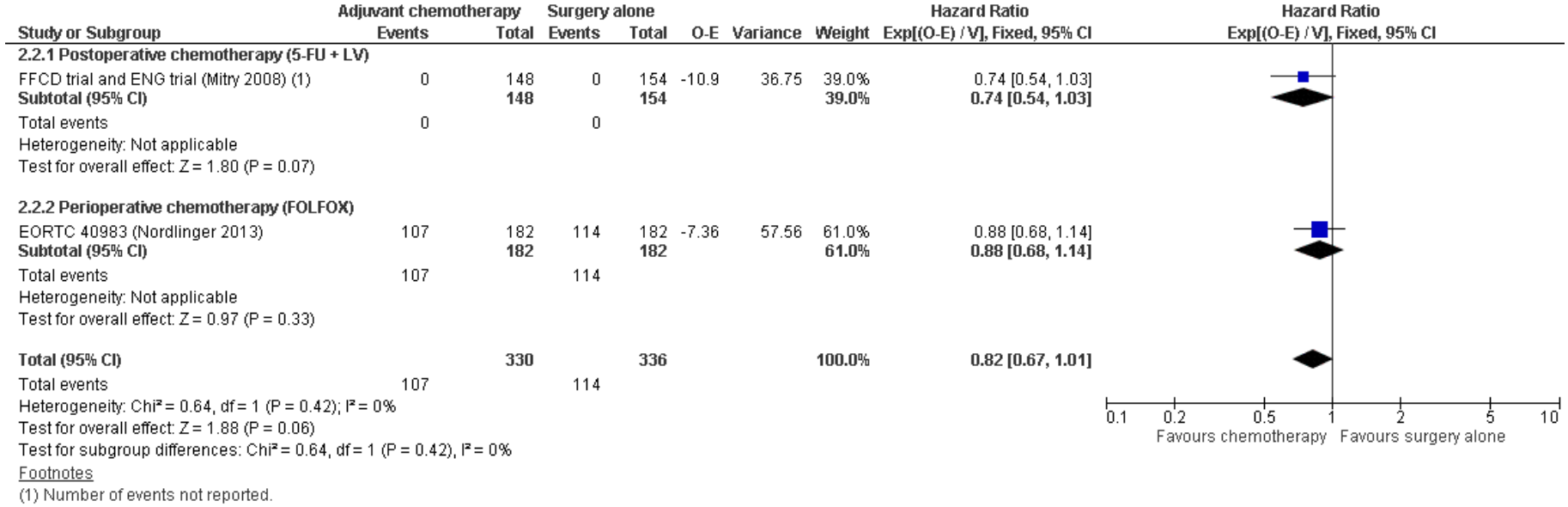
CI: confidence interval

Figure 12: Comparison 1: Simultaneous resection versus staged resection – Postoperative complications



CI: confidence interval; M-H: Mantel Haenszel method

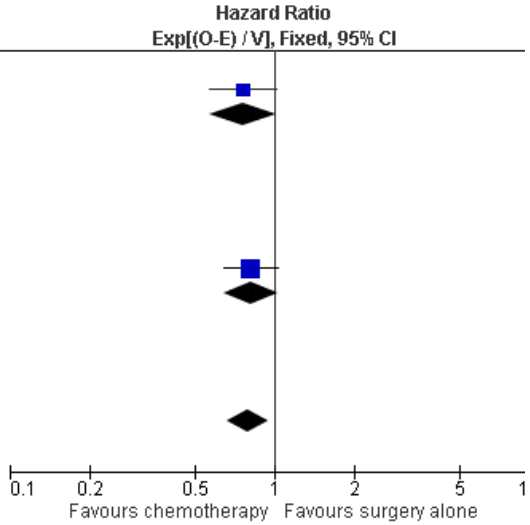
Figure 13: Comparison 2: Adjuvant chemotherapy versus surgery alone – Overall survival



5-FU: fluorouracil; CI: confidence interval; ENG trial: European Organisation for Research and Treatment of Cancer/National Cancer Institute of Canada Clinical Trials Group/Gruppo Italiano di Valutazione Interventi in Oncologia trial; EORTC: European Organisation for Research and Treatment of Cancer; FFCD trial: Federation Francophone de Cancerologie Digestive trial 9002; FOLFOX: leucovorin (folinic acid), fluorouracil, oxaliplatin; LV: leucovorin (folinic acid); O-E: observed minus expected; V: variance

Figure 14: Comparison 2: Adjuvant chemotherapy versus surgery alone – Disease-free survival

Study or Subgroup	Adjuvant chemotherapy Events	Total	Surgery alone Events	Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
2.4.1 Postoperative chemotherapy (5-FU + LV)								
FFCD trial and ENG trial (Mitry 2008) (1)	0	148	0	154	-12.54	45.71	39.3%	0.76 [0.57, 1.02]
Subtotal (95% CI)		**148**		**154**			**39.3%**	**0.76 [0.57, 1.02]**
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.85 (P = 0.06)								
2.4.2 Perioperative chemotherapy (FOLFOX)								
EORTC 40983 (Nordlinger 2013)	136	182	139	182	-14.9	70.73	60.7%	0.81 [0.64, 1.02]
Subtotal (95% CI)		**182**		**182**			**60.7%**	**0.81 [0.64, 1.02]**
Total events	136		139					
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.77 (P = 0.08)								
Total (95% CI)		**330**		**336**			**100.0%**	**0.79 [0.66, 0.95]**
Total events	136		139					
Heterogeneity: Chi² = 0.11, df = 1 (P = 0.74); I² = 0%								
Test for overall effect: Z = 2.54 (P = 0.01)								
Test for subgroup differences: Chi² = 0.11, df = 1 (P = 0.74), I² = 0%								

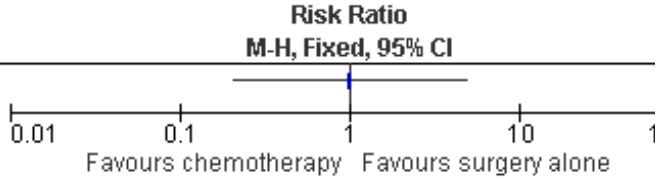


Footnotes
(1) Number of events not reported.

5-FU: fluorouracil; CI: confidence interval; ENG trial: European Organisation for Research and Treatment of Cancer/National Cancer Institute of Canada Clinical Trials Group/Gruppo Italiano di Valutazione Interventi in Oncologia trial; EORTC: European Organisation for Research and Treatment of Cancer; FFCD trial: Federation Francophone de Cancerologie Digestive trial 9002; FOLFOX: leucovorin (folinic acid), fluorouracil, oxaliplatin; LV: leucovorin (folinic acid); O-E: observed minus expected; V: variance

Figure 15: Comparison 2: Adjuvant chemotherapy versus surgery alone – Treatment-related mortality

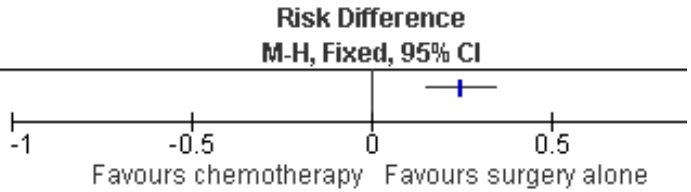
Study or Subgroup	Adjuvant chemotherapy Events	Total	Surgery alone Events	Total	Risk Ratio M-H, Fixed, 95% CI
EORTC 40983 (Nordlinger 2013)	3	182	3	182	1.00 [0.20, 4.89]



CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; M-H: Mantel Haenszel method

Figure 16: Comparison 2: Adjuvant chemotherapy versus surgery alone – Grade 3 or 4 chemotherapy-related adverse events

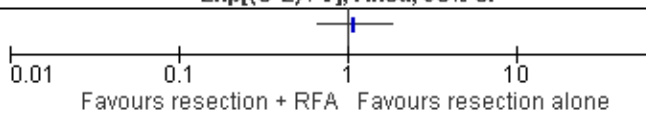
Study or Subgroup	Adjuvant chemotherapy Events	Total	Surgery alone Events	Total	Risk Difference M-H, Fixed, 95% CI
FFCD trial (Portier 2006)	20	81	0	85	0.25 [0.15, 0.34]



CI: confidence interval; FFCD trial: Federation Francophone de Cancerologie Digestive trial 9002; M-H: Mantel Haenszel method

Figure 17: Comparison 3: Liver resection plus RFA versus liver resection alone – Liver progression-free survival

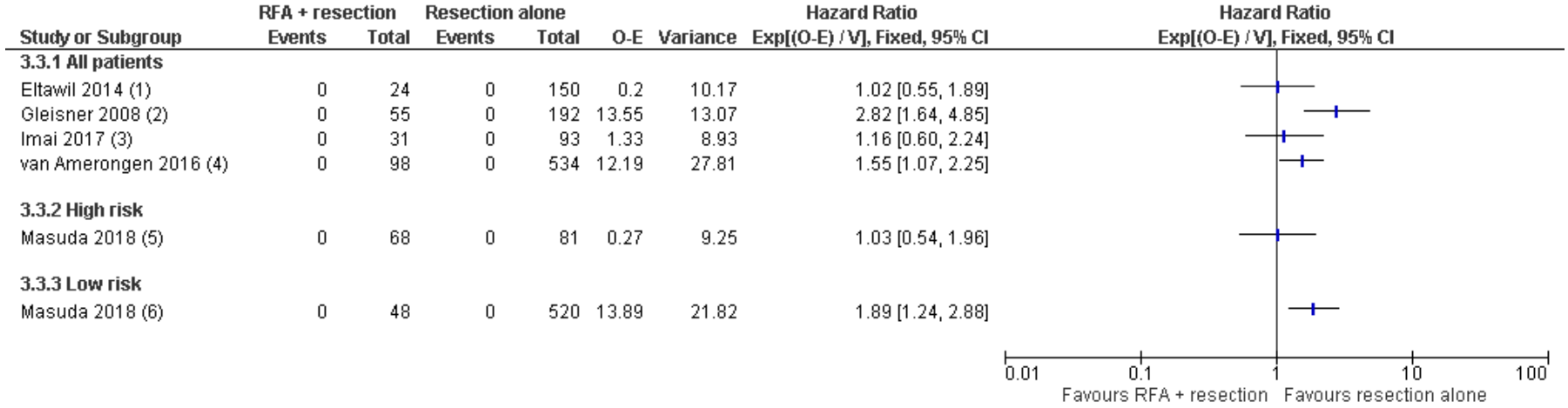
Study or Subgroup	Resection + RFA Events	Total	Resection alone Events	Total	O-E	Variance	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
Imai 2017 (1)	0	31	0	93	1.43	14.97	1.10 [0.66, 1.83]



Footnotes
(1) Number of events not reported.

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

Figure 18: Comparison 3: Liver resection plus RFA versus liver resection alone – Overall survival

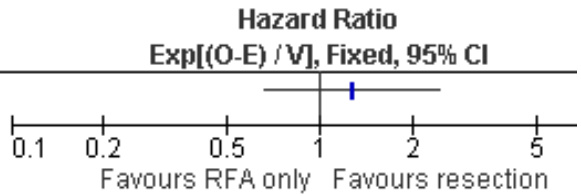


Footnotes
(1) Number of events not reported
(2) Number of events not reported
(3) Number of events not reported
(4) Number of events not reported
(5) Number of events not reported
(6) Number of events not reported

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

Figure 19: Comparison 3: RFA alone versus liver resection alone – Overall survival

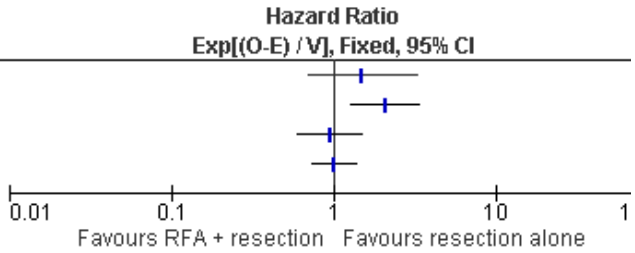
Study or Subgroup	RFA only Events	Total	Resection Events	Total	O-E	Variance	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
Wang 2018	19	46	21	92	2.12	8.89	1.27 [0.66, 2.45]



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

Figure 20: Comparison 3: Liver resection plus RFA versus liver resection alone – Disease-free survival

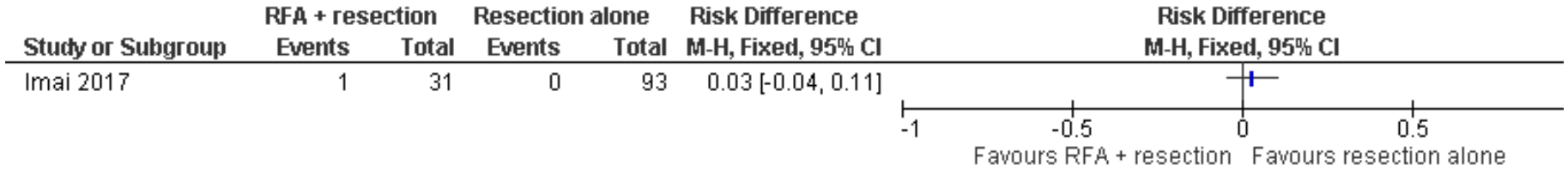
Study or Subgroup	RFA + resection Events	Total	Resection alone Events	Total	O-E	Variance	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
Eltawil 2014 (1)	0	24	0	150	2.64	6.41	1.51 [0.70, 3.27]
Gleisner 2008 (2)	0	55	0	192	11.73	15.91	2.09 [1.28, 3.42]
Imai 2017 (3)	0	31	0	93	-0.75	18.3	0.96 [0.61, 1.52]
van Amerongen 2016 (4)	0	98	0	534	0.52	37.05	1.01 [0.73, 1.40]



Footnotes
(1) Number of events not reported.
(2) Number of events not reported.
(3) Number of events not reported.
(4) Number of events not reported.

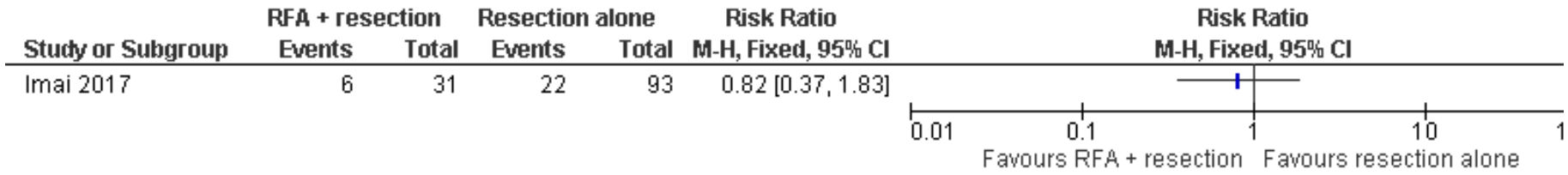
CI: confidence interval; O-E: observed minus expected; RFA: radiofrequency ablation; V: variance

Figure 21: Comparison 3: Liver resection plus RFA versus liver resection alone – 90-day mortality



CI: confidence interval; M-H: Mantel Haenszel method; RFA: radiofrequency ablation

Figure 22: Comparison 3: Liver resection plus RFA versus liver resection alone – Grade 3 or 4 adverse events



CI: confidence interval; M-H: Mantel Haenszel method; RFA: radiofrequency ablation

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 amenable to treatment with curative intent?

Table 7: Clinical evidence profile for comparison 1: Simultaneous resection versus staged resection for metastatic colorectal cancer in the liver amenable to treatment with curative intent

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Simultaneous resection	Staged resection	Relative (95% CI)	Absolute	Quality	Importance
Liver progression-free survival												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	26	14	HR 1.90 (0.68 to 5.50)	Not reported or estimable	VERY LOW	CRITICAL
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	32	42	HR 3.73 (1.49 to 9.29)	At 3 years staged 60%[4], simultaneous 15%	VERY LOW	CRITICAL
1	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	116	21	HR 4.73 (1.72 to 13.06	At 3 years staged 75%[3], simultaneous 26% (2.3% to 61.0%)	VERY LOW	CRITICAL
Overall survival – all patients												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	60	84	HR 1.40 (0.74 to 2.65)	At 3 years staged 65%[5], simultaneous 55% (32% to 73%)	VERY LOW	CRITICAL
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	25	14	HR 2.80 (1.11 to 7.06)	Not reported or estimable	VERY LOW	CRITICAL
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	329	675	HR 1.08 (0.89 to 1.32)	At 5 years staged 44%[6], simultaneous 41% (34% to 48%)	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Simultaneous resection	Staged resection	Relative (95% CI)	Absolute		
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	30/46	32/60	HR 0.95 (0.58 to 1.56)	At 3 years staged 56%, simultaneous 55%	VERY LOW	CRITICAL
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	198	198	HR 0.92 (0.80 to 1.06)	At 3 years staged 65%[5], simultaneous 67% (63% to 71%)	VERY LOW	CRITICAL
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	26	26	Not reported or estimable	At 3 years staged 76%, simultaneous 67%, p=0.78	VERY LOW	CRITICAL
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	106	120	Not reported or estimable	At 5 years staged 43.0%, simultaneous 43.8%, p=0.223	VERY LOW	CRITICAL
1	observational studies	serious[7]	no serious inconsistency	no serious indirectness	serious[2]	none	32	32	Not reported or estimable	At 5 years staged 24%, simultaneous 21%, p=0.84	VERY LOW	CRITICAL
Quality of life												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL
Disease-free survival												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	60	84	HR 1.30 (0.77 to 2.18)	Not reported or estimable	VERY LOW	IMPORTANT
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	26	26	Not reported or estimable	At 1 and 2 years staged 73% and 52%, simultaneous 29% and 13%, p=0.007	VERY LOW	IMPORTANT
Perioperative mortality												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	0/32 (0%)	0/32 (0%)	Risk difference 0 (-0.06 to 0.06)	Not estimable	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Simultaneous resection	Staged resection	Relative (95% CI)	Absolute		
30-day mortality												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	0/61 (0%)	1/61 (1.6%)	Peto OR 0.14 (0.00 to 6.82)	11 fewer per 1000 (from 16 fewer to 115 more)	VERY LOW	IMPORTANT
60-day mortality												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/26 (0%)	0/26 (0%)	Risk difference 0 (-0.07 to 0.07)	Not estimable	LOW	IMPORTANT
Grade 3 or 4 adverse events												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	1/32 (3.1%)	0/32 (0%)	Peto OR 7.39 (0.15 to 372.38)	Not estimable	VERY LOW	IMPORTANT
Major events within 30 days (MI, stroke, PE, shock, in-hospital death)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	99/1088 (9.2%)	35/342 (10.3%)	Adjusted OR 0.72 (0.47 to 1.12)	26 fewer per 1000 (from 52 fewer to 11 more)	VERY LOW	IMPORTANT
Readmission within 30 days												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	190/1088 (17.7%)	74/342 (21.8%)	Adjusted OR 0.71 (0.52 to 0.99)	53 fewer per 1000 (from 90 fewer to 1 fewer)	VERY LOW	IMPORTANT
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	7/61 (11.5%)	8/61 (13.1%)	Not estimable	Not estimable	VERY LOW	IMPORTANT
Return to operating theatre												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	37/1088 (3.4%)	13/342 (3.8%)	Adjusted OR 0.81 (0.41 to 1.59)	7 fewer per 1000 (from 22 fewer to 21 more)	VERY LOW	IMPORTANT
Anastomotic leak												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	153/1088 (14.2%)	39/342 (11.5%)	Adjusted OR 1.29 (0.86 to 1.92)	28 fewer per 1000 (from 15 fewer to 84 more)	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Simultaneous resection	Staged resection	Relative (95% CI)	Absolute		
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	5/61 (8.2%)	4/61 (6.6%)	Not estimable	Not estimable	VERY LOW	IMPORTANT
Acute liver failure												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	1086	341	Adjusted OR 0.38 (0.08 to 1.72)	Not reported or estimable[9]	VERY LOW	IMPORTANT
Liver abscess												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	1086	341	Adjusted OR 1.93 (0.79 to 4.71)	Not reported or estimable[9]	VERY LOW	IMPORTANT
Postoperative complications												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	2/26 (7.7%)	8/26 (30.8%)	RR 0.25 (0.06 to 1.07)	231 fewer per 1000 (from 289 fewer to 22 more)	VERY LOW	IMPORTANT

CI: confidence interval; HR: hazard ratio; MI: myocardial infarction; OR: odds ratio; PE: pulmonary embolism; RR: relative risk
1 Quality of evidence downgraded by 1 because of risk of bias due to confounding (unclear what variables were controlled for in the analysis in one study)
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 Survival percentage at 3 years in the control group estimated using 3-year survival data from Kaibori 2010
4 Survival percentage at 3 years in the control group estimated using 3-year survival data from Yoshidome 2008
5 Survival percentage at 3 years in the control group estimated using 3-year survival data from Vallance 2018
6 Survival percentage at 5 years in the control group estimated using 5-year survival data from Mayo 2013
7 Quality of evidence downgraded by 1 because of risk of bias due to confounding (some important confounding factors were not controlled for)
8 Not estimable due to zero events in both arms
9 Not estimable because number of events not reported

Table 8: Clinical evidence profile for comparison 2: Surgery and SACT versus surgery alone for metastatic colorectal cancer in the liver 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	Surgery and SACT	Surgery alone	Relative (95% CI)	Absolute		
Liver progression-free survival												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgery and SACT	Surgery alone	Relative (95% CI)	Absolute		
0	No evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL
Overall survival - Pooled												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	330	336	HR 0.82 (0.67 to 1.01)	At 5 years surgery alone 47%[2], adjuvant chemotherapy 54% (47% to 60%)	MODERATE	CRITICAL
Overall survival - Postoperative chemotherapy (5-FU + LV)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	148	154	HR 0.74 (0.54 to 1.03)	At 5 years surgery alone 40%[3], adjuvant chemotherapy 50% (38% to 60%)	MODERATE	CRITICAL
Overall survival - Perioperative chemotherapy (FOLFOX)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	107/182 (58.8%)	114/182 (62.6%)	HR 0.88 (0.68 to 1.14)	At 5 years surgery alone 47%[2], adjuvant chemotherapy 51% (42% to 60%)	MODERATE	CRITICAL
Quality of life												
0	No evidence available	-	-	-	-	-	-	-	-	-	-	CRITICAL
Disease-free survival - Pooled												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	330	336	HR 0.79 (0.66 to 0.95)	At 5 years surgery alone 26%[2], adjuvant chemotherapy 35% (28% to 41%)	MODERATE	IMPORTANT
Disease-free survival - Postoperative chemotherapy (5-FU + LV)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	148	154	HR 0.76 (0.57 to 1.02)	At 5 years surgery alone 28%[3], adjuvant chemotherapy	MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Surgery and SACT	Surgery alone	Relative (95% CI)	Absolute		
										38% (27% to 48%)		
Disease-free survival - Perioperative chemotherapy (FOLFOX)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	136/182 (74.7%)	139/182 (76.4%)	HR 0.81 (0.64 to 1.02)	At 5 years surgery alone 26%[2], adjuvant chemotherapy 34% (25% to 42%)	MODERATE	CRITICAL
Treatment-related mortality												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	3/182 (1.6%)	3/182 (1.6%)	RR 1.00 (0.2 to 4.89)	0 fewer per 1000 (from 13 fewer to 64 more)	MODERATE	IMPORTANT
Grade 3 or 4 chemotherapy-related adverse events												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	20/81 (24.7%)	0/85	Risk difference 0.25 (0.15 to 0.34)	250 more per 1000 (from 150 more to 340 more)	MODERATE	IMPORTANT

5-FU: fluorouracil; CI: confidence interval; FOLFOX: leucovorin (folinic acid), fluorouracil, oxaliplatin; HR: hazard ratio; LV: leucovorin (folinic acid); RR: relative risk; SACT: systemic anti-cancer 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 5 years in the control group estimated using 5-year survival data from Nordlinger 2013
3 Survival percentage at 5 years in the control group estimated using 5-year survival data from Mitry 2008

Table 9: Clinical evidence profile for comparison 3: Ablation with or without resection versus liver resection alone for metastatic colorectal cancer in the liver 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	Ablation ± resection	Resection alone	Relative (95% CI)	Absolute		
Liver progression-free survival												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ablation ± resection	Resection alone	Relative (95% CI)	Absolute		
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	31	93	HR 1.10 (0.66 to 1.83)	At 3 years resection alone 40%[2], resection + RFA 37% (19% to 55%)	VERY LOW	CRITICAL
Overall survival												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	24	150	HR 1.02 (0.55 to 1.89)	At 3 years resection alone 61%[3], resection + RFA 60% (39% to 76%)	VERY LOW	CRITICAL
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	55	192	HR 2.82 (1.64 to 4.85)	At 3 years resection alone 75%[4], resection + RFA 44% (25% to 62%)	VERY LOW	CRITICAL
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	31	93	HR 1.16 (0.60 to 2.24)	At 3 years resection alone 80%[2], resection + RFA 77% (61% to 88%)	VERY LOW	CRITICAL
1	observational studies	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	98	534	HR 1.55 (1.07 to 2.25)	At 5 years resection alone 62%[6], resection + RFA 48% (34% to 60%)	VERY LOW	CRITICAL
Overall survival – high risk patients												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	68	81	HR 1.03 (0.54 to 1.96)	Not reported or estimable	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ablation ± resection	Resection alone	Relative (95% CI)	Absolute	Quality	Importance
Overall survival – low risk patients												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	48	520	HR 1.89 (1.24 to 2.88)	Not reported or estimable	VERY LOW	CRITICAL
Overall survival all patients (ablation only versus resection)												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	19/46 (41.3%)	21/92 (22.8%)	HR 1.27 (0.66 to 2.45)	At 3 years resection alone 67%, alblation alone 72%	VERY LOW	CRITICAL
Quality of life												
0	No evidence available									Not reported or estimable[7]		CRITICAL
Disease-free survival												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	24	150	HR 1.51 (0.70 to 3.27)	At 3 years resection alone 29%[3], resection + RFA 15% (2% to 42%)	VERY LOW	IMPORTANT
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	55	192	HR 2.09 (1.28 to 3.42)	At 3 years resection alone 40%[4], resection + RFA 15% (4% to 31%)	VERY LOW	IMPORTANT
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	31	93	HR 0.96 (0.61 to 1.52)	At 3 years resection alone 20%[2], resection + RFA 21% (9% to 38%)	VERY LOW	IMPORTANT
1	observational studies	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	98	534	HR 1.01 (0.73 to 1.40)	At 3 years staged 36%[6], resection + RFA 36% (24% to 47%)	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Ablation ± resection**	**Resection alone**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
90-day mortality												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	1/31 (3.2%)	0/93 (0%)	Risk difference 0.03 (-0.04 to 0.11)	30 fewer per 1000 (from 110 fewer to 40 more)	VERY LOW	IMPORTANT
Grade 3 or 4 adverse events												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	6/31 (19.4%)	22/93 (23.7%)	RR 0.82 (0.37 to 1.83)	43 fewer per 1000 (from 149 fewer to 196 more)	VERY LOW	IMPORTANT

CI: confidence interval; HR; hazard ratio; RFA: radiofrequency ablation; 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 Survival percentage at 3 years in the control group estimated using 3-year survival data from Imai 2017
3 Survival percentage at 3 years in the control group estimated using 3-year survival data from Eltawil 2014
4 Survival percentage at 3 years in the control group estimated using 3-year survival data from Gleisner 2008
5 Quality of evidence downgraded by 1 because of risk of bias due to confounding (some important confounding factors were not controlled for)
6 Survival percentage at 3 years in the control group estimated using 3-year survival data from van Amerongen 2016

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 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 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 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 amenable to treatment with curative intent?

An economic analysis was undertaken to estimate the cost-effectiveness of simultaneous versus staged resection in patients presenting with metastatic colorectal cancer in the liver amenable to treatment with curative intent.

Introduction

Surgical resection is the standard mode of treatment for colorectal cancer presenting with liver metastases when the cancer is amenable to treatment with curative intent. Traditionally, the resection of the primary colorectal cancer and the liver metastasis has taken a staged approach with the resections performed over two surgical operations. In recent times some centres have taken a simultaneous approach performing both resections during the same surgical procedure. A simultaneous approach has potential to both decrease costs and increase patient quality of life and satisfaction through reduced hospitalisation, number of operations and total operating time and reduced perioperative recovery periods. This economic analysis aims to estimate the outcomes, patient quality of life and costs of a simultaneous approach to resection compared to a staged approach in patients with colorectal cancer presenting with liver metastases.

Methods

Population

The model considers patients with colorectal cancer presenting with liver metastases where surgical resection of both the primary cancer and the metastases is considered the most appropriate treatment option. Only patients where the procedure is intended to remove all malignant tissue (R0 margins) are considered by this analysis. Patients were not excluded from analysis based on previous treatment or future planned treatment including systemic anti-cancer therapies (SACTs).

Intervention and comparator

Two approaches to the surgical resection of the cancer were considered in the economic model:

Staged Approach: This approach consists of 2 surgical operations, 1 for the resection of the primary colorectal cancer and 1 for the resection of the liver metastases. The surgical operations are performed during unique hospitalisations and both will consist of standalone pre-operative assessment and preparation, surgical procedure, perioperative recovery and surgical follow-up. Both resections are usually performed within a few months of each other but the model allowed for the second resection to occur within a maximum of 6 months of the first. Whilst the colorectal and liver resection can be performed in either order the majority of staged procedures in England remove the primary colorectal cancer first. This also accounts for the majority of operations used by the studies identified in the accompanying clinical evidence review. The economic model therefore assumes that the colorectal cancer resection is performed prior to the resection of the liver metastases.

Simultaneous Approach: This approach involves 1 surgical operation to resect both the primary colorectal cancer and the liver metastases. Only 1 hospitalisation, pre-operative assessment and preparation, surgical procedure, perioperative recovery period and surgical follow-up is need with this approach.

Other methods of treatment for this patient group were considered by the review protocol including stereotactic ablative radiotherapy (SABR) and adjuvant chemotherapy alongside resection. These were not considered by the economic model as in the case of SABR it was considered unlikely that clinical evidence would be identified to inform the model and there is no clarity on the most appropriate patient group for these techniques or its exact position in any treatment pathway. It was therefore not feasible to meaningfully model such interventions. Adjuvant chemotherapy was not considered by the economic model. It was not considered that having adjuvant radiotherapy could change the preferred option between staged and simultaneous resection. Whilst the use of adjuvant radiotherapy, including whether to use it and what regimen to use, may be of economic interest this question was considered likely to have a greater impact upon quality of life and resource use and was prioritised for bespoke economic modelling.

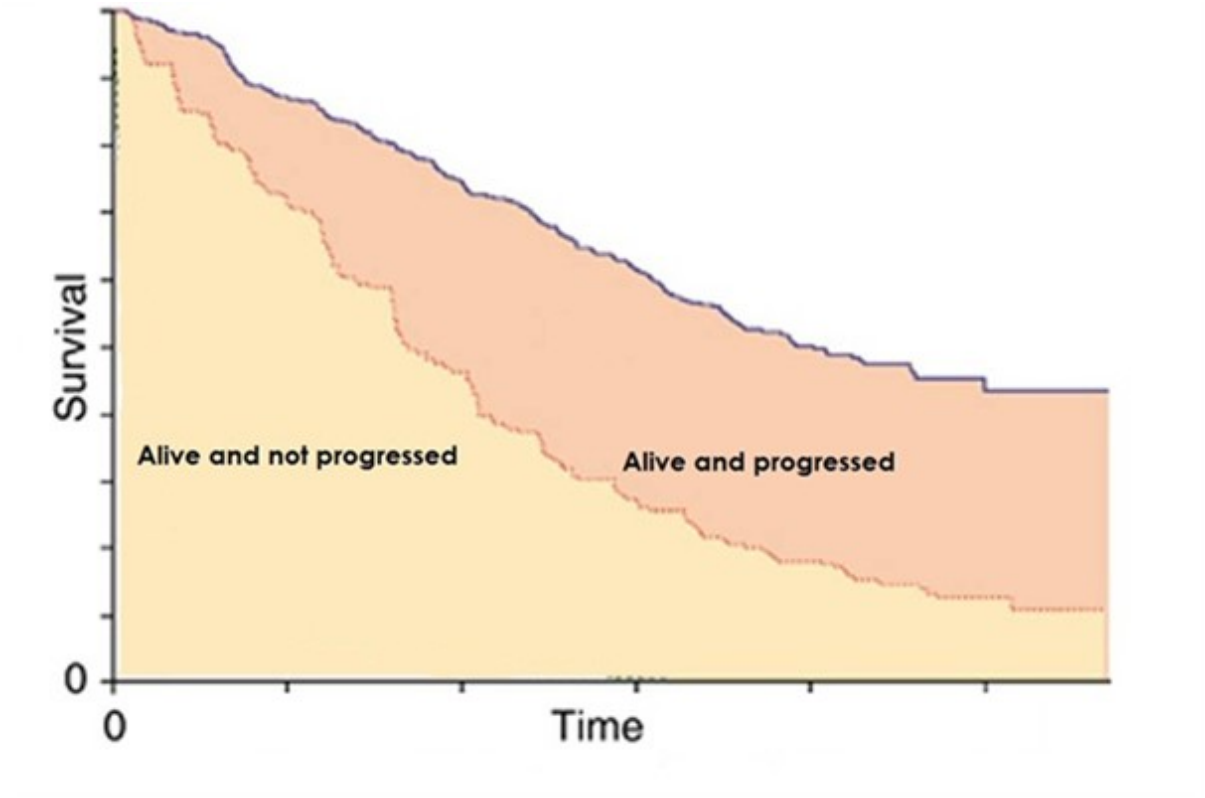
Model Structure

A partitioned survival analysis was developed to estimate the expected life expectancy, quality adjusted life years (QALYs) and costs associated with the 2 approaches considered by this economic analysis. A partitioned survival analysis divides the model cohort between different health states based on survival curves derived for overall survival (OS) and disease-free survival (DFS) derived from the accompanying clinical evidence review. The expected OS and DFS are then calculated from the area under the respective curves. For our model, 3 mutually exclusive health states were derived for the cohort to be partitioned into:

- alive without progressed disease (equal to the area under the DFS curve)
- alive with progressed disease (equal to the area between the DFS curve and the OS curve)
- death (area above the OS curve).

An illustrative example of the structure of the partitioned survival analysis is shown in Figure 23.

Figure 23: Illustrative example of partitioned survival analysis



A partitioned survival analysis approach was chosen over other modelling approaches, for example, a state transition model as only absolute survival estimates at limited set time points were reported by the identified studies and these were the only survival estimates synthesised and reported by the meta-analyses in the accompanying clinical evidence review. Consequently all OS and DFS estimates in the model were derived from these outcomes. Given the scarcity of the time points at which these estimated it was difficult to estimate plausible transition probabilities for use in a state transition model. It was also possible to extrapolate survival beyond that reported by the studies in the accompanying clinical evidence review. How this evidence was used to inform the OS and DFS curves for the economic model is discussed in detail below. This approach is widely used in models of the cost effectiveness of oncology interventions. A review of recent NICE Technology Appraisals in oncology found that this approach was used in 73% of submissions (Woods 2017).

While not a consideration in choosing the most appropriate modelling approach, a partitioned survival analysis is a more intuitive modelling approach for metastases in cancer than state transition models. Evidence from trials and observational studies where survival is a key outcome are almost exclusively reported as median overall and disease or progression-free survival with accompanying hazard ratio and Kaplan Meier survival curves. As these are the primary inputs for partitioned survival analysis the inputs can be easily compared with those

observed in the included trials and other external sources. The model can also be more easily compared, for validity, with any potential future study which consider the relevant interventions.

A partitioned survival analysis was performed for both interventions considered in the economic evaluation and total time spent in each health state for the model cohort was calculated. Each health state was assigned a quality of life weighting so that survival could be adjusted to QALYs.

The economic component of the model was built and run in Microsoft Excel 2013. The model had a cycle length of 1 year. The model had a time horizon of 36 years for which, based on Office of National Statistics (ONS) life tables, over 99.9% of a general population sample would have died (ONS 2018). This percentage would be even higher for a population with metastatic cancer. The model would therefore comfortably cover a sufficient time horizon to capture all outcomes, QALYs and costs. The model took a NHS and Personal Social Services perspective (PSS) and only outcomes relevant to either organisation were considered.

For the reporting of outcomes in the model staged resection was considered the comparator and simultaneous the intervention. The model was run with a hypothetical cohort of 1000 people although costs and outcomes are reported on a per person basis.

Model parameters

Clinical inputs

Socioeconomic and demographics variables

The model assumed a uniform age of the cohort of 60 years of age based and 60% male identical to those reported in the only study (Mayo 2013), identified in the accompanying clinical evidence review, that reported overall survival. The uniform age of the model cohort was not varied during either deterministic or probabilistic sensitivity analysis as evidence was not available, given the 1 study identified, to do this in a meaningful way. The proportion of males was varied using a beta distribution based on the absolute numbers reported (Table 16).

Overall and disease-free survival

Survival curves for the economic model were estimated entirely from the accompanying clinical evidence report. The accompanying clinical evidence review identified one study which reported overall survival for this patient group. (Mayo 2013) The study estimated an absolute overall survival from a staged approach at 44.0% after 5 years. From the same study the hazard ratio for a simultaneous compared to a staged approach was 1.08 (0.89-1.32) suggesting decreased overall survival in the simultaneous approach although the 95% confidence interval crossed the point of no difference. The study was a retrospective cohort study involving 1004 patients. Full details of the study are available in the accompanying clinical evidence review.

It was considered by the committee that retrospective cohort studies would always overestimate the overall survival of the staged approach. This is because there will be a subset of patients in the staged approach who would receive the first stage of the resection, with intention for the second stage, but did not receive both either because of disease progression, change in the frailty of the patient making further surgery inappropriate or through death. This sub patient group is likely to be older, have more aggressive disease or greater comorbidities. Their life expectancy is less than that of the rest of the population. The 3 retrospective studies did not or were unable to identify these patients and they were

excluded from the analysis increasing the mean survival for the cohort. A prospective cohort study or randomised controlled trial would have eliminated this selection bias. Based on single centre cohort studies it is estimated that between 16% and 35% of patients intended to receive both resections in a staged approach will not receive the second operation. (Mayo 2013) The majority of these patients, if simultaneous approach was favoured, would have received both parts of the resection. There is possibly a small number of patients for which performing the first resection, without full intention of performing the second resection (i.e. a planned reevaluation of the disease and patient condition) and that a simultaneous approach maybe inappropriate. Whilst this group is not considered by the economic model they are will be included in the retrospective studies. However, as their number will be small it is unlikely that they will alter the results of the economic model.

Overall survival curves for a staged approach were estimated using the 5 year overall survival and assuming an exponential function in the absence of an estimated Kaplan Meier survival curve. Given the biases in the estimates of survival discussed above it was assumed in the base case that 25.5% of patients intended to receive both resections would only receive the initial one, the median of the two proportions discussed above. It was considered by the committee that such patients would instead receive treatment with non-curative intent given their poor prognosis, advanced cancer or frailty. It was considered by the committee that individuals in this group would follow the prognosis of those enrolled in the FOCUS trial (Seymour 2007). This was an RCT involving 2135 previously untreated patients with advanced colorectal cancer receiving treatment with non-curative intent comparing a number of different treatment strategies. All treatment strategies considered by the RCT reported a median overall survival between 13.9 months and 16.7 months. To approximately account for this omitted group in the base-case overall survival for the staged approach was adjusted to assume that 25.5% of patients had been excluded from the analysis and that these would have a mean survival of 16.7 months the largest median value reported in the FOCUS trial. Mean values were not reported in the trial which would be a more appropriate value to adjust by. The median survival is likely to be an underestimate of the true survival. The overall survival of this subgroup did not vary during the PSA although the proportion of the group was varied on a uniform distribution across the range of reported estimates (16%-35%) from the single centre cohort studies.

The population of the FOCUS trial are about 5 years older, more male and have a worse performance scores compared to the population in Mayo 2013 and assumed for this model. As above though it is assumed tha this subsection of the population would be older and frailer than the rest of the population. The focus study is also reasonably old and survival would now likely be greater. This will be somewhat accounted for in the unadjusted population estimates.

Up to 5 years survival curves for the simultaneous approach were calculated from the hazard ratio reported in the accompanying clinical evidence review and the unadjusted overall survival curve for the staged approach following the usual proportional hazard assumptions. After 5 years in the model equal hazards are assumed. This hazard ratio was varied during probabilistic sensitivity analysis following the 95% confidence interval (0.89-1.32) reported in the accompanying clinical evidence review with a log normal distribution.

Disease-free survival was estimated using similar methods. Again an exponential function was assumed for the 52.0% disease-free survival at 2 years estimated in the accompanying clinical evidence review for the staged approach. Both the baseline rate and relative effect were varied for both overall and disease free survival during PSA. To account for the omitted patients who did not receive both resections it was assumed that all patients in this group would not be disease-free after the first year and the disease-free survival curve was adjusted to account for this. It is unlikely that in a patient in which cancer has not progressed significantly but is fit for surgery that the second resection would not be performed. Disease-

free survival for patients in the simultaneous approach arm was again estimated using the same assumptions as for overall survival using the estimated hazard ratio for disease-free survival (1.30 95% CI 0.77-2.18). Again the hazard ratio was used against the unadjusted disease-free survival curve for the staged approach. The hazard ratio was varied using a log normal distribution. It was assumed there was no correlation between overall and disease-free survival during the PSA although there is some evidence for a weak to moderate relationship between the two outcomes in metastatic colorectal cancer (Cicero 2018). Where during the PSA disease-free survival was estimated to be greater than overall survival it was adjusted to be equal to that of the overall survival estimate. This was to avoid any logical anomalies in the economic model.

A deterministic sensitivity analysis was also performed where no adjustments were made to the overall or disease-free survival estimates from the accompanying clinical evidence review.

All patients who had disease recurrence would receive either further treatment or palliative care. The treatments received did not alter the survival in the model as these were already accounted for in the survival estimates from the observational studies survival estimates are based on. These further treatments were added solely as costs and are discussed in detail below.

Mortality

The model split death into disease specific mortality and other cause mortality. Whilst this made no difference to the overall survival in the economic model it was useful for assigning palliative care costs (discussed below). Other cause mortality was assumed to be identical to that of the general population which was estimated using Office of National Statistics Life Tables for England and Wales 2014-2016. Estimated mortality was weighted by the age and percentage male in the model cohort (ONS 2018). All other death was assumed to be as a result of the metastasised colorectal cancer or related complications.

The accompanying clinical evidence review identified 1 study reporting on treatment-related mortality which did not report on any events. The model therefore assumed that there would be no death as a direct result of the treatment approach received. This assumption was held for all sensitivity analyses.

Adverse events

The proportion of adverse events for either approach was taken from the accompanying clinical evidence review. Only grade 3 and grade 4 adverse events, those deemed either severe or potentially life threatening, were included in the economic model as these were considered to be the only adverse events which would add additional costs, relative to the base resection costs, and reduce quality of life over the usual detriment from significant surgery.

The accompanying clinical evidence review only identified 1 study (Moug 2010) which reported grade 3 and grade 4 adverse events. This study reported 1 adverse event, in the simultaneous group, for the 64 patients divided equally across the arms. This difference was not statistically significant. Adverse events for both arms in the economic model were inputted, in absolute terms, identically to the values reported in Moug 2010 (3% staged, 0% simultaneous). The committee highlighted that they thought such adverse events were likely to be very rare in these patient groups and, if there was to be any difference between the two groups, it was most clinically plausible for it to be higher in the staged group where a greater number of operations are needed.

Perioperative period

For all resections there will be some perioperative period given that this is a relatively major operation. Patients will have to spend some period of time in hospital following resection regardless of whether a staged or simultaneous approach is taken. For the purposes of the model the perioperative period was assumed to be equal to the length of stay in hospital although it is acknowledged that recovery after surgery is likely to continue after discharge from hospital. However, the significant health detriments and costs are most likely to occur during this hospitalised period.

Length of stay in the study was estimated from one US costing study a retrospective study at 1 US hospital of 224 patients undergoing resection either as a staged or simultaneous procedure between 1990 and 2012 (Ejaz 2014). The studied reported a median length of stay of 7 days for the simultaneous approach and 13 days (total across both resections) for the staged approach. These perioperative periods were applied to all patients in the model.

Resource use and costs

Cost of resection and resection related complications

All resection costs were taken from NHS Reference Costs 2016/17 (Department of Health 2018). For the staged approach resection was best matched by the currency description 'Complex Large Intestine Procedure' for the colorectal resection and 'Complex, Hepatobiliary or Pancreatic Procedure' performed on an inpatient basis. Both procedures reported differing reference costs based on the number of clinical complications of the patient. As the model structure modelled complications from surgery separately the cost of either was based on the no complications (CC score 0-2) reference cost. The total costs of a staged approach was equal to the two weighted mean costs combined.

As the model cohort did not exclude any patient based on comorbidities a weighted mean of all costs reported were used for all currency descriptions with complications reported. This weighted cost then had the no complications cost subtracted to estimate a cost of complications. To avoid double counting of complications between the 2 resections a mean cost of the estimated complications cost for both stages was applied in the model. Costs were weighted based on the total number of full consultant episodes (FCE) reported in the reference costs. 'Complex Large Intestine Procedure' reported reference costs for both patients under and over 19 years of age. Given the 60 year average age used for the cohort of the model only the over 19 year of age costs were included (Table 10).

In the staged approach arm of the model for patients who receive the first stage (colorectal cancer resection) but do not proceed to the second stage their total cost of procedure will be equal just the primary colorectal cancer resection cost.

Table 10: NHS reference costs used to estimate the cost of staged resection

Currency Code	Currency Description	FCE Weight	Reference Costs
Primary colorectal cancer resection cost			
FF31D	Complex Large Intestine Procedures, 19 years and over – with CC score 0-2 *(no complications)*		£7,370.66
FF31A	Complex Large Intestine Procedures, 19 years and over – with CC score 9+	9%	£13,567.94

Currency Code	Currency Description	FCE Weight	Reference Costs
FF31B	Complex Large Intestine Procedures, 19 years and over – with CC score 6-8	19%	£10,626.33
FF31C	Complex Large Intestine Procedures, 19 years and over – with CC score 3-5	72%	£8,810.93
		Weighted mean cost	£9,567.27
		Procedure cost	£7,370.66
		Complication cost	£2,196.61
Liver metastases resection cost			
GA04D	Complex, Hepatobiliary or Pancreatic Procedure - without complications-with CC score 0-2 (no complications)		£8,599.49
GA04C	Complex, Hepatobiliary or Pancreatic Procedure - without complications-with CC score 3+		£11,554.36
		Procedure cost	£8,599.49
		Complication cost	£2,954.87
		Total procedure cost	**£15,970.15**
		Average complication cost	**£2,575.74**

FCE: full consultant episode; CC: clinical complications

To estimate the cost of the resections in the simultaneous approach it was not appropriate to combine the 2 costs as undertaken for the staged approach. This is because both sets of costs would include costs for pre-assessment, surgical preparation, anaesthesia, time in surgical theatre and many other items that can be 'shared' between the 2 procedures by combining them. This will lead to both reduced overall operating time and resource use.

No currency description was identified in the NHS Reference Costs which was applicable to the simultaneous approach. To estimate the cost for the simultaneous approach the cost of the staged approach was adjusted using data on total operative time and length of stay in hospital. Abbott 2012, identified in the accompanying clinical evidence review, estimated that total operating time in the simultaneous approach was 144 minutes shorter compared to the staged approach. This was converted into a cost using estimates from Ramsay 2012. Ramsey 2012 was a systematic review and economic model of laparoscopic and robotic surgery for the removal of the prostate in individuals with prostate cancer. The economic model estimated a cost per hour of operating time of £1,266. This was converted into a cost for the 144 minutes difference and subtracted from the staged approach cost. Whilst removal of a prostate is fundamentally a different type of surgical operation, the pay grade and number of personnel in attendance and size of operating theatre would be almost identical

between the 2 and it was the committee's opinion that this was a reasonable estimate of operating costs.

Length of stay in hospital also differed between the 2 arms of the model with simultaneous approach resulting in 6 less days in hospital as discussed above. This reduced time in hospital was again converted into a cost. This was done by using the excess bed day costs for 'Complex Large Intestine Procedures, 19 years and over' again weighted against the FCEs in the NHS Reference Costs. This mean cost was then multiplied by the reduction in days and subtracted from the procedure cost for the staged approach. This was in addition to the adjustment for operative time. The cost of complications was assumed to be identical to that of the staged approach. Full details of how costs for the simultaneous approach were calculated are presented in Table 11.

Table 11: Estimation of the cost of a simultaneous approach

Parameter	Weight	Input	Source
Estimation of reduction in costs due to reduced hospitalisation			
FF31A Complex Large Intestine Procedures, 19 years and over – with CC score 9+ additional bed day	6%	£247.57	NHS Reference Costs
FF31B Complex Large Intestine Procedures, 19 years and over – with CC score 6-8 additional bed day	18%	£298.73	NHS Reference Costs
FF31C Complex Large Intestine Procedures, 19 years and over – with CC score 3-5 additional bed day	23%	£354.04	NHS Reference Costs
FF31D Complex Large Intestine Procedures, 19 years and over – with CC score 0-2 (no complications) additional bed day	53%	£326.78	NHS Reference Costs
Mean cost per day of hospitalisation		£323.36	NHS Reference Costs
Reduction in hospital length of stay simultaneous vs staged		6 days	Ejaz 2014
Total reduction in costs due to reduced hospitalisation (A)		**£1,940.16**	
Estimation of reduction in costs due to reduced operating time			
Cost per hour of operating time		£1,265.90	Ramsey 2012
Reduction in operating time simultaneous vs staged		144 minutes	Abbott 2012
Total reduction in costs due to reduced operating time (B)		**£3,038.16**	
Total reduction in costs of simultaneous vs staged			
Total cost of procedure-staged approach		£15,970.15	
Combined reduction in cost simultaneous approach (A+B)		£4,978.32	
Total cost of procedure-simultaneous approach		**£10,991.83**	

CC: clinical complications

Resource use and cost of further treatment

All patients who have disease recurrence will go on to receive further treatment or if not appropriate palliative care. Of those patients with recurrent disease who go on to receive further treatment three broad types of treatment were identified by the committee-hepatic resection, extrahepatic resection and chemotherapy. Hepatic resection is an identical surgical operation to the liver resection stage of the staged approach. It was assumed that

given the post-surgical surveillance these patients would be under that any recurrence would be identified reasonably quickly and that complications from any operation in this group would be minimal. Extrahepatic resection is defined as where disease has recurred near to but outside of the liver most commonly in the bile ducts. Chemotherapy was the treatment choice for patients with recurrence in either the hepatic or extra-hepatic regions where this is not amenable to treatment or to other parts of the body where surgery would not be considered appropriate.

The proportion of patients going on to receive further treatment was taken from a UK cost utility study comparing operable to non-operable treatments for liver metastases (Roberts 2015). The study was excluded from the economic evidence review as comparisons of operable to non-operable treatments were outside of the scope of the protocol. The proportion for each type of treatment was taken from one prospectively maintained database of individuals undergoing surgery or chemotherapy for liver metastases at 1 UK hospital between 1992 and 2001. Estimates of the proportion of patients undergoing each type of further treatment are presented in Table 12.

Table 12: Estimate of proportions undergoing each type of treatment from Roberts 2015

Parameter	Weight
Hepatic resection	21%
Extrahepatic resection	14%
Non-operable (chemotherapy)	64%

Costs for both hepatic and extrahepatic resection were again taken from NHS Reference Costs. Hepatic resection was costed identically to the resection part of the staged approach although the assumption was made, given the follow-up of these patients, that the recurrence would be identified rapidly and the 'Complex, Hepatobiliary or Pancreatic Procedure - without complications-with CC score 0-2' description and costs were assumed. Extrahepatic resection was costed as 'Complex Thoracic Procedures, 19 years and over' and as for other procedures in the model a weighted average of all CC scores was calculated based on FCEs in an inpatient setting. The estimated costs for both approaches are presented in Table 13.

Table 13: Estimation of hepatic and extrahepatic resection costs

Currency Code	Currency Description	FCE Weight	Reference Costs
Hepatic resection costs			
GA04D	Complex, Hepatobiliary or Pancreatic Procedure - without complications-with CC score 0-2 (no complications)		£8,599.49
Extrahepatic resection costs			
DZ02K	Complex Thoracic Procedures, 19 years and over-with CC score 0-2	37%	£6,522.66
DZ02J	Complex Thoracic Procedures, 19 years and over-with CC score 3-5	39%	£7,562.42
DZ02H	Complex Thoracic Procedures, 19 years and over-with CC score 6+	24%	£9,982.05
		Weighted mean cost	**£7,757.61**

FCE: full consultant episode; CC: clinical complications

For disease recurrence, which was considered not amenable to resection, patients received systemic chemotherapy treatment. Two chemotherapy regimens were used by the economic model which were considered to cover the majority of chemotherapy received in the NHS for this patient group following inoperable disease recurrence-FOLFOX and FOLFIRI. An annual cost for each regimen was estimated based on committee estimates of the quantity of each component and the number of cycles. Patients who had recurred disease and received chemotherapy were assumed to continue receiving it annually until death and the cost was applied for every 1 year model cycle. The resource use and quantity for the chemotherapy regimens used in the study are presented in Table 14 . Prices were taken from the 'Drug and Pharmaceutical Electronic Market Information Tool' (eMit) [Accessed March 2019] for all drug components. Administration costs were taken from NHS Reference Costs 2016/17 using the currency description 'Deliver Complex Chemotherapy, including Prolonged Infusional Treatment, at First Attendance' on a day case and regular day/night basis. Given the costs for both chemotherapy regimens were almost identical (less than £1 difference) no differentiation was made between them in the model and a mean cost of the two regimens was applied to all patients receiving chemotherapy following recurrence.

Table 14: Cost of chemotherapy treatment following recurrence

Component	Cost	Source
FOLFOX		
Deliver complex chemotherapy at first attendance	£385.99	NHS Reference costs 2016/17
Dexamethasone 8mg	£1.52	eMit
Ondansetron 16mg	£0.17	eMit
Chlorphenamine 10mg	£3.01	eMit
Oxaliplatin 85mg/m2	£16.04	eMit
Folinic Acid 350mg	£10.42	eMit
Fluorouracil 400mg/m2	£3.94	eMit
Fluorouracil 2400mg/m2	£8.36	eMit
Cost per cycle	£429.45	
Total cost for 6 cycles	£2,576.72	
FOLFIRI		
Deliver complex chemotherapy at first attendance	£385.99	NHS Reference costs 2016/17
Atropine 250mcg	£0.12	eMit
Irinotecan 180mg/m2	£17.35	eMit
Folinic Acid 350mg	£10.42	eMit
Fluorouracil 400mg/m2	£3.94	eMit
Fluorouracil 2400mg/m2	£8.36	eMit
Cost per cycle	£426.18	
Total cost for 6 cycles	£2,557.09	
Average cost of systemic chemotherapy regimens	**£2,566.91**	

FOLFIRI: folinic acid, fluorouracil and irinotecan; FOLFOX: folinic acid, fluorouracil and oxaliplatin

The committee also considered that cetuximab or panitumumab may be used for patients whose disease recurs but is not amenable to further surgery. Cetuximab or panitumumab is used in the NHS in conjunction with Cetuximab and panitumumab for previously untreated metastatic colorectal cancer (TA439) alongside either the FOLFOX or FOLFIRI chemotherapy regimens. This may either be given to shrink cancer tumours to allow surgery

or to palliate. Resource impact tools for TA439 estimated that 65% of patients receiving either FOLFIRI or FOLFOX for metastatic cancer would receive this alongside cetuximab or panitumumab.

The list prices for cetuximab is £890.50 for a 100ml vial and panitumumab £1,517.16 per 20ml vial Both drugs are currently provided to the NHS, by the manufacturers, under the terms of a confidential patient access scheme (for panitumumab) and commercial access agreement (for cetuximab) and the cost to the NHS is likely to be significantly less than the list price. It has not been possible to transparently include these costs in the economic model. Therefore, costs for cetuximab and panitumumab were not included in the base-case analysis. This does not imply that these costs will not be significant but that the access agreements are priced so that the net benefit, assuming NICE's threshold of £20,000 per QALY gained is identical to society's willingness to pay per QALY gained, then the addition of either drug to FOLFIRI or FOLFOX will have no impact upon the incremental cost effectiveness ratios or ultimately the decision around the preferred approach to resection. A deterministic sensitivity analysis was also undertaken which used the list price for both drugs to investigate if this would alter the preferred approach to resection. These 2 values were considered to cover all plausible costs.

Cost of palliative care

Given the relatively short life expectancy of the model cohort and that the majority of patients would die as a result of their disease a one off cost of palliative care was applied to the entirety of the cohort during their final year of life. This is to represent the increase in resource use experienced during the final months of a patient's life. This one off cost was taken from Georghiou 2014. The study used medical records of over 1,836 patients with cancer at multiple UK hospitals and hospices to estimate resource use and publically available UK costs to estimate a total cost for the final 90 days of life. An average cost for patients with cancer was used from the report. These costs are presented in Table 15.

Table 15: Costs of palliative care for patients with cancer from Georghiou 2014

Type of care	Cost
Cost of all hospital contacts	£5,890
Local authority-funded care	£444
District nursing care	£588
GP contacts	£365
Total palliative care cost per patient	**£7,287**

The above costs includes 'local authority-funded care'. The methods of calculation from the original report may include costs, such as personal contributions to care, which are not strictly covered by the NHS & PSS perspective used for this economic model. A deterministic sensitivity analysis was therefore undertaken which removed this cost from the total palliative care cost estimate.

Quality of life

Quality of life weights for the model were taken from previous cost-effectiveness study of patients (identical in age to our cohort) with rectal cancer (Rao 2017). The Markov simulation model compared radical surgery to a 'watch and wait' and wait approach. The model estimated utility weights both following surgery and radiation (0.86) and following disease recurrence (0.78) based on the authors clinical opinion, a previous Dutch study of resection and a previous cost effectiveness study of treatment for recurrent rectal cancer (Miller 2000). These represented the disease-free and disease recurrence groups in our model. These utility weights were used to adjust overall survival and calculate QALYs. The committee

considered that these utilities were probably an overestimate of the true utility of this cohort given the morbidity from major surgery. The difference between disease-free and recurrent disease was also considered too small with recurrent disease likely to lead to greater anxiety, morbidity from further surgery or adverse events from chemotherapy or other treatment. These values were therefore given a wide range during the PSA.

Utility values for the peri-operative period was taken from an economic evaluation conducted alongside the SANICS II RCT investigating the use of perioperative enteral nutrition in patients undergoing colorectal surgery (Pattamatta 2019). This was an RCT of 265 patients at 3 large Dutch hospitals and 2 Danish hospitals. Participants in the study completed the EuroQol 5 dimension 5 level (EQ-5D-5L) questionnaire and scored using the 'Dutch tariff' preferences elicited from the general population of the Netherlands. It was the committee's opinion that patients in this trial would have identical quality of life during the perioperative period as for the patient group in the model cohort. As the study reported higher quality of life for the perioperative stage then the disease-free state used in our model (0.89 versus 0.86) it would not have been logical to include this value in our model and imply that quality of life is greater during a patients stay in hospital then when they are disease-free. A QALY detriment was therefore calculated for the perioperative period which was equal to the difference of the highest and lowest reported utilities values, in the patient group, during the RCT. This was the difference between presurgery and at 3 months post surgery where quality of life had decreased by 0.06 points. The utility weight for the peri-operative period was therefore the disease-free utility state (0.86) minus this difference. The utility weight used for peri-operative period in the model was therefore 0.80.

Death was given a utility value of 0 in the model as is standard in economic evaluations.

Inflation

All costs in the model were converted and inflated to UK sterling 2017 prices, to match the cost year from the NHS Reference Costs, using the IMF Purchasing Power Parities for Healthcare and inflation indices reported by Curtis 2018 where necessary.

Discounting

All health and cost outcomes were discounted at a rate of 3.5% per annum in line with developing NICE guidelines: the manual. This was not varied during sensitivity analyses.

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis was also conducted to assess the combined parameter uncertainty in the model. In this analysis, the values that are utilised in the base-case are replaced with values drawn randomly from the distributions assigned to them. This was done for 10,000 iterations and the different outcomes of these iterations presented both diagrammatically (in the forms of a cost effectiveness plane and cost effectiveness acceptability curve) and in terms of mean from these iterations to reflect the uncertainty around the inputs and consequently the outcomes of the model. The distributions for all parameters used during the probabilistic sensitivity analysis are presented in Table 16.

Table 16: Distributions used during the probabilistic sensitivity analysis

	Value	Source	PSA Distribution
Demographics			
Age	60	Mayo 2013	Fixed
Gender (%male)	60%	Mayo 2013	Beta(598,406)

	Value	Source	PSA Distribution
Overall survival			
Staged resection	44.0%	Clinical Evidence Review	Beta(297,378)
Simultaneous resection - HR	1.08	Clinical Evidence Review	Log Normal(1.08,0.10)
Disease-free survival			
Staged resection	52.0%	Clinical Evidence Review	Beta(14,12)
Simultaneous resection - HR	1.30	Clinical Evidence Review	Log Normal(1.30,0.27)
Cost and resource use			
Proportion complications 'Complex Large Intestines Procedures, 19 years and over			
with CC Score 9+ (FF31A)	9%	NHS Reference Costs 2016/17	Dirichlet
with CC Score 6-8 (FF31B)	19%	NHS Reference Costs 2016/17	Dirichlet
with CC Score 3-5 (FF31C)	72%	NHS Reference Costs 2016/17	Dirichlet
Complex Large Intestine Procedures, 19 years and over - cost			
with CC Score 9+ (FF31A)	£13,567.94	NHS Reference Costs 2016/17	Gamma(13568,303)
with CC Score 6-8 (FF31B)	£10,626.33	NHS Reference Costs 2016/17	Gamma(10626,136)
with CC Score 3-5 (FF31C)	£8,810.93	NHS Reference Costs 2016/17	Gamma(8811,43)
with CC Score 0-2 (FF31D)	£7,370.66	NHS Reference Costs 2016/17	Gamma(7371,17)
Complex, Hepatobiliary or Pancreatic Procedures - weight			
Complex, Hepatobiliary or Pancreatic Procedures, with CC Score 3+	30%	NHS Reference Costs 2016/17	Dirichlet
Complex, Hepatobiliary or Pancreatic Procedures, with CC Score 0-2	70%	NHS Reference Costs 2016/17	Dirichlet
Complex, Hepatobiliary or Pancreatic Procedures - cost			
Complex, Hepatobiliary or Pancreatic Procedures, with CC Score 3+	£11,554.36	NHS Reference Costs 2016/17	Gamma(11554,170)
Complex, Hepatobiliary or Pancreatic Procedures, with CC Score 0-2	£8,599.49	NHS Reference Costs 2016/17	Gamma(8599,79)
Excess bed day (Complex Large Intestine Procedures, 19 years and over) - weight			
with CC Score 9+ (FF31A)	6%	NHS Reference Costs 2016/17	Dirichlet

	Value	Source	PSA Distribution
with CC Score 6-8 (FF31B)	18%	NHS Reference Costs 2016/17	Dirichlet
with CC Score 3-5 (FF31C)	23%	NHS Reference Costs 2016/17	Dirichlet
with CC Score 0-2 (FF31D)	53%	NHS Reference Costs 2016/17	Dirichlet
Excess bed day (Complex Large Intestine Procedures, 19 years and over) - cost			
with CC Score 9+ (FF31A)	£247.57	NHS Reference Costs 2016/17	Gamma(248,2)
with CC Score 6-8 (FF31B)	£298.73	NHS Reference Costs 2016/17	Gamma(299,4)
with CC Score 3-5 (FF31C)	£354.04	NHS Reference Costs 2016/17	Gamma(354,4)
with CC Score 0-2 (FF31D)	£326.78	NHS Reference Costs 2016/17	Gamma(327,2)
Excess bed day (Complex, Hepatobiliary or Pancreatic Procedures) - weight			
Complex, Hepatobiliary or Pancreatic Procedures, with CC Score 3+	85%	NHS Reference Costs 2016/17	Dirichlet
Complex, Hepatobiliary or Pancreatic Procedures, with CC Score 0-2	15%	NHS Reference Costs 2016/17	Dirichlet
Excess bed day (Complex, Hepatobiliary or Pancreatic Procedures) - cost			
Complex, Hepatobiliary or Pancreatic Procedures, with CC Score 3+	£457.65	NHS Reference Costs 2016/17	Gamma(458,10)
Complex, Hepatobiliary or Pancreatic Procedures, with CC Score 0-2	£535.27	NHS Reference Costs 2016/17	Gamma(535,15)
Complex Thoracic Procedures, 19 years and over - weight			
with CC Score 6+ (DZ02H)	24%	NHS Reference Costs 2016/17	Dirichlet
with CC Score 3-5 (DZ02J)	39%	NHS Reference Costs 2016/17	Dirichlet
with CC Score 0-2 (DZ02K)	37%	NHS Reference Costs 2016/17	Dirichlet
Complex Thoracic Procedures, 19 years and over - cost			
with CC Score 6+ (DZ02H)	£9,982.05	NHS Reference Costs 2016/17	Gamma(9982,30)
with CC Score 3-5 (DZ02J)	£7,562.42	NHS Reference Costs 2016/17	Gamma(7562,43)
with CC Score 0-2 (DZ02K)	£6,522.66	NHS Reference Costs 2016/17	Gamma(6523,32)
FOLFOX			
Deliver complex chemotherapy at first attendance	£385.99	eMIT	Gamma(386,0.45)

	Value	Source	PSA Distribution
Dexamethasone 8mg	£1.52	eMIT	Gamma(1.52,0.00)
Ondansetron 16mg	£0.17	eMIT	Gamma(0.17,0.00)
Chlorphenamine 10mg	£3.01	eMIT	Gamma(3.01,0.00)
Oxaliplatin 85mg/m2	£16.04	eMIT	Gamma(16.04,0.30)
Folinic Acid 350mg	£10.42	eMIT	Gamma(10.42,0.04)
Fluorouracil 400mg/m2	£3.94	eMIT	Gamma(3.94,0.00)
Fluorouracil 2400mg/m2	£8.36	eMIT	Gamma(8.36,0.02)
FOLFIRI			
Deliver complex chemotherapy at first attendance	£385.99	eMIT	Gamma(386,0.45)
Atropine 250mcg	£0.12	eMIT	Gamma(0.12,0.00)
Irinotecan 180mg/m2	£17.35	eMIT	Gamma(17.35,0.02)
Folinic Acid 350mg	£10.42	eMIT	Gamma(10.42,0.04)
Fluorouracil 400mg/m2	£3.94	eMIT	Gamma(3.94,0.00)
Fluorouracil 2400mg/m2	£8.36	eMIT	Gamma(8.36,0.02)
Palliative care costs			
Cost of all hospital contacts	£5,890	Georghiou 2014	Uniform(2945,8835)
Local authority-funded care	£444	Georghiou 2014	Uniform(222,666)
District nursing care	£588	Georghiou 2014	Uniform(294,882)
GP contacts	£365	Georghiou 2014	Uniform(183,548)
Quality of life weights			
Event free or remission	0.86	Rao 2017	Beta(42,7)
Recurrence	0.78	Rao 2017	Beta(19,6)
Peri-operative period	0.80	Pattamatta 2019	Fixed

CC: clinical complications; FOLFIRI: folinic acid, fluorouracil and irinotecan; FOLFOX: folinic acid, fluorouracil and oxaliplatin; GP: general practitioner; PSA: probabilistic sensitivity analysis

Results

Base-case results

The base case results of the analysis are shown in Table 17. The results show an increase in life expectancy of half a year with the simultaneous approach corresponding to a 0.28 QALY increase compared to the staged approach. The simultaneous approach also led to reduction in costs just below £2,500. In the base-case analysis the simultaneous approach dominated (was both cost saving and health increasing).

Table 17: Base-case results

Strategy	Life Expectancy (year)		Cost		QALYs		ICER (cost per QALY)
	Total	Incremental	Total	Incremental	Total	Incremental	
Staged	3.80		£31,749	-	3.22	-	-
Simultaneous	4.30	0.51	£29,282	*-£2,467*	3.51	*0.28*	**Dominant**

ICER: incremental cost-effectiveness ratio; QALYS: quality-adjusted life years

When the unadjusted results of the accompanying clinical evidence review are used to inform the economic model and adjustments for survival have not been made to account for individuals who only received the first resection life expectancy is now higher in the staged group with an associated higher QALY as well (Table 18). The simultaneous approach remains cost saving (even more so given the larger number of liver resections in the staged approach). If a £20,000 per QALY threshold is considered, in line with Developing NICE guidelines: the manual, the reduction in costs would not justify the decrease in QALYs, that is only £16,506 is saved for every QALY forgone.

Table 18: Results of the economic model using values reported in the accompanying clinical evidence review

Strategy	Life Expectancy (year)		Cost		QALYs		ICER (cost per QALY)
	Total	Incremental	Total	Incremental	Total	Incremental	
Staged	4.62		£33,942	-	3.79	-	-
Simultaneous	4.30	0.51	£29,282	*-£4,660*	3.51	*-0.28*	£16,506

ICER: incremental cost-effectiveness ratio: QALYs: quality-adjusted life years

The conclusions of both the base-case and alternative assumption remain when the list prices of cetuximab and panitumumab are included and when local authority costs are removed from the estimate of palliative care. As both of these assumptions are considered the upper bound alternative to the base-case assumptions, and they did not alter the conclusions of the model, intermediate estimate of these value are not presented. The difference between both approaches for the percentage of the cohort receiving cetuximab or panitumumab or palliative care was never greater than 3% and therefore even more extreme assumptions would not alter these results unless unfeasibly large or small.

Table 19: Incremental costs effectiveness ratios from alternative assumptions (simultaneous versus staged approach)

	ICER (cost per QALY)	
	Cetuximab and panitumumab costs included	Local authority costs excluded
Base-case assumptions	Simultaneous dominant	Simultaneous dominant
Clinical evidence review assumptions	£17,034†	£16,532†

ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years
†For both these ICERs the simultaneous approach both cost saving and health decreasing. Lower ICERs are more favourable to the staged approach.

Probabilistic Sensitivity Analysis

Base-case assumptions

The results of 10,000 runs of the PSA are shown using ICER scatterplots and cost-effectiveness acceptability curves (CEAC). The ICER scatter plots show the incremental costs and QALYs associated with each of the 10,000 runs of the PSA along with the mean result. The CEAC graphs show the probability of each strategy being considered cost-effective at the various cost-effectiveness thresholds on the x axis.

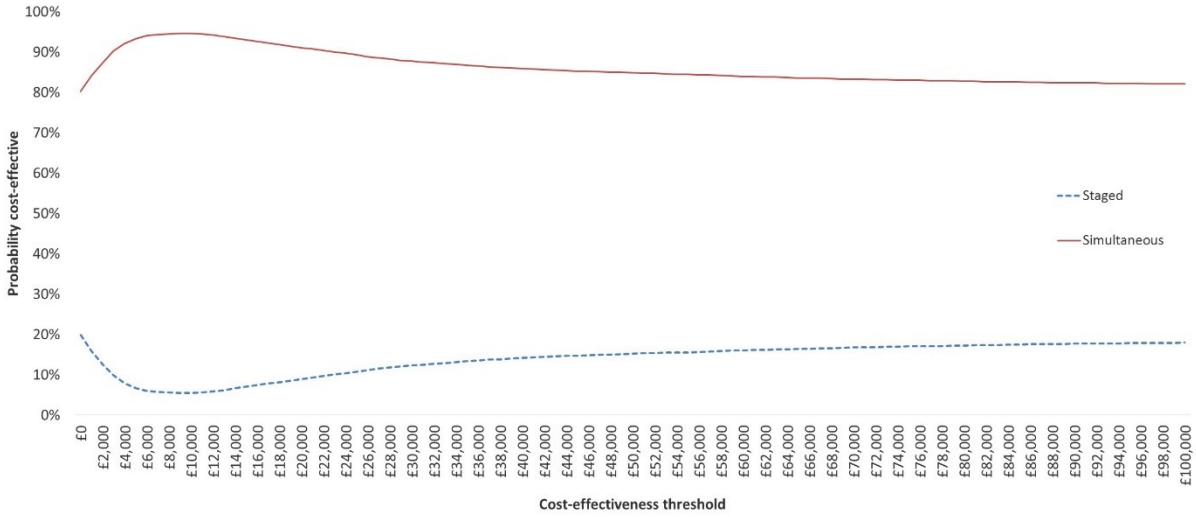
Figure 24 presents the probabilistic results of the base case analysis. Of these 10,000 iterations over 75% of them are health improving (to the right of the Y-axis) and over 80% are cost decreasing (below the X-axis) with the majority of iterations being both cost saving and health increasing.

Figure 24: ICER scatterplot base case results

CE: cost effectiveness; ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years

Figure 24 presents the CEAC for the base case results. The probability that the simultaneous approach is the preferred option is 80% at a cost effectiveness ratio of £0 i.e. where the cheapest option is preferred. At £20,000 threshold there is a 86% probability of the simultaneous approach being the preferred option. This remains above 80% beyond values above the £100,000 threshold. For no threshold does a staged approach become the preferred option.

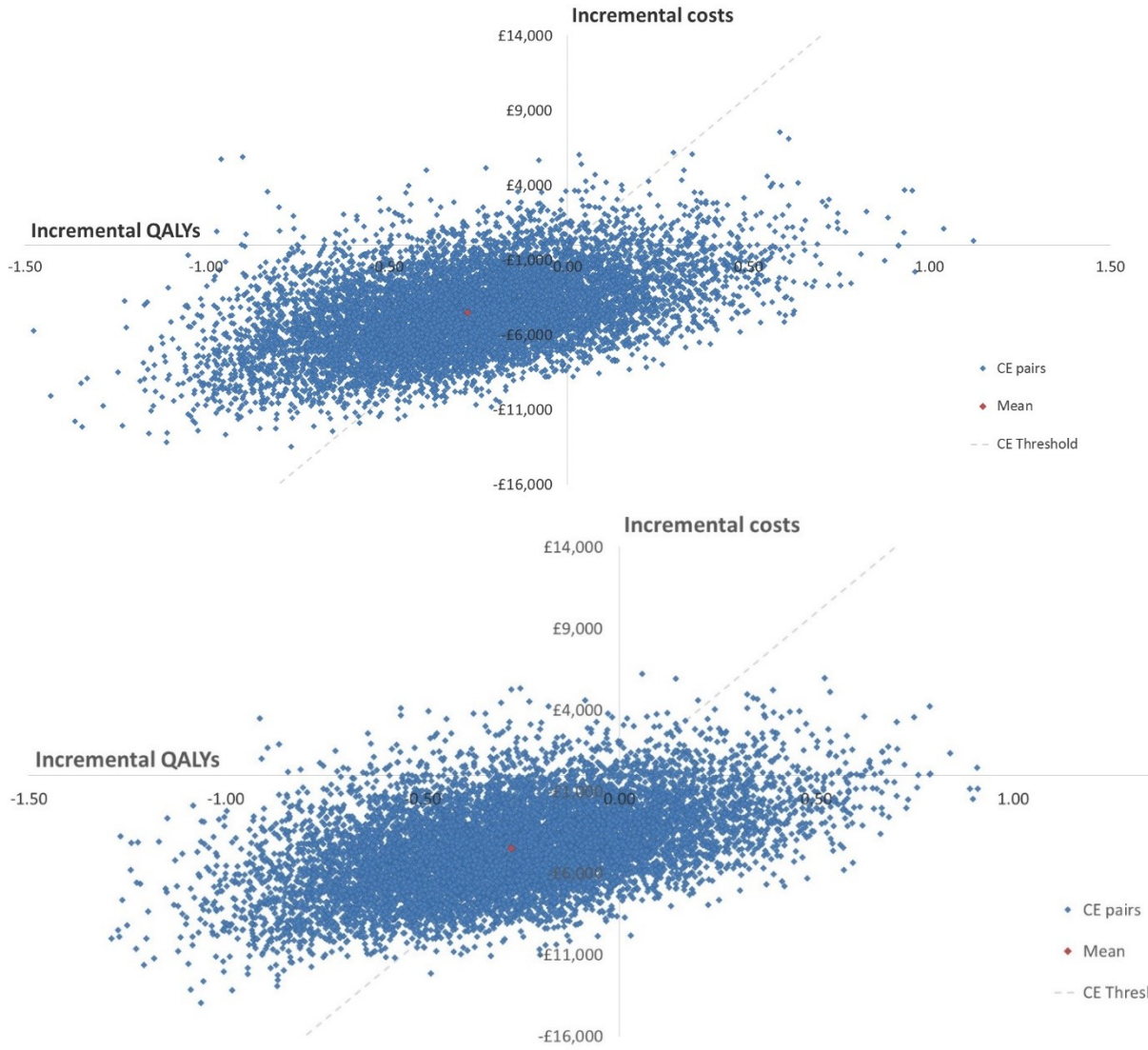
Figure 25: Cost effectiveness acceptability curve base case results



Clinical evidence review values results

When results from the clinical evidence review are used to inform the economic model there is a greater degree of uncertainty around the results. (Figure 26) When these inputs are considered a greater number of iterations show the simultaneous approach as cost saving (94%) but with only 20% of iterations being health improving.

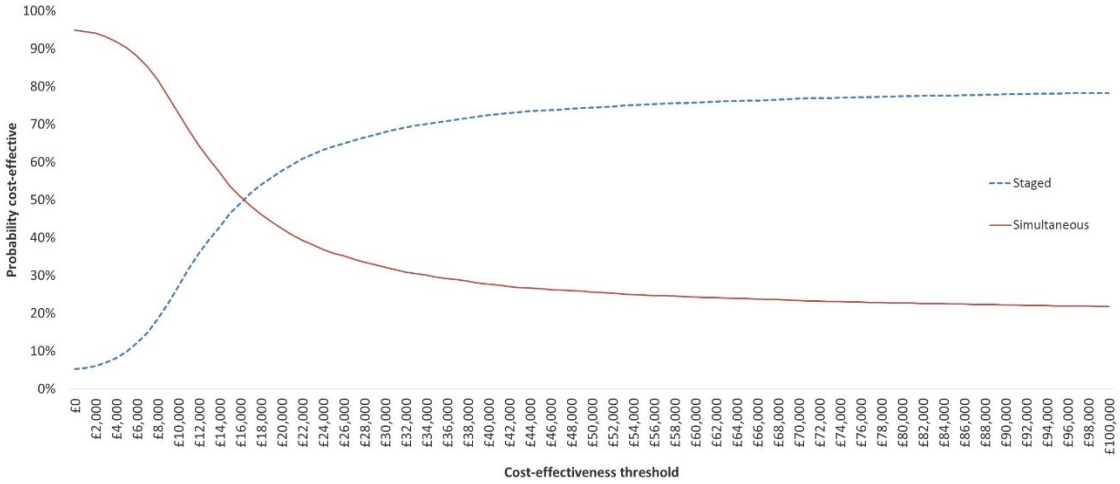
Figure 26: ICER scatterplot clinical evidence review inputs



CE: cost effectiveness; ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life years

The CEAC for this analysis shows uncertainty around the preferred option (Figure 27). At the £20,000 threshold 42% showed the simultaneous approach to be cost effective although as shown by the scatterplot the majority of these would also be health decreasing. As the threshold increases the probability of the staged approach being the most cost effective option also increases. The threshold at which the CEACs cross and we are indifferent between the two options is £17,000 per QALY.

Figure 27: Cost effectiveness acceptability curve clinical evidence review inputs



Conclusions

Both versions of the model gave differing results. The base-case results, where survival in the staged approach had been adjusted, showed the simultaneous approach as both health improving and cost saving. This conclusions was robust to both probabilistic and deterministic sensitivity analysis. The secondary analysis using survival estimates from the accompanying clinical evidence review presented the simultaneous approach as health decreasing and cost decreasing but not cost effective although the PSA highlighted considerable uncertainty around this conclusion. Given the sensitivity of survival estimates to the conclusions of the economic model and the biases with the observational data used to inform the economic model it was difficult to form strong conclusions from either model.

1 Appendix K – Excluded studies

2 Excluded clinical studies for review question: What is the optimal combination 3 and sequence of treatments in patients presenting with metastatic colorectal 4 cancer in the liver amenable to treatment with curative intent?

5 **Table 20: 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, 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
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., 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	Observation study, RCT evidence exists and prioritised
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 and resectable synchronous liver metastases, Clinical Colorectal Cancer, 7, 197-201, 2008	A decision analysis model using existing clinical data, references checked individually
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 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 metastasis of colorectal carcinoma after hepatectomy, Hepato-Gastroenterology, 45, 805-811, 1998	Intervention/comparison not of interest
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	Protocol for a RCT

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	
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 colorectal surgery, Annals of Surgical Oncology, 14, 195-201, 2007	No multivariate analysis
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	No multivariate analysis for relevant comparison and outcome

decisional model, Annals of surgical oncology : the official journal of the Society of Surgical Oncology, 14, 1143-1150, 2007	
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 multivariable 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-Spheres versus SIR-Spheres alone in chemotherapy-resistant colorectal cancer liver metastases, Journal of Gastrointestinal Oncology, 8, 608-613, 2017	Observational study, RCT evidence on SIRT available and prioritised
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., Radiofrequency ablation versus resection for resectable colorectal liver metastases: Time for a randomized trial?, Annals of Surgical Oncology, 15, 11-13, 2008	Editorial

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)
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, (2) (no pagination), 2009	Cochrane review that has been withdrawn in the later updates due to overlap with another 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, 2018 (1) (no pagination), 2018	Protocol for a Cochrane 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 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	Conference abstract
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	Intervention/comparison not relevant (colon resection with MWA or RFA versus colon resection alone)

colorectal liver metastases, American Journal of Surgery, 210, 1185-1191, 2015	
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
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
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	Included in review D2b (liver metastases not amenable to treatment with curative intent)
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 Postoperative Complications, World Journal of Surgery, 41, 1073-1081, 2017	Observational study, RCT evidence exists and prioritised
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
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 (Structured abstract), Health Technology Assessment Database, 2011	Non-English language paper
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 = Huazhong keji daxue xuebao. Yixue Yingdewen ban. 36, 514-518, 2016	Populations are not similar and would not both be candidates for both approaches compared
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
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, Jl, 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	Included in review D2b (liver metastases not amenable to treatment with curative intent)

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., 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 with synchronous colorectal liver metastases, Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract, 14, 1258-1264, 2010	Interventions compared not of interest
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
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.)
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 colorectal cancer: Japan Clinical Oncology Group Study JCOG0603, Japanese Journal of Clinical Oncology, 39, 406-409, 2009	Trial protocol
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	Intervention/comparison not of interest

[corrected to Des Guetz, Gaetan]], Diseases of the Colon & Rectum, 54, 930-8, 2011	
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	Conference abstract

society for radiation oncology, ASTRO 2016. United states, 96, S163, 2016	
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	Populations are not similar and would not both be candidates for both approaches compared

analysis, World Journal of Gastroenterology, 21, 3300-3307, 2015	
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 multivariable 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	Population includes non-colorectal liver malignancies, no

metastases, European Journal of Gastroenterology and Hepatology, 25, 442-446, 2013	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 multivariable 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 case-controlled study, Annals of Surgical Oncology, 14, 3519-3526, 2007	Observational study, RCT evidence exists and prioritised
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. 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	Included in review D2b (liver metastases not amenable to treatment with curative intent)

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
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
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., 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
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
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 chemotherapy, Annals of Surgical Oncology, 16, 1860-1867, 2009	No comparison group
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
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 multivariable 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
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.,	Intervention/comparison not relevant. The original study

Martin, R. C., Single-stage resection and microwave ablation for bilobar colorectal liver metastases, The British journal of surgery, 103, 1048-1054, 2016	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
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-operative chemotherapy, Journal of Surgical Oncology, 113, 456-462, 2016	No relevant outcomes reported by relevant comparison

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
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.,	Included in review D2b (liver metastases not amenable to treatment with curative intent)

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	
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	Included in review D2b (liver metastases not amenable to treatment with curative intent)
Sabanathan, D., Eslick, G. D., Shannon, J., Use of Neoadjuvant Chemotherapy Plus Molecular Targeted Therapy in Colorectal Liver Metastases: A Systematic Review and Meta-analysis, Clinical Colorectal Cancer, 15, e141-e147, 2016	Interventions not relevant for this review
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	Ex[pert review and summarises results from the SIRFLOX trial (reported in another publication)

SIRFLOX Trial?, Current Treatment Options in Oncology, 17 (6) (no pagination), 2016	
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 hepatic metastases from colorectal cancer, Annals of Surgical Oncology, 10, 348-354, 2003	No relevant intervention/comparison
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 simultaneous resection?, ANZ Journal of Surgery, 85, 829-33, 2015	Observational study, no multivariable analysis done
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 liver tumors: A systematic review, Archives of Surgery, 141, 181-190, 2006	No relevant comparative data presented
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
van Amerongen, M. J., Jenniskens, S. F. M., van den Boezem, P. B., Futterer, J. J., de Wilt, J. H. W., Radiofrequency ablation	A systematic review, included studies checked for relevance

compared to surgical resection for curative treatment of patients with colorectal liver metastases - a meta-analysis, Hpb, 19, 749-756, 2017	
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 synchronous liver metastases, British Journal of Surgery, 97, 383-390, 2010	No multivariate analysis
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 in review D2b. No additional relevant outcomes reported in this publication
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	Included in review D2b (liver metastases not amenable to treatment with curative intent)
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.,	Included studies/reviews, checked for relevance

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	
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 approach' for patients with locally advanced rectal cancer and synchronous liver metastases, Diseases of the Colon and Rectum, 52, 23-30, 2009	No comparison group
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
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colorectal liver metastases: A meta-analysis, World Chinese Journal of Digestology, 3349-3355, 2014	
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
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., 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., 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	Included in review D2b (liver metastases not amenable to treatment with curative intent)
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,	A review protocol

Cochrane Database of Systematic Reviews, (1) (no pagination), 2007	
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
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 amenable to treatment with curative intent?

No research recommendations were made for this review question.